LBA4000 **Oral Abstract Session**

Efficacy and safety results from EMERALD-3: A phase 3, randomized study of tremelimumab plus durvalumab with or without lenvatinib combined with trans-arterial chemoembolization (TACE) in participants (pts) with unresectable embolization-eligible hepatocellular carcinoma (eeHCC).

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Camrelizumab (C) plus rivoceranib (R) with transarterial chemoembolization (TACE) vs TACE alone in unresectable hepatocellular carcinoma (uHCC): A randomized, phase 3 trial.

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Background: The combination of C (anti–PD-1 antibody) + R (VEGFR2 tyrosine kinase inhibitor) significantly improved progression-free survival (PFS) and overall survival (OS) vs sorafenib as first-line treatment for advanced HCC, and improved event-free survival vs surgery alone as perioperative treatment for resectable HCC. We conducted a phase 3 trial evaluating C+R with TACE in intermediate-stage HCC and here present data from the protocol-specified PFS interim analysis (IA). **Methods:** In this multicenter, open-label, phase 3 trial, patients (pts) with TACE-eligible uHCC, Child-Pugh A, ECOG performance status (PS) 0–1 and no extrahepatic spread were randomized 1:1 to receive C (200 mg, iv, Q3W) + R (250 mg, po, QD) + TACE or TACE alone. TACE (cTACE or DEB-TACE) was administered at the investigator (INV)'s discretion; C+R continued until loss of clinical benefits, unacceptable toxicities, or other protocol-specified criteria. The primary endpoint was PFS by BIRC per mRECIST. As of Sep.13, 2025, 214 PFS events occurred and a preplanned IA was performed. **Results:** 423 pts (ECOG PS 1, 22.9%; AFP ≥400 ng/mL, 26.7%; portal vein invasion [vp1/2], 9.7%) were randomized to C+R+TACE (n=214) or TACE (n=209). As of data cutoff, median follow-up was 16.4 mo. Median PFS by BICR per mRECIST was significantly longer with C+R+TACE vs. TACE (11.1 vs. 8.3 mo; HR 0.73 [95% CI 0.56–0.96]; 1-sided p=0.0127). PFS by BICR per RECIST v1.1 (13.9 vs 9.5 mo; HR 0.67 [95% CI 0.50–0.91]) and by INV per mRECIST (13.8 vs 7.0 mo; HR 0.61 [95% CI 0.47–0.81]) and per REIST v1.1 (15.7 vs 8.4 mo; HR 0.61 [95% CI 0.45–0.81]) showed consistent findings (Table 1). PFS benefits with addition of C+R persisted across most prespecified subgroups. OS was not mature, with an early trend favoring C+R+TACE (HR 0.76 [95% CI 0.46–1.24]); OS was 91.4% vs 85.5% at 12 mo, and 82.0% vs 73.3% at 24 mo. Among treated pts, grade ≥3 TRAEs occurred in 73.7% (157/213) in C+R+TACE arm vs. 28.7% (60/209) in TACE arm; of them, the most common in C+R+TACE arm were increased AST (20.7% vs 12.9%), hypertension (19.7% vs 4.3%), increased ALT (17.8% vs 9.6%), and decreased platelet count (11.3% vs 2.9%). **Conclusions:** C+R+TACE provided statistically significant and clinically meaningful improvement in PFS vs TACE, with manageable safety, supporting this regimen as a potential new treatment option for TACE-eligible uHCC. Follow-up for OS is ongoing. Clinical trial information: NCT05320692. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

PFS outcomes (ITT set).

	BIRC		INV	
	C+R+TACE (n=214)	TACE (n=209)	C+R+TACE (n=214)	TACE (n=209)
Per mRECIST				
Median (95% CI), mo	11.1 (7.8–14.0)	8.3 (6.9–9.5)	13.8 (8.5–17.3)	7.0 (5.7–9.5)
HR (95% CI)*	0.73 (0.56–0.96); 1-sided p=0.0127†		0.61 (0.47–0.81)	
Per RECIST v1.1				
Median (95% CI), mo	13.9 (10.9–19.4)	9.5 (8.1–11.1)	15.7 (10.3–19.6)	8.4 (6.9–10.8)
HR (95% CI)*	0.67 (0.50–0.91)		0.61 (0.45–0.81)	

*Stratified Cox proportional hazard model.
†Stratified Log-Rank test.

IMbrave251: Final analysis of atezolizumab (atezo) + lenvatinib (lenva) or sorafenib (sora) vs lenva or sora alone in locally advanced or metastatic hepatocellular carcinoma (LA/mHCC) previously treated with atezo and bevacizumab (bev).

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Background: Several immuno-oncology therapies are available for 1L HCC, but data are limited after progression. IMbrave251 (NCT04770896) is the first global randomized Phase 3 trial to assess atezo + lenva or sora (TKIs) vs lenva or sora alone in patients (pts) with LA/mHCC that progressed after atezo + bev treatment (tx). This is the final analysis. **Methods:** Eligible pts had LA/mHCC that was responsive to atezo + bev tx but then progressed (atezo + bev was given for ≥4 cycles and ≥2 tumor assessments, of which ≥1 showed stable disease or complete/partial response). In the atezo + TKI arm, pts received atezo (1200 mg Q3W) + lenva (8 mg for pts < 60 kg or 12 mg for pts ≥60 kg QW) or sora (800 mg QW). Pts in the TKI-only arm received lenva or sora alone. The primary endpoint was OS. Secondary endpoints included PFS, ORR by RECIST 1.1, DOR, time to tumor progression (TTP), quality of life, and safety. Stratification factors were disease etiology (hepatitis B/C infection vs non-viral), ALBI score (1 vs 2/3), AFP (< 400 vs ≥400 ng/mL), and TKI therapy (lenva vs sora). **Results:** IMbrave251 enrolled 557 pts (full analysis population). Median duration of follow-up was 12 mo. Pts were assigned to receive atezo + TKI (n = 279) or TKI-only (n = 278). Most pts in both arms received lenva (92.1%) vs sora (7.9%). At clinical cutoff (Oct 10, 2025), median (m)OS with atezo + TKI vs TKI-only was 14.6 vs 12.5 mo (stratified HR 0.88; *P*= 0.2115) and mPFS was 4.3 vs 4.8 mo (stratified HR 1.05), respectively. Confirmed ORR was 7.5% vs 5.8% with atezo + TKI vs TKI-only. DOR was 10.2 vs 6.9 mo, respectively (stratified HR 0.47) (Table). Additional subgroup analyses and complete duration of systemic therapy will be shown. In the atezo + TKI vs TKI-only arm, the median tx duration was 5.6 vs 4.7 mo for lenva and 2.9 vs 2.3 mo for sora. No new or unexpected safety signals were seen (safety analysis n = 554; Table). **Conclusions:** IMbrave251 did not meet its primary OS endpoint but showed that the addition of atezo to TKIs had a manageable safety profile. This study provides clinically relevant Phase 3 evidence addressing an important, unanswered clinical question regarding 2L tx sequencing after immunotherapy and establishes a new OS benchmark for 2L tx in LA/mHCC. Clinical trial information: NCT04770896. Research Sponsor: F. Hoffmann-La Roche Ltd.

Efficacy (95% CI)	Atezo + lenva or sora (n=279)	Lenva or sora (n=278)	Stratified HR (95% CI)
mOS, mo	14.6 (12.6, 16.8)	12.5 (10.7, 15.5)	0.88 (0.72, 1.08) *P*=0.2115
mPFS, mo	4.3 (4.1, 5.4)	4.8 (4.2, 5.6)	1.05 (0.88, 1.25)
ORR, %	7.5 (4.7, 11.3)	5.8 (3.3, 9.2)	Δ1.77 (−2.72, 6.26)[a]
mDOR, mo	10.2 (5.6, 13.0)	6.9 (5.5, 11.7)	0.47 (0.18, 1.23)
mTTP, mo	4.4 (4.2, 5.5)	5.4 (4.2, 5.6)	1.06 (0.87. 1.28)
Safety, n (%)	**n=279**	**n=275**	
Grade 3/4 | 5 AE	207 (74.2) | 15 (5.4)	182 (66.2) | 16 (5.8)	-
Serious AE | AE leading to withdrawal from any study drugs	112 (40.1) |33 (11.8	101 (36.7) |19 (6.9)	-

[a]Difference in confirmed ORR (95% CI).

First-line treatment of QLS31905 plus chemotherapy in patients with pancreatic cancer and gastric cancer: Data from a phase 1b/2 study.

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Background: QLS31905, a Claudin18.2/CD3 bispecific antibody, showed manageable safety and encouraging efficacy in Claudin18.2-positive patients (pts) with gastrointestinal tumors in a phase 1 trial. Here we report the safety and efficacy of QLS31905 plus chemotherapy in the first-line treatment of Claudin18.2-positive pts with pancreatic cancer (PC) and gastric cancer (GC). **Methods:** This phase 1b/2 trial recruited Claudin 18.2-positive (defined as ≥1% of tumor cells with ≥1+ staining intensity) pts with locally advanced unresectable or metastatic PC and GC who had not received systematic anti-tumor therapy. Pts with PC were administered QLS31905 at 350 μg/kg, 500 μg/kg, or 800 μg/kg Q2W or Q3W combined with gemcitabine plus nab-paclitaxel (Cohort 1). Pts with GC were administered QLS31905 at 500 μg/kg or 800 μg/kg Q3W combined with oxaliplatin plus capecitabine (Cohort 2). The primary endpoints were maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) in phase 1b and was objective response rate (ORR) in phase 2. **Results:** As of Dec 11, 2025, 88 pts with PC and 43 pts with GC were enrolled. No dose-limiting toxicity occurred. MTD was not reached. RP2D was determined as 800 μg/kg Q3W for both pts with PC and GC. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 63 (71.6%) pts and 26 (60.5%) pts in Cohort 1 and Cohort 2, respectively. Ten pts (11.4%) in Cohort 1 and four pts (9.3%) in Cohort 2 discontinued any of the study treatment due to TRAEs. No QLS31905-related death occurred in both cohorts. In 82 efficacy-evaluable pts with PC, ORR and disease control rate (DCR) was 59.8% (95% confidence interval [CI], 48.34%-70.44%) and 89.0% (95% CI, 80.18%-94.86%), respectively. Median progression-free survival (PFS), duration of response (DoR), and overall survival (OS) was 8.74 months (95% CI, 7.16-10.71), 8.94 months (95% CI, 5.32-not evaluable [NE]), and 15.87 months (95% CI, 13.14-NE), respectively. In 15 pts with low Claudin18.2 expression in Cohort 1, ORR, DCR, median PFS, and median OS was 60.0% (95% CI, 32.29%-83.66%), 93.3% (95% CI, 68.05%-99.83%), 11.04 months (95% CI, 7.33-NE), and 15.61 months (95% CI, 3.98-NE), respectively. In 43 efficacy-evaluable pts with GC, ORR and DCR was 74.4% (95% CI, 58.83%-86.48%) and 93.0% (95% CI, 80.94%-98.54%), respectively. Median PFS and DoR was 10.09 months (95% CI, 6.87-NE) and not reached, respectively. In nine pts with low Claudin18.2 expression in Cohort 2, the ORR, DCR, median PFS, and 9-month PFS rate and was 77.8%, 100%, not reached, and 83.33%, respectively. **Conclusions:** QLS31905 plus chemotherapy in first-line treatment for Claudin18.2-positive pts with PC and GC showed manageable safety and potential efficacy. A phase 3 trial is ongoing to further confirm the efficacy and safety of QLS31905 in pts with PC. Clinical trial information: NCT06041035. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

A randomized phase II dose optimization study for alveltamig (ZG006), a trispecific T-cell engager targeting DLL3/DLL3/CD3, as monotherapy in patients with refractory neuroendocrine carcinoma (ZG006-003).

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Background: Alveltamig (ZG006) is an innovative trispecific T cell engager (Tri-TCE) targeting two distinct DLL3 epitopes on tumor cells and CD3 on T cells (DLL3/DLL3/CD3), designed to bridge tumor cells and T cells, thereby mediating T cell specific killing of tumor cells. Here we conducted a dose optimization study in refractory NEC. **Methods:** This is a randomized, multicenter, open-label phase 2 study evaluating ZG006 in NEC patients (pts) who failed at least one prior line of therapy. Pts were randomized 1:1 to receive ZG006 at either 10 mg or 30 mg every two weeks, following a priming dose of 1 mg. The primary endpoint is objective response rate (ORR) assessed by IRC per RECIST1.1. Results are reported for 64 pts who received at least one dose of ZG006. Biomarker based efficacy analyses were performed based on a threshold of ≥50% of tumor cells stained at any intensity for DLL3 with an investigational antibody against DLL3 (SP347, Roche Diagnostics). **Results:** As of Sep. 10, 2025, a total of 64 pts (32 at each dose group) were randomized and received at least one dose of ZG006. The median age was 56 years (range: 25-72), 35 (54.7%) were male. All pts had received ≥1 prior line of systemic therapy, with 65.6% had prior anti-PD-(L)1 treatment. The confirmed ORR in 10 mg and 30 mg groups were 21.9% (7/32) and 37.5% (12/32), respectively; Disease control rate (DCR) were 40.6% (13/32) and 62.5% (20/32), respectively. Among the 19 responders, primary tumor sites included cervix (8), gallbladder (4), stomach (3), rectum (3) and colon (1). Pts with ≥50% DLL3 staining in tumor cells had greater ORR, DCR, and progression-free survival (PFS). The confirmed ORR in 10 mg and 30 mg groups were 33.3% (6/18) and 56.3% (9/16), respectively; DCR were 50.0% (9/18) and 75.0% (12/16), respectively; With a median follow up of 6.4 months, median PFS were 3.02 and 8.41 months, respectively. Median DoR was not yet mature in both groups at data cut-off. Treatment-related adverse events (TRAEs) occurred in all pts. The most frequent events were pyrexia, cytokine release syndrome (CRS) and anaemia. Most CRS were Grade 1-2, with only four grade 3 CRS, resolved with supportive care. TRAEs led to treatment interruption in 15 pts (23.4%) and permanent discontinuation in 2 pts (3.1%, one in each dose group). No grade 5 TRAE. No significant difference was observed in the safety profile between these two dose groups. **Conclusions:** ZG006 demonstrated a robust and durable response and a manageable safety profile in previously treated NEC pts, with superior efficacy observed at the 30 mg dose. The confirmed ORR of 56.3% and median PFS of 8.41 months in pts with ≥50% DLL3 positive tumor cells are particularly encouraging, and support further development of ZG006 for this patient population at the 30 mg dose. Clinical trial information: NCT06440057.
Research Sponsor: None.

Nivolumab plus ipilimumab combined with chemotherapy as first-line treatment for HER2-negative unresectable advanced or recurrent gastric/gastroesophageal junction cancer: A randomized phase 3 trial (ATTRACTION-6).

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Background: Anti-PD-1 antibodies combined with chemotherapy (Chemo) are established as a standard first-line (1L) treatment for HER2-negative gastric/gastroesophageal (G/GEJ) cancer. Nivolumab (NIVO) and ipilimumab (IPI), an anti-CTLA-4 antibody, have complementary mechanisms of action on tumor immunity. Combining NIVO plus Chemo with IPI is expected to suppress disease progression durably and prolong survival, as suggested in other types of tumors. **Methods:** ATTRACTION-6 is a randomized, phase 3 trial conducted in Japan, Korea, and Taiwan. Previously untreated patients with HER2-negative unresectable advanced or recurrent G/GEJ cancer were randomized 1:1 to receive NIVO 360 mg every 3 weeks, IPI 1 mg/kg every 6 weeks in addition to Chemo (S-1 plus oxaliplatin [SOX] or capecitabine plus oxaliplatin [CAPOX]) or Chemo alone. Randomization was stratified by PD-L1 (CPS≥5 or CPS < 5, indeterminate), ECOG PS (0 or 1), countries (Japan or Korea/Taiwan), and disease status (advanced or recurrent). Primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS), objective response rate (ORR) per RECIST v1.1 assessed by site investigator, and safety. **Results:** Between November 2021 and August 2023, 626 patients were randomized 1:1 to the NIVO + IPI + Chemo arm (N = 315) or the Chemo arm (N = 311). At the median follow-up of 31.3 months, the primary endpoint of OS was not met (HR 0.90; 95.8% CI 0.74-1.09; *P*= 0.267; median OS 15.7 vs 15.8 months). Median PFS was 8.9 vs 7.7 months (HR 0.83; 95% CI 0.69-1.00). Among patients with ≥1 measurable lesion at baseline, ORR was 57.9% vs 38.5%. Grade≥3 adverse events (AEs) and grade≥3 treatment-related AEs occurred in 80.0% and 64.8% in the NIVO + IPI + Chemo arm, respectively, and 62.4% and 42.9% in the Chemo arm, respectively. Treatment-related deaths occurred in 0.3% vs 0%, and the only observed event was gastroenteritis in the NIVO + IPI + Chemo arm. **Conclusions:** In ATTRACTION-6 study, NIVO + IPI + Chemo did not improve OS compared with Chemo as 1L treatment for patients with HER2-negative unresectable advanced or recurrent G/GEJ cancer. Although toxicity increased with the addition of NIVO and IPI, no new safety signals were observed. Clinical trial information: NCT05144854. Research Sponsor: Ono Pharmaceutical Co., Ltd.

4007 Oral Abstract Session

ONO-4578 combined with nivolumab (NIVO) and chemotherapy (chemo) as first-line (1L) treatment for patients with HER2-negative unresectable advanced or recurrent (adv/rec) gastric/gastroesophageal junction cancer (G/GEJ): A randomized, double-blind, phase 2 trial (ONO-4578-08).

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Background: Anti-PD-1 antibodies combined with chemo are the standard 1L treatment for HER2-negative G/GEJ cancer. Prostaglandin E_2 (PGE_2)-EP4 signaling is known to induce immunosuppressive tumor microenvironment, by inducing the differentiation of MDSCs and M2 macrophages, potentially contributing to resistance to immunotherapy. ONO-4578, an EP4 antagonist, is expected to modulate tumor immunosuppression through inhibiting the PGE_2-EP4 signaling and to enhance the efficacy of anti-PD-1 antibody. The addition of ONO-4578 appeared to augment the efficacy of NIVO in patients with G/GEJ cancer in the previous phase 1 trial. This study aimed to evaluate the efficacy and safety of ONO-4578 combined with NIVO and chemo compared with placebo combined with NIVO and chemo as 1L treatment for patients with unresectable adv/rec G/GEJ cancer. **Methods:** ONO-4578-08 study is a randomized, double-blind, phase 2 trial conducted in Japan, Korea, and Taiwan. Chemo-naïve patients with HER2-negative adv/rec G/GEJ cancer were randomized in a 2:1 ratio (ONO-4578 group: placebo group), stratified by PD-L1 expression level (CPS $<$ 5 vs CPS$\geq$5), ECOG performance status (0 vs 1), presence of peritoneal metastasis (yes vs no). Patients in each group received ONO-4578 40 mg or placebo once daily, and all received NIVO 360 mg every 3 weeks and chemo (SOX [S-1 + oxaliplatin]/CAPOX [capecitabine + oxaliplatin]). The primary endpoint was investigator-assessed progression-free survival (PFS), powered (two-sided α = 0.10) to detect a HR of 0.65 with 117 events in a planned enrollment of 210 patients; secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. **Results:** Between December 2023 and September 2024, 226 patients were randomized to each group (150 vs 76 patients). With a median follow-up of 8.5 months, PFS was significantly longer in the ONO-4578 group than the placebo group with a hazard ratio (HR) of 0.67 (90% confidence interval [CI]: 0.48–0.92; P = 0.040; median PFS: 9.0 vs 6.9 months). At a minimum follow-up of 7.4 months, OS favored the ONO-4578 group (median OS: not reached vs 12.7 months; HR: 0.60 [95% CI: 0.37–0.96]). ORR was also higher in the ONO-4578 group (62.0% vs 48.7%). The most common treatment-emergent adverse events (TEAEs) in the ONO-4578 group were diarrhea (55.7% vs 45.3%), anemia (55.0% vs 34.7%), and peripheral sensory neuropathy (50.3% vs 46.7%). Serious TEAEs occurred in 53.7% of patients in the ONO-4578 group and 42.7% in the placebo group. **Conclusions:** ONO-4578 combined with NIVO and chemo significantly improved PFS compared with placebo combined with NIVO and chemo in treatment-naive patients with HER2-negative unresectable adv/rec G/GEJ cancer with no new safety concerns. Clinical trial information: NCT06256328. Research Sponsor: Ono Pharmaceutical Co., Ltd.

Izalontamab brengitecan (iza-bren) versus chemotherapy in patients with recurrent or metastatic esophageal squamous cell carcinoma (ESCC): A multicenter, randomized, open-label, phase III study.

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Background: Chemotherapy plus a PD-1/PD-L1 inhibitor is the standard first-line treatment for PD-L1 expressing advanced ESCC. However, most patients (pts) inevitably develop resistance to first-line therapy, and second-line chemotherapy shows an ORR of less than 10% and a median OS of less than 6 mo, highlighting the urgent need for novel therapeutics. Iza-bren is a potentially first-in-class ADC consisting of an EGFR-HER3 bispecific antibody conjugated to a potent topoisomerase I inhibitor Ed-04 via a cleavable linker. Iza-bren has shown promising clinical activity in previously treated ESCC pts in phase I study. Here, we present results from a phase III, randomized, open-label, multicenter study conducted in China evaluating the efficacy and safety of iza-bren versus chemotherapy as second line treatment for advanced ESCC. **Methods:** Pts with recurrent or metastatic ESCC who had progressed after first-line treatment with a PD-1/PD-L1 inhibitor plus platinum-based chemotherapy were randomized (1:1) to receive iza-bren (2.5 mg/kg at D1D8 Q3W) or physician's choice of chemotherapy (irinotecan, paclitaxel, or docetaxel Q3W). Dual primary endpoints were OS and PFS by Blinded Independent Central Review (BICR) per RECIST v1.1. **Results:** As of Oct 17, 2025, a total of 497 pts were randomized to iza-bren (n = 249) or chemotherapy (n = 248). Baseline characteristics were balanced between the two groups. At interim analysis, median follow-up for OS was 7.8 mo in the iza-bren group and 7.6 mo in the chemotherapy group. Iza-bren has demonstrated statistically significant and clinically meaningful improvement in both OS and PFS by BICR compared with chemotherapy. The median OS was 9.8 mo (95% CI, 7.9 to 11.0) with iza-bren and 7.2 mo (95% CI, 6.2 to 8.2) with chemotherapy (HR, 0.64; 95% CI, 0.49 to 0.83; P = 0.0004). The median PFS by BICR was 4.2 mo (95% CI, 3.6 to 4.5) with iza-bren and 2.0 mo (95% CI, 1.6 to 2.7) with chemotherapy (HR, 0.50; 95% CI, 0.40 to 0.63; $P < 0.0001$). ORR by BICR was 35.3% for iza-bren and 13.1% for chemotherapy. Grade≥3 TRAEs, which were predominantly hematologic in nature, occurred in 85.1% in the iza-bren group and 60.2% in the chemotherapy group. TRAEs leading to drug discontinuation were 2.0% in the iza-bren group and 3.3% in the chemotherapy group. TRAEs leading to death were 1.2% in the iza-bren group and 1.6% in the chemotherapy group. **Conclusions:** The study met both dual primary endpoints at prespecified interim analysis. Iza-bren demonstrated statistically significant and clinically meaningful improvements in OS and PFS compared with chemotherapy in pts with recurrent or metastatic ESCC who had progressed after first line PD-1/PD-L1 inhibitor plus platinum-based chemotherapy. The safety profile was manageable. The results support iza-bren as a new second-line standard of care for ESCC. Clinical trial information: NCT06304974. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

4009 Rapid Oral Abstract Session

Neoadjuvant/adjuvant serplulimab vs. placebo combined with chemotherapy for PD-L1–positive gastric cancer: A randomized, double-blind, multicenter phase 3 study.

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Background: The addition of immune checkpoint inhibitors (ICIs) to chemotherapy (chemo) in the neoadjuvant/adjuvant setting for gastric cancer (GC) has yielded mixed efficacy. Target population and treatment regimen remain to be optimized. This study compared the efficacy of serplulimab (anti-PD-1 antibody) plus chemo versus placebo plus chemo as neoadjuvant therapy and serplulimab versus chemo as adjuvant therapy for resectable GC. **Methods:** Patients with PD-L1 positive (PD-L1 CPS $\geq$ 5), histologically confirmed, untreated, resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma were randomized 1:1 to receive 3 cycles of neoadjuvant intravenous (iv) serplulimab (4.5 mg/kg) or placebo, plus chemo (iv oxaliplatin, 130 mg/m^2 and oral S-1, 40-60 mg based on body surface area), followed by post-surgery adjuvant serplulimab monotherapy (up to 17 cycles) or adjuvant chemo (5 cycles), Q3W. The primary endpoint was investigator (INV)-assessed event-free survival (EFS). Efficacy superiority was first evaluated and established in patients with PD-L1 CPS $\geq$ 10 followed by that in the PD-L1 CPS $\geq$ 5 population. **Results:** Between November 26, 2019 and April 19, 2024, 588 patients were enrolled across 57 sites, with 292 randomized to the serplulimab group and 296 to the placebo group. As of the data cutoff date of August 19, 2025 with a median follow-up duration of 35.9 months, INV-assessed median EFS was significantly longer in the serplulimab group (n = 193) than in the placebo group (n = 217) in the PD-L1 CPS $\geq$ 10 population (not reached [NR], 95% CI 43.0–not estimable [NE] vs. 42.0 months, 95% CI 20.5–NE; HR 0.65, 95% CI 0.47–0.90; p = 0.0082), and in the PD-L1 CPS $\geq$ 5 population (NR, 95% CI 37.9–NE vs. 35.9 months, 95% CI 21.3–52.0; HR 0.73, 95% CI 0.56–0.94; p = 0.0152), meeting the protocol-specified superior criteria. Blinded independent central review-assessed median EFS was consistent with that of the investigator. Pathological complete response rate was higher in the serplulimab group than in the placebo group (21.6% vs 6.4%; odds ratio 3.95). Median OS was immature in both groups. Grade $\geq$ 3 treatment-related adverse events (TRAEs) were reported in 136 (46.6%) and 172 (58.5%) patients in the serplulimab and placebo groups, respectively. Discontinuation of any component of the study regimen due to TRAEs occurred in 19 (6.5%) and 31 (10.5%) patients in the respective groups. **Conclusions:** Neoadjuvant serplulimab plus chemo, followed by adjuvant serplulimab monotherapy, significantly prolonged EFS in patients with PD-L1-positive, resectable GC or GEJ adenocarcinoma. Improvements in other efficacy endpoints were also observed along with a favorable safety profile compared to neoadjuvant/adjuvant chemo. This world-first chemotherapy-free regimen (adjuvant) represents a promising treatment option for this indication. Clinical trial information: NCT04139135. Research Sponsor: Shanghai Henlius Biotech, Inc.

Zanidatamab + chemotherapy (CT) ± tislelizumab for first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): PD-L1 subgroup analysis from HERIZON-GEA-01.

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Background: In HERIZON-GEA-01 (NCT05152147), 1L zanidatamab + CT ± tislelizumab significantly improved progression-free survival (PFS) and, with tislelizumab, yielded a statistically significant overall survival (OS) benefit in HER2+ mGEA. Here we report efficacy in PD-L1 subgroups. **Methods:** Eligible patients (pts) with previously untreated HER2+ mGEA, irrespective of PD-L1 status, were randomized (1:1:1) to zanidatamab (1800 mg [<70 kg]/2400 mg [≥70 kg] IV Q3W) + tislelizumab (200 mg IV Q3W) + capecitabine/oxaliplatin (CAPOX) or 5-FU/cisplatin (FP); zanidatamab + CAPOX or FP; or tras + CAPOX or FP. PD-L1 expression was retrospectively assessed using the VENTANA SP263 assay according to tumor area positivity (TAP) score and combined positive score (CPS). Primary endpoints were PFS (BICR) and OS; efficacy by PD-L1 status (TAP) was prespecified. **Results:** With 26 mo median follow-up, PFS (HR, 0.63; P <0.001) and OS (HR, 0.72; P = 0.004) were significantly prolonged with zanidatamab + tislelizumab + CT vs tras + CT in the ITT population. In pts treated with zanidatamab + tislelizumab + CT, similarly prolonged PFS and OS were observed in PD-L1–negative and PD-L1–positive pts (Table); data were consistent between TAP and CPS. In PD-L1 TAP <1% and ≥1% pts, the 18-mo PFS was 50.3% and 42.6%, respectively, and the 24-mo OS was 63.7% and 53.5% with zanidatamab + tislelizumab + CT. In the tras + CT arm, OS was prolonged in PD-L1–positive vs –negative pts. Of note, in the tras + CT arm, 15% of pts received subsequent checkpoint inhibitors and 29% received subsequent HER2-targeted therapies vs 2% and 13%, respectively, in the zanidatamab + tislelizumab + CT arm. Additional details on these subgroups will be presented at the congress. **Conclusions:** In HERIZON-GEA-01, zanidatamab + tislelizumab + CT demonstrated meaningful improvements in PFS and OS in both PD-L1–positive and PD-L1–negative pts as determined by TAP or CPS. The longer OS observed with tras + CT in PD-L1–positive vs –negative pts may be at least partially explained by differences in subsequent therapies. These findings are notable as they demonstrate benefit for this regimen regardless of PD-L1 status. Clinical trial information: NCT05152147. Research Sponsor: Jazz Pharmaceuticals; BeOne Medicines; Zymeworks Biopharmaceuticals.

	Zanidatamab + Tislelizumab + CT	Tras + CT
ITT		
N	302	308
mPFS (95% CI), mo	12.4 (9.8, 18.5)	8.1 (7.0, 8.9)
mOS (95% CI), mo	26.4 (21.5, 30.3)	19.2 (16.8, 21.8)
TAP <1%		
n (%)	90 (29.8)	98 (31.8)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	7.9 (5.8, 9.6)
mOS (95% CI), mo	29.7 (24.7, NE)	15.8 (12.6, 21.4)
CPS <1		
n (%)	78 (25.8)	80 (26.0)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	8.1 (5.8, 9.8)
mOS (95% CI), mo	30.3 (25.7, NE)	15.7 (12.6, 21.4)
TAP ≥1%		
n (%)	187 (61.9)	188 (61.0)
mPFS (95% CI), mo	11.3 (9.6, 18.5)	8.3 (6.9, 9.7)
mOS (95% CI), mo	26.4 (18.7, 35.9)	21.2 (17.7, 25.2)
CPS ≥1		
n (%)	198 (65.6)	206 (66.9)
mPFS (95% CI), mo	12.3 (9.7, 18.5)	8.2 (6.9, 9.1)
mOS (95% CI), mo	26.4 (18.7, 34.6)	20.8 (17.3, 23.9)

A phase 2 pivotal study of savolitinib in patients with *MET*-amplified gastric cancer or gastroesophageal junction adenocarcinomas.

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Background: MET amplification is a poor prognosis for survival in patients (pts) with gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJa). Currently no approved targeted therapy is available for MET-amplified GC/GEJa. Savolitinib is a potent and highly selective oral MET-TKI. Here we reported the primary analysis results from a pivotal phase 2 trial investigating savolitinib in MET-amplified GC/GEJa, conducted with registration intent (NCT04923932). **Methods:** Eligible pts had locally advanced or metastatic GC/GEJa with MET amplification (gene copy number ≥10 by FISH) and had failed ≥2 lines of prior standard therapy. Pts received savolitinib 200 mg (BW < 50 kg) or 300 mg (BW ≥50 kg) BID. The primary endpoint was ORR assessed by an Independent Review Committee (IRC) per RECIST 1.1, with a pre-specified efficacy threshold defined as the lower limit of the 95% CI of ORR exceeding 15%. Secondary endpoints mainly included DCR, DoR, TTR, PFS, OS and safety. An exploratory OS analysis was conducted in pts with MET-amplified GC/GEJa, who had previously received first-line, second-line, or later-line standard therapies, but were ineligible for study enrollment and did not receive the study drug. Plasma samples were also collected at baseline and end of treatment (EOT) for comprehensive genomic profiling using a 671-gene sequencing panel (Benrui GCP, OrigiMed). **Results:** As of Oct 8, 2025, 65 eligible pts were enrolled and received savolitinib. Baseline characteristics were: median age of 57.4 years, ECOG PS of 0 (13.8%) or 1 (86.2%), primary tumor sites of GC (84.6%) or GEJa (15.4%), and baseline ctDNA MET-positive rate of 64.6% (42 pts). Per the IRC assessment, ORR was 32.3% (95%CI: 21.2%, 45.1%), which exceeded the pre-specified efficacy threshold; in baseline ctDNA MET-positive pts (42 pts), IRC-assessed ORR was 45.2% (95%CI: 29.8%, 61.3%). IRC-assessed secondary efficacy endpoints were: DCR of 63.1%; mTTR of 1.4 months; mDoR of 9.7 months; and mPFS 4.0 of months. mOS was 6.9 months in the 65 treated pts, versus 4.8 months in 139 pts who received alternative treatments rather than the study drug in the exploratory OS analysis. Savolitinib-related TEAEs of Grade ≥3 occurred in 23 pts (35.4%). Exploratory ctDNA biomarker analysis showed that pts (N = 14) harboring baseline alterations in FGFR2, EGFR, PIK3CA, BRAF, or KRAS had lower ORR (14.3%, 2/14) and shorter mPFS (1.4 months). Additionally, in pts (N = 26) who provided PD/EOT samples, 12 pts developed alterations in these genes that were identified as putative acquired resistance mechanisms, and 4 pts had acquired MET mutations. **Conclusions:** Savolitinib showed clinical efficacy and a tolerable safety profile in pts with MET-amplified GC/GEJa who had received ≥2 lines of prior therapy, supporting it to be a future treatment option for this genetically defined population. Clinical trial information: NCT04923932. Research Sponsor: HUTCHMED Limited; AstraZeneca.

Randomized phase II trial of olaparib and pembrolizumab vs olaparib alone as maintenance therapy in metastatic pancreatic cancer patients with germline BRCA1 or BRCA2 (gBRCA1/2) mutations: SWOG S2001.

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Background: Preclinical studies have demonstrated that PARP inhibitors modulate the immune microenvironment by increasing genomic instability, PD-L1 expression and activating the immune inflammatory stimulator of interferon genes (STING) pathway. The POLAR trial demonstrated promising results combining pembrolizumab with olaparib as maintenance therapy in patients (pts) with homologous recombination deficiency (HRD) mutations. S2001 is a randomized phase II trial evaluating the addition of pembrolizumab to olaparib as maintenance therapy in patients with gBRCA1/2. **Methods:** Eligible pts had mPDA with gBRCA1/2 mutations and had received a minimum of 4 months of platinum-based chemotherapy without progression. Pts were randomized 1:1 to olaparib 300 mg twice per day plus pembrolizumab 200 mg every 3 weeks or olaparib alone. The primary endpoint was progression-free survival (PFS) with a target hazard ratio (HR) of 0.6 (median PFS 7.0 vs 11.7 months) with 1-sided alpha=0.1 and 80% power. Secondary outcomes were safety and tolerability, overall survival (OS), overall response rate (ORR), and disease control rate (DCR). The accrual goal was 88 pts to have 78 eligible for analysis. Differences in PFS by treatment arm were assessed via stratified log-rank test, with first line platinum-based chemotherapy, Zubrod PS, and disease status after first line treatment as stratification factors. Tissue and blood samples for correlative studies were banked. **Results:** The study enrolled 73 patients, with 68 eligible, and was closed for futility after a planned interim analysis showed that PFS was not improved in the pembrolizumab + olaparib arm (p=0.82), despite higher ORR (p=0.20) (Table). Treatment was well tolerated, with no grade 4-5 treatment-related adverse events and similar toxicity profiles across arms. Autoimmune toxicities on the experimental arm included adrenal insufficiency, hyperthyroidism, and hypothyroidism. Grade 3 adverse events in both arms included neutropenia, anemia, thrombocytopenia, gastrointestinal toxicity and fatigue. **Conclusions:** S2001 is the first randomized controlled trial evaluating the addition of pembrolizumab to olaparib in pancreas cancer. Despite doubling the ORR and improvement in DCR and PFS in the experimental arm, the high bar of improving PFS to 11.7 months was not met. Activity seen in the experimental arm of S2001 is comparable to the HRD cohort of the POLAR trial which demonstrated ORR 35%, DCR 90% and PFS of 8.2 months. Further follow-up for mature survival outcomes and translational analysis of DNA and RNA are planned. Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819 with additional support from by Merck & Co, Inc. Clinical trial information: NCT04548752. Research Sponsor: NIH/NCI/NCTN grants; U10CA180819; Merck & Co., Inc.

	Pembrolizumab + Olaparib (n=34)	Olaparib (n=34)
Median PFS	8.2 months	6.4 months
Median OS	20.0 months	22.1 months
ORR	28.1%	14.3%
DCR	84.4%	64.3%

Results from a phase 2a study of atebimetinib in combination with mGnP in advanced or metastatic pancreatic cancer.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is driven predominantly by oncogenic KRAS signaling, yet prior attempts to target the MAPK pathway have been limited by toxicity and emergence of resistance. Atebimetinib is a next-generation, deep cyclic inhibitor (DCI) of MEK designed to achieve pulsatile pathway inhibition with improved tolerability. We report a Phase 2a cohort evaluating atebimetinib in combination with modified gemcitabine/nab-paclitaxel (mGnP) in the first-line treatment of advanced or metastatic PDAC (NCT05585320). **Methods:** In this multicenter, open-label, nonrandomized Phase 2a study, patients with previously untreated advanced or metastatic PDAC were eligible for participation and were treated with orally administered atebimetinib daily in combination with mGnP (modification: every other week dosing). The primary endpoint was objective response rate (ORR) per investigator assessment using RECIST 1.1 criteria in response-evaluable patients. The cohort was powered (~80%, one sided alpha 0.05) using an optimal Simon's 2-stage design. **Results:** Fifty-five patients were enrolled and treated with 320 mg atebimetinib daily + mGnP. ECOG performance status was 0-1 (100%); median age was 68 years (range 42-85 years), 62% were ≥65 years, and 55% were male. No grade 5 treatment-related adverse events (AE) were observed. No AE related to atebimetinib were higher than grade 3. Grade 3 AE related to atebimetinib occurred in 29% of participants, with the most frequent being rash (5%), ALT increased (5%), and AST increased (5%). Among the 50 response-evaluable patients, best overall response (BOR) achieved were 21 PR, 21 SD, 7 PD, 1 NE. The ORR was 42%, and DCR was 84%. With a median follow-up of 10.4 months (data cutoff Jan 7, 2026), 6- and 9-month OS rates were 88% and 79%, respectively; median PFS was 8.3 months and median OS was not reached. **Conclusions:** Atebimetinib in combination with mGnP demonstrated favorable safety and promising efficacy compared to historic standard-of-care (SoC) GnP.[1] A phase 3 registrational trial is planned to start in mid-2026 for evaluation of atebimetinib + mGnP versus SoC GnP. 1. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703. doi:10.1056/NEJMoa1304369 (PMID: 24131140). Clinical trial information: NCT05585320. Research Sponsor: None.

Nilvanstomig (ZG005), an anti-PD-1/TIGIT bispecific antibody, plus bevacizumab vs. sintilimab plus bevacizumab biosimilar as first-line therapy for advanced hepatocellular carcinoma: A randomized, multi-center, phase II trial.

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Background: Checkpoint inhibitors combined with anti-angiogenic therapy represents one of the standard first-line therapies for advanced hepatocellular carcinoma (aHCC). Nilvanstomig (ZG005) is a recombinant humanized anti-PD-1/TIGIT bispecific antibody. By blocking both pathways, it can synergistically activate T cells and enhance the anti-tumor activity of NK cells. This study evaluated ZG005 plus bevacizumab vs. sintilimab plus IBI305 (a bevacizumab biosimilar) as first-line therapy for aHCC. **Methods:** In this randomized, open-label, multi-center, phase 2 trial conducted in China, patients with aHCC who had not previously received systemic treatment were randomly assigned (1:1:1) to receive ZG005 10 mg/kg plus bevacizumab 15 mg/kg (Arm A); ZG005 20 mg/kg plus bevacizumab 15 mg/kg (Arm B); or sintilimab 200 mg plus IBI305 15 mg/kg (Arm C). All treatments were administered intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by baseline AFP level (< 400 vs. ≥ 400 ng/mL), macrovascular invasion or extrahepatic metastasis (presence vs. absence). The primary endpoint was IRC-assessed PFS per RECIST v1.1, with key secondary endpoints including PFS per mRECIST, ORR and DCR by both criteria, and OS. **Results:** As of the data cutoff (Nov 25, 2025), 95 patients were enrolled and received at least one dose of treatment (Arm A, n = 31; Arm B, n = 32; Arm C, n = 32). Baseline characteristics were well-balanced across the treatment arms. For all patients enrolled, the median age was 61 years (range, 37-75), with 85.3% of patients being male. Disease characteristics included BCLC stage B (28.4%) or C (71.6%), Child-Pugh score A5 (83.2%) or A6 (16.8%), baseline AFP ≥ 400 ng/mL in 45.3% of patients, and HBV positivity in 73.7%. Macrovascular invasion and/or extrahepatic metastasis were present in 71.6% (68/95) of patients. With a median follow-up of about 5 months, the IRC-assessed ORR was 32.3% in Arm A, 37.5% in Arm B, and 25.0% in Arm C per RECIST v1.1; the corresponding ORRs per mRECIST were 54.8%, 50.0%, and 34.4%. The IRC-assessed median PFS per RECIST v1.1 was not reached in Arm A or B, compared with 5.8 months in Arm C (Arm A vs. C: HR 0.40, 95% CI 0.15-1.05; Arm B vs. C: HR 0.28, 95% CI 0.10-0.79). The safety profiles were comparable across the three arms. No grade ≥ 3 hemorrhagic adverse events were reported in either Arm A or B. **Conclusions:** The combination of ZG005 and bevacizumab as first-line treatment in patients with aHCC demonstrated an early encouraging efficacy with an acceptable safety profile. Higher response rates and prolonged PFS were observed with the ZG005-based regimens. Longer follow up of the current study and future phase 3 trials are warranted to validate the efficacy and safety of ZG005 in combination with bevacizumab in aHCC. Clinical trial information: NCT06558227. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co.,Ltd.

4015 Rapid Oral Abstract Session

Tegavivint, a downstream Wnt/β-catenin inhibitor: Dose-finding results from a phase 1/2 trial in advanced hepatocellular carcinoma (aHCC).

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Background: Wnt/β-catenin pathway activation is a hallmark of many cancers, with Wnt pathway mutations (WPMs) present in ~40% of advanced HCC (aHCC). Tegavivint is a first-in-class small-molecule inhibitor of TBL1, a transcriptional co-factor required for nuclear β-catenin–dependent oncogenic gene expression. Binding of TBL1 by tegavivint disrupts the TBL1/β-catenin complex, resulting in selective degradation of nuclear β-catenin while preserving cytoplasmic and membrane-bound β-catenin functions associated with normal tissue homeostasis. This mechanism inhibits Wnt-driven oncogenicity while avoiding toxicities observed with upstream Wnt inhibitors. Here, we report dose-finding results from an ongoing phase 1/2 study of tegavivint in aHCC (NCT05797805). **Methods:** This multicenter, open-label phase 1/2 study employs a 3+3 dose-escalation design with backfill, followed by dose optimization. Eligible patients (pts) had aHCC previously treated with ≥1 systemic therapy, BCLC stage C or B disease not amenable to locoregional therapy, and Child-Pugh class A or B (score ≤ 7). WPM status was assessed by liquid biopsy. Tegavivint was administered intravenously once weekly. Primary objectives were safety and tolerability; secondary objectives included preliminary efficacy and PK/PD. **Results:** As of 21 Jan 2026, 39 pts were enrolled (median age 68 years [range 34–84]); 28 had WPMs, and the median number of prior systemic therapies was 2 (range 1–6). Pts were treated across four dose levels (3–8 mg/kg), demonstrating dose-proportional increases in exposure. At 8 mg/kg, 2 of 5 pts experienced Grade 3 anemia within the DLT window, establishing 3–6.5 mg/kg as the recommended dose range (RDR). Across all doses, the most common (all grade/grade ≥ 3; n/n) TRAEs were fatigue (9/0), hyperbilirubinemia (7/4; isolated, asymptomatic and reversible), anemia (5/5; reversible), myalgia (4/0), and decreased appetite (4/0). Among WPM pts evaluable for efficacy within the RDR (n = 18), those with ≤ 3 previous lines of therapy (n = 9) achieved an overall response rate (ORR) of 22%, disease control rate (DCR) of 89%, and median progression-free survival (mPFS) of 8 mo, compared with 0% ORR, 56% DCR, and 4 mo mPFS in pts treated in later lines (n = 9). No significant clinical benefit was observed in pts without WPMs. Pts remaining on treatment for ≥ 4 months (n = 9) demonstrated concordant improvements in liver enzymes, alpha-fetoprotein, platelet counts, and/or ctDNA variant allele frequency. **Conclusions:** Tegavivint is the first Wnt/β-catenin inhibitor to demonstrate monotherapy clinical activity and a manageable safety profile in heavily pretreated aHCC pts with WPMs. Observed partial responses, durable disease control, and on-target PD effects in 2L and 3L pts support further development of tegavivint as a monotherapy or in combination with other treatments for this population. Clinical trial information: NCT05797805. Research Sponsor: Iterion Therapeutics.

A phase Ib/II trial of first-line trastuzumab, nivolumab, gemcitabine, and cisplatin in HER2-positive biliary tract cancer (HERBOT): A multi-institutional study from the Korean Cancer Study Group.

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Background: Several phase II trials support HER2 as a promising actionable target in advanced biliary tract cancers (BTCs). However, the efficacy of adding anti-HER2 therapy to the current first-line standard-of-care (ICI plus gemcitabine/cisplatin [GemCis]) remains unknown. We report the results of the HERBOT trial evaluating this quadruplet combination. **Methods:** This multi-institutional, open-label, phase Ib/II study (KCSG-HB23-05; NCT05749900) enrolled treatment-naïve pts with locally advanced/unresectable or metastatic, HER2-positive BTC (defined as centrally confirmed HER2 IHC3+, or IHC2+/ISH+, or *ERBB2* gene copy number ≥6.0 by NGS). Pts received trastuzumab 6mg/kg (after 8mg/kg load) D1, nivolumab 360mg D1, cisplatin 25mg/m^2 D1,8, and gemcitabine 1000mg/m^2 (dose level 0) or 800mg/m^2 (dose level -1) D1,8 every 3 weeks. The primary endpoints were recommended phase II dose (RP2D, phase Ib) and ORR per RECIST v1.1 (phase II). Secondary endpoints included PFS, DCR, OS, safety. Exploratory biomarker analyses included AI-powered whole-slide image (WSI) profiling of HER2 expression and immune phenotype assessment. **Results:** Dose level 0 was established as RP2D with no DLT. Among total of 40 pts, 29 (72.5%) had gallbladder cancer and 26 (62.5%) were HER2 IHC 3+. The primary endpoint was met with an ORR of 55% (95%CI: 38.5 – 70.7; 1 CR, 21 PR) and a DCR of 95% (95%CI: 83.5 – 99.4); median duration of response was 12.6 months (95%CI: 5.7 – NR). With a median follow-up of 17.0 months, median PFS was 10.6 months (95% CI: 7.8 – 17.4) and median OS was not yet reached. Three pts (7.5%) underwent curative-intent conversion surgery. Pts with HER2 IHC 3+ showed a numerically longer PFS compared to IHC 2+/ISH+ (17.4 vs 9.7 months; HR 0.46, 95%CI: 0.20 – 1.07). Common grade ≥3 treatment-related adverse events (TRAEs) included neutropenia (57.5%), anemia (30.0%), and thrombocytopenia (22.5 %). A grade 2 decreased ejection fraction occurred in 1 pt (2.5%); no grade ≥3 immune-related AEs were observed. AI-based WSI analyses revealed that ≥10% HER2 3+ tumor cells proportion was associated with higher ORR (80% vs 36.4%, P = 0.009) and numerically superior PFS (17.4 vs 9.1 months; HR 0.54, 95%CI: 0.23 – 1.28). Pts with inflamed immune phenotype (n = 4) showed durable responses (ORR 75%; mPFS and mOS NR). **Conclusions:** The HERBOT trial demonstrates that adding trastuzumab to first-line ICI plus GemCis provides robust antitumor activity and manageable safety in HER2-positive BTC. This study is the first to report the efficacy of a HER2-targeted quadruplet regimen in the first-line setting, providing strong clinical rationale for integrating HER2-targeted strategies into first-line treatment and complementing ongoing global phase III trials in this molecularly defined subgroup. Clinical trial information: NCT05749900. Research Sponsor: Korean Cancer Study Group; Boryung Corp; ONO/BMS.

Pemigatinib for untreated unresectable/metastatic cholangiocarcinoma (mCCA) with fibroblast growth factor receptor-2 (FGFR2) rearrangement: Phase 3 FIGHT-302 results.

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Background: First-line mCCA treatment is chemotherapy and immunotherapy. Based on the phase 2 FIGHT-202 trial, pemigatinib was the first FGFR1-3 inhibitor approved in second line and beyond for mCCA with *FGFR2* rearrangement. Results from the phase 3, randomized, global FIGHT-302 trial evaluating pemigatinib as first-line therapy are reported here (NCT03656536). **Methods:** Patients (pts) aged ≥18 y with previously untreated mCCA with *FGFR2* rearrangement were randomized 1:1 to receive oral pemigatinib (13.5 mg once daily q21) or intravenous chemotherapy (1000 mg/m^2 gemcitabine + 25 mg/m^2 cisplatin d1,8 q21 ≤8 cycles) stratified by previous receipt of 1 chemotherapy cycle, geographic region, and tumor burden. Pemigatinib crossover was allowed for control arm pts progressing on chemotherapy. Primary end point was progression-free survival (PFS). Secondary efficacy, safety, and exploratory end points were also analyzed. **Results:** After prescreening >4000 pts, only 196 had *FGFR2* rearrangement and were screened; 167 were randomized to receive pemigatinib (n=83) or chemotherapy (n=84) before closing the study early due to slow accrual. Baseline characteristics and demographics were similar between arms. Median PFS (mPFS) with pemigatinib versus chemotherapy was 8.3 versus 6.8 mo, respectively (hazard ratio [95% CI], 0.58 [0.39-0.87]; nominal *P*=.0078); secondary efficacy endpoints generally supported primary results (Table). Median OS was similar, although these results are confounded by FGFR inhibitor administration as second-line treatment. In the crossover group (n=42, second-line pemigatinib), mPFS was 8.1 mo. Safety was consistent with previous results (Table). Exploratory analyses of genetic co-alterations associated with treatment response will be presented. **Conclusions:** FIGHT-302 was the first phase 3 trial of a targeted therapy for untreated mCCA. Pemigatinb demonstrated superior activity and prolonged mPFS compared with first-line chemotherapy. The results confirm the current management paradigm of pemigatinib administration after disease progression on chemotherapy. Clinical trial information: NCT03656536. Research Sponsor: Incyte Corporation; N/A.

	Pemigatinib	Gemcitabine + cisplatin
mPFS (95% CI), mo[a]	8.3 (6.5-12.2)	6.8 (6.1-8.3)
Objective response rate, n/N (%)[a]	39/83 (47)	13/84 (15.5)
Median duration of response (95% CI), mo[a]	14.2 (8.7-24.7)	6.3 (4.3-not estimable)
Median overall survival (95% CI)[a,b]**, mo**	24.4 (18.6-35.9)	25.0 (18.7-34.2)
Treatment related TEAEs, n/N[c] **(%)**	80/83 (96)	70/73 (96)
Serious TEAEs, n/N (%)[c,d]	23/83 (28)	17/73 (23)
Grade ≥3 TEAEs, n/N (%)[c]	65/83 (78)	49/73 (67)
TEAEs leading to treatment discontinuation, n/N (%)[c]	5/83 (6)	8/73 (11)
Fatal TEAE, n/N (%)[c,d]	3/83 (4)	0

[a]All randomized pts.
[b]Interpretation limited by second-line treatment with FGFR inhibitor in gemcitabine + cisplatin arm.
[c]Pts who received ≥1 study dose.
[d]None deemed treatment related.

H&E 2.0: Artificial intelligence–driven prediction of N256-glycosylated CEACAM5/6 expression in esophageal and gastric adenocarcinomas.

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Background: The antibody-drug conjugate (ADC) EBC-129 has shown promising clinical responses in a Phase 1A/B trial, where higher H-scores correlate with responses, slated to start Phase 2. It specifically targets N256-glycosylated CEACAM5/6, highly expressed on solid tumours, including gastro-oesophageal adenocarcinomas. Recent advances in deep learning enabled the extraction of morphological features from stained pathological images to predict protein expression from haematoxylin and eosin (H&E) images. We investigated the feasibility of training deep learning models on H&E images of gastro-oesophageal carcinomas and assessed the models' ability to predict EBC-129 antigen (Ag) expression directly from H&E images. **Methods:** H&E and immunohistochemistry (IHC) images from same sections of oesophageal and gastric adenocarcinoma TMA tissues (n = 103 cores) were acquired at the same magnification. Tumour and EBC-positive areas were annotated in FIJI, with images pre-processed in Python to obtain 112x112-pixel H&E image patches. Cell patches with $tumour^{+}EBC^{+}$ labels were classified positive while patches with all other labels were classified negative. Six cores were held-out for testing while class balancing was conducted for the remaining 97 cores, where image patches were split 80:20 for training and validation respectively. Deep learning prediction of Ag was tested using two model architectures (DenseNet121 and ResNet50 - with no pre-trained weights) employing k-fold cross validation (k = 5). Performance metrics were recorded for the best model of each split, with mean and standard deviation values tabulated across 5 splits to determine the best performing model architecture family, followed by core-level metrics to determine the best performing individual model. **Results:** Feasibility and predictive potential of deep learning models was demonstrated, with superior performance metrics exhibited by the DenseNet121 model. It outperformed ResNet50 across all metrics for the combined held-out test set: AUC (0.796 ± 0.092 vs 0.748 ± 0.105), balanced accuracy (0.727 ± 0.075 vs 0.664 ± 0.100), F1 score (0.756 ± 0.059 vs 0.742 ± 0.070) and AUPRC (0.426 ± 0.132 vs 0.404 ± 0.157). Friedman test and post-hoc Conover's test revealed significant ($p < 0.05$) differences in metrics amongst the 10 models, where subsequent rank sum of mean metric values showed that DenseNet121 fold2_epoch09 performed best across the held-out test cores, displaying robustness and generalisability. **Conclusions:** There is potential of deep learning models to predict EBC-129 Ag expression from H&E images and suggest possible triaging of patients suitable for treatment. Immediate next steps include examining virtual stain plots for comparison to ground truth IHC images. Future work will extend to pancreatic ductal adenocarcinoma, building on encouraging findings from the Phase 1 trial. Research Sponsor: Singapore National Medical Research Council; OFLCG23may-0039,OFLCG24MAY-0028,OFLCG24may-0025,CIAINV25jan-0001,MOH-001067, MOH-001610-00; A*STAR GAP Funding; I24D1AG059; Industry Alignment Fund-Industry Collaboration Fund; I2001E0065.

4019 Poster Session

A machine learning algorithm for optimizing treatment selection for patients with up to three hepatocellular carcinomas measuring ≤ 3 cm.

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Background: Liver resection (LR) and radiofrequency ablation (RFA) are recommended for patients with early-stage hepatocellular carcinoma (HCC) with three nodules measuring ≤3 cm and preserved liver function. This study aimed to develop a predictive model to guide treatment decisions based on survival outcomes. **Methods:** This study included 18,958 patients with up to three HCCs measuring ≤3 cm from the nationwide survey of Japan. The Recurrent Deep Survival Machines (RDSM) model was employed for deep survival analysis. We employed 10-fold cross-validation, the concordance index (C-index), and overall survival (OS) to assess model performance. Survival curves were compared using the log-rank test. To identify potential confounding factors, 1:1 propensity score matching (PSM) was performed. **Results:** Patients undergoing LR demonstrated significantly longer OS than those receiving RFA (5-year survival rate 81.4% vs. 73.1%; $P < 0.005$). The trained RDSM model achieved a C-index of 0.68. In the deep learning (DL) model, patients undergoing recommended treatment demonstrated significantly longer survival than those who did not (5-year survival rate 81.2% vs. 73.9%; $P < 0.005$; PSM, 81.9% vs. 76.7%; $P < 0.005$). The DL modeling recommended LR in 6,966 (84.5%) patients undergoing RFA, especially those showing typical imaging patterns (early enhancement and washout in the computed tomography images [85.9% vs. 61.7% and 84.1 vs.74.3%, respectively]). **Conclusions:** DL modeling effectively helped treatment allocation for patients with up to three HCCs measuring ≤3 cm. Our study indicates the potential utilization of DL modeling in the treatment allocation of patients with up to three HCCs measuring ≤3 cm. Research Sponsor: Small Business Innovation Research.

Multi-modal AI modeling to predict clinical trial outcomes and benchmarks pan-RAS versus KRAS G12D inhibition in KRAS G12D–mutant PDAC.

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Background: In pancreatic ductal adenocarcinoma (PDAC), uncertainty persists regarding the optimal positioning of pan-RAS inhibitors, allele-specific KRAS inhibitors, and chemotherapy backbones. While patient-derived organoids (PDOs) provide functional resolution of drug response, their clinical utility has been limited by cohort size and insufficient validation against trial outcomes. **Methods:** A biobank of 135 colorectal cancer (CRC) and PDAC PDOs was assembled with matched clinical annotation, omics characterization, and functional drug profiling. Multi-modal AI models integrating molecular features, PDO drug response, and clinical covariates were trained to predict patient-level progression-free survival (PFS) and longitudinal response, and to aggregate these predictions into cohort-level clinical trial outcomes. Model performance was evaluated by benchmarking predicted outcomes against published results across 22 treatment arms from multiple clinical trials. A pan-RAS inhibitor (daraxonrasib), a KRAS G12D-directed inhibitor (zoldonrasib), and FOLFIRINOX (FFX) were compared as single agents or in combination in a KRAS G12D-mutant PDAC subset (n = 23), with external benchmarking to published clinical data. **Results:** The AI models demonstrated robust predictive performance at both the patient and cohort levels. Patient-level predictions were driven by functional PDO drug response and established clinical factors, including performance status and prior treatment exposure. At the cohort level, predicted and published outcomes showed good agreement ($R^2 = 0.63$), with correct ranking of treatment arms by efficacy in 78% of cases. In pairwise arm-to-arm comparisons, the model identified the superior regimen in 80% of comparisons. When applied to KRAS G12D-mutant PDAC, virtual clinical trial simulations preserved the relative efficacy hierarchy observed in external datasets. Zoldonrasib showed heterogeneous predicted activity (simulated ORR 20% vs reported 30%), whereas daraxonrasib demonstrated more favorable predicted outcomes (simulated ORR 35% vs reported 36%). Combination with FFX further improved predicted efficacy for zoldonrasib, particularly in first-line simulations (simulated ORR 38% vs reported 63%). **Conclusions:** Multi-modal AI modeling trained on clinically annotated PDO collections enables calibrated simulation of clinical trial outcomes and comparative assessment of therapeutic strategies in KRAS-mutant PDAC. By capturing patient-level heterogeneity and cohort-level efficacy trends, this framework provides a scalable decision-support tool for arm selection, therapeutic positioning, and trial design in KRAS-directed drug development. Research Sponsor: Fondation Jean-Jacques et Felicia Lopez-Loreta pour l'Excellence Académique; Banque Publique d'Investissement.

Benchmarking the KEYNOTE-811 standard of care using AI-reconstructed external control arms in advanced gastric cancer.

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Background: Randomized controlled trials in rare cancers and biomarker-enriched populations face significant recruitment burdens. External control arms (ECA) derived from historical Individual Patient Data (IPD) can mitigate these challenges, yet cross-trial heterogeneity often confounds comparisons. This study evaluates the feasibility of an AI-powered pipeline to reconstruct IPD from historical HER2+ advanced gastroesophageal adenocarcinoma trials and validates the cohort against a modern standard-of-care benchmark (KEYNOTE-811). **Methods:** An LLM-computer vision pipeline digitized KM curves from 10 historical trials (2011–2022) and the KEYNOTE-811 control arm (2023). IPD was reconstructed using a modified Guyot algorithm with risk-table guidance and least-squares optimization. Accuracy was validated against published HR and median survival. A propensity score matched (PSM) analysis (1:1 nearest-neighbor) compared the KEYNOTE-811 control arm (n=348) to historical controls (n=395). Sensitivity analyses addressed geographic imbalance (34% vs. 95% Asian) and early-period confounding via 3- and 6-month landmarking. **Results:** Technical validation demonstrated high fidelity: median OS concordance was 100%, with a reconstructed-to-published OS HR delta of only 0.01 (0.85 vs 0.84). The initial PSM suggested significantly worse outcomes for the KEYNOTE-811 control (OS HR 1.69, $p<0.0001$). However, this discrepancy was primarily driven by regional heterogeneity. After region-specific matching, OS HR stabilized at 1.13 ($p=0.40$). A 6-month landmark analysis further resolved early-period bias, achieving statistical equivalence for OS (HR 1.26, $p=0.057$) and PFS (HR 0.97, $p=0.84$). Residual imbalances in ECOG (SMD 0.25) and primary site (SMD 0.32) persisted but did not negate the trend toward equivalence. **Conclusions:** AI-powered IPD reconstruction achieves high fidelity to original trial data. While naive pooled ECAs may display era-specific survival artifacts, rigorous causal inference frameworks can resolve cross-trial heterogeneity. This study confirms that AI-reconstructed ECAs are viable tools for benchmarking novel therapies when paired with robust methodological guardrails for regional and baseline covariate alignment. Research Sponsor: None.

PSM sensitivity analyses with covariate balance.

Analysis	OS HR (95% CI)	PFS HR (95% CI)	Pairs	Key Imbalances (SMD >0.2)
Main PSM	1.69 (1.37–2.08) ***	1.30 (1.05–1.61) *	217	Age (0.86), ECOG (0.42), Primary site (0.49), Region (0.65)
+ Geographic matching	1.13 (0.85–1.50)	0.87 (0.66–1.16)	119	ECOG (0.25), Primary site (0.32)
+ 3-month landmark	1.16 (0.93–1.45)	1.17 (0.93–1.48)	194/177	ECOG (0.25), Primary site (0.32)
+ 6-month landmark	1.26 (0.99–1.60)	0.97 (0.73–1.30)	174/115	ECOG (0.25), Primary site (0.32)

***$p<0.001$, *$p<0.05$; SMD = standardized mean difference; All other covariates SMD <0.2.

First-line (1L) trastuzumab deruxtecan (T-DXd)–based regimens in advanced HER2-expressing gastric cancer (GC), gastroesophageal junction adenocarcinoma (GEJA), or esophageal adenocarcinoma (EA): Safety results from DESTINY-Gastric03 (DG-03) Part 2 arms D and F, and Part 4.

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Background: T-DXd 6.4 mg/kg monotherapy is approved in several countries for advanced HER2+ (IHC 3+ or IHC 2+/ISH+) GC/GEJA after an indicated HER2-directed regimen. Early data have shown promising antitumor activity with 1L T-DXd + immunotherapy + chemotherapy for advanced HER2+ GCs. Here, we report an approximate time-matched analysis of safety results for DG-03 Part 2 arms D and F, and Part 4. **Methods:** DG-03 (NCT04379596) is a Phase 1b/2, open-label, multipart trial. Part 2 (arms A–F) enrolled patients (pts) with previously untreated advanced HER2+ (IHC 3+ or IHC 2+/ISH+) GC/GEJA/EA. Pts in arm D received T-DXd 6.4 mg/kg + pembrolizumab (pembro) + fluoropyrimidine (FP; 5-fluorouracil or capecitabine), and pts in arm F received T-DXd 5.4 mg/kg + pembro + FP. In Part 4, pts with previously untreated advanced HER2-expressing (IHC 3+, IHC 2+/ISH+, IHC 2+/ISH−, or IHC 1+) GC/GEJA/EA were enrolled and received T-DXd 5.4 mg/kg + rilvegostomig (rilve; a monovalent, Fc-reduced, bispecific IgG1 antibody against PD-1 and TIGIT receptors) + FP. HER2 status was based on local testing. Secondary endpoints included frequency of adverse events (AEs) and serious AEs. **Results:** As of Feb 15, 2023, Aug 19, 2024, and Oct 16, 2025, 43, 32, and 62 pts received treatment (Tx) in Part 2 arm D, Part 2 arm F, and in Part 4, respectively. Median (range) total duration of Tx for both T-DXd and pembro was 6.1 (0.5–13.3) months (mo) in Part 2 arm D, and 6.9 (0.7–10.3) mo for T-DXd and 7.5 (0.7–10.3) mo for pembro in Part 2 arm F. Median (range) total duration of Tx for both T-DXd and rilve was 6.5 (0.7–14.7) mo in Part 4. A summary of safety data is shown in the Table. Drug-related adjudicated interstitial lung disease (ILD)/pneumonitis events occurred in 2 pts (5%) in Part 2 arm D, no pts in Part 2 arm F, and 2 pts (3%) in Part 4. **Conclusions:** Results with T-DXd (5.4 mg/kg)–based regimens were generally consistent with the known safety profiles of each agent; no new signals were observed. Safety data support use of pembro/rilve as combination partners for T-DXd (5.4 mg/kg) in advanced HER2-expressing GCs. Clinical trial information: NCT04379596. Research Sponsor: AstraZeneca.

n (%)	Part 2 arm D T-DXd 6.4 mg/kg + pembro + FP (n=43)	Part 2 arm F T-DXd 5.4 mg/kg + pembro + FP (n=32)	Part 4 T-DXd 5.4 mg/kg + rilve + FP (n=62)
AEs	43 (100)	31 (97)	60 (97)
Drug-related AEs*	40 (93)	27 (84)	55 (89)
Grade ≥3 AEs	38 (88)	15 (47)	31 (50)
Drug-related Grade ≥3 AEs*	33 (77)	11 (34)	24 (39)
Serious AEs	25 (58)	12 (38)	22 (36)
Drug-related serious AEs*	19 (44)	5 (16)	12 (19)
AEs leading to discontinuation of any IP	16 (37)	7 (22)	7 (11)
Drug-related AEs leading to death	4 (9)†	0	1 (2)‡

*Assessed by the investigator as possibly related to any investigational product (IP); †ILD/pneumonitis (n=2), respiratory failure due to pneumonitis/pneumocytis jirovecii infection (n=1), febrile neutropenia (n=1); ‡pneumonia.

Sonesitatug vedotin (Sone-Ve) monotherapy in patients (pts) with claudin 18.2–positive (CLDN18.2+) advanced or metastatic gastric or gastroesophageal junction (GEJ) cancers: Data from CLARITY-PanTumor01.

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Background: Sone-Ve (AZD0901), an antibody-drug conjugate comprising an anti-CLDN18.2 antibody and monomethyl auristatin E, showed promising antitumor activity and a manageable safety profile in pts with advanced or metastatic gastric/GEJ cancers in the first-in-human study conducted in China. **Methods:** CLARITY-PanTumor01 is an ongoing, global, phase 2 study (NCT06219941) evaluating Sone-Ve in gastric/GEJ cancers, PDAC, and BTC outside of China. Here we report data for pts with CLDN18.2+ advanced or metastatic gastric/GEJ cancers and ≤2 lines of prior systemic therapy (substudy 1) receiving Sone-Ve 2.2 mg/kg IV Q3W (pts randomized to 1.8 mg/kg are not reported). Primary endpoints were safety and objective response rate (ORR; 30 pts were selected to estimate ORR; lack of efficacy is concluded if ≤6 confirmed responses). Secondary endpoints included duration of response (DoR) and progression-free survival (PFS). Molecular responses (MRs) based on circulating tumor DNA (ctDNA) were evaluated. **Results:** As of Oct 31, 2025, 67 pts received Sone-Ve 2.2 mg/kg, including 30, 31, and 6 pts from the randomized (RC), paired biopsy (PBC), and Japanese safety (JSC) cohorts, respectively. All pts had adverse events (AEs; grade ≥3 in 34.3% overall, 36.7% of the RC, and 35.5% of the PBC). The most common grade ≥3 AEs were neutrophil count decreased (7.5%), anemia (7.5%), vomiting (6.0%), and nausea (6.0%). Dose reductions were most commonly due to gastrointestinal (GI) AEs and occurred in 40.3% of pts overall, 56.7% of the RC, and 19.4% of the PBC (adoption of a 4-drug antiemetic regimen improved GI tolerability in the PBC). The ORR was 28.4% (95% CI: 18.0–40.7). Median DoR has not yet been reached. Additional data are in the Table. Among evaluable pts, 58.6% (17/29) had sufficient baseline ctDNA levels to enable MR analysis; of these, 10 (58.8%) had at least a partial MR (>50% ctDNA reduction) within 2 cycles of Sone-Ve initiation. **Conclusions:** Sone-Ve 2.2 mg/kg demonstrated clinically meaningful efficacy and a manageable safety profile consistent with the first-in-human study. ctDNA MRs were observed in over half the evaluable pts. Clinical trial information: NCT06219941. Research Sponsor: AstraZeneca.

	RC (n=30)	PBC (n=31)	Total* (n=67)
ORR, % (95% CI)†	26.7 (12.3–45.9)	29.0 (14.2–48.0)	28.4 (18.0–40.7)
Best overall response, n (%)†			
Complete response	2 (6.7)	1 (3.2)	3 (4.5)
Partial response	6 (20.0)	8 (25.8)	16 (23.9)
Stable disease	14 (46.7)	18 (58.1)	35 (52.2)
Progressive disease	7 (23.3)	4 (12.9)	12 (17.9)
Not evaluable	1 (3.3)	0	1 (1.5)
6-month response rate, % (95% CI)	87.5 (38.7–98.1)	NC (NC–NC)	71.9 (39.2–89.1)
PFS†			
Events, n/N (%)	22/31 (71.0)	19/31 (61.3)	47/68 (69.1)
Median, months (95% CI)	4.2 (2.9–8.6)	3.1 (2.8–5.5)	4.2 (3.0–7.0)
6-month, % (95% CI)	44.8 (26.5–61.6)	30.3 (13.3–49.3)	39.9 (27.7–51.9)

NC, not calculable.
*Includes the JSC.
†Investigator-assessed per RECIST v1.1.

An open-label phase Ib/II study of trastuzumab deruxtecan combined with nivolumab and CAPOX in patients with HER2-low gastroesophageal adenocarcinoma (EPOC2203).

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Background: Trastuzumab deruxtecan (T-DXd) is standard of care for previously treated patients with HER2-positive metastatic gastroesophageal adenocarcinoma (mGEA) with exploratory analyses of the DESTINY-Gastric01 trial suggested activity in HER2-low (IHC 1+/2+ ISH-negative) disease and preclinical synergy with anti-PD-1 therapy. **Methods:** EPOC2203 (jRCT2031230477) is a prospective, multicenter, phase Ib/II study evaluating first-line T-DXd combined with nivolumab and CAPOX in HER2-low mGEA. Patients received T-DXd (5.4 or 4.4 mg/kg, day1) in combination with nivolumab (360mg/body, day1) and CAPOX (capecitabine 750 mg/m^2 twice daily on days 1–14; oxaliplatin 70 mg/m^2 on day 1) every 3 weeks. The primary endpoints were DLT rate to determine RP2D in phase Ib and ORR in phase II. Assuming a threshold ORR of 58% and an expected ORR of 80%, 28 patients in the full analysis set (FAS) treated at the RP2D were planned (one-sided α = 0.10; power = 80%). **Results:** A total of 30 patients were enrolled. The median age was 59 years; 83.3% had HER2 IHC 1+ disease, 63.3% had gastric primary, and 96.7% had PD-L1 CPS $\geq$1. Two DLTs, both febrile neutropenia, occurred at T-DXd 5.4 mg/kg, while none were observed at 4.4 mg/kg in phase Ib part, which was selected as the RP2D. Among patients in the FAS (n = 28), the investigator-assessed ORR was 89.3% (80% CI, 77.7–96.0; $P< 0.001$), exceeding the prespecified threshold. At median follow-up of 10.1 months, median PFS was 8.1 months (95% CI, 5.6–not estimable). The 6-month OS was 89.3% (95% CI, 70.4–96.4). Six patients underwent conversion surgery, including three with pathological complete response. Grade $\geq$3 treatment-emergent adverse events occurred in 46.4% of patients who were treated at the recommended dose (n = 28). The most common grade $\geq$3 adverse events were neutropenia (25.0%), anemia (14.3%), febrile neutropenia (3.6%), and diarrhea (3.6%). Interstitial lung disease was observed in 3 patients (10.7%), with no grade $\geq$3 events. No treatment-related deaths were observed. **Conclusions:** T-DXd (4.4 mg/kg) combined with nivolumab and CAPOX demonstrated encouraging antitumor activity with a manageable safety profile as first-line treatment for HER2-low mGEA, supporting further evaluation. Clinical trial information: jRCT2031230477. Research Sponsor: Daiichi Sankyo.

Application of unsupervised genetic clustering to identify biologically distinct cholangiocarcinoma subtypes with differential survival.

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Background: Cholangiocarcinoma (CCA) is a genetically heterogeneous malignancy for which current anatomic and histologic classifications inadequately predict survival. We hypothesized that unsupervised machine learning clustering of mutations and copy number alterations(CNA) could identify biologically distinct CCA subgroups with clinically meaningful differences in survival. **Methods:** Genomic and clinical data were obtained from the MSK cholangiocarcinoma dataset from cBioPortal. 790 patients with intrahepatic and extrahepatic CCA with available mutation and CNA data were included. Multiple unsupervised approaches were evaluated, including k-means, hierarchical clustering, non-negative matrix factorization, PCA–k-means, and UMAP–k-means. Model performance was assessed using silhouette scores, with UMAP–k-means (n=4 clusters) selected as the optimal method. Clusters were defined by dominant genetic alterations and compared for overall survival using Kaplan–Meier analysis with pairwise log-rank testing. Subgroup analyses included patients without curative-intent surgery and a young-onset cohort. **Results:** UMAP–k-means delineated four distinct genomic clusters ordered by progressively worse median survival. Cluster 1, defined by *ARID1A* or *BAP1* mutations, demonstrated the most favorable survival outcomes. Cluster 2 consisted of tumors wild type for recurrent driver alterations. Cluster 3 was characterized by *TP53*, *KRAS*, or *IDH1* mutations. Cluster 4, defined by *CDKN2A* double deletion or *ERBB2* amplification, exhibited the poorest median survival. Overall survival differed significantly across clusters, with all pairwise Kaplan–Meier comparisons reaching statistical significance except between clusters 1 and 2. These survival differences remained significant in patients who did not undergo curative-intent surgery. Notably, cluster 4 remained associated with significantly worse survival within the young-onset cohort. **Conclusions:** Unsupervised genomic clustering using UMAP–k-means identified biologically distinct subtypes of cholangiocarcinoma, with clinically significant survival differences that persist across surgical and age-based subgroups. These findings support future genomic subtyping as a prognostic framework and a rationale for biology-driven clinical trial stratification in cholangiocarcinoma. Research Sponsor: None.

Unsupervised genetic clustering identifies biologically distinct cholangiocarcinoma subtypes with differential survival.

Cluster	Primary Genetic alterations	N patients	Median OS	log-rank test P-value vs cluster 2	log-rank test P-value vs cluster 3	log-rank test P-value vs cluster 4
1	ARID1A or BAP1 mutant	120	28.0	0.308	<0.001	<0.001
2	Wild types	224	26.7	-	0.003	<0.001
3	TP53, KRAS or IDH1 mutant	319	22.0		-	0.002
4	CDKN2A deletion or ERBB2 amplification	127	16.9			-

LBA4026 **Poster Session**

Disitamab vedotin (DV) plus toripalimab (Tor) and chemotherapy (Chemo)/ trastuzumab (Tra) for first-line (1L) HER2-expressing locally advanced or metastatic (la/m) gastric cancer (GC): Updated results from the RC48-C027 trial.

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A phase 2 clinical study of nimotuzumab plus S-1 and concurrent radiotherapy in 75 years and older patients with esophageal squamous cell carcinoma.

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Background: Concurrent chemoradiotherapy is the standard treatment method for inoperable and locally advanced esophageal cancer. Nevertheless, due to decreased physical function and the presence of multiple complications, older patients often have reduced tolerance to radiotherapy and chemotherapy. **Methods:** We conducted this prospective, single-center, phase II study to evaluate the efficacy and safety of nimotuzumab (an epidermal growth factor receptor antibody) plus concurrent radiotherapy and S-1 in 75 years and older patients with stage II-IVB esophageal squamous cell carcinoma (ESCC). The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS), objective response rate (ORR), disease control rate (DCR), safety, nutritional indicators, and quality of life (QOL). Most nutritional indicators remained stable after treatment. **Results:** As of June 2024, a total of 56 patients were enrolled in this study. The median follow-up was 24.1 months (95% CI: 8.8, 34.1). 11 patients had complete response, 39 patients had partial response, 5 patients had stable disease, and 1 patient had progressive disease. The ORR was 89.2%, and the DCR was 98.1%. The 1- and 3-year PFS rates were 67.8% (95% CI: 55.5%, 80.1%) and 35.8% (95% CI: 17.6%, 54.0%), with the median PFS was 25.3 months (95% CI: 16.5, 34.1). The 1- and 3-year OS rates were 79.6% (95% CI: 68.8%, 90.4%) and 40.1% (95% CI: 21.1%, 59.1%), with the median OS was 28.2 months (95% CI: 24.1, 32.3). Most adverse events were grade 1-2 (85.7%). Among survivors, 45.5% patients reported high satisfaction with their QOL, and 84.8% patients did not experience weight loss. **Conclusions:** Our treatment combination of nimotuzumab plus S-1 and concurrent radiotherapy indicated favorable efficacy and safety profile. This might be an underlying treatment choice for older patients with ESCC. Clinical trial information: NCT06048913. Research Sponsor: None.

Preclinical efficacy of the anti-EBV agent brincidofovir (BCV) in EBV-associated gastric carcinoma (EBVaGC).

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Background: Immune checkpoint inhibitor (ICI) plus chemotherapy is an approved therapy for EBVaGC whose tumors express PD-L1 (CPS ≥1). However, some patients are resistant to ICI or exhibit myelosuppression, making them unable to tolerate chemotherapy. BCV, an antiviral drug with no myelotoxicity, is effective against EBV (EC50: 30 nM), and has demonstrated anti-tumor activity against head and neck cancer and EBV-associated lymphoma. Recently, we found that SNU-719, an EBVaGC cell line, is sensitive to BCV *in vitro* (IC50: 1.95 μM). To seek conventional chemo-free regimens for EBVaGC, we have studied the preclinical efficacy of BCV monotherapy and combination therapy with ICI against EBVaGC. **Methods:** BCV was tested for its ability to induce dsDNA breaks in SNU-719 cells by γ-H2A.X immunostaining. To assess synergy of BCV with ICI, we analyzed BCV-induced immunogenic cell death (ICD) in SNU-719 cells using calreticulin and HMGB-1 assays. Additionally, we assessed BCV-induced expression of PD-L1 using qPCR and FACS. Since BCV induced both ICD and PD-L1 expression *in vitro*, we then evaluated the *in vivo* anti-tumor activity of BCV with or without ICI in humanized NOG mice bearing SNU-719 xenografts. Specifically, mice received intraperitoneal administration of vehicle, BCV, pembrolizumab (Pembro), or Pembro+BCV. Subcutaneous tumor growth was monitored for each group. After euthanasia, the SNU-719 xenografts were also used to measure the mRNA expression levels of EBV genes including *EBNA1*. **Results:** BCV induced both dsDNA breaks and ICD in SNU-719 cells, similar to the positive control bleomycin. It also induced PD-L1 mRNA and protein expression. Subsequent *in vivo* studies showed that, while BCV or Pembro monotherapy showed partial efficacy, the combination therapy of BCV and Pembro was effective in all mice. Notably, treatment with BCV significantly reduced the expression levels of *EBNA1* mRNA ($p < 0.05$) in the tumor tissue of SNU-719 xenografts. **Conclusions:** EBV is an oncovirus and its gene product EBNA1 is an oncoprotein for EBVaGC. This study showed a significant reduction of *EBNA1* mRNA expression by BCV. Therefore, in addition to its own anti-tumor effects, BCV may contribute significantly to the suppression of EBVaGC tumorigenesis via its anti-EBV activity. From a clinical perspective, BCV was effective against EBVaGC xenografts when combined with ICI. This less toxic regimen may be beneficial for EBVaGC patients, especially those with myelosuppression. Research Sponsor: SymBio Pharmaceuticals Limited.

Early treatment failure despite first-line immunotherapy in real-world MSI-H/dMMR gastroesophageal cancer.

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Background: Clinical trials of first-line (1L) immunotherapy (IO) in gastroesophageal cancer (GEC) demonstrate greater benefit in patients with microsatellite instability–high or mismatch repair–deficient (MSI-H/dMMR) tumors compared with the overall trial population. However, the benefit is not universal, and outcomes remain suboptimal for a subset of patients. Real-world (RW) evidence describing outcomes with 1L IO in MSI-H/dMMR GEC is limited. This study characterized treatment patterns and outcomes among RW MSI-H/dMMR GEC patients treated with 1L IO to better define residual unmet need. **Methods:** Using the Flatiron Health electronic health record-derived deidentified database, adults (≥18 years) diagnosed with locally advanced unresectable, metastatic, or recurrent gastric (GC), gastroesophageal junction (GEJ), or esophageal cancer (EC) between 17 Apr 2021 and 31 Dec 2024 were identified. Patients were required to have documented MSI-H or dMMR status and no trastuzumab exposure. Data were available through 08 Sep 2025. Time to next treatment or death served as a RW proxy for progression. **Results:** Among 3,047 eligible patients, MSI-H/dMMR prevalence varied by disease site and stage, ranging from 5.8% in metastatic GC to 17.6% in locally advanced GC; from 2.4% to 10.4% in GEJ disease; and from 3.4% to 4.4% in EC. A total of 199 MSI-H/dMMR GEC patients were identified (median age 75 years [IQR 66–82]; 36% female; 37% metastatic at diagnosis; 95% adenocarcinoma). Of the 155 MSI-H/dMMR patients who received 1L therapy, 32% received IO alone, 31% IO plus chemotherapy, and 37% chemotherapy alone. Among patients treated with 1L IO ± chemotherapy, 37% initiated 2L therapy or died within 6 months, increasing to 47% and 54% by 9 and 12 months, respectively. Baseline characteristics were largely similar between patients with and without progression within the first 12 months (Table). **Conclusions:** In this real-world cohort of MSI-H/dMMR GEC patients, a substantial proportion experienced early treatment failure despite 1L IO. More than one-third initiated second line therapy or died within 6 months, and over half progressed or died within 1 year. These findings underscore heterogeneity in benefit from 1L IO and highlight an ongoing need for improved risk stratification and alternative precision-based treatment approaches. Research Sponsor: None.

Characteristics of MSI-H/dMMR GEC patients by progression status at 12 months post start of 1L IO therapy.

		Progressors N=35	Non-progressors** N=30
Age, Median [IQR]		72 [66, 83]	73 [64, 80]
Female, %		34.3	40.0
Location, %	GC	62.9	63.3
	GEJ	8.6	13.3
	EC	28.6	23.3
Status*, %	Metastatic	48.6	46.7
	Non-metastatic	45.8	50.0
ECOG at 1L*, %	0/1	25.7	26.7
	2+	57.1	50.0

*Some patients are missing disease status and/or ECOG.
**Patients included in non-progressors were required to have activity in the data at least 12 months after 1L IO initiation.

Tislelizumab (Tisle) combined with POFI (irinotecan, paclitaxel, oxaliplatin, and 5-FU/levoleucovorin) as first-line treatment for advanced gastric/gastroesophageal junction adenocarcinoma (AGC): Update from a single-arm, open-label phase I/II trial (SYLT-023).

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Background: Tisle is an anti-PD-1 antibody. The combination of Tisle + XELOX/FP is a first-line treatment of AGC in China. Both irinotecan and paclitaxel have also shown antitumor activity in AGC. This Phase I/II study evaluated the efficacy and safety of Tisle + POFI in this population. **Methods:** This single-center, single-arm phase I/II study enrolled treatment-naïve patients with pMMR/MSS AGC, aged 18-75, who have at least one measurable lesion according to RECIST 1.1 and an ECOG PS of 0-1. Eligible participants received POFI (irinotecan/paclitaxel (mg/m2): 135/45 (dl #1), 150/45 (dl #2), 135/67.5 (dl #3), and 135/90 (dl #4), oxaliplatin 85 mg/m^2, levoleucovorin 200 mg/m^2, and 5-FU 2400 mg/m^2 for 46 hours every 2 weeks) in combination with Tisle 200mg every 2 weeks. The primary endpoint was the objective response rate (ORR) per RECIST 1.1. **Results:** As of Dec. 23, 2025, 47 patients were enrolled (median age: 58 years, range: 31–72; 26%(12/47) ECOG PS 1; 74% poorly differentiated; 68%(32/47) with ≥2 metastatic sites; 34% with programmed death-ligand 1 combined positive score [PD-L1 CPS] ≥1). The confirmed ORR was 76.6% (36/47), and the disease control rate was 95.7%. Median progression-free survival (PFS) was 11.1 months (95% CI: 8.8, 13.4) (versus 6.9 months (5.7-7.2) for ITT population for RATIONALE 305, ESMO 2023). Median duration of response was 9.7 months (95% CI: 6.7, 12.2). Median overall survival was 16.0 months (95% CI: 12.4, 23.0). All patients experienced treatment-emergent adverse events. The most common grade 3/4 adverse events included neutropenia (53.2%), leukopenia (27.7%), and anemia (21.3%). No new safety signals were identified. **Conclusions:** Tisle + POFI showed promising efficacy and a manageable safety profile as first-line treatment for HER2-negative, pMMR/MSS AGC, warranting further investigation. Clinical trial information: NCT05319639. Research Sponsor: None.

4031 Poster Session

CLDN18.2–targeting antibody-drug conjugate BA1301 in advanced solid tumors: Results from a phase I clinical trial.

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Background: Aberrant expression of claudin18.2 (CLDN18.2) has frequently been observed in various solid tumors, making it a promising therapeutic target for those aggressive cancers. BA1301 is an ADC consisting of a fully humanized anti-CLDN18.2 monoclonal antibody conjugated to monomethyl auristatin E, a potent cytotoxic agent via site-specific glycol conjugation and a cleavable linker with a drug-to-antibody ratio of 4. Here we reported the results from a phase 1 dose escalation and dose expansion study of BA1301. **Methods:** Eligible pts failed or intolerant to standard therapy were enrolled. BA1301 was intravenously administered with accelerated titration (0.1/0.4 mg/kg Q3W) and traditional 3+3 design (1.2/2.0/2.5/3.0mg/kg Q3W). Dose expansion was evaluated at 1.6/2.0/2.5mg/kg Q3W. CLDN18.2 was test by immunohistochemistry [IHC] Claudin18.2 (EPR19202-244) Assay developed by Medx. Moderate to high expression of CLDN18.2 defined as IHC membrane staining intensity ≥2 in ≥40% of tumor cells. Endpoints were safety and efficacy per RECIST v1.1. **Results:** As of Dec 22, 2025, a total of 91 patients with advanced cancers (gastric cancer [59, 64.8%], biliary tract cancer [14, 15.4%], pancreatic cancer [11, 12.1%], gynecologic cancers [3, 3.3%] and other 4 tumor types) were enrolled, 49 (53.8%) patients had received ≥2 systemic therapies (median 2, range 1-7). In dose escalation (n = 24), No DLTs were observed.80 (87.9%) patients had at least one treatment-related adverse events (TRAEs), and 33 (36.3%) had grade 3 or 4 TRAEs. The most common TRAEs were corneal disorder (51, 56.0%) and anemia (30, 33.0%). 3(3.3%) pts discontinued treatment due to TRAEs, and no treatment related death reported. Among patients with CLDN18.2 moderate to high expression (N=76), 69 at the ≥1.6 mg/kg dose level had at least one post-baseline tumor assessment. Key efficacy outcomes are presented (Table). **Conclusions:** BA1301 was well-tolerated with a manageable safety profile and demonstrated promising anti-tumor activity in patients with CLDN18.2 moderate to high expression. The findings support further development of BA1301 as a new therapeutic approach to treat CLDN18.2-positive solid tumors. The trial (NCT06927349) is ongoing in China. Clinical trial information: NCT06927349. Research Sponsor: None.

Cancer Type	ORR n (%) [95%CI]	DCR n (%) [95%CI]
Gastric cancer (N=49)	14 (28.6) [16.6, 43.3]	35 (71.4) [56.7, 83.4]
Biliary tract cancer (N=10)	3 (30.0) [6.7, 65.2]	6 (60.0) [26.2, 87.8]
Pancreatic cancer (N=7)	1 (14.3) [0.4, 57.9]	5 (71.4) [29.0, 96.3]
Gynecologic cancer (N=3)	1 (33.3) [0.8, 90.6]	3 (100.0) [29.2, 100.0]
In total (N=69)	19 (27.5) [17.5, 39.6]	49 (71.0) [58.8, 81.3]

Prognostic impact of AXL expression in upper gastrointestinal cancer in MONSTAR-SCREEN-2: An international collaborative study between United States and Japan.

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Background: AXL, a receptor tyrosine kinase of the TAM family, promotes epithelial-mesenchymal transition (EMT) and tumor progression. Elevated AXL expression is reported as poor prognostic factor with immunosuppressive features in colorectal cancer (Karam Ashouri, et al. J Immunother Cancer. 2025). We investigated the prognostic impact of AXL expression and its associated molecular and tumor microenvironment (TME) features in upper gastrointestinal (GI) cancers. **Methods:** Treatment-naïve patients with gastric cancer (GC) and esophageal cancer (EC) enrolled in MONSTAR-SCREEN-2 with available RNA-seq data (Caris MI TumorSeek) were analyzed. AXL expression was dichotomized by median into high and low groups within each cancer type. Molecular alteration, including somatic mutations and copy number alterations, and expression of receptor tyrosine kinases, including FGFRs, VEGFRs, and EGFR were compared between groups. Overall survival (OS) was evaluated using Kaplan-Meier analysis and Cox proportional hazards models. Tumor microenvironment (TME) cell infiltration, assessed using xCell deconvolution and gene set enrichment analysis (GSEA) performed using Hallmark gene sets, was compared between AXL-high and AXL-low groups. **Results:** A total of 320 patients were analyzed (GC: n = 270; EC: n = 50). In GC, AXL-high patients were older than AXL-low patients (median 71 vs 66 years, p = 0.012), while no other baseline characteristics, including sex, histology, primary site, metastatic sites, microsatellite instability-high, and tumor mutation burden-high status, differed between groups. *ARID1A* mutations were enriched in AXL-high GC ($p < 0.05$), while *CCNE1* amplification was associated with AXL-low ($p < 0.05$). Across both cancer types, AXL-high tumors exhibited significantly higher expression of FGFR1, VEGFR1-3, and MET ($p < 0.01$). In GC, AXL-high was associated with significantly shorter OS compared to AXL-low (median 12.9 vs 16.6 months; HR 1.44, 95% CI 1.03-2.02; p = 0.034). Similarly in EC, AXL-high showed worse OS compared to AXL-low (median 10.4 vs not reached; HR 2.46, 95%CI 1.08-5.62; p = 0.027). TME analysis revealed increased stromal scores, endothelial cells, M1/M2 macrophages, and regulatory T cells, along with higher expression of immune checkpoint molecules, including PD-L2 and CTLA4, in AXL-high tumors. GSEA showed enrichment of EMT, IFN-γ response, and PI3K/AKT/mTOR pathways in AXL-high GC. **Conclusions:** AXL overexpression is a prognostic biomarker in upper GI cancers, and is associated with worse survival and a distinct molecular and immune landscape characterized by EMT activation and immune-suppressive TME. These findings support AXL as a potential therapeutic target and warrant further investigation of AXL-targeted therapy in upper GI cancers. Research Sponsor: None.

4033 Poster Session

CDH17 expression and tumor microenvironment composition in gastric cancer.

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Background: Cadherin 17 (CDH17), commonly referred to as liver-intestine cadherin, is a calcium-dependent cell adhesion molecule, is overexpressed across multiple gastrointestinal epithelial malignancies and is implicated in tumorigenesis and aggressive tumor phenotypes through diverse signaling pathways. Preclinical studies have demonstrated the therapeutic potential of anti-CDH17 approaches across multiple therapeutic modalities. However, the relationship between CDH17 and cellular characteristics within the gastric cancer tumor microenvironment (TME) is yet to be sufficiently characterized. **Methods:** To systematically investigate the association between CDH17 expression and TME composition in gastric cancer, we conducted a comprehensive multi-cohort analysis of clinically annotated gastric cancer samples with RNA sequencing data. Within each cohort, CDH17 expression levels were quantified and dichotomized into high and low expression groups based on cohort-specific median transcripts per million (TPM) values. We applied the xCell immune deconvolution algorithm to estimate the relative immune and stromal cell populations enrichment across all samples. **Results:** In total, we studied 1,811 samples within ten datasets. CDH17 high-expressing gastric cancers demonstrated a distinctive TME signature characterized by selective cellular depletion rather than generalized immune suppression. Natural killer (NK) cell enrichment was identified in three cohorts; however, this pattern lacked pan-cohort consistency. Notably, CDH17 high expression was associated with significant depletion in multiple critical effector populations, including CD8+ cytotoxic T lymphocytes (CD8+ T-cells: 6/10 cohorts $p < 0.05$), myeloid dendritic cells and cancer-associated fibroblasts (8/10 cohorts, $p < 0.05$), and hematopoietic stem cells (5/10 cohorts, $p < 0.05$). In contrast, other immune and stromal cell populations demonstrated heterogeneous patterns of association with CDH17 expression, with no clear or uniform enrichment or depletion across cohorts. **Conclusions:** CDH17 high-expressing gastric cancers harbor an immunologically "cold" tumor microenvironment characterized by selective depletion of critical effector immune and stromal cell populations. Research Sponsor: None.

Quality-adjusted survival comparison for tislelizumab (TIS) + chemotherapy (CT) versus placebo (PBO) + CT as first-line (1L) treatment in gastric/gastroesophageal junction adenocarcinoma (GC/GEJC) patients with peritoneal metastasis (PM): Long-term follow-up from RATIONALE-305.

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Background: There is an unmet need for better treatment among patients (pts) with PM. A post hoc analysis of the phase 3 RATIONALE-305 (NCT03777657) trial showed that TIS + CT as 1L treatment for GC/GEJC pts with PM improved survival compared to PBO + CT (Qiu et al, 2025). The current study evaluated whether this survival benefit translated into quality of life (QoL) adjusted survival gains. **Methods:** This post hoc analysis used long-term follow-up data from the RATIONALE-305 trial (minimum follow-up 3 years; data cutoff February 28, 2024). The analysis focused on the intent-to-treat (ITT) population and subgroups defined by programmed death ligand-1 (PD-L1) ≥1% as well as ≥5% by Tumor Area Positivity (TAP) score. The well-established Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) methodology was used. QoL adjusted survival was calculated as the average time spent in three distinct health states during the trial follow-up: survival time with grade 3/4 toxicity, survival without progression/toxicity, and survival post progression, each weighted by QoL utility parameters specific to that state. A sensitivity analysis (SA) using trial-derived, treatment-specific EQ-5D utility values was also conducted. QoL adjusted relative survival gains ≥15% were considered "clearly clinically important," in line with commonly accepted Q-TWiST benchmarks (DOI 10.1007/s11136-005-1579-7). **Results:** At the maximum follow-up of 57 months in all randomized pts in RATIONALE-305, TIS + CT (n=501) pts experienced greater mean QoL adjusted survival than PBO + CT (n=496) (16.3 vs 13.1 months). Among pts with PM, TIS + CT (n=220) showed higher mean QoL adjusted overall survival than PBO + CT (n=214) (13.4 vs 10.8 months; 17.7% relative Q-TWiST gain) that was clearly clinically important. QoL adjusted survival benefit was also clearly clinically important in TIS + CT pts with PM with PD-L1 TAP score ≥1% (16.8% gain) and PD-L1 score ≥5% (33.0% gain) compared with PBO + CT. SA results further favored TIS + CT (Table). **Conclusions:** Treatment with TIS + CT resulted in clinically meaningful improvement in long-term quality-adjusted survival for GC/GEJC pts with PM versus those receiving CT alone. Clinical trial information: NCT03777657. Research Sponsor: BeOne Medicines, Ltd.

TIS + CT vs PBO + CT treatment difference.

	Mean Q-TWiST, months (95% CI)	Relative Q-TWiST Gain
Pts with PM[a]		
ITT pts (n=434)	2.6 (0.1 to 5.0), *P*=0.04	17.7%
PD-L1 TAP ≥1% (n=386)	2.5 (0.1 to 5.1), *P*<0.05	16.8%
PD-L1 TAP ≥5% (n=217)	4.7 (1.1 to 8.6), *P*=0.02	33.0%
Pts with PM (SA using EQ-5D scores)[b]		
ITT pts (n=434)	3.1 (0.8 to 5.5), *P*<0.01	21.3%
PD-L1 TAP ≥1% (n=386)	3.1 (0.5 to 5.6), *P*=0.02	20.8%
PD-L1 TAP ≥5% (n=217)	4.8 (1.3 to 8.2), *P*<0.01	33.9%

[a]Using standardized base case Q-TWiST utility weights.
[b]Using US mapping algorithm weights.

4035 Poster Session

Real-world adoption and sequencing of CLDN18.2, PD-L1, and HER2 testing in advanced gastric and gastroesophageal junction adenocarcinoma.

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Background: The FDA approval of zolbetuximab for CLDN18.2-positive advanced gastric and gastroesophageal junction adenocarcinoma (GEA) in Oct 2024, based on the SPOTLIGHT and GLOW trials, represents an important advance in biomarker-driven therapy. We aimed to describe real-world adoption of CLDN18.2 testing in the US, and CLDN18.2 co-expression with other clinically relevant biomarkers. **Methods:** Using the US-based, electronic health record-derived deidentified Flatiron Health Research Database, we evaluated biomarker testing patterns among patients diagnosed after 2016 across three periods: pre-SPOTLIGHT publication (2016–2022), post-SPOTLIGHT/pre-FDA approval (Jan 2023–Sep 2024), and post-FDA approval (Oct 2024 onward). We assessed CLDN18.2 testing uptake and co-expression with PD-L1 and HER2. **Results:** In total, our study included 11,099 patients (7,515 pre-SPOTLIGHT, 2,364 pre-FDA, 1,220 post-FDA). Compared to HER2 testing, 1.1% had CLDN18.2 testing pre-SPOTLIGHT, 21.3% pre-FDA and 39.5% post-FDA. The prevalence of biomarker positivity was as follows: HER2 20.1% (2,617/13,033), PD-L1 25.6% (1,913/7,487), CLDN18.2 42.6% (473/1,109). Among patients tested for all three biomarkers with available result dates, 69.9% underwent upfront comprehensive testing (HER2, PD-L1, CLDN18.2 within one week), while 30.1% had sequential testing, with a median interval of 91 days between tests. Among 1,034 patients tested for all three biomarkers, 13.9% were dual PD-L1/CLDN18.2 positive, and 4.4% were triple-positive. **Conclusions:** In this real-world analysis, CLDN18.2 testing uptake increased following SPOTLIGHT but remained incomplete, and nearly one-third underwent sequential rather than upfront comprehensive biomarker testing, resulting in clinically meaningful delays. These findings highlight the need for improved education and implementation of upfront, comprehensive biomarker testing strategies to optimize treatment sequencing and preserve therapeutic options for patients with GEA. Research Sponsor: None.

Phase I/II trial of anti-CLDN18.2/PD-L1 recombinant humanized bispecific antibody Q-1802 plus XELOX in treatment-naive CLDN18.2-positive advanced GC/GEJ.

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Background: First-line therapy for HER2-negative advanced GC/GEJ remains a huge unmet clinical need. Claudin 18.2 (CLDN18.2), a tight junction protein, is specifically expressed in normal gastric mucosa but aberrantly overexpressed in various cancers, making it a high-value therapeutic target. Q-1802 is a first-in-class humanized bispecific antibody targeting both CLDN18.2 and PD-L1. Q-1802 can bind CLDN18.2 on tumor cells and kill them through Fc mediating antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP). Meanwhile, it can activate immune system to eliminate tumor cells by blocking PD-1/PD-L1 binding. **Methods:** Qure-1802-201 was a multicenter, open-label, nonrandomized phase I/II trial. Eligible pts: CLDN18.2-positive (≥40% tumor cells with 2+/3+ membranous staining), HER2-negative, treatment-naïve, histologically confirmed unresectable locally advanced/metastatic GC/GEJ. Pts received Q-1802 (10 mg/kg or 20 mg/kg Q2W) plus standard XELOX (oxaliplatin IV d1; capecitabine PO d1-14 Q3W). Primary endpoints: DLT/MTD (Phase I) and ORR per RECIST v1.1 (Phase II). Secondary endpoints: efficacy, safety, pharmacokinetics, pharmacodynamics, immunogenicity. **Results:** As of Dec 11, 2025, 62 pts were enrolled (45 in 10 mg/kg, 17 in 20 mg/kg). No DLT observed; MTD not reached. All pts had TEAEs and Q-1802-related TEAEs; the latter mainly included nausea (75.8%), AST increase (61.3%), nausea (59.7%), ALT increase (51.6%), fatigue (50.0%). Incidences of ≥3 Grade TEAEs and Q-1802-related ≥3 Grade TEAEs: 74.2% and 43.5%, respectively. Most common Q-1802-related ≥3 Grade TEAE: thrombocytopenia (8.1%), followed by neutropenia (6.5%), anemia, WBC decrease, hypokalemia (4.8% each). Rate of Q-1802 permanent discontinuation due to TEAEs: 6.5%; no treatment-related death. ORR and median progression-free survival (mPFS) in 60 efficacy-evaluable pts were 70.0% (42/60; 95% CI: 56.8%–81.2%) and 11.3 months (95% CI: 8.0–16.8). A correlated trend was observed between efficacy and CLDN18.2 expression. In the 10 mg/kg cohort, ORR and mPFS were 73.0% (27/37; 95% CI: 55.9%–86.2%) and 11.3 months (95% CI: 7.1–16.8) in pts with CLDN18.2 high expression (2+/3+≥70%, N = 37), which were improved to 81.8% (9/11; 95% CI: 48.2%–97.7%) and 12.2 months (95% CI: 2.7–NE) when CLDN18.2 high expression companied with PD-L1 CPS≥5 (N = 11). DCR was nearly complete (non-response in 1 of 60 pts). ORR in the 20 mg/kg cohort (70.6%, 12/17; 95% CI: 44.0%–89.7%) was similar to 10 mg/kg (69.8%, 30/43; 95% CI: 53.9%–82.8%.). Overall survival (OS) in all pts and PFS in the 20 mg/kg cohort are under follow-up. **Conclusions:** Q-1802 plus XELOX has manageable safety and promising antitumor activity as first-line therapy for CLDN18.2-positive/HER2-negative advanced GC/GEJ, supporting a phase III trial (Q-1802 10 mg/kg as recommended dose). Clinical trial information: NCT05964543. Research Sponsor: None.

4037 Poster Session

A phase 1 study of SHR-3821, an ADCC-enhanced CLDN18.2/4-1BB bispecific antibody, in patients with advanced solid tumors.

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Background: CLDN18.2 is a highly selective tumor-associated antigen overexpressed in gastrointestinal malignancies, and has emerged as a promising therapeutic target. 4-1BB is a co-stimulatory receptor expressed on activated immune cells; its activation enhances antitumor immunity. SHR-3821 is an ADCC-enhanced bispecific antibody that specifically targets CLDN18.2 and activates 4-1BB in a CLDN18.2-dependent manner, enabling tumor-specific killing while minimizing systemic toxicity. This phase 1 study aims to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of SHR-3821 in patients with CLDN18.2-positive advanced solid tumors. **Methods:** Eligible patients had CLDN18.2-positive advanced solid tumors that had progressed on or lacked standard therapies. Patients received SHR-3821 via intravenous infusion every 3 weeks at prespecified dose levels: 0.1, 1, 3, 10, 15, 20 and 30 mg/kg during dose escalation (using a Bayesian optimal interval design), followed by dose expansion and efficacy expansion at 15 and 20 mg/kg. Primary endpoints included safety, maximum tolerated dose, and recommended phase 2 dose. **Results:** As of November 30, 2025, 40 patients with CLDN18.2-positive advanced solid tumors (23 gastric cancer [GC], 17 pancreatic cancer [PC]) were treated with SHR-3821 at doses ranging from 0.1 to 20 mg/kg. No dose-limiting toxicities occurred, and the maximum tolerated dose was not reached across the evaluated dose range. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 15 patients (37.5%), most commonly decreased neutrophil count (20.0%), decreased lymphocyte count (7.5%), and vomiting (5.0%). No TRAEs led to death; one (2.5%) patients discontinued treatment due to TRAEs. Preliminary pharmacokinetic analyses demonstrated dose-proportional increases in systemic exposure following a single 1–20 mg/kg administration, with terminal elimination half-lives ranging from 4.2 to 7.0 days. ORR in GC were 22.2% at 15 mg/kg and 37.5% at 20 mg/kg (Table). **Conclusions:** SHR-3821 showed tolerable safety and promising antitumor activity in patients with CLDN18.2-positive GC and PC. These data support further clinical development of SHR-3821. Clinical trial information: NCT06618651. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

Efficacy in GC and PC.

	GC		PC	
	15 mg/kg (N=9)	20 mg/kg (N=8)	15 mg/kg (N=4)	20 mg/kg (N=7)
Confirmed ORR, %	11.1	0	0	0
(n/N; 95% CI)	(1/9; 0.28-48.25)	(0/8; 0.00-36.94)	(0/4; 0.00-60.24)	(0/7; 0.00-40.96)
Confirmed DCR, %	55.6	62.5	50.0	42.9
(n/N; 95% CI)	(5/9; 21.20-86.30)	(5/8; 24.49-91.48)	(2/4; 6.76-93.24)	(3/7; 9.90-81.59)
Unconfirmed ORR*, %	22.2	37.5	0	0
(n/N; 95% CI)	(2/9; 2.80-60.01)	(3/8; 8.52-75.51)	(0/4; 0.00-60.24)	(0/7; 0.00-40.96)
Unconfirmed DCR, %	55.6	62.5	50.0	42.9
(n/N; 95% CI)	(5/9; 21.20-86.30)	(5/8; 24.49-91.48)	(2/4; 6.76-93.24)	(3/7; 9.90-81.59)

ORR, objective response rate; DCR, disease control rate.
*Four patients were pending efficacy confirmation.

Randomized phase II trial of trifluridine/tipiracil (FTD/TPI) plus ramucirumab (RAM) versus FTD/TPI for previously treated patients with advanced gastric or gastro-esophageal junction adenocarcinoma: Final analysis of RETRIEVE study (WJOG 15822G).

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Background: Promising activity of trifluridine/tipiracil (FTD/TPI) plus ramucirumab (RAM) has been reported in single-arm phase II trials as third- or later-line treatment for advanced gastric cancer (GC) and gastroesophageal junction (GEJ) adenocarcinoma (Lancet Gastroenterol Hepatol. 2021; 6: 209-217). We previously reported the primary analysis of the RETRIEVE study at ASCO-GI 2026, which demonstrated no significant difference in progression-free survival (PFS; median 2.69 vs 2.07 months) between FTD/TPI plus RAM and FTD/TPI alone. Here, we present the final analysis, including overall survival (OS) as a key secondary endpoint, along with updated results of other endpoints. **Methods:** RETRIEVE study is a multicenter, prospective, open-label, randomized phase II trial comparing FTD/TPI plus RAM versus FTD/TPI alone in patients with unresectable or recurrent GC or GEJ adenocarcinoma who were refractory or intolerant to fluoropyrimidine, taxane, or irinotecan, and refractory to RAM. Treatment is repeated every 4 weeks until disease progression or unacceptable toxicity. Key eligibility criteria include age of ≥20 years; ECOG performance status of 0 or 1, and at least a measurable lesion per RECIST 1.1. **Results:** Between January 2023 and June 2024, 111 patients were randomly assigned to receive FTD/TPI plus RAM (n = 56) or FTD/TPI alone (n = 55). At a median follow-up of 18.4 months, median OS was 6.08 months in the combination arm and 7.36 months in the monotherapy arm (hazard ratio [HR], 1.233; 95% CI, 0.817–1.862; P = 0.318). The proportion of patients who received subsequent treatment was 64.3% in the combination arm and 56.4% in the monotherapy arm. In the updated analysis, median PFS was 2.69 months in the combination arm and 2.07 months in the monotherapy arm (HR, 1.010; 80% CI, 0.781–1.307; P = 0.959). Objective response rate (ORR; 5.4% vs 9.1%, P = 0.489) and disease control rate (DCR; 50.0% vs 47.3%, P = 0.850) were consistent with the primary analysis. No novel adverse events were identified from the primary analysis. Any grade of n (49.1% vs 25.5%) and diarrhea (29.1% vs 14.5%) were more frequently observed in the combination arm than in the monotherapy arm. **Conclusions:** The final analysis demonstrated that FTD/TPI plus RAM did not provide a significant OS benefit compared with FTD/TPI alone in third- or later-line treatment for advanced GC and GEJ adenocarcinoma. Updated results of PFS, tumor response, and safety profile were consistent with the primary analysis. Clinical trial information: jRCTs041220120. Research Sponsor: Taiho Pharmaceutical Co., Ltd.

Evaluation of homologous recombination deficiency (HRD) in gastric cancer: Real-world prevalence and outcomes with first-line (1L) platinum-based therapy.

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Background: Metastatic gastric and gastroesophageal junction cancers (GC/GEJ) have poor outcomes with limited predictive biomarkers to guide first-line (1L) therapy. HRD predicts sensitivity to platinum chemotherapy and PARP inhibition in several malignancies, but its clinical relevance is not well defined in GC/GEJ. We evaluated the association between HRD alterations, genomic context, and clinical outcomes following 1L platinum-based therapy (PBT) in metastatic GC/GEJ. **Methods:** We queried the de-identified Tempus multimodal database using the Tempus Lens Platform to analyze a cohort of patients with advanced GC/GEJ. All patients had DNA (xT, 648 gene DNA-seq panel) and/or RNA sequencing (xR, whole transcriptome RNA-seq). Patients were classified as HRD-altered (HRD-alt) if they harbored pathogenic or likely pathogenic germline or somatic alterations in at least one of 23 predefined HRD-associated genes; all others were classified as HRD wild-type (HRD-wt). Tumor mutational burden (TMB-H, $\geq$ 10 mut/Mb) and microsatellite instability (MSI) were assessed. Real-world (rw) overall survival (rwOS) was estimated using Kaplan–Meier methods. Hazard ratios (HRs) from Cox-proportional hazards models were adjusted for relevant clinical and molecular covariates at a significance level of $p < 0.05$. **Results:** Among 1,066 eligible patients, 257 (24%) were HRD-alt and 809 (76%) were HRD-wt. HRD-alt tumors were associated with TMB-H (21% vs 5.9%, $p< 0.001$) and MSI-high status (12% vs 1.2%, $p< 0.001$). Median OS was longer in HRD-alt compared with HRD-wt patients (15 vs 12 months, HR:0.79, p = 0.033). Notably, HRD-alt tumors were strongly enriched for ERBB2 alterations compared to HRD-wt tumors (30% vs 8.8%, $p< 0.001$), predominantly driven by amplification (86%). Further stratification by HRD and ERBB2 status showed reduced HRs for rwOS in HRD-alt only (HR 0.78; 95%, p = 0.034), dual ERBB2/HRD-alt tumors (HR 0.63; 95% CI, 0.45–0.88, p = 0.006), and ERBB2-alt only (HR 0.52; 95% CI, 0.36–0.76, $p < 0.001$) compared to the wt/wt group. ERBB2-alt tumors demonstrated distinct co-mutation patterns enriched for cell-cycle and proliferative genes (*CCNE1, TOP2A)*, whereas *ERBB2*–wt tumors more frequently harbored *KRAS*, *ARID1A*, and *CDH1* alterations. **Conclusions:** In this large rw-cohort of metastatic GC/GEJ, HRD alterations identified a biologically distinct subgroup with improved OS and greater durability on 1L PBT. HRD status was associated with *ERBB2* amplification, and the HRD/ERBB2 status was associated with improved survival. These findings support HRD as a clinically relevant biomarker in GC/GEJ and justify prospective evaluation of HRD-informed treatment strategies. Research Sponsor: None.

KEYNOTE-811: 6-year median follow-up of pembrolizumab plus trastuzumab and chemotherapy for previously untreated advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma.

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Background: At the final analysis of the phase 3 KEYNOTE-811 trial (NCT03615326), first-line (1L) pembrolizumab (pembro) plus trastuzumab and chemotherapy (chemo) showed superior OS and consistently improved PFS and ORR with durable responses vs placebo plus trastuzumab and chemo in participants (pts) with HER2-positive (HER2+) advanced or metastatic gastric or gastroesophageal (G/GEJ) adenocarcinoma, particularly in pts with PD-L1 combined positive score (CPS) ≥1 tumors. Results supported the approval of pembro plus trastuzumab and chemo for 1L treatment of advanced or metastatic HER2+ G/GEJ adenocarcinoma with PD-L1 CPS ≥1. We report results after an additional 20 months of follow-up. **Methods:** Eligible pts with untreated advanced or metastatic HER2+ G/GEJ adenocarcinoma, measurable disease, and ECOG PS 0 or 1 were randomly assigned 1:1 to receive pembro 200 mg or placebo IV Q3W for up to 35 cycles plus trastuzumab 6 mg/kg (after loading dose of 8 mg/kg) and chemo (CAPOX or FP). Dual primary end points were OS and PFS per RECIST v1.1 by BICR. Secondary end points included ORR and DOR (per RECIST v1.1 by BICR), and safety. Data cutoff date was November 12, 2025. **Results:** Overall, 698 pts were randomly assigned to the pembro group (n = 350) or placebo group (n = 348). Median follow-up was 70.0 months (range, 50.9-84.2). In the intention-to-treat (ITT) population (all randomly assigned pts), median OS was 20.0 months (95% CI, 17.8-22.1) in the pembro group vs 16.8 months (95% CI, 14.9-18.7) in the placebo group. In pts with PD-L1 CPS ≥1, median OS was 20.1 months (95% CI, 17.9-22.9) vs 15.7 months (95% CI, 13.5-18.5). PFS, ORR, and DOR were also consistent between the ITT population and pts with PD-L1 CPS ≥1 (Table). Treatment-related AEs occurred in 341 pts (97.4%; grade ≥3, 206 [58.9%]) in the pembro group and 335 (96.8%; grade ≥3, 177 [51.2%]) in the placebo group. **Conclusions:** Pembro plus trastuzumab and chemo continued to show improved OS, PFS, and ORR vs placebo plus trastuzumab and chemo after a median study follow-up of 70 months, especially in pts with PD-L1 CPS ≥1. No new safety signals were seen. The findings continue to support pembro plus trastuzumab and chemo as the preferred 1L treatment for advanced or metastatic HER2+ G/GEJ adenocarcinoma. Clinical trial information: NCT03615326. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	ITT N = 698		PD-L1 CPS ≥1 n = 594	
	Pembro group n = 350	Placebo group n = 348	Pembro group n = 298	Placebo group n = 296
OS, median (95% CI), months	20.0 (17.8-22.1)	16.8 (14.9-18.7)	20.1 (17.9-22.9)	15.7 (13.5-18.5)
HR (95% CI)	0.81 (0.69-0.95)		0.79 (0.66-0.94)	
PFS, median (95% CI), months	10.0 (8.6-12.2)	8.1 (7.0-8.5)	10.9 (8.5-12.5)	7.3 (6.8-8.4)
HR (95% CI)	0.73 (0.61-0.87)		0.72 (0.60-0.87)	
ORR, % (95% CI)	72.6 (67.6-77.2)	60.1 (54.7-65.2)	73.2 (67.7-78.1)	58.4 (52.6-64.1)
DOR, median (range), months	11.3 (1.1+ to 80.0+)	9.5 (1.4+ to 79.6+)	11.3 (1.1+ to 80.0+)	9.6 (1.4+ to 79.6+)

Efficacy and safety of PD-1 inhibitor plus chemotherapy vs chemotherapy alone in advanced gastric cancer patients with low or negative PD-L1 expression.

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Background: Advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma remains a major global health challenge with limited treatment options and poor prognosis in metastatic or unresectable disease. Immune checkpoint inhibitors targeting the programmed death-1 (PD-1) pathway, when combined with standard chemotherapy, have improved outcomes in overall populations, as shown in pivotal trials such as CheckMate-649 and KEYNOTE-859. However, efficacy is strongly influenced by tumor PD-L1 expression, with patients exhibiting low or negative PD-L1 expression (combined positive score [CPS] <1 or <5, or tumor area positivity [TAP] <5%) derive less pronounced benefit. Subgroup analyses from ORIENT-16 and RATIONALE-305 show heterogeneous results, leaving uncertainty regarding the benefit of PD-1 inhibitors in this subgroup. We aimed to evaluate the efficacy and safety of first-line PD-1 inhibitor–chemotherapy combinations versus chemotherapy alone in this clinically important population. **Methods:** A systematic search of PubMed/MEDLINE, Embase, Cochrane Library, Scopus, ClinicalTrials.gov, and major oncology conferences was conducted through January 16, 2026. We included Phase III randomized controlled trials comparing PD-1 inhibitor plus chemotherapy with chemotherapy alone in adults with treatment-naïve advanced gastric or GEJ adenocarcinoma and low/negative PD-L1 expression (CPS <1, <5, or TAP <5%). Meta-analyses were conducted using RevMan 5.4 with the generic inverse variance method for time-to-event outcomes (HR) and Mantel–Haenszel method for dichotomous outcomes (RR). Heterogeneity was assessed using I^2. Primary outcomes were overall survival (OS) and progression-free survival (PFS); secondary outcomes included objective response rate and safety. **Results:** Four Phase III RCTs (CheckMate-649, KEYNOTE-859, ORIENT-16, RATIONALE-305) comprising 4,761 patients were included. Subgroup data from patients with low/negative PD-L1 expression were analyzed. PD-1 inhibitors did not improve OS (HR 0.92, 95% CI 0.81–1.03, P=0.16; I^2=0%) or PFS (HR 0.84, 95% CI 0.70–1.02, P=0.08; I^2=47%). Results were consistent across CPS and TAP methods. Toxicity was significantly increased, with higher grade ≥3 adverse events (RR 1.48, P<0.001) and immune-related adverse events (any grade RR 2.80; grade ≥3 RR 4.30). **Conclusions:** In advanced gastric/GEJ adenocarcinoma with low/negative PD-L1 expression, first-line PD-1 inhibitor plus chemotherapy provides no survival benefit and substantially increases toxicity. These findings support biomarker-guided treatment selection and highlight the need for alternative therapeutic strategies. Research Sponsor: None.

Characterization and management of gastrointestinal (GI) adverse events (AEs) with zanidatamab + chemotherapy (CT) ± tislelizumab in first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): Analysis from HERIZON-GEA-01.

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Background: In HERIZON-GEA-01, replacing 1L trastuzumab (tras) + CT with zanidatamab + CT ± tislelizumab significantly improved progression-free survival and, with tislelizumab, yielded a statistically significant overall survival benefit in HER2+ mGEA. The safety profile was manageable; diarrhea was the most common AE. Here we further characterize GI AEs and diarrhea management. **Methods:** Eligible patients (pts) with previously untreated HER2+ mGEA were randomized 1:1:1 to zanidatamab (1800 mg [<70 kg]/2400 mg [≥70 kg] IV Q3W) + tislelizumab (200 mg IV Q3W) + capecitabine/oxaliplatin (CAPOX) or 5-FU/cisplatin (FP); zanidatamab + CAPOX or FP; or tras + CAPOX or FP. CT could be discontinued per physician preference after cycle 6. Tras dose reductions were not permitted. Diarrhea prophylaxis (loperamide 4 mg orally BID) was mandatory in zanidatamab-containing arms for the first 7 days of cycle 1. **Results:** Median treatment duration was 43.1 wk with zanidatamab + tislelizumab + CT, 31.0 with zanidatamab + CT, and 30.0 with tras + CT. Median number of CT cycles was 6, 6, and 7, respectively. Diarrhea was the most common GI AE in all arms; other GI AEs were generally similar across arms. Among pts who experienced diarrhea, most had first onset in cycle 1 (76% in ≤3 wk) with median duration <2.5 wk (Table). Few pts had their first onset of diarrhea occur after cycle 6 when pts could discontinue CT. HER2-targeted therapy discontinuations (4.1%, 1.3%, 0.3%, respectively) and dose reductions (9.9%, 10.8%, NA) or delays (13.6%, 13.4%, 7.6%) due to diarrhea were infrequent. Diarrhea was more often managed with CT dose reduction (21.8%, 23.6%, 14.2%, respectively). Immune-mediated colitis occurred in 2.7% of pts with zanidatamab + tislelizumab + CT. Additional incidence and management data will be presented. **Conclusions:** In zanidatamab-treated pts, most diarrhea events were grade 1/2, and first-onset events tended to occur in cycle 1 and resolved in <3 wk. Diarrhea rarely led to zanidatamab discontinuation. The safety of zanidatamab-containing regimens appears favorable given the survival benefits; diarrhea should be managed with prophylactic loperamide and CT dose modifications as needed. Clinical trial information: NCT05152147. Research Sponsor: Jazz Pharmaceuticals; BeOne Medicines; Zymeworks Biopharmaceuticals.

Diarrhea	Zanidatamab + Tislelizumab + CT n = 294	Zanidatamab + CT n = 305	Tras + CT n = 302
Any-grade, n (%)	244 (83.0)	241 (79.0)[a]	161 (53.3)
Grade 1	79 (26.9)	80 (26.2)	84 (27.8)
Grade 2	92 (31.3)	99 (32.5)	38 (12.6)
Grade ≥3	73 (24.8)	61 (20.0)	39 (12.9)
Time to first onset, n (%), wk			
≤3	188 (77.0)	192 (79.7)	108 (67.1)
>3 to ≤6	25 (10.2)	27 (11.2)	22 (13.7)
>6 to ≤9	7 (2.9)	14 (5.8)	11 (6.8)
>9 to ≤12	4 (1.6)	4 (1.7)	2 (1.2)
>12 to ≤18	8 (3.3)	3 (1.2)	7 (4.3)
>18	12 (4.9)	1 (0.4)	11 (6.8)
Duration of first onset, median (95% CI), wk	2.0 (1.6, 2.6)	2.4 (1.9, 2.9)	1.4 (1.0, 2.1)

[a]Grade missing for 1 pt.

Clinicopathologic and molecular features of Krukenberg tumors from gastric cancer (GC): A single-institution experience.

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Background: Krukenberg tumors (KTs), ovarian metastases most commonly arising from gastric adenocarcinoma, represent an aggressive and understudied metastatic phenotype, frequently associated with diffuse-type gastric cancer (GC). The molecular determinants underlying this metastatic pattern remain poorly characterized. We aimed to define the clinicopathologic and genomic landscape of GC-associated KTs. **Methods:** We conducted a retrospective review of 103 patients with metastatic gastric or gastroesophageal junction adenocarcinoma treated at City of Hope (2020–2025). Twenty-two patients with confirmed KTs were identified. Clinicopathologic data were extracted from electronic medical records. Next-generation sequencing (NGS) for KTs was performed on primary or metastatic tumor specimens. Survival outcomes were estimated using the Kaplan-Meier method, with progression-free survival (PFS) and overall survival (OS) reported with 95% confidence intervals (CIs). **Results:** The median age at diagnosis was 45 years (range, 30–64). HER2 positivity was infrequent (14%), and PD-L1 expression was heterogeneous across tumors. Genomic profiling demonstrated recurrent alterations in *TP53* (53%), *ARID1A* (20%), *CDH1* (13%), *KRAS* (13%), and *PIK3CA* (13%). Notably, 86.4% of KTs exhibited CLDN18.2 immunohistochemical expression $>$ 75%, and 80% of patients had low PD-L1 CPS scores ($<$ 5). The CLDN18::ARHGAP26 fusion was detected in 30% of sequenced tumors, representing a highly recurrent structural alteration. Median PFS was 9 months (95% CI, 4–15), and median OS was 17 months (95% CI, 5–30). **Conclusions:** GC–associated KTs demonstrate a distinct molecular architecture enriched for diffuse-type genomic features, including frequent *TP53* mutations and recurrent CLDN18::ARHGAP26 fusions, aligning with the poor prognosis observed in this cohort. Our findings establish CLDN18 fusions as a recurrent molecular hallmark of GC–associated ovarian metastases, providing novel clinicopathologic insight into mechanisms of ovarian metastatic tropism. Importantly, the high prevalence of CLDN18.2 protein expression identifies a biologically actionable therapeutic vulnerability. CLDN18.2-directed strategies may represent an effective biomarker-driven treatment approach capable of achieving disease control without reliance on surgical intervention. These data define a high-risk, biologically distinct metastatic phenotype and support precision-guided therapeutic targeting, in this clinically aggressive patient population. Research Sponsor: None.

SYS6010 combined with SYH2051 in advanced solid tumors: Results from a phase Ib/II trial.

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Background: SYS6010 is an antibody-drug conjugate (ADC) composed of an epidermal growth factor receptor (EGFR)-specific antibody, a cleavable linker, and the topoisomerase I inhibitor JS-1. SYH2051 is an ATM inhibitor that disrupts DNA repair. The combination of SYS6010 and SYH2051 has shown preliminary antitumor activity (ASCO 2025) in advanced gastrointestinal tumors, particularly gastric cancer (GC). Here, we report the safety and preliminary efficacy of SYS6010 plus SYH2051 in patients with advanced solid tumors in phase Ib. **Methods:** This was a multi-center, open-label study. Phase Ib enrolled patients with advanced, EGFR-positive or EGFR-mutant solid tumors, including gastric cancer (GC) with EGFR expression (≥1+) in ≥30% of tumor cells, who were refractory or intolerant to standard treatment. Phase Ib consisted of dose escalation and expansion parts. Dose escalation followed a 3+3 design, exploring SYS6010 at doses of 3.2 mg/kg and 3.6 mg/kg (both Q2W) in combination with SYH2051 at 20 mg, 40 mg, 60 mg, and 80 mg (QD). The primary endpoints were safety, maximum tolerated dose (MTD), and recommended phase II dose (RP2D). **Results:** As of October 31, 2025, a total of 117 patients (median age, 58 years; male, 73.5%; ECOG PS 1, 72.6%; metastasis, 100%) were enrolled. Most common tumor types included gastric cancer (GC, n = 66), colon cancer (n = 24), and rectal cancer (n = 15). One dose-limiting toxicity (grade 4 thrombocytopenia) was reported in the regimen of SYS6010 3.2 mg/kg plus SYH2051 60 mg. The RP2D was determined to be SYS6010 3.6 mg/kg plus SYH2051 40 mg. Overall, 94.0% (110/117) of enrolled patients reported at least one treatment-related adverse event (TRAE). The common TRAEs (≥30%) were anemia (68.4%), leukopenia (50.4%), neutropenia (48.7%), decreased appetite (47.0%), nausea (43.6%), hypoalbuminemia (40.2%), fatigue (39.3%), and thrombocytopenia (33.3%). Grade ≥ 3 TRAEs occurred in 44.4% (52/117) of patients. Treatment discontinuations due to TRAEs were reported in 0.9% (1/117) of patients for SYS6010 and in 0.9% (1/117) for SYH2051. No deaths were reported due to TRAEs. Among all efficacy-evaluable GC patients treated with the RP2D regimen (n = 33), the confirmed objective response rate (cORR) was 15.2%, disease control rate (DCR) was 69.7%, and median progression-free survival (mPFS) was 4.5 mo (95% CI, 2.1–5.7). For the 17 patients receiving RP2D regimen as ≥3rd-line therapy, cORR was 23.5%, DCR was 88.2%, and mPFS was 5.4 mo (95% CI, 2.5–NR). The 3-mo and 6-mo PFS rates were 72.4% and 36.2%, respectively. Overall survival data were immature. **Conclusions:** The combination of SYS6010 and SYH2051 showed acceptable safety and tolerability in patients with advanced solid tumors. Promising antitumor activity was observed in patients with advanced GC, particularly among those receiving the regimen as ≥3rd-line therapy. Clinical trial information: NCT07104877. Research Sponsor: CSPC Megalith Biopharmaceutical Co.,Ltd.

Efficacy and safety of tecotabart vedotin plus toripalimab with or without chemotherapy as first-line treatment for CLDN18.2-positive advanced gastric or gastroesophageal junction adenocarcinoma: Phase II study results.

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Background: Tecotabart vedotin (TV; LM-302) is a novel and potent MMAE-based ADC targeting CLDN18.2. Previous data (ASCO 2025, abstract#4039) demonstrated promising efficacy and manageable safety profile of TV plus PD-1 inhibitor in patients (pts) with systemic therapy-naive advanced gastric or gastroesophageal junction (G/GEJ) cancer. Updated phase II results of TV plus toripalimab (T) with or without chemotherapy in this first-line setting are presented. **Methods:** Eligible pts had histologically confirmed, no prior systemic therapy, HER2-negative G/GEJ adenocarcinoma with CLDN18.2 positivity (IHC 2+/3+ in ≥1% of tumor cells). Pts received TV (1.8 mg/kg Q2W) plus T (3 mg/kg Q2W), with or without capecitabine or S-1. The primary endpoint was PFS per RECIST v1.1. Secondary endpoints were efficacy, safety, PK, and biomarker analysis. Data cutoff: November 25, 2025. **Results:** A total of 71 pts with G/GEJ adenocarcinoma were enrolled: 39 in the TV+T cohort and 32 in the TV+T+Chemo cohort. Baseline CLDN18.2 high expression (≥25%) was presented in 82.1% of pts in the TV+T cohort and 84.4% in the TV+T+Chemo cohort. PD-L1 CPS ≥1 was observed in 61.5% and 81.3% of pts, respectively. Median follow-up was 16.16 months in the TV+T cohort and 14.82 months in the TV+T+Chem cohort. The median PFS (95% CI) was 10.68 months (6.28, NE) and 12.55 months (6.80, NE), respectively. Among pts with CLDN18.2 ≥25%, the median PFS (95% CI) was 12.22 months (6.87, NE) and NE (8.44, NE), the median DOR (95% CI) was 13.86 months (9.36, NE) and NE (7.10, NE), ORR was 64.5% and 69.2%, and DCR was 96.8% and 96.2%, respectively. Median OS was not reached in either cohort. In pts with CLDN18.2 <25%, TV+T (N=7) and TV+T+Chemo (N=5) showed a median PFS (95% CI) of 5.72 (1.15, NE) and 6.80 (5.55, NE) months, ORR of 14.3% and 40.0%, DCR of 71.4% and 100%, and OS (95% CI) of 10.78 (2.56, NE) months and NE (8.25, NE), respectively. TRAEs occurred in all pts. Grade ≥3 TRAEs occurred in 66.7% of pts in the TV+T cohort and 81.3% of pts in the TV+T+Chemo cohort. The most common Grade ≥3 TRAEs (incidence ≥20%) were decreased neutrophil count in the TV+T cohort, and decreased neutrophil count and decreased white blood cell count in the TV+T+Chemo cohort. TEAEs leading to dose reduction occurred in 17.9% (Grade ≥3: 12.8%) and 43.8% (Grade ≥3: 18.8%) of pts, respectively. TEAEs led to treatment discontinuation occurred in 15.4% (Grade ≥3: 7.7%) and 31.3% (Grade ≥3: 28.1%), respectively. No treatment-related deaths were reported. **Conclusions:** TV+T, with or without chemotherapy, demonstrated encouraging anti-tumor activity and manageable safety as first-line treatment for CLDN18.2-positive advanced G/GEJ cancer. The doublet shows comparable efficacy to the triplet with enhanced tolerability, supporting further large-scale clinical investigation. Clinical trial information: NCT05934331. Research Sponsor: LaNova Medicines Limited.

Phase II trial of SYS6010, an EGFR antibody-drug conjugate (ADC) in patients with advanced esophageal squamous cell carcinoma (ESCC).

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Background: SYS6010 is an EGFR- ADC composed of an EGFR-specific antibody, a cleavable linker, and the topoisomerase I inhibitor (TOPOi) JS-1. Preliminary clinical data from the phase I study of SYS6010 monotherapy in patients with solid tumors showed an acceptable safety and encouraging preliminary efficacy (ChiCTR2300072141). Here, we report the efficacy and safety results of SYS6010 in patients with ESCC in the phase II trial. **Methods:** Patients with advanced ESCC that was refractory or intolerant to standard therapy were enrolled. In the dose-expansion part, SYS6010 was administered intravenously at a dose of 3.6 mg/kg every 2 weeks (Q2W). The primary endpoint was objective response rate (ORR) assessed by the investigator. **Results:** As of Jan 14, 2026, 48 patients with ESCC (median age, 64.5 years; male, 89.6%; ECOG PS 1, 87.5%; metastatic disease, 93.8%) were enrolled and received SYS6010. Ten patients (20.8%) had received ≥3 prior lines of systemic therapy. The median follow-up was 3.9 months (mo; Q1-Q3: 3.1-5.6). Among 40 efficacy-evaluable patients, the confirmed ORR (cORR) was 35% (95%CI 20.6-51.7), and the disease control rate (DCR) was 67.5% (95%CI 50.9-81.4). Median progression-free survival (mPFS) was 4.6 mo (95% CI, 2.7–NR; 48% maturity). The 3-mo and 6-mo PFS rates were 56.3% and 41.4%, respectively. 15 patients remain on treatment with SYS6010. For TOPOi-naïve patients (n = 34), cORR and DCR were 41.2% (95%CI 24.7-59.3) and 70.6% (95%CI 52.5-84.9), respectively. mPFS was 4.6 mo (95%CI 2.8-NR; 45% maturity), with 3-mo and 6-mo PFS rates of 62.5% and 43.2%, respectively. 14 patients remain on treatment with SYS6010. Overall, 97.9% (47/48) of patients experienced treatment-related adverse events (TRAEs). Grade ≥3 TRAEs occurred in 31 (64.6%) patients. Common grade ≥3 TRAEs (≥5%) included neutropenia (29.2%), anemia (18.8%), leukopenia (18.8%), thrombocytopenia (12.5%), lymphocytopenia (8.3%), vomiting (8.3%), and nausea (6.3%). TRAEs led to treatment discontinuation in 4 (8.3%) patients. One death of unknown reason was reported and assessed by the investigator as related to the study drug. **Conclusions:** SYS6010 demonstrated a manageable safety profile and promising antitumor activity, supporting further development in patients with advanced ESCC, especially TOPOi-naïve patients. A phase 3 study is planned to compare SYS6010 with standard of care (SOC) in patients with TOPOi-naïve ESCC. Clinical trial information: ChiCTR2500099933. Research Sponsor: CSPC Megalith Biopharmaceutical Co., Ltd.

Cadonilimab in combination with ivonescimab and chemotherapy as first-line (1L) therapy in patients with advanced gastric (G) or gastroesophageal junction adenocarcinoma (GEJA): Updated results from an open-label phase II trial.

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Background: Cadonilimab (AK104), an anti-PD-1/CTLA-4 bispecific antibody, plus chemotherapy significantly improved OS versus chemotherapy and had a tolerable safety profile in first-line (1L) treatment of advanced G/GEJA patients (pts), including those with low PD-L1 expression. Currently, it has been approved by NMPA. Ivonescimab (AK112), also approved in China, is a novel bispecific antibody against PD-1 and VEGF and has shown a clinically significant improvement in efficacy with favorable safety for advanced NSCLC in two phase 3 studies (HARMONi-2 and HARMONi-A). Here, we presented the updated data for the safety and efficacy of AK104 combined with AK112 and chemotherapy as 1L treatment in advanced G/GEJA. **Methods:** Pts with previously untreated advanced G/GEJA were enrolled. The phase II trial consisted of a dose-escalation part (part 1) and a dose expansion part (part 2). Eligible pts were firstly enrolled into sequential part1 including 10mg/kg and 15mg/kg AK104 (Q6W, D8) combined with AK112 (20mg/kg, Q3W, D1) and chemotherapy (SOX or XELOX) following the conventional 3+3 design. If the starting dose of 10mg/kg AK104 led to ≥2 dose-limiting toxicities (DLTs), 6mg/kg AK104 would be administered. After the part 1 completed, eligible pts were enrolled into the part 2 and received AK104 (the recommended dose, Q6W, D8) combined with AK112 (20 mg/kg, Q3W, D1) and chemotherapy (SOX or XELOX). The primary outcomes were safety and ORR. Secondary endpoints included DCR, PFS, OS, biomarkers of drug activity and pharmacokinetics. **Results:** As of 19 January 2026, 54 pts were enrolled with a median age of 60 years (range: 39-75). 55.6% were PD-L1 CPS < 5, 42.6% had liver metastases and 40.7% had peritoneal metastases. Among efficacy evaluable pts, the ORR was 71.7% and DCR was 95.7%. The median PFS (mPFS) was 8.4 months (mo) (95%CI: 6.0-13.1) and OS analysis was immature. In the pts with liver metastases, the ORR was 81.8%, DCR was 90.9% and mPFS was 10.7 mo (95%CI: 5.7-13.1). In the pts with peritoneal metastases, the ORR was 72.2%, DCR was 100.0% and mPFS was 6.4 mo (95%CI: 5.45-NR). Grade 3-4 treatment-related adverse events (TRAEs) were reported in 18.5% pts, mainly including hypokalemia (5.6%), decreased neutrophil count (3.7%), decreased platelet count (3.7%) and hyperbilirubinemia (3.7%). There were no grade 4/5 TRAEs or treatment-related deaths. **Conclusions:** Updated results demonstrated that AK104 combined with AK112 and chemotherapy as 1L treatment continued to show highly encouraging anti-tumor activity with a manageable safety profile in pts with advanced G/GEJA, including those with liver or peritoneal metastases. Clinical trial information: NCT06196697. Research Sponsor: None.

Molecular circulating tumor DNA (ctDNA) profiling from patients (pts) treated with zanidatamab + chemotherapy (CT) in first-line (1L) HER2-positive (HER2+) advanced or metastatic gastroesophageal adenocarcinoma (mGEA).

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Background: Zanidatamab is a dual HER2-targeted bispecific antibody that binds to HER2 extracellular domains 2 and 4. In the phase 3 HERIZON-GEA-01 trial, 1L zanidatamab ± tislelizumab + CT significantly prolonged progression-free survival (PFS) and, with tislelizumab, yielded significant overall survival benefits versus trastuzumab + CT in HER2+ mGEA. Consistent results were previously reported in a phase 2 trial of zanidatamab + CT. ctDNA profiling provides a noninvasive approach to identify pts who could benefit from HER2-targeted therapies, and on-treatment ctDNA reductions may be associated with response. Here we report ctDNA profiling from the phase 2 trial. **Methods:** The phase 2 trial (NCT03929666) evaluated zanidatamab + CT (mFOLFOX6, CAPOX, or 5-FU/cisplatin [FP]) in 1L mGEA. Pts in part 1 had HER2-expressing (IHC 3+ or 2+) mGEA. Pts in part 2 had HER2+ (IHC 3+ or IHC 2+/FISH+) mGEA by central assessment (ccHER2+). Primary endpoint was confirmed objective response rate (cORR). PFS was a secondary endpoint. Plasma ctDNA samples were collected prior to cycle 1 of zanidatamab (baseline [BL]) and on treatment (cycle 2 day 15 for zanidatamab + CAPOX or FP; cycle 3 day 1 for zanidatamab + mFOLFOX6) for NGS by Guardant360 and/or Guardant Infinity. **Results:** 46 pts were enrolled (zanidatamab + mFOLFOX6 [n = 24], CAPOX [n = 20], FP [n = 2]). Most (41 [89%]) pts had ccHER2+ mGEA. cORR was 76.2% (95% CI 60.5, 87.9) and median PFS was 12.5 (95% CI 8.2, 21.8) mo. BL ctDNA was available from 39 pts; 29 had on-treatment samples, and 16 had matched BL and on-treatment samples. The concordance was 94% (34/36) between centrally assessed *ERBB2* amplification by FISH in tissue and *ERBB2* amplification in plasma ctDNA by NGS. Among 34 pts with detectable *ERBB2* amplification at BL, median PFS was 18.6 (95% CI 12.0, NE) mo. All pts with available samples and confirmed complete (CR) or partial (PR) response or stable disease (SD) had undetectable on-treatment *ERBB2* amplification in ctDNA. Most pts with *ERBB2* indel, fusion, or SNV (79% [15/19]) or with *PIK3CA* amplification or SNV (86% [12/14]) at BL had CR or PR. Nearly all (94% [15/16]) pts with available matched samples had a $>$ 80% decrease in ctDNA from BL to on-treatment assessment on the Guardant Infinity panel. On-treatment ctDNA samples from pts with progressive disease or SD showed recurrence/persistence of *ERBB2* alterations and co-alterations across PI3K/AKT and RAS/MAPK pathways. Additional data will be presented. **Conclusions:** Molecular ctDNA profiling showed that 1L zanidatamab + CT in HER2+ mGEA could markedly reduce total ctDNA levels and *ERBB2* amplification detection early in treatment. Antitumor activity was observed among pts whose tumors harbored *ERRB2* and *PIK3CA* mutations, both of which are associated with resistance to standard HER2-targeted therapies. Clinical trial information: NCT03929666. Research Sponsor: Jazz Pharmaceuticals; Zymeworks Biopharmaceuticals.

Survival outcomes according to ramucirumab (RAM)-related hypertension (HTN) in patients (pts) with advanced HER2-negative gastric (G) or gastro-esophageal junction (GEJ) cancer: An exploratory analysis of the phase III ARMANI trial.

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Background: Retrospective studies suggest an association between treatment-related HTN and improved outcomes with anti-angiogenic agents, with most evidence derived from colorectal cancer pts treated with bevacizumab. Data on the prognostic significance of RAM-induced HTN are limited. We therefore explored the association between treatment-related HTN and survival outcomes in the ARMANI trial. **Methods:** ARMANI was a phase III trial enrolling pts with advanced HER2-negative G/GEJ cancer who had disease control after a 3-month first-line fluoropyrimidine and oxaliplatin (FOX) induction chemotherapy. Pts were randomized to switch maintenance with paclitaxel plus RAM (PTX-RAM) or the continuation of FOX. The objectives of this exploratory analysis were to evaluate the association between grade (G)≥2 HTN and survival outcomes across treatment arms (using the FOX arm as reference [ref]) and within the PTX–RAM arm. To mitigate time-related bias, Cox proportional hazards models were fitted with HTN modeled as a time-dependent covariate, considering pts ‘non-HTN’ until G≥2 HTN onset and ‘HTN’ thereafter. Because HTN is a post-randomization event, survival analyses in the PTX-RAM arm by HTN status were adjusted for baseline characteristics using inverse probability weighting based on propensity scores derived from a logistic regression model. **Results:** Among 276 pts (141 in PTX-RAM and 135 in FOX arm), G≥2 HTN occurred in 20 cases (7.2%), all observed in the PTX-RAM arm (20/141, 14.2%). The incidence of G≥2 HTN was similar between males and females (15.8% versus 10.9%) and between pts aged < 70 and ≥70 years (14.4% versus 13.5%). Median time to G≥2 HTN-onset was 3 months. In the between-arm comparison, the PTX–RAM arm showed improved progression-free survival (PFS) versus FOX regardless of HTN development (p = 0.192). In contrast, the overall survival (OS) benefit was greater in the HTN group (p = 0.071). These findings are detailed in the Table below. In analyses restricted to the PTX–RAM arm, G≥2 HTN onset was associated with improved OS (HR 0.43; 95% CI, 0.22-0.83; p = 0.033), whereas no significant difference was observed for PFS (HR 0.88; 95% CI, 0.50-1.57; p = 0.735). **Conclusions:** The development of G≥2 HTN was associated with a significant OS benefit in pts treated with PTX–RAM in the ARMANI trial. These findings support further research to identify biomarkers predictive of HTN onset to refine pts selection for switch maintenance strategies. Clinical trial information: NCT02934464. Research Sponsor: None.

	Median PFS (months) (95% CI)	HR (95% CI)	Median OS (months) (95% CI)	HR (95% CI)
FOX	3.5 (2.8–4.2)	ref	10.5 (8.5–13.5)	ref
PTX-RAM (non-HTN)	6.5 (5.8–7.7)	0.44 (0.32–0.60)	12.2 (10.6–14.4)	0.65 (0.49–0.87)
PTX-RAM (HTN)	9.0 (4.2–16.9)	0.61 (0.38–0.99)	24.6 (13.3–64.4)	0.39 (0.22–0.69)

Genomic biomarkers of primary resistance to anti-EGFR monoclonal antibodies (mAbs) by comprehensive genomic profiling (CGP) in *EGFR*-amplified (ampl) advanced gastroesophageal adenocarcinoma (aGEA) and correlative analysis from a single-arm study with panitumumab.

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Background: *EGFR* ampl is found in up to 6% of patients with aGEA and accounts for the efficacy of anti-EGFRs in this patients' subgroup. The AMNESIA panel with *KRAS*/*PIK3CA*/*MET* mutations and *KRAS*/*EGFR*/*MET* amplifications represented a paradigm of negative selection to trastuzumab in HER2+ aGEA. Here, we aimed to characterize the prevalence and prognostic relevance of genomic drivers of primary resistance to EGFR blockade in *EGFR*-ampl aGEA. **Methods:** Patients with *EGFR*-ampl aGEA were retrieved from 3 CGP screening sources, i.e. the ARMANI phase 3 trial, an observational cohort established at the Fondazione IRCCS Istituto Nazionale dei Tumori (INT) of Milan and 11 patients with *EGFR* ISH positive aGEA treated with panitumumab as ≥2L from the 117/15 INT screening platform (thereafter Panitumumab study). CGP was performed by means of FoundationOne CDx next-generation sequencing (NGS). AMNESIA-EGFR panel grouped genomic alterations with clinical and biological rationale as driver of primary resistance to anti-EGFR mAbs, i.e. *EGFR* rearrangements, *FGFR2*/*HER2*/*MET*/*RAS* co-ampl, *RAS*/*MEK1*/*PIK3CA* ex20 mut, *AKT1/2* mut and *PTEN* loss. We evaluated prevalence of AMNESIA-EGFR alterations in the ARMANI and observational cohort. Then, we explored the prognostic impact of AMNESIA-EGFR panel and lack of *EGFR* ampl by NGS in the Panitumumab study. **Results:** *EGFR*-ampl by NGS was found in 3/130 (2.3%) and 7/128 (5.5%) pts in the ARMANI and observational cohort. *EGFR* ampl was confirmed by NGS in 8/11 pts (73%) in the panitumumab cohort. Among patients with *EGFR*-ampl tumors by NGS, AMNESIA-EGFR alterations were found in 9/18 (50%) pts, including: *KRAS* ampl (16.7%), *EGFR* rearrangement (11.1%), *PTEN* loss (11.1%), *FGFR2* co-ampl (5.6%), *MET* co-ampl (5.6%) and *MEK1* mut (5.6%). AMNESIA-EGFR panel alterations were mutually exclusive, except for one case with concurrent *MET* co-ampl and *MEK1* mutation. In the Panitumumab study, disease control rate (DCR) was 18.2% including a partial response and a stable disease. Median progression-free survival (PFS) and overall survival (OS) were 2.0 months (95%CI, 1.8-NA) and 5.3 months (95%CI, 3.38-NA). 7/11 pts had tumors with AMNESIA-EGFR alterations or lacked *EGFR* ampl by NGS. AMNESIA-EGFR+ or lack of *EGFR* ampl were associated with inferior DCR (0% vs 50%), PFS (median PFS 2.0 vs 3.8 months; HR 3.17 [95% CI, 0.64-NA] and OS (median OS 5.3 vs 6.4 months; HR 1.80 [95%CI, 0.45–7.14]). **Conclusions:** Genomic drivers of primary resistance to anti-EGFR mAbs are common in *EGFR*-ampl aGEA. A negative selection paradigm based on CGP may optimize outcomes with anti-EGFRs. Innovative drugs that may bypass resistance mechanisms to mAbs, such as bispecific antibodies, antibody-drug conjugates and bispecific T-cell engagers, are awaited. Research Sponsor: None.

Real-world treatment patterns and overall survival (OS) in patients (pts) with HER2-positive (HER2+) advanced or metastatic gastroesophageal adenocarcinomas (mGEA) in the US.

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Background: The first-line (1L) standard of care for pts with HER2+ mGEA is HER2-targeted therapy (HER2 Tx) plus platinum-based chemotherapy (CT). Recent immunotherapy (IO) addition to this regimen prolonged OS of pts with HER2+ programmed death-ligand 1 (PD-L1)-positive (PD-L1+) mGEA. Here, we describe real-world treatment patterns and OS in pts with HER2+ mGEA in the US since the FDA approval of 1L IO. **Methods:** Adults with HER2+ mGEA who initiated 1L systemic therapy between May 2021 and 2025 and had ≥6 mo of follow-up (or died within 6 mo) after 1L initiation, were identified from the Flatiron Health Electronic Health Records database. OS from 1L initiation was evaluated with the Kaplan-Meier method in the overall HER2+ cohort and in a subset of pts with PD-L1+ disease. Outcomes were also reported with HER2 Tx + CT ± IO use. **Results:** Of 2237 pts with known HER2 status prior to 1L therapy, 21% were HER2+, defined as immunohistochemistry (IHC) 3+, IHC 2+/*ERBB2*-amplified, or per physician's note. Mean (SD) age was 66.1 (11.7), 20% of pts were female, and 66% had an Eastern Cooperative Oncology Group performance status ≤1. Of 292 pts with HER2+ mGEA and known PD-L1 status prior to 1L, 81% were PD-L1+ (combined positive score ≥1 or per physician's note). Of the 467 pts with HER2+ mGEA who received 1L therapy, 60% had HER2 Tx, 28% had CT alone, and 10% received IO-based regimens without HER2 Tx. Of the 281 pts on 1L HER2 Tx, 58% had HER2 Tx + IO + CT and 37% had HER2 Tx + CT. Overall, 228/467 (49%) pts treated in the 1L went on to receive second-line (2L) therapy. In the 2L setting, 70% of pts received HER2 Tx, including 38% pts who only received CT or IO-based regimens without HER2 Tx in 1L treatment. A total of 42% of pts on 2L therapy received 1L and 2L HER2 Tx. Among the 467 pts with HER2+ mGEA, median OS (mOS) from 1L initiation was 17.4 mo. In the PD-L1+ subgroup, mOS was 19.0 mo in pts on HER2 Tx + IO + CT, and 17.2 mo in pts on HER2 Tx + CT without IO (Table). Across treatment groups, mOS remained <2 years, and the 24-mo OS rate was <40%. **Conclusions:** Despite the availability of HER2 Tx, a significant unmet need remains, as 40% of pts with HER2+ mGEA did not receive this option in 1L regimens. OS was numerically longer with HER2 Tx + IO + CT vs without IO in the HER2+/PD-L1+ mGEA subgroup. These data underscore the need to improve OS and the opportunity to enhance biomarker-guided management of HER2+ mGEA. Research Sponsor: Jazz Pharmaceuticals.

OS analysis.

	HER2+			HER2+/PD-L1+ Subgroup		
	HER2+ (Overall) (n = 467, 100%)	1L HER2 Tx + IO + CT (n = 164, 35%)	1L HER2 Tx + CT (n = 103, 22%)	PD-L1+ (all) (n = 237, 100%)	1L HER2 Tx + IO + CT (n = 95, 40%)	1L HER2 Tx + CT (n = 40, 17%)
Median OS, mo (95% CI)	17.4 (15.7, 20.5)	19.3 (15.7, 22.3)	17.2 (13.5, 21.3)	17.2 (15.0, 20.9)	19.0 (15.6, 24.6)	17.2 (12.6, 24.4)
OS Rate, (%)						
6-mo	83.0	85.5	79.8	82.3	87.2	77.5
12-mo	65.5	67.6	66.4	64.1	67.9	66.2
18-mo	48.9	52.4	46.3	47.2	53.0	41.7
24-mo	34.7	37.2	26.3	36.0	39.5	30.6

Updated results of benmelstobart plus anlotinib combined with SOX in the first-line treatment of advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma with low PD-L1 expression: A single-arm, multicenter phase II clinical trial.

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Background: While PD-1 inhibitors plus chemotherapy have become standard first-line therapy for advanced HER2-negative gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, patients with low PD-L1 expression (Combined Positive Score (CPS) < 5) derive limited benefit. Anti-angiogenic agents can modulate the tumor immune microenvironment and synergize with immune checkpoint inhibitors. Anlotinib, a multi-targeted tyrosine kinase inhibitor approved in China, offers a promising combination strategy. This study evaluates the efficacy and safety of benmelstobart (a PD-L1 inhibitor) combined with anlotinib and SOX (S-1 plus oxaliplatin) as first-line therapy in patients with advanced G/GEJ adenocarcinoma and low PD-L1 expression. **Methods:** Patients with HER2-negative, unresectable, locally advanced, or metastatic G/GEJ adenocarcinomas and PD-L1 CPS < 5, who had not received prior systemic therapy were included. They received benmelstobart (1200mg, iv, d1, q3w) combined with anlotinib (10mg, po, d1~14, q3w), oxaliplatin (130mg/m^2 , d1, iv, q3w) and S-1 (40mg, po, bid, d1~14, q3w) for 6 cycles as initial therapy. Maintenance therapy with benmelstobart (1200mg, iv, d1, q3w) plus anlotinib (10mg, po, d1~14, q3w) followed for non-progressive disease until PD or unacceptable toxicity occurred. Tumor responses were evaluated by RECIST 1.1 criteria. The target sample size was 37, with ORR as the primary endpoint, and safety, DCR, DoR, PFS, and 1-year OS rate as secondary endpoints. **Results:** From June 2023 to June 2025, 37 patients were enrolled. At the data cut-off date (December, 2025), the best overall response indicated that there were 31 PR (83.8%) and 6 SD (16.2%). Therefore, the preliminary ORR was 83.8% (95%CI: 68-93.8), DCR was 100% (95%CI: 90.5-100). The preliminary prognostic result exhibited that the median PFS of the 37 patients was 11.3 months (95%CI: 8.07-14.53). The 1-year OS rate was 91.33% (95%CI: 75.46–97.12). Safety was manageable, common TRAEs > 20% included platelet count decreased (54.1%), white blood cell decreased (32.4%), anemia (24.3%). **Conclusions:** The combination of benmelstobart, anlotinib, and SOX demonstrated promising efficacy with a manageable safety profile as first-line therapy for advanced G/GEJ adenocarcinoma with low PD-L1 expression. These findings warrant validation in larger cohorts. Clinical trial information: NCT06939452. Research Sponsor: None.

Nimotuzumab combined with paclitaxel and cisplatin as first-line treatment for metastatic esophageal squamous cell carcinoma: A prospective, multicenter, double-blind, randomized controlled clinical study.

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Background: Chemotherapy for advanced esophageal squamous cell carcinoma (ESCC) is limited due to the lack of effective drugs. Such as traditional two drugs chemotherapy (5-Fluorouracil and Cisplatin) as first-line treatment for metastatic and recurrent ESCC has an efficacy of 25-35%. Nimotuzumab is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody. Previous studies have shown that its combination with paclitaxel and cisplatin (TP regimen) has a good efficacy, with an objective response rate (ORR) of up to 55%, median overall survival (mOS) 13.9 months in some small-sample trials. **Methods:** Eligible patients from 36 centers in China, who were randomly assigned to receive nimotuzumab (400 mg once per week, up to 2 years) or placebo followed by TP regimen (paclitaxel 175 mg/m^2, cisplatin 60 mg/m^2, Day 1, with a 21-day cycle, up to 6 cycles) until disease progression or unacceptable toxicity. The primary end point was overall survival (OS) and the secondary end points were progression-free survival (PFS), response rates, quality of life (QoL) and safety. **Results:** A total of 640 patients were screened. 503 patients were enrolled and 161 patients with EGFR gene amplification tumors were eligible. In the full analysis set of 497 patients who had took at least one dose of medication, there were no differences in baseline characteristics. The mOS were 12 vs 11.5 months, and the median PFS were 5.6 vs 5.4 months respectively, suggesting survival benefit trend in the trial. ORR were 55.5% and 50.4% for both arms. In the EGFR gene amplification subgroup, the mOS was 13.3 vs 9.5 months (log-rank test, hazard ratio [HR] = 0.66 (95%CI, [0.47-0.93]), P = 0.016) for two groups. Patients who were with ESCC at stage IV, as well as who had not undergone surgery, radical radiotherapy, or neoadjuvant and adjuvant therapy showed significant survival benefits after the addition of nimotuzumab. Median PFS were 6.0 vs 5.5 months for two arms (log-rank test, HR = 0.63 [0.43-0.91], P = 0.014). Both OS and PFS were longer in the nimotuzumab group than in the placebo group. The ORR of the two groups were 61.3% and 44.0%, respectively (P = 0.029). There were no statistically significant differences in the QoL scores of the FAS population at each time point before and after treatment. The incidence of adverse events were comparable in the experimental group and the control group. Such as the incidence of serious adverse event (SAE) was 30.7% and 34.5%, serious adverse drug reaction (SADR) was 2.7% and 8.3%, the incidence of above grade 3 treatment emergent adverse event (TEAE) was 85.3% and 83.3%, respectively, etc. **Conclusions:** In patients with metastatic EGFR gene amplification ESCC, nimotuzumab plus TP as first-line treatment significantly improved OS and PFS with a good safety profile. Research Sponsor: None.

Heterogeneity in biomarkers for advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC/GEJC/EAC) across regions: Insights from CheckMate-649.

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Background: In CheckMate 649, first-line nivolumab plus chemotherapy showed improved clinical efficacy vs chemotherapy in patients (pts) with advanced GC/GEJC/EAC, with varied benefit across regions in a subgroup analysis. To identify biomarkers predictive of differential efficacy outcomes, we did post hoc exploratory biomarker analyses by region. **Methods:** Post hoc exploratory analyses were done with whole-exome sequencing (WES) and RNA-seq of baseline tumor tissue. Pts were grouped by region: China (CN), Asia (including CN), United States + Canada + European Union (UCE), Latin America (LA). For WES-evaluable pts, gene alterations were profiled and pts grouped into genomic subtypes: chromosomal instability (CIN), genomically stable (GS), hypermutated (H), and Epstein–Barr virus (EBV)-positive. Gene expression signatures (GES) related to mitogen-activated protein kinase (MAPK) pathway, stroma, and angiogenesis were assessed by RNA-seq, and pts were stratified into tertiles based on GES score: high, medium, or low. **Results:** Of 1512 pts randomized, 647 were WES-evaluable (79, 141, 351, 155 in CN, Asia, UCE, and LA, respectively) and 769 RNA-evaluable (50, 106, 423, 240, respectively). A numerically lower proportion of CIN subtype and higher proportion of EBV subtype was seen in LA vs other regions (Table). Percentage (%) of select gene alterations was generally comparable across regions: of note, there was numerically higher % of altered *FGFR2* (10%) in CN, altered *TP53* (58%), *KRAS* (16%), *CDKN2A* (11%), and *CDH1* (7%) in UCE, and altered *PIK3CA* (10%) and *ERBB2* (22%) in LA. By contrast, there was numerically lower % of altered *EGFR* (4%) in Asia and altered *ARID1A* (8%) in LA. GES profile was broadly similar across regions, with numerically higher % of MAPK-high subgroup in UCE, stroma-medium/low subgroup in LA, and angiogenesis-low subgroup in CN (Table). **Conclusions:** While the biomarker profile was largely comparable across regions, differential features were noted for certain subgroups; clinical utility of these biomarkers requires validation in future trials. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.

	Regions	CN	Asia(including CN)	UCE	LA
Genomic subtypes	CIN	53 (67)	86 (61)	223 (64)	81 (52)
	GS	22 (28)	47 (33)	99 (28)	49 (32)
	H	4 (5)	6 (4)	18 (5)	6 (4)
	EBV	0	2 (1)	11 (3)	19 (12)
GES					
5-gene MAPK	High	15 (30)	31 (29)	145 (34)	74 (31)
	Medium	13 (26)	29 (27)	153 (36)	79 (33)
	Low	22 (44)	46 (43)	125 (30)	87 (36)
15-gene stroma	High	20 (40)	38 (36)	151 (36)	70 (29)
	Medium	11 (22)	34 (32)	138 (33)	79 (33)
	Low	19 (38)	34 (32)	134 (32)	91 (38)
5-gene angiogenesis	High	15 (30)	35 (33)	137 (32)	81 (34)
	Medium	14 (28)	34 (32)	138 (33)	89 (37)
	Low	21 (42)	37 (35)	148 (35)	70 (29)

Data are n (%). % was calculated as events divided by number of WES- or RNA-seq–evaluable pts.

Sintilimab combined with short-course intensified chemotherapy regimen nab-POF in the treatment of metastatic gastric cancer (FDZL-GC002): A single-arm, phase 2 trial.

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Background: This prospective phase II study investigates a novel therapeutic strategy combining PD-1 inhibitor sintilimab (Sin) with short-course intensified chemotherapy regimen Nab-POF as first-line treatment for metastatic gastric cancer (MGC), based on the hypothesis that short-duration, high-intensity chemotherapy may potentiate antitumor immunity while reducing the cumulative immunosuppressive burden of prolonged chemotherapy. **Methods:** Eligible patients (pts) received Sin (200mg IV), nab-paclitaxel (125mg/m^2), oxaliplatin (85mg/m^2), and fluorouracil (2400mg/m^2 as a 48-hour infusion) (plus trastuzumab for HER2+ pts) Q2W. After 6 cycles, pts without disease progression received maintenance treatment (capecitabine + Sin). Upon disease progression, HER2- pts underwent reinduction with the Nab-POF regimen ± Sin, for up to 6 cycles, followed by maintenance therapy (S-1 +/- Sin). Tumor response was assessed every 3 cycles. PFS1 was defined as the time from informed consent to first progression. PFS2 was defined as the time from consent to second progression. If reinduction therapy was not performed, PFS2 equals to PFS1. The primary endpoint was PFS2 in HER2- pts. **Results:** In total, 123 pts were enrolled up to 09/2025. 118 pts were evaluable. This report presents the results for the HER2- population. Among 90 HER2- pts, the median age was 60 (23-83), with 72.2% male. The common metastatic sites included the liver (36.7%), peritoneum (26.7%), bone (13.3%), and lungs (6.7%). ORR was 82.2% (74/90) and DCR was 100%. Nine pts received complete response and CR rate was 10.0%. 2-year DFS and OS rate were both 100% among pts with CR. 60 pts progressed and 47 patients died. 25 pts experienced reinduction with the Nab-POF regimen ± Sin. Median PFS1 was 13.6mo (95%CI 9.8-16.1) and median PFS2 was 16.2mo (95%CI 11.0-23.2). Median OS was 21.3mo (95%CI 11.3-NR). 1-year OS rate was 72.2% (95%CI 63.5-82.1) and 2-year OS rate was 44.2% (95%CI 33.9-57.6). Subgroup analysis showed whether signet ring cells are present or not, whether liver metastasis occurs or not, and the level of CPS were not related to the therapeutic effect. All pts experienced treatment-related adverse events (AEs). Grade 3/4 AEs were 55.6% (50/90) and neutrophil decrease was the most common at 36.7% (33/90). Immune-related AEs occurred in 22(24.4%) pts, including 6 (6.7%) grade 3/4 events, which were effectively controlled. **Conclusions:** Sin plus short-course intensified chemotherapy regimen Nab-POF demonstrates high response and CR rate, and remarkable long-term effects. This approach may represent a feasible first-line treatment strategy, warranting further evaluation in randomized trials. Clinical trial information: NCT05982301. Research Sponsor: None.

Radiogenomic biomarkers for identifying surgery-sparing candidates in locally advanced gastric or gastro-esophageal junction cancer treated with perioperative immunochemotherapy: A discovery and validation study.

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Background: Perioperative immunochemotherapy has markedly increased pathologic complete remission (pCR) rates in patients with locally advanced gastric cancer or gastroesophageal junction cancer (LAGC/GEJC), raising the possibility of surgery-sparing strategies in selected patients. However, reliable non-invasive tools to identify pCR preoperatively are lacking. This study aimed to develop and validate a radiogenomic model integrating CT radiomics and peripheral blood single nucleotide polymorphism (SNP) data to predict pCR. **Methods:** This retrospective multicenter study included 642 patients with LAGC/GEJC from 14 institutions who received perioperative immunochemotherapy. Patients were assigned to a primary cohort (n = 442; training n = 309, internal validation n = 133) and an external validation cohort (n = 200). Radiomic features were extracted from preoperative CT images, and SNPs were genotyped from peripheral blood. Feature selection was performed using LASSO, generating radiomic (Rad-score) and genomic (Gen-score) signatures. A combined radiogenomic model incorporating Rad-score, Gen-score, and clinical variables was developed using multivariable logistic regression. Model performance was evaluated using AUC and decision curve analysis (DCA). **Results:** Fourteen radiomic features and eight SNPs were selected. The radiogenomic model consistently outperformed single-modality models across cohorts. In the training set, the combined model achieved an AUC of 0.915 (95% CI 0.880–0.950), exceeding Rad-score (AUC 0.832) and Gen-score (AUC 0.798; both $P < 0.001$). In the internal validation set, the AUC was 0.882 (95% CI 0.825–0.939), and in the external validation set, 0.852 (95% CI 0.795–0.909), remaining superior to either modality alone. DCA demonstrated greater net clinical benefit of the combined model. At the optimal cutoff, 91.5% of true pCR cases were correctly identified in the validation cohort. **Conclusions:** A radiogenomic model integrating CT radiomics and peripheral blood SNP signatures enables accurate, non-invasive prediction of pCR in LAGC/GEJC patients undergoing perioperative immunochemotherapy and may support identification of candidates for surgery-sparing management. Research Sponsor: National Nature Science Foundation for Distinguished Young Scholars of Guangdong Province; National Natural Science Foundation of China; Guangdong Basic and Applied Basic Research Foundation; Fundamental Research Funds for the Central Universities, Sun Yat-sen University.

Induction chemotherapy plus camrelizumab followed by concurrent chemoradiotherapy for unresectable locally advanced esophageal squamous cell carcinoma (ImpactCRT): Long-term outcomes of a single-arm phase II trial.

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Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for unresectable locally advanced esophageal squamous cell carcinoma (ESCC), with 3-year overall survival (OS) approximately 30%. Induction chemoimmunotherapy followed by CCRT appears promising, but long-term efficacy remains unclear. In the ImpactCRT study, induction chemotherapy plus camrelizumab followed by CCRT has shown promising efficacy in patients with unresectable locally advanced ESCC. Here, we reports long-term outcomes with ≥3-year follow-up. **Methods:** ImpactCRT was a prospective, single-arm, phase II study at the First Affiliated Hospital of Sun Yat-sen University. Eligible patients were aged 18–75 years with untreated, unresectable locally advanced ESCC (cT1–4bN0–3M0 or M1 limited to supraclavicular nodes). Patients received two 21-day cycles of induction therapy with albumin-bound paclitaxel (260 mg/m^2), carboplatin (AUC 5), and camrelizumab (200 mg) on day 1, followed by two 28-day cycles of fluorouracil (750 mg/m^2 per 24 h for 5 days) and cisplatin (75 mg/m^2 on day 1) administered concurrently with radiotherapy (50–63 Gy in 25–28 fractions). The primary endpoint was the 1-year OS rate in the per-protocol set (PPS). The trial was registered with ChiCTR (ChiCTR2000034304). **Results:** Between July 12, 2020, and October 14, 2022, 49 patients were enrolled; all completed induction chemoimmunotherapy, and 46 received CCRT and comprised the PPS. As of January 1, 2026, median follow-up among surviving patients was 53.7 months (range 41.1–65.5). In the PPS, the 1-, 2-, 3-, and 4-year OS rates were 87.0% (95% CI 77.7–97.3), 73.9% (95% CI 62.3–87.8), 65.2% (95% CI 52.8–80.5), and 60.9% (95% CI 48.3–76.7), respectively. Corresponding PFS rates were 71.7% (95% CI 59.8–86.0), 63.0% (95% CI 50.5–78.7), 56.5% (95% CI 43.9–72.8), and 50.0% (95% CI 37.5–66.8). Median OS was not reached (95% CI 40.7 months–not reached), and median PFS was 45.5 months (95% CI 26.7–not reached). Disease progression occurred in 17 patients (37.0%), all within 3 years after treatment (median 6.1 months; range 2.9–35.2): locoregional failure in 7 (15.2%), distant metastasis in 5 (10.9%), and simultaneous locoregional and distant failure in 5 (10.9%). During follow-up, 20 patients (43.5%) died, including 12 (26.1%) due to disease progression. Grade 3 late toxicities occurred in three patients, all esophageal strictures; no grade ≥3 late toxicities were observed in the lung, heart, or other organs. **Conclusions:** Induction chemotherapy plus camrelizumab followed by CCRT showed improved long-term survival and acceptable late toxicity in unresectable locally advanced ESCC. Median PFS exceeded three years and appeared superior to previous reports. This regimen warrants further evaluation in randomized controlled trials. Clinical trial information: ChiCTR2000034304. Research Sponsor: None.

Impact of molecular profile on switch maintenance to paclitaxel plus ramucirumab (PTX-RAM) versus continuation of first-line fluoropyrimidine and oxaliplatin (FOX) chemotherapy (ChT) in patients (pts) with advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: An exploratory endpoint of the ARMANI phase 3 randomized trial.

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Background: The ARMANI trial proved the superiority of PTX-RAM switch maintenance over continuation of FOX first-line ChT in patients with advanced HER2-negative G/GEJ cancer. Here, we present the prognostic and predictive impact of baseline gene alterations. **Methods:** ARMANI was an Italian, multicenter, open-label, randomized phase 3 trial in which patients with HER2-negative G/GEJ cancer who achieved disease control after 3 months of induction FOX chemotherapy were randomized to either PTX-RAM switch maintenance or continuation of FOX. Pre-induction chemotherapy samples were sequenced by means of FoundationOne CDx, a panel comprising 324 cancer-related genes. Variants of unknown significance were filtered out. Presence of at least one pathogenic alteration was used to classify samples as altered or wild-type for the respective pathway (Cell cycle, PI3K, RAS, RTK, TGFβ, TP53 and WNT). Homologous repair deficiency (HRD) positivity was defined as the presence of a positive HRD signature (HRDsig+) as defined by FoundationOne CDx. **Results:** Sequencing data was available for 130 patients, with 65 patients treated in each arm, and 103 were evaluable for HRDsig. The most frequently altered pathways were TP53 (69.2%), Cell cycle (43.1%), PI3K (24.6%), RTK (24.6%) and RAS (23.1%). Presence of at least one alteration in the WNT pathway was observed for 22/130 patients (16.9%) and was associated with significantly higher rate of objective response to maintenance regimen (55.6% vs 17.3%, p = 0.002), longer mPFS (8.8 vs 6.0 months; HR = 0.54, 95%CI: 0.33-0.89; p = 0.017) and longer mOS (18.1 vs 14.1 months; HR = 0.53, 95%CI: 0.31-0.91, p = 0.021). TP53 pathway status was predictive for OS as switching maintenance to PTX+RAM improved OS in patients without TP53 pathway alterations (mOS 16.8 vs 8.8 months; HR 0.40, 95% CI 0.20—0.78) but not in those with at least one TP53 pathway alteration (mOS 14.7 vs 17.4 months; HR 0.94, 95% CI 0.60—1.48) (p for treatment interaction = 0.044). Ten out of 103 (9.7%) were HRDsig+. HRDsig+ status was not associated with neither PFS nor OS advantage (p = 0.676 and p = 0.623) and was not predictive of better outcomes in the FOX arm (p for treatment interaction for PFS = 0.919 and p for treatment interaction for OS = 0.558). **Conclusions:** Alterations in the WNT pathway have a positive prognostic significance in patients with G/GEJ cancer who achieved disease control after 3 months of FOX. TP53 pathway alterations bear potential for guiding the choice of PTX+RAM switch maintenance. HRDsig+ is not predictive of sensitivity of FOX in this setting. Clinical trial information: NCT02934464. Research Sponsor: None.

4061 Poster Session

Comparison of CLDN18/CLDN18.2 IHC assays (43-14A vs EPR19202) and the correlation with clinical efficacy in patients with gastric/gastroesophageal junction adenocarcinoma treated by the novel antibody-drug conjugate XNW27011.

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Background: Claudin 18.2 (CLDN18.2), the dominant isoform of CLDN18 in gastric tissues, is a highly specific tight junction protein of the gastric mucosa with considerably retained expressions in gastric and gastroesophageal junction (G/GEJ) adenocarcinoma, making it a clinically actionable therapeutic target. Accurate immunohistochemical (IHC) assessment of CLDN18.2 expression is critical for patient selection in CLDN18.2-targeted therapies. Here, we report the findings of the analytical comparability, concordance and clinical efficacy outcomes between two CLDN18/CLDN18.2 antibodies (VENTANA CLDN18 [43-14A] and Abcam CLDN18.2 [EPR19202]), from a Phase I/II study of a novel antibody-drug conjugate XNW27011 (NCT06792435). **Methods:** This retrospective study utilized formalin-fixed paraffin-embedded (FFPE) samples of 121 patients with G/GEJ adenocarcinoma enrolled in the Phase I/II study of XNW27011. Each sample was stained with CLDN18 (43-14A) and CLDN18.2-specific (EPR19202) antibodies. Efficacy in objective response rate (ORR) was evaluated across CLDN18/CLDN18.2 expression strata defined by each assay antibody in patients treated with XNW27011 at doses of 2.4–6.0 mg/kg administered intravenously every 3 weeks. Concordance between the two assay antibodies was assessed by the percentage of the overall agreement (positive or negative) primarily at the cutoff of ≥20% tumor cells with 2+ to 3+ membranous staining. **Results:** Therapeutic efficacy outcomes of XNW27011 in ORR were highly consistent across expression strata defined by either 43-14A or EPR19202 assay antibody. In patients with CLDN18/CLDN18.2 expression defined as IHC ≥2+ in ≥20% of tumor cells, ORRs were 45.5% and 45.3% using EPR19202 and 43-14A assay antibody, respectively. EPR19202 and 43-14A IHC assays demonstrated high concordance, with an overall agreement of 90.1%. **Conclusions:** The IHC assays of CLDN18.2 expression with EPR19202 or CLDN18 expression with 43-14A demonstrate comparable analytical performance with high concordance. The alignment of efficacy outcomes across the two antibody-defined strata supports that CLDN18 and CLDN18.2-specific antibodies can identify patient populations with similar clinical benefit. Both antibodies can support the clinical development of XNW27011 in the treatment of patients with G/GEJ adenocarcinoma. Research Sponsor: None.

Phase II study of ceralasertib (ATR inhibitor) plus durvalumab in patients with advanced gastric cancer (AGC) who progressed on prior anti-PD-(L)1 therapy.

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Background: The standard first-line therapy for advanced gastric cancer (AGC) now includes immune checkpoint inhibitors (ICIs), but resistance is inevitable. ATR inhibition may sensitize tumors to ICIs by enhancing DNA damage and activating the cGAS-STING pathway. We evaluated the efficacy and immunologic impact of ceralasertib (ATRi) plus durvalumab in IO-pretreated AGC. **Methods:** This open-label phase II trial (NCT03780608) enrolled patients with metastatic gastric adenocarcinoma who progressed on prior anti-PD-(L)1 therapy. Patients received ceralasertib (240mg BID, Days 1–7) and durvalumab (1500mg IV, Day 8) every 28 days. The primary endpoint was ORR (RECIST v1.1). Serial endoscopic biopsies were collected at baseline (BL), post-ATRi monotherapy (FU1), and post-durvalumab combination (FU2) for multi-omics analysis (WES/WTS/scRNA-seq). **Results:** Thirty patients were enrolled (median 4 prior lines; all HER2-negative). ORR was 33.3% (10/30) and DCR was 56.7%. Median PFS was 4.3 months (95% CI, 1.45–7.10); median OS was not reached. Patients receiving study treatment immediately after prior IO failure had significantly longer PFS than those with intervening non-IO lines ($p < 0.05$). Grade 3 TRAEs occurred in 10% (3/30) of patients, with no new safety signals identified. Dose reductions of ceralasertib occurred in 4 patients. Multi-omics revealed that higher baseline scarHRD scores correlated with shorter PFS ($p = 0.031$). scRNA-seq showed that responders (R) had significant depletion of aneuploid clones post-treatment, whereas non-responders (NR) exhibited clonal persistence. Mechanistically, R showed baseline enrichment of the ATR-ATRIP axis, indicating functional dependency on replication stress tolerance. ATR inhibition in R induced replication fork collapse and ATM-CHEK2-mediated apoptosis. Conversely, NR displayed base excision repair deficiency signatures and adaptive G1-phase retention, facilitating evasion of ATRi-induced lethality. **Conclusions:** Ceralasertib plus durvalumab is efficacious and well-tolerated in IO-refractory AGC. The higher efficacy observed in patients treated immediately after prior IO failure suggests that ATR inhibition may effectively reverse acquired resistance to PD-1 blockade. This biomarker-driven approach warrants further validation in a larger cohort. Clinical trial information: NCT03780608. Research Sponsor: None.

4063 Poster Session

Biomarker-driven assessment of immunochemotherapy with or without fruquintinib as first-line treatment for advanced gastric/GEJ adenocarcinoma: Initial clinical results and subgroup analysis from the MGC-FLORA study.

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Background: The MGC-FLORA study is a prospective biomarker-exploratory trial primarily designed to identify predictive biomarkers (including gut microbiota and blood-based biomarkers) for first-line immunochemotherapy in advanced gastric/gastroesophageal junction (G/GEJ) adenocarcinoma. A key exploratory question is whether adding anti-angiogenic therapy (fruquintinib) modifies the efficacy landscape and its associated biomarkers. This interim analysis compares clinical outcomes between chemotherapy plus immunotherapy (CHEM cohorts) and chemotherapy plus immunotherapy plus fruquintinib (FRUQ cohorts). The FRUQ cohort is concurrently registered as an independent phase II clinical study (NCT06158919). **Methods:** This analysis included patients enrolled before September 30, 2025, with follow-up until January 15, 2026. Patients with previously untreated, unresectable locally advanced or metastatic G/GEJ adenocarcinoma were enrolled into two cohorts in this non-randomized study: CHEM (PD-1 inhibitor plus XELOX/SOX) and FRUQ (PD-1 inhibitor plus XELOX/SOX plus fruquintinib 4mg QD, days 1-14). After 6 induction cycles, oxaliplatin was discontinued in both cohorts, and maintenance therapy consisted of S-1/capecitabine plus PD-1 inhibitor, with or without continued fruquintinib. Blood and stool samples were collected at baseline (C1D1), after two treatment cycles, and at progression for future biomarker analysis (gut microbiota, cfDNA/cfRNA); the present report focuses on clinical outcomes. **Results:** A total of 126 patients were included (CHEM: n = 83; FRUQ: n = 43), with a median follow-up of 10.97 months. In the overall population, median PFS was 8.38 months and median OS was 18.53 months. Among evaluable patients, ORR was 47.1% (16/34) in the CHEM cohort versus 76.7% (33/43) in the FRUQ cohort, indicating a higher response rate with the addition of fruquintinib. Median PFS was 8.38 months for CHEM and 10.35 months for FRUQ (HR = 0.63, 95% CI 0.37-1.08; p = 0.09). After propensity score matching for sex, age, liver metastasis status, number of target lesions, and Claudin18.2 expression (n = 29 per cohort), the PFS benefit associated with fruquintinib became more pronounced (HR = 0.45, 95% CI 0.20-1.02; p = 0.05). **Conclusions:** This initial analysis from the biomarker-oriented MGC-FLORA study suggests that the addition of fruquintinib to first-line immunochemotherapy may improve clinical efficacy in advanced G/GEJ adenocarcinoma. Consistent trends toward prolonged PFS were observed in both the overall and propensity score–matched populations, supporting a potential therapeutic benefit of fruquintinib. These findings warrant further validation in randomized trials and integrated biomarker analyses.
Research Sponsor: None.

Toripalimab plus chemotherapy and radiotherapy for treatment-naïve advanced esophageal squamous cell carcinoma: Long-term survival and recurrence patterns.

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Background: Concurrent chemoradiotherapy plus PD-1 blockade is standard for locally advanced esophageal squamous cell carcinoma (ESCC), but its role in advanced disease remains undefined. We investigated the safety and efficacy of Toripalimab combined with chemotherapy and radiotherapy (RCIT) as first-line treatment for advanced ESCC, analyzing long-term survival, recurrence patterns, and immune biomarkers. **Methods:** This single-arm, phase II trial enrolled treatment-naïve patients with stage IV ESCC (N3 nodal or oligometastases; 5 lesions in 3 organs). Treatment comprised induction chemoimmunotherapy (2 cycles) followed by concurrent radiotherapy (Cycles 3-4) and maintenance immunotherapy. Patients received Paclitaxel (135-175 mg/m2) and Carboplatin (AUC 4-6) plus Toripalimab (240 mg) on day 1 (Q3W). Intensity-modulated radiotherapy (50-50.4 Gy/25-28f) targeted primary/regional lesions, while SBRT (30-40 Gy/3-5f) targeted oligometastases. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), recurrence patterns, health-related quality of life (HRQOL), and biomarker analysis via multiplex immunofluorescence (mIF). **Results:** Thirty-three patients were enrolled. At a median follow-up of 33.4 months, the 2-year PFS and OS rates were 30.3% (95% CI: 18.1-50.8) and 48.5% (95% CI: 34.1-68.9), respectively. In the efficacy-evaluable population completing radiotherapy (n = 26), outcomes were significantly superior to those who did not, with a median OS of 27.4 months and a 2-year OS of 61.5% (HR = 0.26, p = 0.004). Recurrence occurred in 26 (78.8%) patients, comprising locoregional only (27.3%), distant only (18.2%), and combined failure (33.3%). Notably, among patients completing RT, in-field recurrence (57.7%) remained a predominant failure pattern despite multimodal therapy. HRQOL analysis demonstrated significant post-induction improvement in pain and social functioning scores, whereas radiotherapy transiently worsened dysphagia at 3 months post-RT (p = 0.041). Translational analysis revealed that high baseline tumor infiltration of CD8+ T cells, PD-L1+ dendritic cells, and PD-L1+ macrophages, alongside elevated serum IL-4, IL-17, and IFN-γ\gamma, were significantly associated with long-term survival (OS $\geq$24 months; $p < 0.05$). **Conclusions:** First-line RCIT yields promising long-term survival in advanced oligometastatic ESCC, particularly in patients completing the full radiotherapeutic course, achieving a 2-year OS of 61.5%. However, high rates of in-field recurrence suggest a need for further optimization of local control strategies. Baseline immune infiltrates and cytokine profiles offer potential predictive value for patient stratification. Randomized trials are warranted to validate these findings. Clinical trial information: ChiCTR2100046715. Research Sponsor: This work was supported by the NSFC program (82573448).

4065 Poster Session

Disitamab vedotin (RC48), tislelizumab, and S-1 as first-line therapy for HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): Updated survival and exploratory biomarker results from the RCTS trial.

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Background: Anti-PD1 antibody has significantly improved survival in patients with HER2-overexpressing and PD-L1 combined positive score (CPS) ≥1 GC/GEJC when added to trastuzumab and chemotherapy. Recent trials revealed that HER2-targeted antibody-drug conjugates combined with anti-PD1 antibody, have also shown promising efficacy in this population. We report updated survival, safety, and exploratory biomarker results of RC48 combined with tislelizumab and the oral fluoropyrimidine S-1 as first-line therapy for patients with HER2-overexpressing GC/GEJC. **Methods:** This single-arm, multicenter clinical trial enrolled patients with unresectable or metastatic HER2-overexpressing (IHC 3+ or 2+, regardless of FISH status) GC/GEJC. Patients received RC48 (2.5 mg/kg), tislelizumab (200 mg), and S-1 (40–60 mg BID for 14 days) every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. Exploratory analyses included dynamic peripheral T-cell receptor (TCR) sequencing and longitudinal circulating tumor DNA/cell-free DNA (cfDNA) profiling. **Results:** 57 patients were enrolled, 71.9% HER2 IHC 3+, 17.5% IHC 2+/FISH+, and 10.5% IHC 2+/FISH-; 45.6% had CPS ≥1. Until Dec 31, 2025, the median follow-up was 28.2 months. In the ITT population, the confirmed ORR was 89.5% (95% CI: 78.5–96.0%), including 8.8% complete responses; disease control rate was 98.2%. Median PFS was 13.8 months (95% CI: 10.3–24.0), and median OS was 31.9 months (95% CI: 22.1–not reached). In the CPS ≥1 and CPS < 1 subgroups, ORRs were 92.3% (95% CI: 74.9–99.1%) and 87.1% (95% CI: 70.2–96.4%), with median PFS 16.7 vs 10.0 months and median OS 31.9 vs 25.4 months, respectively. Grade ≥3 treatment-related adverse events occurred in 64.9%, mainly decreased white blood cell count (29.8%), decreased neutrophil count (12.3%), anemia (10.5%), and peripheral motor neuropathy (10.5%). In patients with paired TCR samples, higher treatment-induced clonal expansion score was associated with improved PFS (HR 0.34; P = 0.017) and OS (HR 0.33; P = 0.037), with particularly prognostic discrimination in the CPS < 1 subgroup. In patients with longitudinal cfDNA, cfDNA tumor fraction increases preceded imaging-defined progression in most patients who progressed. **Conclusions:** The combination of RC48, tislelizumab and S-1 as a first-line therapy shows encouraging response rates and updated survival with manageable safety in HER2-overexpressing GC/GEJC, including patients with CPS < 1. TCR clonal expansion may serve as a robust biomarker of antitumor immune activation, independent of PD-L1 expression levels. Clinical trial information: NCT05586061. Research Sponsor: None.

Efficacy of nimotuzumab combined with concurrent chemoradiotherapy for patients with postoperative loco-regional recurrent esophageal squamous cell carcinoma: A phase II study.

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Background: The clinical therapeutic effect for patients with postoperative loco-regional recurrent esophageal squamous cell carcinoma (ESCC) is not satisfactory. Nimotuzumab, an EGFR-targeted humanized antibody, showed efficacy in the treatment of ESCC. We explored the efficacy of nimotuzumab combined with concurrent chemoradiotherapy (CCRT) for patients with postoperative loco-regional recurrent ESCC. **Methods:** Eligible patients (18-75 years) with postoperative loco-regional recurrent ESCC were enrolled in this single-arm phase II study, received nimotuzumab (400mg on D1, 200mg/w for 6 weeks) combined with CCRT (chemotherapy:TP regimen, radiotherapy: 45-50.4Gy/25-28f/5-6w), sequentially nimotuzumab 200mg every 3 weeks plus chemotherapy (patients with partial response or stable disease). The primary endpoint was objective response rate (ORR), the second endpoints were disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and local-regional control (LRC) and adverse events. **Results:** From Sep 2021 to Apr 2024, 44 patients were screened, ultimately 42 patients were included in the Full Analysis set. The median age was 69 years (range: 48-75). 12 (28.57%) patients achieved complete response, 24 (57.14%) patients with partial response, 5 (11.90%) patients with stable disease, and 1 (2.38%) patient with progressive disease. ORR was 85.71%, and DCR was 97.62%. The failure patterns showed that 10 (23.81%) patients had loco-regional recurrence, and 9 (21.43%) had distant metastases after CCRT. The median follow-up was 29.3 months (95%CI: 25.7-38.0). 3-year OS was 51.8% (95% CI: 36.9-72.8%), with the median OS was not reached. 3-year PFS was 33.4% (95%CI: 20.4-54.7%), and the median PFS was 15.1 months (95%CI: 11.8-NE), 3-year LRC was 46.1% (95%CI: 29.9-71.0%), the median LRC was 30.8 (95%CI: 16.6-NE). The most common Graded 3-5 adverse events (AEs) included leukopenia, thrombocytopenia, hemoglobin decreased, radiation esophagitis, radiation-induced lung injury, fatigue, and radiodermatitis. 4 patients experienced Grade 3-5 radiation esophagitis, in which 2 patients developed esophageal fistulas (1 patient died). No nimotuzumab-related serious AEs occurred. **Conclusions:** Nimotuzumab combined with CCRT showed promising ORR and survival with tolerable toxicity in patients with postoperative loco-regional recurrent ESCC. Clinical trial information: ChiCTR2200063875. Research Sponsor: None.

Survival outcome of sandwich therapy with induction chemoimmunotherapy followed by concurrent chemoradiotherapy and sequential immune maintenance therapy in locally advanced unresectable esophageal squamous cell carcinoma (ESCC) patients: A multi-center prospective study.

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Background: PD-1 inhibitor, combined with chemotherapy, is recommended in first-line treatment for metastatic ESCC, but its role remains undefined in locally advanced ESCC. This trial aimed to investigate the survival outcome and safety of the 'Sandwich Therapy' consisting of induction chemoimmunotherapy followed by definitive chemoradiotherapy (dCRT) and sequential immune maintenance therapy. **Methods:** This is a multicenter, prospective study. Patients with histologically confirmed, clinical stage I—IVA and unresectable esophageal squamous cell carcinoma (ESCC) were included. Patients received 1-8 cycles of chemoimmunotherapy (intravenous paclitaxel (175 mg/m^2) plus platinum-based chemotherapy), then concurrent chemoradiotherapy followed by tislelizumab (200mg intravenously, every 3 weeks) until disease progression or the end of the study. The primary outcome was progression-free survival (PFS). The secondary outcomes included overall survival (OS) and the incidence of adverse events (AE). **Results:** Between August 2022 and Aug 2025, 77 patients were enrolled and all proceeded to the immune maintenance therapy phase. The median age was 61 years (IQR 55-69), and 78% had clinical stage III or IV disease. With median follow-up of 19 months (95CI), median PFS was 17.0 months (95% CI:12.0—36.0) , with 1-, 2- and 3-year PFS rate of 56.4%, 39.9% and 25.6%, respectively. The median OS was 45.0 months (95%CI:20.1-69.3), with 1-, 2- and 3-year OS rate of 74.9%, 63.2% and 50%, respectively. The objective response rate (ORR) was 55.8%, and the disease control rate was 92.2%. Grade ≥3 AE occurred in 27 (35.1%) patients during the treatment. The most common grade ≥3 AE was lymphopenia, which was reported in 22 (28.6%) patients. **Conclusions:** For locally advanced ESCC, induction chemoimmunotherapy followed by dCRT and subsequent maintenance of immunotherapy may improve PFS and OS with a manageable safety profile. Clinical trial information: NCT05515315. Research Sponsor: None.

Incidence and prognostic impact of recurrence in esophageal carcinoma patients achieving complete pathological response after neoadjuvant chemoradiotherapy or perioperative chemotherapy.

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Background: Esophageal carcinoma remains a global challenge, ranking 7th in cancer-related mortality. While the CROSS trial established neoadjuvant chemoradiotherapy (nCRT) as a standard of care with a 29% pathological complete response (pCR) rate, real-world data in diverse histological populations—particularly Squamous Cell Carcinoma (SCC)—are evolving. We aimed to evaluate the impact of pCR on Overall Survival (OS) and Disease-Free Survival (DFS) in a high-volume surgical cohort. **Methods:** A retrospective analysis of a prospective database was conducted for patients undergoing curative-intent esophagectomy at a tertiary cancer center (2019–2023). Inclusion: Patients receiving neoadjuvant therapy (nCRT or perioperative chemotherapy). Exclusion: Patients with upfront surgery, palliative resections, or incomplete records. Survival outcomes were analyzed using Kaplan-Meier curve. **Results:** Of 546 patients, 51% were male with a mean age of 44 ± 9 years. nCRT was the primary neoadjuvant modality (92.3%), followed by perioperative chemotherapy (7.7%). pCR was achieved in 54.8% of patients. At a median follow-up of 5 years, the overall recurrence rate was 27.1%; notably, only 28.3% of the pCR group experienced recurrence compared to the non-pCR group ($p < 0.001$). Recurrence patterns distant (48.6%), followed by locoregional (44.6%), and both (6.8%). The pCR group demonstrated superior survival outcomes: Mean OS: 57 ± 0.7 months vs 52 ± 1 months in non-pCR ($p = 0.001$); Mean DFS: 52 ± 1 months vs 35 ± 1 months in non-pCR ($p < 0.001$). Total study mortality was 8.4%. **Conclusions:** In this large South Asian cohort, pCR was achieved in over half of the patients following neoadjuvant therapy and served as a robust predictor of both OS and DFS. These findings reinforce pCR as a critical surrogate endpoint for long-term oncological success and suggest that tumor biology in this region may be particularly sensitive to multimodality protocols. Research Sponsor: None.

Clinical characteristics and survival outcomes.

Variable	Value (n=546)
Tumor Location	Distal Esophagus: 52.6% Mid Esophagus: 25.3% Gastroesophageal Junction: 12.6%
Histology	Squamous Cell Carcinoma (SCC): 85.7% Adenocarcinoma: 14.3%
Neoadjuvant Therapy	Chemoradiotherapy (nCRT): 92.3% Chemotherapy: 7.7%
Surgical Procedure	McKeown Esophagectomy: 78.6% Ivor Lewis Esophagectomy:18.7% Trans-hiatal Esophagectomy: 2.7%
Pathological Stage (TNM) I/II/III/IV	69.5% / 10.5% / 16.6% / 3.4%
Resection Margin	R0 (Negative): 95.1% R1 (Microscopic Positive): 4.9%
Pathological Complete Response (pCR)	Overall: 54.8% Squamous cell Carcinoma: 95.3% Adenocarcinoma: 4.6%
Recurrence	Overall Rate: 27.1% Recurrence within PCR group: 7.6%
Overall Survival (Months)	pCR = 57±0.7 Residual Disease = 52±1 months p=0.001
Disease-Free Survival (Months)	pCR = 52±1 Residual Disease = 35±1 p= <0.001

Efficacy of durvalumab and safety by treatment period in MATTERHORN: A randomized, phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy in resectable gastric/gastroesophageal junction (G/GEJ) cancer.

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Background: In MATTERHORN (NCT04592913), perioperative durvalumab (D) + FLOT significantly improved event-free survival (EFS) and overall survival vs placebo (Pbo) + FLOT in participants (pts) with resectable G / GEJ cancer. Here, we report EFS by treatment period completion status. **Methods:** In this global, double-blind, Phase 3 study, pts with histologically confirmed, resectable, untreated G / GEJ adenocarcinoma were randomized 1:1 to D 1500 mg or Pbo every 4 weeks (Q4W) on Day 1 + FLOT every 2 weeks on Days 1 and 15 for 4 cycles (2 cycles each neoadjuvant and adjuvant [adjuvant: 4–12 weeks post-surgery]), followed by D 1500 mg or Pbo Q4W for 10 additional cycles (adjuvant monotherapy). EFS (time from randomization to progression, local or distant recurrence, or death) was assessed by treatment period completion status (Table). Safety was also assessed. Landmark EFS rates were calculated by the Kaplan–Meier method. Hazard ratios and their confidence intervals were estimated by the Cox proportional hazards model. **Results:** The number of pts who received treatment in each period was similar in the D + FLOT and Pbo + FLOT treatment arms (Table). EFS landmark rates at 12 and 24 months were highest in pts who completed all adjuvant D / Pbo in both arms; EFS was improved in the D + FLOT vs Pbo + FLOT arm irrespective of treatment periods started / completed (Table). A smaller proportion of Grade 3–4 adverse events (AEs) and serious AEs (SAEs) were reported in the adjuvant monotherapy period with D + FLOT and Pbo + FLOT (Grade 3–4: 21.2% and 20.5%; SAEs: 14.5% and 14.5%, respectively) when compared with the overall treatment period (Grade 3–4: 71.6% and 71.2%; SAEs: 48.2% and 44.1%, respectively). In the adjuvant monotherapy period, the rate of any AEs leading to discontinuation of D / Pbo was 5.8% in the D + FLOT vs 2.7% in the Pbo + FLOT arm. **Conclusions:** EFS landmark rates were greatest for pts who completed the full adjuvant regimen compared with those who discontinued prematurely in both arms. Moreover, the addition of D to FLOT improved EFS regardless of treatment periods started / completed. Safety was manageable and tolerable in the adjuvant monotherapy period. Clinical trial information: NCT04592913. Research Sponsor: AstraZeneca.

	Received any neoadjuvant treatment but did not complete surgery (N=132)		Received any neoadjuvant treatment and completed surgery (N=96)*		Received any adjuvant treatment but did not complete D / Pbo (N=223)		Completed all adjuvant D / Pbo (N=493)	
	D + FLOT (n=62)	Pbo + FLOT (n=70)	D + FLOT (n=48)	Pbo + FLOT (n=48)	D + FLOT (n=116)	Pbo + FLOT (n=107)	D + FLOT (n=248)	Pbo + FLOT (n=245)
EFS landmark rate, %								
12 mo	16.0	8.3	59.0	41.6	67.4	66.4	99.6	98.8
24 mo	10.0	6.2	49.2	33.3	46.7	29.8	91.8	87.2
EFS hazard ratio (95% CI)	0.80 (0.55–1.18)		0.65 (0.38–1.13)		0.65 (0.46–0.91)		0.63 (0.41–0.97)	

*These pts did not receive adjuvant treatment.

Non-invasive strategy for gastric cancer detection: Integration of cell-free DNA fragmentomics and protein biomarkers.

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Background: Gastric cancer (GC) ranks the fifth most common cancer worldwide. Although gastroscopy is widely acknowledged as the gold standard for GC detection, its invasiveness limits its utility in large-scale screening. Accurate, non-invasive diagnostic modalities are urgently needed. Cell-free DNA (cfDNA) fragmentomics has emerged as a promising tool for cancer detection. This study aimed to develop and validate a novel non-invasive model for GC detection based on cfDNA fragmentomics and protein biomarkers. **Methods:** A total of 257 participants, comprising 120 GC patients and 137 non-cancer individuals, were enrolled and divided into a training cohort (n = 129) and a test cohort (n = 128). Low-coverage whole-genome sequencing was performed on plasma cfDNA. We evaluated eight multi-dimensional cfDNA fragmentomics features individually, and selected four, including fragment size ratio, copy number variation, 9-bp end motif, and fragment size at transcription starting sites, to build an ensemble model (GaFraD) to detect GC. Furthermore, conventional protein biomarkers of GC were assessed and integrated with GaFraD model to generate a CONFIRM model aimed at improving diagnostic performance. **Results:** The GaFraD model achieved an area under the receiver-operating characteristic curve (AUC) of 0.953 (95% CI: 0.918 – 0.979) in the training cohort and 0.970 (95% CI: 0.944 – 0.990) in the test cohort, with a sensitivity of 95.0% and a specificity of 80.9%. By incorporating protein biomarkers CA19-9 and PG-I/PG-II, the CONFIRM model further reached an AUC of 0.967 (95% CI: 0.929 – 0.992) in the training cohort and 0.986 (95% CI: 0.966 – 1.000) in the test cohort, attaining a sensitivity of 95.0% and specificity of 95.6%. Moreover, the CONFIRM model also exhibited remarkable performance in discriminating early-stage GC patients from controls (AUC = 0.983, sensitivity: 95.6%, specificity: 94.2%). **Conclusions:** Our model exhibits high discriminatory power in distinguishing GC patients from controls, highlighting the strong clinical potential of combining cfDNA fragmentomics with protein biomarkers for non-invasive, early GC detection. This approach offers a promising pathway towards earlier, accurate, and non-invasive clinical diagnosis of GC. Research Sponsor: the Scientific Research Project of Jiangsu Provincial Health Commission; Z2022039; Suzhou Gusu Health Talent Plan; GSWS2022115; the Science and Technology Project Foundation of Suzhou; SKY2023034; SS202093; SYW2024164; the Key Scientific Research Projects of Jiangsu Provincial Health Commission; ZD2021053.

Prevalence of *CDH1* germline variants in gastric cancer patients with exome-inferred ancestry.

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Background: Germline pathogenic or likely pathogenic (P/LP) *CDH1* variants increase the lifetime risk of developing diffuse gastric cancer (DGC). Given that the epidemiology and prognosis of gastric cancer vary based on patient ancestry, and Hispanic and Black/African-American patients have been underrepresented in clinical and translational research, we sought to determine the prevalence of *CDH1* variants in a diverse population of gastric cancer patients. **Methods:** Germline whole exome sequencing (WES) data from gastric cancer patients were obtained as part of commercial ordering of personalized circulating tumor DNA testing (Signatera, Natera, Inc.) from March 2024 to June 2025. Ancestry was inferred by EthSeq and classified into predefined groups: European (EUR), admixed American (AMR), African (AFR), and East Asian (EAS). Germline single-nucleotide variants and short insertions/deletions were identified and annotated with Variant Effect Predictor (v.105), and the pathogenicity of variants in *CDH1* was determined using classifications available in the ClinVar database. The prevalence of P/LP variants and variants of uncertain significance (VUS) were compared across ancestries. Potential pathogenicity of VUS was evaluated using *in silico* predictors SIFT (v5.2.2), Polyphen (v2.2.2), and AlphaMissense (hg19). **Results:** Among 2,567 patients, 55% (1,414/2,567) were male and the median age was 67 years. Ancestry inference identified 47% (n=1,201) as EUR, 22% (n=575) as AMR, 18% (n=457) as AFR, and 13% (n=334) as EAS. Patients with AMR ancestry were younger compared to EUR ancestry patients (median 62 years vs 69 years; adj $p<0.0001$), and less likely to be male (51% [295/575] vs. 58% [693/1201]; OR, 0.7; 95% CI, 0.63–0.94; p=0.015). No significant differences in age or sex were observed in patients with AFR (median 68 years, 55% male) or EAS (median 68 years, 52% male) ancestry compared to EUR. Overall, 0.7% (n=17) gastric cancer patients had a P/LP variant, and there was no difference across ancestries (0.8% of EUR, 0.5% of AMR, 0.4% of AFR, and 0.6% of EAS patients). We found that 1.1% (n=27) of the cohort had a *CDH1* VUS, the rate for which did not vary across ancestries (1.2% of EUR, 0.52% of AMR, 0.84% of AFR, 0.60 of EAS). Of the 21 unique VUS, 33% (n=7) were each predicted to be pathogenic by all three *in silico* predictors. One unique VUS was observed in two unrelated patients: NM_004360.5:c.635G>T (p.Gly212Val). The predicted-pathogenic VUS were similarly distributed across ancestries. **Conclusions:** This real-world analysis highlights that *CDH1* VUS were similarly distributed across ancestries. Notably, we found that one-third of VUS identified were predicted to have pathogenic function across three *in silico* prediction tools. This highlights the need for functional assays to determine the variant biology to improve gastric cancer risk assessment. Research Sponsor: None.

Neoadjuvant and adjuvant pembrolizumab plus chemotherapy for locally advanced gastric or gastroesophageal junction adenocarcinoma: Outcomes from the microsatellite instability-high population of the phase 3 KEYNOTE-585 study.

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Background: In the randomized phase 3 KEYNOTE-585 study (NCT03221426), perioperative pembrolizumab (pembro) plus chemotherapy (chemo) significantly improved pathologic complete response (pCR) vs placebo (pbo) plus chemo (diff, 10.9%; 95% CI, 7.5-14.8; $P < 0.00001$), with no new safety signals in participants (pts) with locally advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. We present outcomes for the microsatellite instability-high (MSI-H) population. **Methods:** Eligible pts had untreated resectable locally advanced G/GEJ adenocarcinoma (including Siewert type 2 or 3 tumors); MSI was centrally assessed. Pts enrolled in the main cohort (n = 804) received neoadjuvant pembro 200 mg intravenously (IV) every 3 weeks (Q3W) or pbo plus chemo (cisplatin + capecitabine or 5-FU) for 3 cycles; after surgery, pts received adjuvant pembro or pbo plus chemo Q3W for 3 cycles, then adjuvant pembro or pbo Q3W for 11 cycles. Pts in the fluorouracil, docetaxel, and oxaliplatin (FLOT) cohort (n = 203) received neoadjuvant pembro 200 mg IV Q3W or pbo Q3W for 3 cycles plus FLOT Q2W for 4 cycles; after surgery, pts received adjuvant pembro or pbo Q3W for 3 cycles plus FLOT Q2W for 4 cycles, then adjuvant pembro or pbo Q3W for 11 cycles. End points were pCR (blinded independent central review [BICR]), event-free survival (EFS; RECIST v1.1 by BICR), overall survival (OS), and safety. We report outcomes in the main and FLOT cohorts combined. The data cutoff date was February 16, 2024 (final analysis). **Results:** Data from the 81 pts with MSI-H status were analyzed (n = 43, pembro + chemo; n = 38, pbo + chemo). The pCR rate was 39.5% (95% CI, 25.0-55.6) in the pembro group and 0% (95% CI, 0.0-9.3) in the pbo group (diff, 39.5%; 95% CI, 26.3-54.5). The median EFS was not reached (NR; 95% CI, 49.9-NR) and 60.1 months (95% CI, 18.6-NR), respectively (HR, 0.58; 95% CI, 0.26-1.31); 24/48-month EFS rates were 78%/73% in the pembro group and 68%/68% in the pbo group. The median OS was NR (95% CI, NR-NR) in both treatment groups (HR, 0.50; 95% CI, 0.19-1.30); 24/48-month OS rates were 91%/86% in the pembro group and 76%/74% in the pbo group. Treatment-related adverse events (AEs) occurred in all 43 pts (100%) in the pembro group and 37 (97%) in the pbo group. Grade 3-5 treatment-related AEs occurred in 32 (74%) and 25 (66%) pts, respectively. Discontinuation of any drugs due to treatment-related AEs occurred in 15 pts (35%) in the pembro group and 12 (32%) in the pbo group. No deaths due to treatment-related AEs were reported. **Conclusions:** In this post hoc analysis, efficacy outcomes for pts with MSI-H G/GEJ adenocarcinoma suggested a consistent trend with numerically more pronounced difference between the treatment groups, with a manageable safety profile. Further studies in this population are warranted. Clinical trial information: NCT03221426. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

LBA4075 **Poster Session**

Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by D2 gastrectomy and adjuvant chemotherapy for locally advanced gastric cancer (Neo-CRAG): A randomized, multicenter, phase 3 trial.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

A multicenter non-randomized phase III study of sentinel node navigation surgery for early gastric cancer.

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Background: Sentinel node navigation surgery (SNNS) has the potential to minimize the extent of gastrectomy, thereby improving quality of life (QOL) after surgery for patients with early gastric cancer (GC). This prospective, multicenter, non-randomized, phase III study aims to evaluate the long-term outcomes of SNNS for early GC. **Methods:** A total of 13 institutions enrolled clinically diagnosed primary T1N0M0 gastric cancer patients with a single lesion (≤40 mm) and without previous endoscopic treatment. Sentinel nodes (SNs) were identified using dye and radioisotope tracers, then subjected to intraoperative rapid pathology. Patients with negative SN metastasis underwent individualized surgery consisting of limited stomach resection and SN basin dissection, while those with positive SN metastasis underwent standard gastrectomy with D2 lymph node dissection. The primary endpoint was five-year relapse-free survival (RFS). The secondary endpoints were overall survival (OS), SN detection rate, diagnostic accuracy for SNs, SN distribution, and the distribution of metastatic and non-SNs. Postoperative QOL was also assessed. RFS was assessed in the full analysis set (FAS), excluding patients who did not undergo intraoperative SN biopsy and pathological assessment during surgery. The data cutoff date for the analysis was May 31, 2025. Clinical trial information: jRCTs031180432. **Results:** A total of 187 patients were enrolled from May 2014 to May 2020. Of the 180 patients in FAS, 62.2% were male. The median (range) age was 64 (27–85). cT1a/cT1b was 18.3%/81.7%, respectively. The median follow-up time was 60.2 months (range: 9.0–62.8). The 5-year RFS rate (95% CI) was 95.6% (91.43–98.06). Since the lower boundary of the 95% CI exceeded the predefined threshold of 90%, the study met its primary endpoint. Events for RFS included one recurrence and three non-cancer deaths. SNs were identified in all patients, and LN metastasis was detected in 17 patients (9.4%) during surgery. Finally, 143 patients (79.4%) underwent individualized surgery consisting of limited stomach resection and SN basin dissection. The 5-year RFS rate (95% CI) for this cohort was 96.5% (92.03 - 98.86). There was no mortality after surgery. **Conclusions:** SNNS for early GC has been shown to be non-inferior to standard gastrectomy, with an acceptable toxicity profile. SNNS represents a promising alternative as a potential new standard treatment for early GC. Clinical trial information: jRCTs031180432. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

FGF4-mediated resistance to combined anti-angiogenic and immunotherapy in esophageal squamous cell carcinoma via suppression of high endothelial venules and tertiary lymphoid structure formation.

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Background: Many patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC) fail to achieve a pathological complete response (pCR) following neoadjuvant immunochemotherapy plus anti-angiogenic therapy, which is associated with a poor prognosis. The identification of predictive biomarkers and the elucidation of resistance mechanisms constitute a major challenge. This study aims to identify relevant biomarkers and elucidate the underlying mechanisms to improve therapeutic outcomes. **Methods:** Exploratory analyses were conducted on 70 untreated LA-ESCC patients from a phase II clinical trial (ChiCTR2100051763) treated with two 21-day cycles of neoadjuvant treatment with intravenous camrelizumab (200mg), albumin-paclitaxel (260mg/m^2), carboplatin (AUC=5) on day 1, and oral apatinib (250mg) on days 1-14, followed by the third cycle without apatinib. Pretreatment tumor tissues were subjected to transcriptomic and whole-exome sequencing to identify differential pathways and genetic alterations between patients achieving pCR and non-pCR. Candidate biomarkers were further validated by immunohistochemistry. In vitro and in vivo experiments were employed to elucidate the mechanisms underlying treatment resistance. **Results:** Pathway analysis identified significant enrichment of the fibroblast growth factor receptor (FGFR) signaling pathway in non-pCR patients, with FGF4 as the most upregulated factor. FGF4 alterations were primarily gene amplifications, occurring in 40% of cases. FGF4 expression predicted treatment resistance (non-pCR) with an AUC of 0.857 (95% CI: 0.744–0.97). Multiplex immunohistochemistry revealed that tumors overexpressing FGF4 exhibited impaired vascular normalization, evidenced by significantly reduced pericyte coverage and basement membrane integrity. These tumors also showed lower densities of high endothelial venules (HEVs), CD8+ T cells, and tertiary lymphoid structures (TLSs) following combination therapy. In vivo experiments confirmed that FGF4 overexpression led to decreased pericyte and basement membrane coverage, reduced HEV density, and diminished CD8+ T cell infiltration. Notably, pharmacological inhibition of FGFR signaling reduced tumor growth and increased the pCR rate, effectively reversing the resistance mediated by FGF4. **Conclusions:** Aberrant FGF4 expression drives resistance to combined immunochemotherapy and anti-angiogenic therapy by impeding vascular normalization, which subsequently suppresses the formation of HEVs and tertiary TLSs. Targeting FGFRs might be a promising strategy to overcome FGF4-driven treatment resistance in ESCC. Clinical trial information: ChiCTR2100051763. Research Sponsor: National Natural Science Foundation of China; 82373307; the Natural Science Foundation of Guangdong Province; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

Non-operative management in mismatch repair deficient (dMMR) esophagogastric cancer (EGC) following immune checkpoint inhibition (ICI).

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Background: ICI achieves deep and durable responses in patients with dMMR and microsatellite instability-high (MSI-H) EGC, creating an opportunity for non-operative management (NOM) of localized disease. However, limited data exists regarding long-term outcomes with NOM and factors associated with ICI failure, which we evaluated in this retrospective cohort study. **Methods:** We identified patients with EGC managed at MSK from 2007-2025 whose tumors were dMMR by IHC or MSI-H by next generation sequencing and analyzed patient/tumor characteristics and clinical outcomes in those who received curative-intent therapy (systemic therapy and/or surgery; ICI was first introduced in 2018). Clinical complete response (cCR) was defined as the absence of disease by available clinical, radiographic, and endoscopic assessment. **Results:** A total of 211 patients with localized dMMR/MSI-H EGC were identified, with median follow-up of 48 months (IQR 24-77). Primary tumor sites were stomach (71%), GE junction (17%), and esophagus (12%). Among 122 patients who underwent germline testing, 15 (12%) had Lynch syndrome. Initial treatment was upfront surgery in 85 patients (40%), chemotherapy (chemo) in 68 (32%), ICI alone in 44 (21%), and chemo/ICI in 14 (7%). Among 58 patients treated with ICI +/- chemo, 27 (47%) achieved a cCR. 6 patients underwent surgery despite cCR, with pathologic complete response (pCR) rate of 4/6 (67%); pCR rate in those without cCR was 3/16 (19%), yielding an overall pCR rate of 32%, higher than the pCR rate observed with chemo alone (5/48 [10%]). 21 patients elected for NOM after cCR; among those with $\geq$1 year of follow-up, 16 of 17 (94%) remain alive and surgery-free at 1 year. cCR rates were similar between those receiving ICI alone (45%) and chemo/ICI (50%). Notably, 2/2 (100%) patients treated with dual ICI therapy achieved cCR. Lower cCR rates were observed in patients with shorter time on ICI therapy (5/17 [29%] with $\leq$3 months of ICI vs 14/30 [47%] with $>$ 3 and $<$ 6 months vs 8/11 [73%] with $\geq$6 months) and in those with clinical nodal involvement (6/17 [35%] vs 14/19 [74%] in N0); 3 patients who underwent surgery had pCR at tumor but residual nodal disease. cCR rate was also numerically lower in the 19% of patients with MMR heterogeneity, defined by focal loss of MMR proteins on IHC or discordant MMR status between tissue specimens (4/11 [36%] vs 23/47 [49%] in non-heterogeneous cases). **Conclusions:** In this MSK cohort, ICI induced deep responses in nearly half of patients with localized dMMR/MSI-H EGC. Patients achieving cCR who pursued NOM demonstrated excellent outcomes, with most remaining surgery-free at 1 year, supporting the viability of NOM after careful multidisciplinary review. Research Sponsor: National Cancer Institute; P30 CA008748; U.S. National Institutes of Health; UL1TR00457; Brian Piccolo Endowed Cancer Research Fellowship.

4079 Poster Session

Total neoadjuvant immunotherapy plus chemotherapy in Borrmann type IV gastric cancer (PERISCOPE-01 study): An open-label, single-arm, phase 2 trial.

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Background: Borrmann type IV (Borrmann-IV) gastric cancer (GC), or linitis plastica, is marked by diffuse infiltration, early metastasis, and poor prognosis, with limited benefit from conventional therapies. This study evaluated the efficacy and safety of a total neoadjuvant regimen combining immunotherapy and chemotherapy in Borrmann-IV GC. **Methods:** This trial (NCT06451211) enrolled patients with Borrmagnn-IV gastric cancer without distant metastasis. Participants received a total neoadjuvant regimen consisting of tislelizumab (an anti–PD-1 antibody) combined with platinum-based chemotherapy (oxaliplatin plus capecitabine or S-1) for 6 cycles at 3-week intervals, followed by radical surgical resection. The prespecified primary endpoint was the pathological response rate, defined as tumor regression grade (TRG) 0/1. **Results:** A total of 56 patients were enrolled, all patients had no distant metastasis confirmed by laparoscopic exploration and ascitic fluid cytology. The median age was 58 years; all patients were pMMR. In the efficacy analysis population (n=47), 41 patients completed 5–6 cycles and 6 patients completed 3–4 cycles of preoperative chemotherapy plus immunotherapy, no patients experienced disease progression leading to tumor metastasis during preoperative treatment. 47 patients underwent radical surgical resection, including 42 total gastrectomy, with an R0 resection rate of 98% (46/47). The prespecified primary endpoint of TRG 0/1 was achieved in 32% of patients (15/47; 95% CI, 21%–48%). Notably, 17% (n = 8) achieved pCR (ypT0N0), and 53% (n =25) were ypN0. Pathological response (TRG 0/1) was significantly higher in Lauren intestinal/mixed versus diffuse types (53% vs. 21%; $p < 0.05$), while efficacy was comparable between PD-L1 CPS ≥ 5 and <5 (44% vs. 30%). Grade 3/4 treatment-related adverse events occurred in 32% of patients (n=18), mainly thrombocytopenia and liver function impairment. Surgical morbidity (Clavien–Dindo grade II/III) occurred in 10.6% of surgical patients (5/47), including 1 patient with postoperative bleeding and 3 patients with anastomotic leakage; no perioperative mortality was observed. **Conclusions:** Total neoadjuvant tislelizumab plus chemotherapy demonstrated promising efficacy and an acceptable safety profile in patients with Borrmann-IV gastric cancer. Lauren classification may serve as a potential predictive biomarker and warrants further study. Clinical trial information: NCT06451211. Research Sponsor: None.

Perioperative chemotherapy plus disitamab vedotin (RC48) and toripalimab in HER2-overexpressed locally advanced gastric or gastroesophageal junction cancer (PERISCOPE-02): An open-label, single-arm, phase 2 trial.

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Background: The use of Disitamab vedotin (RC48) and programmed death-1 (PD-1) inhibitor is effective in patients with HER2-expressing advanced gastric or gastroesophageal junction (G/GEJ) cancer. However, their use has not been investigated in patients with localized disease. This trial evaluated the safety and anti-tumor activity of perioperative chemotherapy combined with RC48 and toripalimab in the treatment of locally advanced HER2-overexpressed (defined as IHC 2+ or 3+) G/GEJ cancer. **Methods:** This study was an investigator-initiated, open-label, single-arm, phase 2 trial was conducted at Sun Yat-sen University Cancer Center. Eligible patients with HER2-overexpressed locally advanced G/GEJ cancer received 3-4 cycles of neo-adjuvant XELOX plus RC48 and toripalimab, followed by surgery. The primary endpoint was TRG 0/1 after neoadjuvant treatment. This study is registered at Chinese Clinical Trial Registry (ChiCTR2400081677). **Results:** Between July 11, 2024, and July 11, 2025, of 26 patients screened for eligibility, 25 patients were enrolled, all patients had no distant metastasis confirmed by laparoscopic exploration and ascitic fluid cytology, 20 (80%) patients had clinical stage III disease and 5(20%) with stage II. Of these 25 patients, the median age was 58 (IQR, 37-74) years. Tumors were located in the stomach in 21(84%) patients and in the gastroesophageal junction in 4 (16%) patients. The patients with HER2 IHC expression of 2+ and 3+ was 21 (84%) and 4 (16%) respectively. 15 (60%) patients had the PD-L1 CPS of 1 or more, 24 (96%) patients were pMMR. The primary endpoint of TRG 0/1 was met in 16 (64%) patients, 9 (36%) patients achieved pCR (ypT0N0), and 24 (96%) were ypN0. 10 (40%) patients experienced grade 3 treatment-related adverse events, the most common treatment-related adverse events were increased ALT or AST (5 [20%] patients) and neutropenia (3 [12%] patients), no grade 4 treatment-related adverse events. Surgical morbidity (Clavien-Dindo II/III) occurred in 2 of 25 (8%) patients, with no 30-day surgical mortality. **Conclusions:** Our findings suggested that perioperative chemotherapy plus RC48 and toripalimab had controllable safety and showed encouraging efficacy in patients with HER2-overexpressed G/GEJ cancer. Clinical trial information: ChiCTR2400081677. Research Sponsor: None.

4081 Poster Session

Whole-genome sequencing–based ultra-sensitive ctDNA molecular residual disease assessment in resectable gastric cancer: Results from MONSTAR-SCREEN-3.

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Background: Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for post-surgical molecular residual disease (MRD) detection; however, its clinical utility in gastric cancer remains poorly defined. The MONSTAR-SCREEN-3 evaluates the clinical performance of a whole-genome sequencing (WGS)–based MRD assay in a pan-cancer cohort, including patients with gastric cancer. **Methods:** MONSTAR-SCREEN-3 is a prospective multicenter study targeting 1,100 patients with solid tumors curative-intent treatment, including gastric cancer. Personalized panels were constructed using Precise MRD (Myriad Genetics), incorporating up to 1,000 tumor-specific alterations identified through whole-genome sequencing (WGS) of matched tumor tissue. Serial plasma samples were collected at baseline, post-neoadjuvant treatment (NAT) when applicable, 1-month post-surgery, every 3 months in year 1, and every 6 months thereafter up to 2 years. Assay performance was evaluated for ctDNA detection and recurrence monitoring. **Results:** As of November 2025, 88 patients with resectable gastric cancer were enrolled. Median age was 69 years (range: 33-87), with female predominance (52.2%). Treatment strategies included upfront surgery (56%, n = 49) and NAT (44%, n = 39). MRD results were available for 220 samples from 57 patients. Clinical staging included Stage I (6%), Stage II (39%), Stage III (51%), and Stage IV (5%). Personalized panel creation succeeded in 100% of patients (57/57), yielding panels containing 588-1,000 alterations. Baseline ctDNA detection was achieved in 96.4% (54/56), with 31.5% at ultra-sensitive levels (tumor fraction $<$ 100 parts per million [ppm]). Post-operative MRD positivity was 7.8% (4/51) at 1 month and 19.5% (8/41) at 3 months, with 25.0% and 50.0% detected at ultra-sensitive levels, respectively. Among 24 patients receiving NAT with pathological assessment, post-NAT MRD status demonstrated 70.0% sensitivity and 100% specificity for pathological complete response (pCR) (MRD positivity, 70% in non-pCR vs. 0% in pCR; $P <$ 0.01); 57.1% of MRD-positive cases were detected at ultra-sensitive levels. Two MRD-positive patients developed radiological recurrence, with MRD detection preceding imaging by 2.0 and 4.3 months. **Conclusions:** This WGS-based personalized ctDNA assay demonstrated high technical feasibility and baseline detection sensitivity in gastric cancer, with notable ultra-sensitive detection capability. Post-NAT MRD status demonstrated potential as a predictor of pathological complete response. Extended follow-up and comprehensive longitudinal ctDNA dynamics will be presented. Research Sponsor: SCRUM-Japan Funds (https://scrum-japan.ncc.go.jp/) and Myriad Genetics.

LBA4082 **Poster Session**

Pathological complete response and ctDNA analyses in SCIENCE: Results from a randomized, phase III trial of neoadjuvant chemotherapy plus sintilimab and chemoradiotherapy plus sintilimab versus chemoradiotherapy in resectable locally advanced esophageal squamous cell carcinoma.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

Perioperative durvalumab plus neoadjuvant chemoradiotherapy (CROSS) with and without tremelimumab in esophageal adenocarcinoma: The prospective phase II RICE trial (NCT04159974).

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Background: Anti-PD-(L)1 is effective in esophageal adenocarcinoma (EGA). The phase II RICE trial (NCT04159974) evaluated the addition of neoadjuvant and adjuvant durvalumab, with or without tremelimumab, to neoadjuvant chemoradiotherapy (CROSS). **Methods:** Patients with locally advanced (≥uT3/Nx or uT2/N+) non-metastatic EGA received two doses of neoadjuvant durvalumab in addition to CROSS, followed by surgery. Adjuvant therapy was randomized 1:1 to durvalumab (12 doses) alone (arm A) or durvalumab plus one dose of tremelimumab (arm B). Translational analyses included HLA-I genotyping, immunohistochemistry, whole-exome sequencing and RNA-sequencing. Clinical outcomes were analyzed in patients who received at least one neoadjuvant dose (mITT) and in those who were randomized and received at least one adjuvant dose (R-mITT). **Results:** In the mITT set (n=56), 95% completed neoadjuvant therapy and 93% underwent resection. The rate of grade ≥3 non-hematologic adverse events during neoadjuvant treatment was 25% (13/56 G3, 1/56 G4). Surgery was feasible with a rate of anastomotic leakage of 6%. Major pathological response (MPR, <10% viable tumor cells) was achieved in 54% (30/56) including a 23% (13/56) pathological complete response rate (pCR, ypT0/ypN0). The rate of MPR was higher than in propensity-based comparisons with FLOT (25%) and CROSS (37%). Two-year overall (OS) and progression-free (PFS) survival of the mITT set were 72.7% and 53.1%, respectively. After completion of Stage I of the trial (safety run in), 38 patients were included in the R-mITT set. 80% in arm A (durvalumab monotherapy, n=20) and 44% in arm B (durvalumab plus tremelimumab, n=18) completed at least 80% of adjuvant immunotherapy. Combined immunotherapy in the R-mITT set was associated with higher grade ≥3 toxicity (22% G3/ 22% G4 in Arm B vs. 15% G3 / 0% G4 in arm A) and did not improve survival (2-year OS/PFS 95.0%/80.0% [arm A] vs. 82.4%/54.2% [arm B]). Tumor mutational burden, heterozygosity of HLA-I, expression of genes related to antigen presentation and T-cell abundance were associated with pathological response. However, discordant cases across all biomarkers underscore the complexity of tumor-immune interactions underlying response to immunotherapy. **Conclusions:** RICE demonstrates safety and feasibility of adding anti-PD-L1 to neoadjuvant CROSS in EGA and shows promising response rates. While CROSS is no longer considered standard of care, our results support efficacy of durvalumab, consistent with results for FLOT plus durvalumab in the MATTERHORN trial. Addition of tremelimumab to durvalumab is not supported by our study. Clinical trial information: NCT04159974. Research Sponsor: Astra Zeneca.

Paclitaxel/cisplatin (TP) vs cisplatin/5-fluorouracil (PF) neoadjuvant chemoradiotherapy for locally advanced esophageal squamous cell carcinoma (ESCC): A randomized trial.

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Background: Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is standard treatment for patients with resectable locally advanced ESCC. A direct comparison of taxane/platinum nCRT versus PF nCRT in prospective randomized clinical trials has never been reported. **Methods:** This is a single-center, open-label, randomized phase II/III trial (registered as NCT0623737 at ClinicalTrial.gov). Patients with locally advanced ESCC (T3/4aN0M0 or T1-3N1-3M0 per AJCC 7th ed.) were randomized 1:1 to TP (paclitaxel 50 mg/m2 weekly plus cisplatin 30 mg/m2 weekly for 5 weeks) or PF (cisplatin 75 mg/m2 day 1 plus 5-FU 1,000 mg/m2 days 1-4 on weeks 1 and 5) chemotherapy with concurrent radiotherapy 45 Gy/25 fractions. Esophagectomy was performed 6 to 10 weeks after completing CRT. Primary endpoint was pathological complete response (pCR) rate for phase II part. If significant pCR benefit of TP versus PF nCRT was found in phase II part, the trial would continue enrolment for the phase III part with overall survival as primary endpoint. **Results:** From Mar 2017 to Jul 2025, 128 patients were enrolled in the phase II part; 6 withdrew before treatment. The intention-to-treat (ITT) population included 122 patients (61 patients per arm); median age was 61 (35-77) years with TP and 58 (39-77) with PF; 90% and 89% were male, respectively. Esophagectomy was performed in 51/61 (84%) vs. 49/61 (80%), and R0 resection was achieved in 43/51 (84%) vs. 36/49 (73%) (p=0.183), respectively. The pCR rate per ITT population was 23/61 (37.7%) with TP vs 17/61 (27.9%) with PF (p=0.247). The difference of pCR rate did not meet the boundary to continue the trial to the phase III part. Median overall survival was 54 vs 43 months (HR 0.76; p=0.284) and median progression-free survival was 33 vs 25 months (HR 0.74; p=0.193) for TP vs PF. Median recurrence free survival was not reached in both arms. Grade 3-4 adverse events during nCRT occurred in 29/61 (47.5%) with TP and 40/61 (65.6%) with PF (p=0.045); most common grade ≥3 events were leucopenia (23.0% vs 32.8%), esophagitis (11.5% vs 29.5%), and dysphagia (14.8% vs 27.9%). Postoperative 90-day mortality was 0% in both arms. **Conclusions:** TP-nCRT did not significantly improve pCR versus PF-nCRT in patients with locally advanced ESCC. Clinical trial information: NCT0623737. Research Sponsor: None.

Efficacy and safety outcomes for TP-nCRT versus PF-nCRT.

	TP	PF	Statistics
ITT, n	61	61	-
Resection, n (%)	51 (84)	49 (80)	p=0.638
R0 resection rate (%)	43/51 (84)	36/49 (73)	p=0.183
pCR (ITT) rate (%)	23/61 (37.7)	17/61 (27.9)	p=0.247
pCR (resected population) rate (%)	23/51 (45.1)	17/49 (34.7)	p=0.288
OS, median (mo)	54	43	HR 0.76; p=0.284
PFS, median (mo)	33	25	HR 0.74; p=0.193
Grade 3-4 AEs during nCRT, n (%)	29 (47.5%)	40 (65.6%)	p=0.045
Postoperative 90-day mortality	0	0	-

Phase II study of adjuvant nab-paclitaxel plus S-1 after D2 resection in stage III diffuse gastric cancer (NORDICA study).

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Background: Stage III diffuse-type gastric cancer (DGC) is highly aggressive, with a substantial risk of postoperative recurrence. Adjuvant chemotherapy with nab-paclitaxel plus S-1 (AS regimen) has shown potential efficacy in early studies, but its safety and effectiveness in this high-risk population remain unclear. **Methods:** This single-center, prospective phase II trial enrolled patients with stage III DGC who underwent D2 gastrectomy between January 2020 and October 2023. All patients first received one cycle of S-1 monotherapy as a pre-screening tolerance test. Eligible patients then received adjuvant AS therapy: nab-paclitaxel 260 mg/m^2 on day 1 every 3 weeks (maximum 400 mg) plus S-1 80–120 mg/day on days 1–14 every 3 weeks for 6 cycles, followed by 8 cycles of S-1 monotherapy. The primary endpoint was 1-year disease-free survival (DFS); secondary endpoints included 3-year DFS, overall survival (OS), and safety. To explore potential molecular correlates of treatment response, whole-exome sequencing was performed on tumor specimens obtained from surgical resection in 24 patients, including 12 patients who experienced recurrence within 2 years (resistant group) and 12 patients with DFS of 2 years or longer (sensitive group). **Results:** The 1-year DFS and OS rates were 84.9% (95% CI, 75.3–95.9%) and 100%, respectively. The 3-year DFS and OS rates were 45.2% (95% CI, 32.5–63.0%) and 62.5% (95% CI, 49.0–79.8%), with a median DFS of 27.7 months (95% CI, 16.5–NR). The most common ≥grade 3 treatment-related adverse events were neutropenia (29.2%), leukopenia (20.8%), rash (6.3%), febrile neutropenia (6.3%), and oral mucositis (4.2%). CDH1 and OBSCN mutations were more frequent in the resistant group, suggesting a potential link to early recurrence. **Conclusions:** Adjuvant AS therapy is feasible and demonstrates promising efficacy for stage III DGC, with an acceptable safety profile. Molecular findings may help identify patients at higher risk of recurrence, supporting further evaluation in larger, randomized phase III trials. Clinical trial information: NCT03977220. Research Sponsor: None.

Interim results from a prospective phase II study of stratified treatment of localized cervical esophageal squamous cell carcinoma by induction immunochemotherapy (SCENIC trial).

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Background: Definitive concurrent chemoradiotherapy (dCRT) is the standard treatment for cervical esophageal squamous cell carcinoma (CESCC). However, when dCRT fails, salvage esophagectomy is technically challenging. Moreover, optimizing patient selection for dCRT remains an unresolved concern. We propose a stratified screening strategy by incorporating induction immunochemotherapy, aiming to identify suitable candidates for organ-sparing dCRT and timely surgical treatment. **Methods:** This prospective interventional phase II study (SCENIC, ChiCTR2200057732) enrolled patients with clinical stage T_{2-4} N_{any} M0 (AJCC TNM 8th) resectable CESCC. Eligible participants received induction therapy (IT) of intravenous PD-1 inhibitor tislelizumab (200mg, day 1) plus nab-paclitaxel (100 mg/m^2, day 1,8,15) and carboplatin (area under curve of 5 mg/mL/min, day 1), administered over two 3-week cycles. Four weeks after IT, treatment response was evaluated via endoscopy and PET-CT. Patients were then divided into 3 groups: remarkable response (RR); limited partial response (LPR); and poor response (POR). RR patients received dCRT, while LPR and POR patients underwent radical surgery. Tislelizumab was maintained after dCRT in RR patients, and postoperative adjuvant therapy was dependent on the patient's condition, including chemotherapy, radiotherapy, immunotherapy, or follow-up. The primary endpoint is 2-year event-free survival (EFS). **Results:** From Jul 2022 to Sep 2024, 42 patients were enrolled, with 40 completing two-cycle IT and response evaluation. Post-IT responses were RR in 62.5% (25/40), LPR in 25.0% (10/40), and POR in 12.5% (5/40). All RR patients received subsequent dCRT. In 11 non-RR patients,7 underwent total phryngo-laryngo-esophagectomy(TPLE), 4 received dCRT. Overall, 40 patients (96.0%) had any-grade treatment-related adverse events with leukocytopenia being most prevalent. 5 patients (12.5%) had adverse events of grade 3 or worse. With a median follow-up of 22.3 months (range, 4.5-40.9 months), 2-years EFS rate and overall survival (OS) rate in ITT population was 60.9% and 76.6%. 2-years EFS rate and OS rate in RR group and non-RR group is 78.8% vs 28.0%(p = 0.0011) and 84.8% vs 70.1%(p = 0.0703), respectively. **Conclusions:** The 2-year survival of RR patients with dCRT followed by IT appears promising compared to historical data. This stratified strategy of induction immunochemotherapy is effective in identifying candidates suitable for dCRT in patients with resectable CESCC. Clinical trial information: ChiCTR2200057732. Research Sponsor: None.

Perioperative therapy with tifcemailmab plus toripalimab and chemotherapy for resectable thoracic esophageal squamous cell carcinoma (BT-NICE trial): A prospective phase II study.

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Background: Tifcemailmab is a first-in-class humanized monoclonal antibody targeting B- and T-lymphocyte attenuator (BTLA), a novel inhibitory immune checkpoint. This phase II BT-NICE trial represents the first clinical study designed to evaluate the efficacy and safety of a perioperative treatment regimen that combines a BTLA inhibitor (tifcemailmab), a PD-1 inhibitor (toripalimab), and chemotherapy for resectable thoracic ESCC. **Methods:** Patients(pts) with histologically confirmed, resectable thoracic ESCC (clinical stage cT1b-3N1-3M0 or cT2-3N0M0) were enrolled. They received 2 cycles of neoadjuvant therapy with tifcemailmab, toripalimab, and standard chemotherapy (every 3 weeks). Following radical esophagectomy, pts with a pathological complete response (pCR) received up to 15 cycles of adjuvant dual immunotherapy (tifcemailmab + toripalimab). Pts without a pCR received 2 cycles of adjuvant chemotherapy plus dual immunotherapy, followed by dual immunotherapy for up to 13 cycles. The primary endpoint was pCR rate. Secondary endpoints included major pathological response (MPR) rate, objective response rate (ORR), R0 resection rate, adverse events (AEs), event-free survival (EFS), and overall survival (OS). **Results:** Between October 20, 2024, and September 30, 2025, a total of 25 patients were successfully enrolled and underwent surgery after completing neoadjuvant therapy. The median age was 63 years (range 53-75), and 19 (76.0%) were male. Most pts (23/25, 92.0%) had stage III disease. The R0 resection rate was 100% (25/25). The ORR (neoadjuvant) was 96.0% (24/25). The MPR rate was 56.0% (14/25), and the pCR rate was 40.0% (10/25). Pathologic downstaging was achieved in 84.0% of patients. Grade 3-4 treatment-related AEs occurred in 24.0% (6/25) of pts, and grade 3-4 immune-related AEs occurred in 20.0% (5/25); the most common were rash and hypothyroidism. Overall postoperative complications were 20% (5/25). One pt experienced postoperative complications (pulmonary infection and anastomotic leakage). No treatment-related surgical delays or 30-day mortality occurred. **Conclusions:** The BT-NICE regimen demonstrates promising efficacy and is feasible with a manageable safety profile in pts with locally advanced, resectable ESCC. This study provides the first clinical evidence supporting the incorporation of a BTLA inhibitor into a perioperative treatment paradigm for ESCC. Clinical trial information: NCT06588335. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

The early-onset paradox of gastric cancer: Assessment of geographic clustering, biology, treatment, and outcomes.

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Background: Early-onset gastric cancer (EOGC), defined as diagnosis before age 45, represents an increasingly recognized and clinically distinct subset of gastric cancer (GC) in the United States. While prior studies largely from Asian cohorts suggest more aggressive tumor biology, contemporary U.S. data characterizing demographic patterns, treatment strategies, geographic variation, and outcomes in resectable disease is limited. **Methods:** Using a U.S. cancer registry (2006–2022), we studied patients aged 18–90 with stage II–III gastric cancer post-gastrectomy. Excluding palliative or incomplete cases, we analyzed overall survival (OS) via Cox models, adjusting for demographics and treatment. P-values were calculated using the Chi-square test to compare racial distribution across age groups. **Results:** Among eligible patients, 1,943 (7.4%) had EOGC. EOGC disproportionately affected Hispanic (23.8%; $p < 0.001$), Black (14.2%; $p < 0.001$), and Asian (10.2%; $p < 0.001$) populations, with White patients accounting for 49.4%, with a male predominance (2:1). Demographic and socioeconomic profiles were distinct within the EOGC population. A greater proportion of EOGC patients resided in areas with a median household income < $38,000 (17.1%; $p = 0.025$). The ≤45 group was more frequently uninsured (7.6%) or Medicaid insured (19.7%) and represented the highest proportion of residents from areas with the lowest educational attainment (21.6%). Geographic clusters emerged in the South/Middle Atlantic and Pacific (TX, CA, AK, HI). EOGC tumors more frequently exhibited diffuse or signet-ring histology (~30%) and advanced nodal involvement. Despite receiving more intensive multimodality therapy, including perioperative or neoadjuvant chemotherapy (74.1%), EOGC patients had lower pathologic response rates and no survival advantage. Median OS was 49.8 months (36-month OS: 58.3%). **Conclusions:** Even with aggressive treatment, EOGC shows worse pathology and no better survival rates than older-onset cases. New U.S. data confirms this aggressive biology and highlights significant demographic and socioeconomic disparities. To improve outcomes, the focus should shift from just intensifying treatment to prioritizing earlier detection and targeted regional screening. Research Sponsor: None.

Demographic characteristics stratified by age groups.

Variable	≤45 Years (n=1943)	46–69 Years (n=15927)	≥70 Years (n=8397)	Total Cohort (N=26267)	p-value
Race, n (%)					<0.001
White	960 (49.4)	10912 (68.5)	5918 (70.5)	17790 (67.7)	
Black	276 (14.2)	1890 (11.9)	838 (10.0)	3004 (11.4)	
Hispanic	462 (23.8)	1611 (10.1)	766 (9.1)	2839 (10.8)	
Asian	198 (10.2)	1166 (7.3)	731 (8.7)	2095 (8.0)	
Other	47 (2.4)	348 (2.2)	144 (1.7)	539 (2.1)	

Neoadjuvant cadonilimab plus CapeOX in patients with clinical stage III gastric or esophagogastric junction adenocarcinoma (GC/EGJC): A prospective, single-arm phase II study.

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Background: Perioperative PD-L1 inhibitor plus chemotherapy has shown survival benefit in PD-L1-positive patients with locally advanced GC/EGJC. However, evidence for neoadjuvant PD-1/CTLA-4 bispecific blockade remains limited. This study evaluates neoadjuvant cadonilimab plus CapeOX in patients with clinical stage III GC/EGJC. **Methods:** This prospective, single-arm phase II study (NCT06310473) enrolled patients (pts) with cT3-4aN1-3M0 disease (AJCC 8th), staged by contrast-enhanced CT and staging laparoscopy with peritoneal cytology to exclude peritoneal metastasis and positive peritoneal cytology (CY1). Pts received cadonilimab (10 mg/kg) plus standard-dose CapeOX every 3 weeks for 3 cycles. Pts without progressive disease on repeat CT and laparoscopy underwent curative-intent surgery, followed by 3-5 cycles of adjuvant CapeOX. The primary endpoint was the pathologic complete response rate (pCR, defined as no residual tumor in stomach and lymph node). The data cutoff was January 15, 2026. **Results:** From May 2024 to August 2025, 30 pts with GC/EGJC were enrolled (GC, n = 21; EGJC, n = 9); 83.3% (25/30) were cT4a and 73.3% (22/30) were cN2-3. PD-L1 CPS < 1 was observed in 14.8% (4/27) of evaluable pts. All pts completed 3 neoadjuvant cycles. Three pts did not undergo surgery: one refused resection and subsequent antitumor therapy after achieving a cCR to neoadjuvant therapy; one had a PR and continued systemic therapy; and one had PD with liver invasion on repeat laparoscopy and initiated second-line therapy. The other 27 pts underwent resection; one had CY1 on postoperative assessment and was considered PD, with an R0 resection rate of 96.3% (26/27). The pCR and major pathologic response (MPR) rates were 22.2% (6/27) and 37.0% (10/27), respectively. The tumor downstaging rate was 74.1% (20/27), including a ypN0 rate of 55.6% (15/27). Adjuvant therapy was administered in 23/27 (85.2%), with four pts still on therapy. Treatment-related adverse events occurred in 100% (30/30), including grade≥3 events in 20.0% (6/30). Notable events included one perioperative cardiovascular death (G5); one pulmonary embolism (G3) diagnosed 5 weeks postoperatively that resolved with anticoagulation; one patient with concomitant anastomotic leakage (G4), intra-abdominal infection (G4), and immune-related adrenal insufficiency (G2) who recovered after endoscopic covered-stent placement and conservative management; additional G3 events included ascites, neutropenia, and peripheral neuropathy (n = 1 each). No postoperative recurrence was observed among resected pts at data cutoff. **Conclusions:** Neoadjuvant cadonilimab plus CapeOX appears safe and effective in patients with clinical stage III GC/EGJC, achieving a moderate pCR rate and warranting further exploration of neoadjuvant immunochemotherapy combination strategies. Clinical trial information: NCT06310473. Research Sponsor: None.

Neoadjuvant adebrelimab combined with chemotherapy in locally advanced esophageal squamous cell carcinoma: A single-arm, phase II trial.

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Background: Neoadjuvant therapy is the standard treatment for patients with locally advanced resectable esophageal squamous cell carcinoma (ESCC). This study evaluated the efficacy and safety of adebrelimab (anti-PD-L1 antibody) combined with neoadjuvant chemotherapy and explored immune correlates associated with treatment response (ChiCTR2400085858). **Methods:** Patients with locally advanced ESCC (cT1b-T2N+M0 or cT3-4NanyM0) received three preoperative cycles of adebrelimab (1200 mg, IV, d1, Q3W) plus nab-paclitaxel (125 mg/m^2, IV, d1, d8, Q3W) and carboplatin (AUC 5 mg/mL/min, IV, d1, Q3W). The primary endpoint was pathological complete response (pCR). Secondary endpoints included major pathological response (MPR), R0 resection rate, disease-free survival (DFS), overall survival (OS) and safety. PD-L1 expression was measured by immunohistochemistry using the combined positive score (CPS). Multiplex immunohistochemistry was performed to assess spatial immune microenvironment changes. **Results:** Forty-three patients were enrolled from October 2023 to June 2025. The median age was 61 years (range, 42-75), and 39 patients (91.0%) were male. Patients with cStage II/III/IVA were 6/16/22. Among the 35 patients who underwent surgery, all achieved R0 resection (100%), with pCR and MPR rates of 22.9% (8/35) and 45.7% (16/35), respectively. The median follow-up was 13.2 months (range 2.4-21.9), with 1-year DFS and OS estimates of 94.2% (95%Cl: 86.7%-100.0%) and 86.8% (95%Cl: 76.5%-98.4%). Patients with PD-L1 CPS $\geq$ 10 (57%, 20/35) demonstrated a higher pCR rate compared with those with PD-L1 CPS $<$ 10 (43%, 15/35), specifically 30% (6/20) vs 13.3% (2/15). Multiplex immunohistochemistry revealed distinct spatial immune remodeling during neoadjuvant therapy. At baseline, PD-L1 expression was predominantly associated with CD11b$^+$ myeloid cells in peritumoral regions and was enriched in good responders (TRG 0-1), accompanied by higher peritumoral CD3$^+$ T-cell infiltration. Post-treatment analyses demonstrated divergent T-cell dynamics, with decreased peritumoral T-cell density in good responders (TRG 0-1) and increased infiltration in poor responders (TRG 2-3). Treatment-related adverse events were consistent with the known safety profile. The most common treatment-related grade 3/4 AEs were leukopenia (41.9%), alopecia (27.9%), thrombocytopenia (9.3%), anemia (7.0%), and hepatic dysfunction (2.3%). **Conclusions:** Neoadjuvant adebrelimab combined with chemotherapy demonstrated promising efficacy and manageable toxicity in patients with locally advanced ESCC. Myeloid-associated PD-L1 expression and treatment-induced T-cell redistribution may represent immune correlates of response and warrant further investigation. Clinical trial information: ChiCTR2400085858. Research Sponsor: None.

Neoadjuvant tislelizumab plus oxaliplatin and S-1 for locally advanced Siewert type II esophagogastric junction adenocarcinoma: A prospective multicenter phase II study.

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Background: Adenocarcinoma of the esophagogastric junction (AEG) is a malignant tumor with high morbidity and mortality globally. Among subtypes, Siewert type II AEG remains a clinical challenge owing to its unique anatomical location and distinct clinicopathological features. This study aimed to evaluate the efficacy and safety of Tislelizumab in combination with oxaliplatin and S-1 as neoadjuvant therapy for patients with locally advanced Siewert type II AEG. **Methods:** This is a prospective, multicenter clinical trial. Eligible patients were aged 19-75 years with pathologically confirmed Siewert type II adenocarcinoma of the esophagogastric junction, clinical stage T2-4N0-3M0, ECOG performance status 0-1, and adequate major organ function. All patients received 3 cycles of neoadjuvant therapy consisting of: tislelizumab (200 mg, D1, Q3W), oxaliplatin (130 mg/m^2, D1, Q3W), and S-1 (40-60mg based on BSA, po, bid, D1-14, Q3W). Following efficacy evaluation, patients underwent resection of the esophagogastric junction adenocarcinoma 4-8 weeks after completion of neoadjuvant therapy. The primary endpoint is pathologic complete response (pCR). Secondary endpoints include major pathologic response (MPR), objective response rate, R0 resection rate, overall survival (OS), disease-free survival (DFS), and safety. **Results:** As of June 2025, a total of 40 patients were enrolled in this study. The median age was 66 years (range, 37-76), 87.5% were male, and 92.5% had an ECOG performance status of 0. Among them, 87.5% (n = 35) of the patients completed 3 cycles of neoadjuvant therapy. The remaining 5 cases completed 1 (n = 1, due to grade≥3 TRAEs), 2 (n = 2, due to grade≥3 TRAEs and patient decision, respectively), and 4 (n = 2, patient decision) cycles of treatment. All patients underwent resection of the esophagogastric junction adenocarcinoma. The R0 resection rate was 97.5% (39/40), with no patients requiring re-operation or experiencing perioperative mortality. The pathologic complete response (pCR) rate was 25% (10/40). The primary tumor pCR rate reached 30% (12/40), and the major pathologic response (MPR) rate was 37.5% (15/40). Treatment-related adverse events (TRAEs) of any grade occurred in 95% (38/40) of patients, with grade ≥3 TRAEs observed in 15% (6/40). **Conclusions:** Neoadjuvant therapy with Tislelizumab in combination with oxaliplatin and S-1for locally advanced Siewert type II esophagogastric junction adenocarcinoma yields a favorable pathological complete response (pCR) rate and shows a good safety profile. Clinical trial information: ChiCTR2300075638. Research Sponsor: Excellent Talents Program of the Department of Finance of Hebei Province; ZF2025209.

SCALE-2: A phase 2 trial evaluating neoadjuvant short-course radiotherapy combined with chemotherapy and toripalimab in resectable locally advanced esophageal squamous cell carcinoma.

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Background: The SCALE-1 Phase Ib trial demonstrated that short-course neoadjuvant radiotherapy combined with toripalimab and chemotherapy, followed by esophagectomy, exhibited manageable toxicity and promising efficacy in patients (pts) with resectable locally advanced ESCC (RLaESCC). This Phase II trial aims to further valuate efficacy and safety of this novel short-course regimen in a larger cohort. **Methods:** RLaESCC pts with clinical stages cT3-4aN0M0/cT1-4aN+M0 received neoadjuvant paclitaxel (135 mg/m^2), carboplatin (AUC=5), and toripalimab (240 mg) every 3 weeks for two cycles. Short-course neoadjuvant radiotherapy (30 Gy/12f; 5 days per week) was administered between the two doses of neoadjuvant immune-chemotherapy. Compared to SCALE-1, high-risk nodal regions were selectively included in the irradiation volume. Weekly weight changes were used to assess preoperative waiting time. Esophagectomies were scheduled 8-10 weeks after completing neoadjuvant treatment. The primary endpoint was pathological complete response (pCR) rate, with secondary endpoints included disease free survival (DFS), overall survival (OS) and safety. **Results:** From April 28, 2024 to February 26, 2025, 63 pts were enrolled (intention-to-treat population, ITT), with stage distribution:I (3.2%), II (14.3%), III (63.5%) and IVA (19%). Following the exclusion of 3 pts who refused surgery, pathological assessment of the surgical specimens revealed that 56.7% (34/60) pts achieved pCR (ypT0N0 or ypTisN0) and 91.7% (55/60) achieved MPR. The median number of resected lymph nodes was 19 (range: 6–45). At a median follow-up of 23.9 months (cutoff date: Jan 19, 2026), median OS and DFS were not reached. In the ITT population, the 2-year OS and DFS rates were 90.4% (95% Cl: 82.4-98.4%) and 81.5% (95% Cl: 70.5-92.5%), respectively. Postoperative complications occurred in 45% (27) pts, with 18.3%(11) experiencing Grade ≥3 events. The most frequent Grade 3 and above complications were anastomotic leakage (n=4) (with or without pleural effusion or hemothorax) and airway mucus obstruction (n=4). Moreover, one case of postoperative delirium was observed (Grade IV), and one patient died of septic shock secondary to an anastomotic leak. All 63 pts completed neoadjuvant radiotherapy. However, 2 pts discontinued the second dose of toripalimab, and 16 pts required dose reductions during the second cycle of neoadjuvant chemotherapy. The most frequent grade 3/4 adverse events were neutropenia (n=27, 42.9%) and leukopenia (n=21, 33.3%). Notably, no grade 3 esophagitis or pneumonitis occurred. **Conclusions:** The SCALE regimen demonstrated potent antitumor activity, achieving 56.7% pCR and 91.7% MPR. Favorable 2-year OS and DFS further highlight its potential to improve long-term outcomes for RLaESCC pts. Clinical trial information: NCT05424432. Research Sponsor: None.

Noninvasive detection of early gastric cancer via red blood cell DNA features associated with tumor-induced hematopoietic stress.

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Background: Early detection of gastric cancer (GC) is limited by invasive endoscopy and the low sensitivity of current blood-based biomarkers for early-stage disease. Emerging evidence indicates that GC engages in complex crosstalk with the bone marrow microenvironment, imposing stress on hematopoiesis. Tumor-derived exosomal and inflammatory mediators reprogram transcriptional and epigenetic profiles in hematopoietic progenitors, driving abnormal hematopoiesis and inducing genomic instability. Here, we report a noninvasive strategy for GC detection based on genome-wide profiling of DNA remnants in mature red blood cells (rbcDNA) and validate its performance for early-stage disease across independent multicenter cohorts. **Methods:** We analyzed rbcDNA from 1–2 mL peripheral blood of 865 individuals, including 434 treatment-naive patients with stage I–III GC (~60% stage I) and 431 non-GC controls with benign gastric conditions. Shallow whole-genome sequencing revealed reproducible rbcDNA read-depth features that distinguished GC from non-cancer states. A machine-learning classifier was trained on dimensionally reduced rbcDNA features in a discovery cohort (n = 435), with a cutoff fixed at 90% specificity. The locked model was then evaluated in a test cohort (n = 109) and three independent validation cohorts from distinct medical centers (n = 321). **Results:** In a discovery cohort, we identified GC-associated rbcDNA features that were significantly enriched in hematopoietic regulation and cell-cycle pathways, reflecting systemic hematopoietic stress rather than tumor-derived copy-number alterations. The resulting classifier achieved AUCs of 93% in the discovery cohort and 95% in the test cohort. At the predefined cutoff, the classifier yielded 83% overall sensitivity and 79% sensitivity for stage I GC in the test cohort. Across three independent medical center cohorts, the model achieved sensitivities of 83%, 90%, and 86%, with specificities ranging from 89% to 94%, consistent with the discovery and test cohorts. The assay effectively distinguished early-stage GC from precancerous lesions, including atrophic gastritis and intestinal metaplasia, while showing limited detection in non-gastric solid tumors. Importantly, rbcDNA identified ~80% of GC cases that were negative for conventional serum tumor markers. **Conclusions:** These findings establish rbcDNA as an effective biomarker for accurate, noninvasive detection of early-stage GC. Research Sponsor: None.

Prognostic value of perioperative ctDNA monitoring in patients with esophageal squamous cell carcinoma (ESCC) undergoing neoadjuvant chemotherapy (NAC) and surgery.

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Background: Recent results from a multicenter phase II clinical trial (jRCTs031200094) demonstrated that neoadjuvant FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) improves survival outcomes of patients with resectable ESCC. In this analysis, we evaluated the value of circulating tumor DNA (ctDNA) dynamics after FLOT and curative-intent surgery to predict treatment response and long term outcomes. **Methods:** The jRCTs031200094 clinical study enrolled 37 patients with ESCC to receive neoadjuvant FLOT followed by curative-intent surgery. Plasma samples were collected NAC, post-NAC (prior to surgery), and within 2–12 weeks post surgery [molecular residual disease (MRD) window]. A clinically validated, personalized, tumor-informed mPCR-NGS assay (Signatera, Natera, Inc.) was used on the banked specimens for ctDNA detection. Survival analyses were performed to calculate progression-free survival (PFS) stratified by ctDNA status at the post-NAC and post surgery timepoints. **Results:** This retrospective analysis included the 34 patients with ESCC and available ctDNA results. Patients had a median age of 66 years (range: 44–80), and the majority were male (79% [27/34]). Tumor locations included the middle (53%, 18/34), lower (41%, 14/34), and upper esophagus (5.9%, 2/34). The clinical stage distribution was 8.8% (3/34) stage I, 21% (7/34) stage II, 56% (19/34) stage III, and 15% (5/34) stage IV. R0 resection was achieved in 94% (29/31) of resected patients; 3 patients did not undergo esophagectomy due to disease progression or patient preference. Baseline ctDNA positivity was observed in 97.1% (33/34) of patients. Among 33 patients with ctDNA data available at the post-NAC timepoint, ctDNA-positivity was associated with significantly inferior PFS (HR: 3.17, 95% CI: 1.22-8.21; P=0.018), higher rate of lymph node positivity and higher tumor regression grade (TRG). Of the 29 patients with ctDNA data in the MRD window 31.3% (9/29) were ctDNA-positive and ctDNA-positivity in the MRD window was associated with significantly inferior PFS (HR: 5.89; P=0.001) and overall survival (OS; HR: 7.23; P=0.019). In addition, ctDNA dynamics in response to NAC and surgery were highly predictive of long term outcomes. Sustained clearance after NAC correlated with 80% 24m PFS. Inferior survival was observed in patients who remained ctDNA positive after NAC but cleared after surgery (HR 3.17) and in patients without clearance after surgery (HR 7.63). **Conclusions:** This study demonstrates prognostic and predictive value of single timepoint and longitudinal ctDNA status in the neoadjuvant and postsurgical management of patients with ESCC. Persistent ctDNA positivity following NAC and in the MRD window was strongly associated with inferior PFS, and early ctDNA clearance conferred the most favorable outcomes. Clinical trial information: jRCTs031200094. Research Sponsor: None.

Individualized estimation of benefit from adjuvant docetaxel plus S-1 in stage III gastric cancer using deep learning–based counterfactual survival analysis of the START-2 trial.

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Background: The START-2 trial demonstrated that docetaxel plus S-1 (DS) was superior to S-1 alone in terms of relapse-free survival (RFS) and overall survival (OS) as adjuvant chemotherapy for patients (pts) with stage III gastric cancer (GC) (J Clin Oncol 2019; Gastric Cancer 2022). We conducted the START-2 AR study, a retrospective analysis, to develop a neural network–based model for predicting RFS and estimating individual-level treatment benefit. **Methods:** Among 912 pts enrolled in the START-2 trial, 599 provided written informed consent to participate in the START-2 AR study. Pts were randomly divided into training (70%) and test (30%) cohorts. Missing data were addressed using multiple imputation. A deep learning–based Cox proportional hazards model was trained in the training cohort and evaluated in the test cohort. Using this model, we estimated individual-level treatment benefit among pts in the DS group, quantified as the difference in restricted mean survival time (dRMST) between counterfactual survival curves comparing DS with S-1 alone. Subsequently, a LightGBM regressor was applied to identify clinicopathological factors associated with treatment benefit using SHapley Additive exPlanations (SHAP). In an exploratory analysis, the top-ranked variables were used to identify a subgroup with limited additional benefit from DS. **Results:** Among 599 pts (training cohort, n = 419; test cohort, n = 180), 249 RFS events were observed (174 and 75 events, respectively). The pooled Antolini C-index was 0.686 (95% confidence interval [CI], 0.643–0.726) in the training cohort and 0.628 (95% CI, 0.565–0.697) in the test cohort. The estimated dRMST in the DS group was 2.71 months (95% CI, 2.58–2.84). SHAP analysis of dRMST indicated that a lower number of metastatic lymph nodes, a higher platelet count, a higher number of dissected lymph nodes, and differentiated histology were the key factors associated with a smaller dRMST, indicating limited treatment benefit. When continuous variables were dichotomized at their median values and pts were stratified by the cumulative number of these four factors, the subgroup with < 3 factors (n = 454) showed significantly improved RFS with DS compared with S-1 alone (hazard ratio [HR], 0.67; 95% CI, 0.51–0.88; p = 0.004). In contrast, no significant benefit was observed in the subgroup with ≥ 3 factors (n = 145; HR, 1.32; 95% CI, 0.70–2.50; p = 0.396). **Conclusions:** Using a deep learning–based counterfactual dRMST framework, we identified a subgroup of pts with resected stage III GC who derived limited additional benefit from adjuvant DS therapy. Stratification based on four clinicopathological factors may facilitate personalized de-escalation of DS treatment. External validation in independent cohorts is warranted. Clinical trial information: UMIN000011438. Research Sponsor: Taiho Pharmaceutical Co., Ltd.

Long-term survival results of perioperative chemoimmunotherapy with DCF and avelumab in locally advanced gastro-esophageal adenocarcinoma.

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Background: We have shown that avelumab, an anti-PD-L1 antibody, added to perioperative modified DCF chemotherapy (aDCF regimen), improves the pathologic complete response rate from 7% to 14% in locally advanced gastro-esophageal adenocarcinoma (GEA), in comparison to historical controls from our own institution. Little is known about the long-term survival results obtained with perioperative chemoimmunotherapy, a new standard of care. We are here reporting the 5-year survival results of our cohort of patients treated with aDCF. **Methods:** Single-arm phase II study of aDCF given every 2 weeks for 4 cycles before and after surgery with planned sample size of 50 operated patients in order to test hypothesis that pCR rate would improve from 7 to 20%. Main inclusion criteria were: histologically proven GEA, locally advanced disease (cT3-4 and/or N+), adequate organ function, WHO performance status 0-1. Main exclusion criteria were: histology other than adenocarcinoma, metastatic disease (M1), use of immunosuppressants, serious autoimmune disease, daily intake of more than 10 mg of prednisone. Pathological response (Tumour Regression Grade -TRG) was determined by the College of American Pathologists criteria: 0 = complete;1 = near complete/microscopic residual disease; 2 = moderate; 3 = poor/no response. MPR was defined as TRG 0 or 1. Data presented as median (range), KM determined survival. Patients with less than 5 years follow-up and who were disease free / alive were censored. **Results:** One of the 51 patients enrolled into the trial withdrew consent, leaving 50 patients in the survival analysis. Clinical disease burden was high (cT3 44/50, 88%, N+ 31/50, 62%) with 49/50 (98%) completing neoadjuvant aDCF. All patients proceeded to surgery with MPR found in 9/50 (18%) patients. The median follow-up for the cohort was 71.5 months (range 43-105) with an estimated mean DFS and OS of 62.5 months and 68.5 months corresponding to a 5-year DFS and OS of 55.3% and 61.1%. For patients with MPR, 5-year DFS and OS were 100%. There were no new safety signals. **Conclusions:** Perioperative aDCF resulted in long-term survival in the majority of patients treated on our trial, bringing more evidence that chemoimmunotherapy improves outcomes of patients with locally advanced GEA. Those outcomes seem enhanced among patients with MPR. Clinical trial information: NCT03288350. Research Sponsor: EMD/Serono.

Integrating tumor-infiltrating iymphocytes (TILs) in the biomarker landscape of gastroesophageal adenocarcinoma: Going beyond PD-L1.

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Background: Immune checkpoint inhibitors (CPI) are standard of care in perioperative and metastatic gastro-esophageal adenocarcinoma (GEA). PD-L1 scoring remains heterogeneous, with multiple assays and substantial interobserver variability. In breast cancer, immunotherapy responses occur even in PD-L1–negative tumors when tumor-infiltrating lymphocytes (TILs) are present. Exploratory analyses from CM649 suggest that immune infiltration and T-cell signatures may better capture CPI benefit than PD-L1 alone, particularly with ipilimumab–nivolumab. We evaluated TILs and their relationship with established biomarkers in a large GEA cohort. **Methods:** We performed a single-center retrospective study including localized and metastatic GEA patients diagnosed between 2019–2023. Histopathology included MMR status, HER2 (IHC/SISH), PD-L1 CPS, and CLDN18.2 (≥75% tumor cells). TILs were blindly reviewed by an expert pathologist using international TILs-WG guidelines (in press). Baseline characteristics and follow-up were collected until August 2024. **Results:** A total of 230 patients were included (140 localized, 90 metastatic). MMR, PD-L1 CPS, CLDN18.2, and HER2 status were available for all. By Lauren classification, 83 tumors were diffuse (36%), 131 intestinal (57%), and 17 mixed (7%). TILs were dichotomized at $< 20\%$ and $< 10\%$. TIL density differed significantly across Lauren subtypes ($p = 0.0007$): diffuse tumors showed markedly lower infiltration (76% with TILs $< 20\%$) compared with intestinal tumors (60% with TILs ≥20%). Using the $< 10\%$ cutoff, diffuse tumors again showed lower immune infiltration (78% vs. 22%; $p < 0.001$). PD-L1 CPS categories ($< 1, 1–4, 5–9, \geq 10$) did not differ by subtype. Notably, in CPS $<$ 1 tumors, 28/48 (58%) were TIL-high (≥10%), whereas CPS ≥10 tumors showed strong concordance with TIL-high status (25/30, 83%). HER2-positive tumors had a higher proportion of TIL-high cases than HER2-negative tumors (OR 3.55; 95% CI 1.64–8.39; $p = 0.0004$). CLDN18.2 positivity showed no association with TILs ($p = 0.44$; OR 0.80; 95% CI 0.46–1.37). **Conclusions:** Using international TILs-WG guidelines, TIL assessment is feasible in routine GEA pathology. TIL density varied significantly across Lauren subtypes, with diffuse tumors showing consistently low immune infiltration. PD-L1 CPS did not reflect these differences and showed substantial discordance with TILs, particularly in PD-L1–negative but TIL-high tumors, suggesting potential CPI sensitivity. HER2 positivity, but not CLDN18.2, was associated with higher TIL levels. These findings support further evaluation of TILs alongside PD-L1 CPS/TAP score as improved predictive biomarkers for anti-PD-1 or anti-PD-1/CTLA-4 therapy. Research Sponsor: None.

4099 Poster Session

Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma: Long-term follow-up of the GERCOR NEONIPIGA phase II study.

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Background: Neoadjuvant nivolumab and ipilimumab in localized MSI/dMMR gastric cancer were evaluated in the NEONIPIGA study (NCT04006262). The primary endpoint was pathological complete response (pCR) and has been previously reported. Here, we report on the long-term follow-up analysis and the secondary objectives of event-free survival (EFS) and overall survival (OS). **Methods:** This phase II, single-arm study evaluated neoadjuvant nivolumab 240 mg q2w x 6 and ipilimumab 1 mg/kg q6w x 2, followed by surgery 5 weeks (±1 week) after the last injection of nivolumab and adjuvant nivolumab 480 mg q4w x 9 in patients with resectable MSI/dMMR, T2-T4 NxM0 oeso-gastric adenocarcinoma. EFS and OS were evaluated through Kaplan-Meier curves. **Results:** 32 patients were included: 16 (50%) with gastric location and 16 (50%) with gastro-esophageal junction; 28 (88%) were initially classified as usT3 and four (12%) as usT2; 23 (72%) were lymph node positive. Three patients did not undergo surgery (one metastatic progression, two refusals). 27 (84%) patients completed the planned 6 cycles of neoadjuvant therapy, and 14 (44%) received the full neoadjuvant and adjuvant treatment. Median follow-up was 48.3 months (44.8-52.0). In the ITT population, 4-year OS was 84.1% (65.8-93). In the population eligible for surgery, 4-year EFS was 83.5% (64.8-92.8). Only one patient (classified as ypT0N1 and TRG1b at surgery) relapsed with cerebral metastases 29 months after initiation of neoadjuvant treatment. Six deaths were reported, including two related to gastric cancer (one post-operative due to surgery complications, one from cerebral metastases). The four remaining deaths were unrelated to gastric cancer or treatment toxicity and were due to pulmonary infections (n = 2; 33 and 60 months after initiation of neoadjuvant treatment), perforation of a strangulated hernia (13 months), and metastatic tongue cancer (30 months). All three patients without surgery achieved a clinical complete response after immunotherapy (including one deceased patient reported above). Combined with the 17 (59%) patients in pCR previously reported, 20 of 32 (62.5%) patients achieved complete response. No new safety signals were reported during extended follow-up. **Conclusions:** Neoadjuvant nivolumab and ipilimumab before surgery and adjuvant nivolumab in localized MSI/dMMR oeso-gastric adenocarcinoma achieved a high curative rate. These findings strongly support further investigation of a watch-and-wait approach in case of clinical complete response after immune checkpoint inhibitors, which is currently being evaluated in the DEWI GERCOR phase II study (NCT06059495). Clinical trial information: NCT04006262. Research Sponsor: BMS.

Neoadjuvant cadonilimab plus chemotherapy for locally advanced gastric/gastroesophageal junction cancer: A single-arm, phase II trial.

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Background: Cadonilimab plus chemotherapy is a promising treatment option in the first-line setting of gastric cancer; however, its activity in the neoadjuvant setting remains unclear. The study evaluated the efficacy and safety of cadonilimab plus chemotherapy in neoadjuvant treatment for locally advanced gastric or gastroesophageal junction (G/GEJ) cancer. **Methods:** Eligible patients with locally advanced G/GEJ cancer (cT3-4a N+ M0) were enrolled and treated with 3 cycles of SOX chemotherapy (oxaliplatin 130mg/m^2, IV, d1; S-1 40-60 mg, PO, bid, d1-d14; q21d) plus cadonilimab (10mg/Kg IV, d1, q21d), followed by radical gastrectomy with D2 lymphadenectomy. The primary endpoint was pathological complete response (pCR) rate, and the secondary endpoints included R0 resection rate, major pathological response (MPR) rate, 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate and safety. Moreover, a single-cell spatial proteomic atlas was constructed to identify the mechanisms of immune resistance in patients with G/GEJ cancer who received neoadjuvant cadonilimab combined with SOX chemotherapy. **Results:** From September 2023 to July 2024, 45 patients were screened, and 37 patients were enrolled in this study. The median age was 58 years (range 27–72). 26 (70.3%) patients had cT4a disease, and 32 (86.5%) patients had a primary tumor in the stomach. All patients underwent preoperative evaluation. Two (5.4%) patients refused surgery, and 35 (94.6%) patients underwent gastrectomy with D2 lymphadenectomy. pCR (TRG1a) was observed in nine patients (ITT set: 24.3% (95% CI: 11.8% to 41.2%); surgery set: 25.7% (95% CI: 12.5% to 43.3%)). The MPR (TRG1a/b) rate was 70.3% (95% CI: 53.0% to 84.1%). As of the cutoff date of January 1, 2026, the median follow-up time was 24.1 months (range 14.3-28.4). One patient who refused surgery died, and three patients in the surgery set relapsed. 2-year DFS and OS rates were 90.2% and 97.3, respectively. Most of the TRAEs were grade 1-2. Nine (24.3%) patients experienced grade 3-4 TRAEs. The most common grade 3-4 TRAEs were thrombocytopenia (n = 4, 10.8%) and rash (n = 2, 5.4%). Single-cell spatial atlas demonstrates that recurrence following cadonilimab combined with SOX chemotherapy in gastric cancer is associated with distinct spatial immune ecosystems, which is characterized by immune deserts or suppressive fibrotic–myeloid networks that spatially and functionally incapacitate CD8 T cells. **Conclusions:** Based on the encouraging pCR rate, survival outcome and manageable safety in this study, cadonilimab plus SOX chemotherapy is a promising neoadjuvant treatment option for patients with locally advanced gastric cancer. Moreover, targeting stromal and myeloid components may be necessary to unlock the full therapeutic potential of immune checkpoint blockade. Clinical trial information: NCT05948449. Research Sponsor: None.

4101 Poster Session

Diagnostic and predictive utility of peritoneal tumor DNA in gastroesophageal cancer: A prospective multicenter study.

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Background: Gastric and gastroesophageal cancers (G/GEC) commonly spread to the peritoneum. Accurate peritoneal staging is critical for guiding intent and therapy, however staging PET, CT and peritoneal cytology have low sensitivity for peritoneal micro-metastases. Whilst circulating tumor DNA (ctDNA) poorly correlates with peritoneal disease, tumor DNA from the peritoneum (ptDNA) may identify early peritoneal metastases missed by conventional staging. We developed a tumor-informed whole-genome sequencing (WGS) platform to detect ptDNA and evaluated its accuracy in diagnosing peritoneal metastases and predicting survival in curative-intent G/GEC. **Methods:** This Australian multicenter prospective cohort study enrolled patients receiving curative-intent treatment for G/GEC (upfront surgery, perioperative FLOT or neoadjuvant CROSS/nivolumab). Tumor biopsies, blood, and peritoneal lavage fluid were collected at staging laparoscopy, and at surgery for those receiving neoadjuvant therapy. Tumor-informed WGS was used to identify ctDNA and ptDNA, which were correlated with disease free survival (DFS), peritoneal recurrence free survival (pRFS), non-peritoneal recurrence free survival (npRFS), and overall survival (OS) using multivariate Cox regression. The diagnostic utility of ptDNA for peritoneal metastases was evaluated by comparing true-negative patients ($>$ 2 years disease-free post-surgery alone) with an independently enrolled cohort of true-positive patients (macroscopic/cytology-positive peritoneal disease). **Results:** ptDNA was detected in 28 (30.4%) of 92 consecutive non-metastatic patients (59 with and 33 without neoadjuvant therapy). ptDNA-positivity significantly correlated with advanced cT and (y)pT stage. At a median follow-up of 17 months, there were 12 (13.0%) peritoneal and 10 (10.9%) non-peritoneal recurrences. ptDNA-positivity independently predicted poorer pRFS (HR 26.74, 95%CI 3.94-181.66), DFS (HR 4.51, 95%CI 1.77-11.47) and OS (HR 6.65, 95%CI 1.72-25.76), but not npRFS (HR 0.87, 95%CI 0.16-4.78). Importantly, 9 (60%) patients converted from ptDNA-positive to ptDNA-negative post-neoadjuvant treatment. Patients who remained ptDNA-positive had significantly worse pRFS (3/6 recurrences, HR 45.4, 95%CI 3.5-595.2) than those who were ptDNA-negative (0/25 recurrences). The diagnostic accuracy of ptDNA was validated in 10 true negative and 12 true positive patients. In this cohort, ptDNA achieved 100% sensitivity, specificity, positive and negative predictive values (95%CI 75.8-100%) for detecting peritoneal metastases. ctDNA data will be presented at the meeting. **Conclusions:** Tumor-informed WGS-based ptDNA accurately diagnoses peritoneal disease and predicts peritoneal recurrence post curative-intent treatment, informing its potential to personalize clinical management using intraperitoneal therapies. Research Sponsor: Victorian Cancer Agency; Australian Gastro-Intestinal Trials Group; Peter MacCallum Cancer Foundation; Cancer Council Victoria.

Perioperative cadonilimab (AK104) in locally advanced MSI-H/dMMR gastric or gastroesophageal junction adenocarcinoma and colorectal adenocarcinoma: A basket study.

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Background: Microsatellite instability-high (MSI-H) / deficient mismatch repair (dMMR) tumors generate abundant neoantigens and are sensitive to PD-1 blockade. However, evidence supporting the use of PD-1/CTLA-4 blockade in the neoadjuvant setting for MSI-H/dMMR gastric and colorectal cancers remains scarce. **Methods:** In this multicenter, single-arm, dual-cohort basket study (NCT04556253), we used a Simon's two-stage design to evaluate perioperative cadonilimab in patients with locally advanced MSI-H/dMMR gastric/gastroesophageal junction (GEJ) or colorectal adenocarcinoma. 29 patients were enrolled in cohort 1 (gastric/GEJ adenocarcinoma) and 18 patients were enrolled in cohort 2 (colorectal adenocarcinoma). The main inclusion criteria include newly diagnosed, histologically confirmed cT3–T4aNxM0 MSI-H/dMMR gastric/GEJ adenocarcinoma or colorectal adenocarcinoma, with an ECOG score of 0-1. Both cohorts received 3 cycles of neoadjuvant cadonilimab (10 mg/kg q3w) followed by radical resection, then 6 cycles of adjuvant cadonilimab (10 mg/kg q3w). The primary endpoint was pathologic complete response (pCR). Secondary endpoints included overall survival (OS), event-free survival (EFS), disease-free survival (DFS), major pathologic response (MPR) rate and incidence of adverse events (AEs). **Results:** As of the data cutoff date of January 24, 2026, the median follow-up was 14.6 months for cohort 1 and 12.6 months for cohort 2. In cohort 1, 2 patients were pathologically confirmed as pMMR prior to treatment. Among the 26 patients (mITT population), pCR rate was 69.2% (95% CI: 48.2%-85.7%), and MPR rate was 80.8% (95% CI: 60.6%-93.4%). The 12-month OS, EFS, and DFS rates were each 100% in mITT population. All 29 patients (ITT population) received neoadjuvant therapy. AEs during neoadjuvant treatment occurred in 24 patients (82.8%), with 3 patients (10.3%) experiencing grade 3-4 AEs. Common AEs (incidence ≥10%) included rash, anemia, constipation, and insomnia, which were primarily grade 1-2. Among the 18 patients (mITT population) in cohort 2, the postoperative pCR rate was 66.7% (95% CI: 41.0%-86.7%), and the MPR rate was 72.2% (95% CI: 46.5%-90.3%). The 12-month OS, EFS, and DFS rates were each 100% in mITT population. All 18 patients (ITT population) received neoadjuvant therapy. AEs during neoadjuvant treatment occurred in 17 patients (94.4%), with 2 patients (11.1%) experiencing grade 3-4 AEs. Common AEs (incidence ≥10%) included rash, infusion-related reaction, anemia, and cough, which were primarily grade 1. No grade 5 AEs were reported in this study. **Conclusions:** Perioperative cadonilimab demonstrates excellent antitumor activity and a manageable safety profile in patients with locally advanced MSI-H/dMMR gastric/GEJ adenocarcinoma and colorectal adenocarcinoma. Clinical trial information: NCT04556253. Research Sponsor: National Natural Science Foundation of China (82272655); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2025ZD0552019); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2025ZD0545201); Science Foundation of Peking University Cancer Hospital (BJCH2025BJ01); National Natural Science Foundation of China (92259302); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2024ZD0520600); National Natural Science Foundation of China (82373438); Beijing Municipal Public Welfare Development and Reform Pilot Project for Medical Research Institutes (PWD&RPP-MRI) (JYY2023-3).

Neoadjuvant immunochemotherapy plus thymalfasin in locally advanced gastric cancer: A prospective clinical trial.

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Background: Neoadjuvant immunochemotherapy has emerged as a promising strategy for locally advanced gastric and gastroesophageal junction (G/EGJ) adenocarcinoma, but a substantial proportion of patients derive limited benefit. Thymalfasin is an immunomodulatory peptide that may amplify antitumor immunity while attenuating toxicity. We conducted a phase II trial to evaluate anti-PD-1 plus SOX immunochemotherapy combined with thymalfasin as neoadjuvant treatment for G/EGJ adenocarcinoma. **Methods:** The prospective trial enrolled patients aged 18–75 with cStage III G/EGJ adenocarcinoma, ECOG 0–1, and adequate organ function. Treatment included three 21-day cycles of serplulimab (anti-PD-1) plus SOX (S-1 and oxaliplatin) and nine weeks of thymalfasin, followed by curative gastrectomy. The primary endpoint was pathological complete response (pCR). Secondary endpoints included major pathological response (MPR), safety, survival, and other efficacy measures. Peripheral immune remodeling was assessed by flow cytometry, and bulk RNA sequencing of peripheral blood mononuclear cells (PBMCs) interrogated thymalfasin-associated transcriptional programs. **Results:** Thirty patients were enrolled and all underwent curative-intent minimally invasive gastrectomy. pCR was achieved in 30.0% (9/30), and MPR in 56.7% (17/30). ypN0 status was observed in 63.3% (19/30), with N-stage downstaging in 80.0% (24/30). The objective response rate was 73.3% and the disease control rate was 100.0%. At a median follow-up of 14.0 months (range 10.0-17.2), only one retroperitoneal nodal relapse had occurred at 14.4 months after diagnosis; no deaths were documented. Any-grade adverse events (AEs) occurred in 93.3% of patients, grade ≥3 AEs in 26.7%, and immune-related AEs in 23.3%, with no grade ≥3 irAEs. Flow cytometry showed expansion of $CD8^+$ T cells with increased CD69 expression and a concurrent reduction in HLA-DR-positive T cells, suggesting dynamic remodeling from broad systemic activation toward a more focused effector or memory response. RNA-seq revealed thymalfasin-associated upregulation of genes involved in antigen processing and presentation, type I interferon signaling, innate immune sensing, and immune metabolic reprogramming, and identified immune co-expression modules linked to treatment and response. **Conclusions:** Neoadjuvant serplulimab, SOX, and thymalfasin produced encouraging pathological response, substantial nodal clearance, and an acceptable safety profile in stage III G/EGJ adenocarcinoma. Peripheral immune and transcriptomic profiling are consistent with a hypothesis in which thymalfasin may help preserve and coordinate systemic antitumor immunity without excessive toxicity. These findings warrant confirmation in larger randomized trials. Clinical trial information: NCT06461910. Research Sponsor: This work was supported by National Natural Science Foundation of China; 82102723, 82373335.

CheckMate-9DW 4-year follow-up: Overall survival by depth of response and outcomes in long-term survivors.

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Background: Nivolumab plus ipilimumab (NIVO + IPI) was globally approved as a first-line (1L) treatment for unresectable hepatocellular carcinoma (HCC) based on the phase 3 CheckMate 9DW trial (NCT04039607). We report 4-year follow-up results and overall survival (OS) by depth of response (DpR). **Methods:** Methods were reported previously (Yau T. *Lancet* 2025). Briefly, adults with previously untreated unresectable HCC were randomized 1:1 to receive NIVO + IPI (then NIVO for ≤ 2 years) or lenvatinib/sorafenib (LEN/SOR). OS analyses were done by best percentage change in tumor burden from baseline. We also present exploratory analyses on long-term survivors (survival ≥ 4 years after randomization). **Results:** A total of 668 patients (pts) were randomized to NIVO + IPI (n = 335) or LEN/SOR (n = 333); among 325 pts treated with LEN/SOR, 275 (85%) received LEN. At a median (range) follow-up of 52.5 (44.0–66.1) mo, NIVO + IPI continued to show OS benefit (95% CI) vs LEN/SOR (HR 0.78 [0.65–0.93]) with higher objective response rate (ORR; 95% CI) by blinded independent central review (BICR; 36% [31–42] vs 13% [10–17]) and more durable responses. Pts with deeper tumor reduction had numerically improved median OS on both NIVO + IPI and LEN/SOR; the trend was more pronounced with NIVO + IPI specifically in pts with tumor shrinkage ≥ 30% (Table). More pts treated with NIVO + IPI (n = 62) were long-term survivors vs pts treated with LEN/SOR (n = 33). In long-term survivors, ORR by BICR was higher with NIVO + IPI vs LEN/SOR (76% vs 24%), with higher rates of complete response (CR; 21% vs 6%; Table); median duration of response was not reached in either group. Among long-term survivors, median (range) treatment-free interval was 23.3 (0.1–56.6) mo with NIVO + IPI and 0.5 (0.1–54.0) mo with LEN/SOR; 26 of 62 (42%) and 2 of 33 (6%) patients, respectively, were off study treatment and remained free from subsequent treatment. Baseline characteristics and incidence of TRAEs in long-term survivors were consistent with all randomized pts. **Conclusions:** 1L NIVO + IPI continued to show sustained efficacy benefit vs LEN/SOR in unresectable HCC with no new safety concerns at the 4-year follow-up. These analyses suggest deeper responses with NIVO + IPI may be associated with improved survival outcomes. Long-term survivors treated with NIVO + IPI had higher ORR and CR rates vs LEN/SOR, and were more likely to remain free of subsequent treatment. These results reinforce NIVO + IPI as a 1L treatment for unresectable HCC. Clinical trial information: NCT04039607. Research Sponsor: Bristol Myers Squibb.

DpR,[a] %	NIVO + IPI (n = 290)[b]	LEN/SOR (n = 286)[b]
	Median OS (95% CI), mo	**Median OS (95% CI), mo**
−100 to ≤−60	NR (NE)	NR (28.3–NE)
−60 to ≤−30	31.1 (19.9–40.4)	20.9 (15.1–30.9)
−30 to 20	17.0 (14.8–22.0)	20.5 (17.1–22.9)
≥20	14.3 (6.0–17.5)	7.8 (4.8–19.3)
Best overall response in long-term survivors[a]	**NIVO + IPI (n = 62)**	**LEN/SOR (n = 33)**
ORR (95% CI), %	76 (63–86)	24 (11–42)
CR, %	21	6

[a]By BICR.
[b]Response evaluable pts. NE, not estimable; NR, not reached.

First-line rilvegostomig (R) + chemotherapy (CTx) in advanced biliary tract cancer (BTC): Updated analysis of GEMINI-Hepatobiliary substudy 2 cohort A.

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Background: Addition of PD-(L)1 inhibitors to CTx has transformed advanced BTC treatment but survival is limited for most patients (pts). R is a monovalent, Fc-reduced PD-1xTIGIT bispecific antibody that delivers coordinated and synchronous PD-1 and TIGIT blockade on immune effector cells. The primary analysis of substudy 2 Cohort A of GEMINI-Hepatobiliary (NCT05775159), a global phase 2 study evaluating R + CTx in pts with advanced BTC, demonstrated promising efficacy and a manageable safety profile. We report updated analyses after ≥18 months of follow-up for the last enrolled pt. **Methods:** Pts ≥18 years with previously untreated unresectable/metastatic BTC and ECOG PS 0/1 received intravenous R every 3 weeks (Q3W; ≤2 years) + gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 on days 1 and 8 Q3W (≤8 cycles). Coprimary endpoints were 6-month progression-free survival (PFS) and safety/tolerability. Secondary endpoints included median PFS, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and overall survival (OS). Response and progression were investigator-assessed per RECIST v1.1. **Results:** As of Oct 24, 2025, the median follow-up for OS was 16.2 months (IQR 10.4–21.5); 6 pts (20.0%) received ≥20 cycles of R. Median OS was 16.8 months (95% confidence interval [CI] 11.0–not calculable [NC]) overall; 18-month OS was 44.8% (95% CI 26.5–61.6). Median OS was > 13 months across all subgroups based on age (< 65/≥65 years), ECOG PS (0/1), geography, initially unresectable/recurrent disease at enrollment, and primary tumor location (gallbladder or bile duct). Two unconfirmed responses were identified after > 85 weeks follow-up: one complete and one partial response. The safety profile was consistent with the primary analysis. The most common treatment-related adverse events (AEs) were anemia (53.3%), neutrophil count decreased (50.0%), and platelet count decreased (43.3%). Detailed efficacy and safety data are in the Table. **Conclusions:** R + CTx demonstrated promising efficacy and a manageable safety profile. This study and phase 3 studies of R in BTC (ARTEMIDE-Biliary01, ARTEMIDE-Biliary02, DESTINY-BTC01) are ongoing. Clinical trial information: NCT05775159. Research Sponsor: AstraZeneca.

	N=30*
PFS	
Events, n (%)	25 (83.3)
6-month, % (95% CI)	73.0 (53.2–85.5)
12-month, % (95% CI)	25.6 (11.4–42.6)
Median (95% CI), months	8.2 (6.7–11.1)
Confirmed ORR, % (95% CI)	31.0 (15.3–50.8)
Best objective response, n (%)	
Partial response	9 (31.0)
Stable disease	18 (62.1)
Progressive disease	2 (6.9)
DCR, % (95% CI)	93.1 (77.2–99.2)
DoR, median (95% CI), months	6.9 (2.8–NC)
OS	
Events, n (%)	19 (63.3)
12-month, % (95% CI)	65.5 (45.4–79.7)
18-month, % (95% CI)	44.8 (26.5–61.6)
Median (95% CI), months	16.8 (11.0–NC)
Any / R-related AEs, n (%)	30 (100) / 22 (73.3)
Grade ≥3	27 (90.0) / 5 (16.7)
Serious	14 (46.7) / 3 (10.0)
Led to R discontinuation	2 (6.7) / 1 (3.3)†
Led to death	2 (6.7) / 0

*N=29 for responses.
†Hepatic function abnormal.

Safety and efficacy of puxitatug samrotecan (Puxi-Sam, AZD8205) in patients with biliary tract cancer (BTC): A first-in-human phase 1/2a study (BLUESTAR).

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Background: B7-H4 is a transmembrane glycoprotein that negatively regulates T-cell function and is highly expressed in many cancers, including BTC, making it an attractive target for an antibody–drug conjugate (ADC). Puxi-Sam (also known as AZD8205), a novel B7-H4–directed topoisomerase I inhibitor (TOP1i) ADC, demonstrated favorable toxicity and promising anti-tumor activity during the dose escalation phase of the first-in-human Phase 1/2a BLUESTAR (NCT05123482) trial. Here, we report the pooled analyses for patients with BTC in the dose-escalation and dose-expansion phase of BLUESTAR. **Methods:** Eligible patients were ≥18 years old with nonresectable, recurrent, or metastatic B7-H4-positive BTC, with measurable disease per RECIST v1.1, and an ECOG performance status of 0 or 1. B7-H4 positivity was defined as ≥25% tumor cell staining by central immunohistochemistry in archival tumor samples. Patients must have received prior adequate standard-of-care therapy; prior treatment with a TOP1i was not allowed for patients in the dose-expansion phase. Patients received Puxi-Sam 2.4 mg/kg IV Q3W until disease progression, unacceptable drug-related toxicity, or consent withdrawal. The primary objective was assessment of safety; secondary objectives included assessment of antitumor activity. **Results:** As of 30 October, 2025, 20 patients received 2.4 mg/kg Puxi-Sam. The median (min–max) age was 61.5 years (44–88) and patients had received a median (min–max) of 2 (1–4) prior lines of treatment. Sixteen (80.0%) patients had treatment-related adverse events (TRAE), most commonly nausea (55.0%), and anemia (50.0%). Eleven (55.0%) patients had Grade ≥3 TRAEs, most commonly anemia (50.0%) and neutropenia (30.0%). Dose interruptions, reductions, and discontinuations due to TRAEs were required in six, two, and one patient, respectively. Two patients achieved a partial response (PR), corresponding to a confirmed objective response rate (ORR) of 10.0%. Disease stabilization was observed in a meaningful proportion of patients; 10 patients (50%) had stable disease (SD), and 12-week disease control rate (DCR) was 25.0% (5/20). Median progression-free survival (PFS) was 2.2 months, with a median follow-up of 2.2 months, supporting early signals of disease control (Table). **Conclusions:** Puxi-Sam demonstrated a favorable safety profile and showed modest clinical activity with prolonged disease stabilization observed in a subset of heavily pretreated patients with nonresectable, recurrent, or metastatic BTC. Clinical trial information: NCT05123482. Research Sponsor: AstraZeneca.

Efficacy summary (interim response evaluable patients).

	Puxi-Sam 2.4 mg/kg N=20
ORR, % (95% CI)	10.0 (1.2–31.7)
PR, n (%)	2 (10.0)
SD, n (%)	10 (50.0)
PD, n (%)	7 (35.0)
NE, n (%)	1 (5.0)
DCR at 12 weeks, % (95% CI)	25.0 (8.7–49.1)
Median PFS, months (95% CI)*	2.2 (1.4–4.6)

*Full analysis set.
NE, not evaluable; PD, progressive disease.

Efficacy and safety of transarterial chemoembolization combined with donafenib for hepatocellular carcinoma with rupture and bleeding: A retrospective, cohort study.

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Background: The incidence of hepatocellular carcinoma (HCC) ranks 6th in the world, and rupture and bleeding of HCC is its fatal complication. Transarterial chemoembolization (TACE) is an effective measure for acute hemostasis, but the prognosis of TACE alone is limited. The ZGDH3 study showed that donafenib was the only targeted agent with better overall survival (OS) than sorafenib in monotherapy for HCC. This study aims to investigate the efficacy and safety of TACE combined with donafenib compared with TACE monotherapy in the treatment of HCC with rupture and bleeding. **Methods:** This study retrospectively analyzed patients with rupture and bleeding of HCC who received TACE combined with donafenib or TACE monotherapy in Qinghai University Affiliated Hospital from January 2022 to August 2024. Patient criteria for inclusion: (1) Definitive diagnosis of HCC with rupture and bleeding by imaging and laboratory examination; (2) Child-Pugh class A and B; (3) No previous systemic therapy. The efficacy and safety were evaluated by mRECIST and CTCAE 5.0. **Results:** A total of 62 patients were included in the study, of whom 35 in the TACE monotherapy group and 27 in the TACE plus donafinib group, and there was no significant difference in baseline characteristics between the two groups. Patients in TACE plus donafenib group demonstrated a significantly higher objective response rate (ORR) compared with TACE monotherapy group (55.6%vs 25.7%, P=0.008). The median progression-free survival (PFS) significantly better than TACE monotherapy group (13.6 months [95%CI: 4.354 - 22.846] vs 4.6 months [95% CI: 1.637 - 7.563]; HR=0.404, P=0.003). The median OS was longer in the TACE plus donafenib group compared to TACE monotherapy group (17.4 months [95%CI: 8.478 - 26.322] vs 7.6 months [95%CI: 1.301 - 13.899]; HR=0.479, P=0.012). Additionally, multivariate COX regression analysis showed that PVTT, Child-Pugh grade, tumor diameter and total bilirubin were independent prognostic factors for OS. The incidence of treatment-related adverse events (TRAEs) significantly higher in TACE plus donafenib group, the most common were skin-related adverse events (37% vs 0%), diarrhea (29.6% vs 0%) and alopecia (18.5% vs 0%), which can be controlled by symptomatic treatment. There were no grade ≥3 TRAEs. But there was no significant difference in the incidence of rebleeding, stomachache and fever. **Conclusions:** TACE combined with donafenib showed significant efficacy and controllable safety in HCC with rupture and bleeding. Research Sponsor: None.

Dual BRAF/MEK inhibition in *BRAF*^{V600E}–mutated biliary tract cancer with exploratory histology-dependent response: A systematic review and meta-analysis.

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Background: The BRAF V600E mutation defines an actionable subset of rare cancers. Metastatic BTC carries a poor prognosis, with median survival under one year on standard chemotherapy. Given the rarity of BRAF V600E-mutated BTC and the absence of RCTs, rigorous evidence synthesis is needed; existing data for dabrafenib plus trametinib come only from single arm basket trials such as ROAR and NCI-MATCH. The low prevalence of this mutation limits the feasibility of large randomized studies. This SRMA aimed to quantify the efficacy of dual BRAF/MEK inhibition in BTC and explore potential histology dependent differences in response. **Methods:** We performed a systematic review and meta-analysis (SRMA) pooling single arm Phase II basket trial cohorts (N = 53 BTC; N = 17 CNS). Seven case reports were summarized qualitatively and excluded from pooled analyses. The primary endpoint was pooled overall response rate (ORR). A random effects model was used. Subgroup and heterogeneity analyses were performed given the tissue-specific behavior of V600E-driven tumors. Histology was evaluated as an exploratory moderator and heterogeneity was quantified. **Results:** In the pooled cohort of 70 patients (53 BTC and 17 CNS), the overall ORR was 45.3% (95% CI: 24.5-66.9%). Heterogeneity for the BTC subgroup was moderate (I^2 = 62.6%), while overall pooled heterogeneity across all studies was low (I^2 = 14%). ORR in BTC was numerically higher than in Central nervous system (CNS) cohorts (34.9%) but subgroup differences did not reach statistical significance (P = 0.3386). The observed median OS of 13.5 months in the ROAR BTC cohort compares favourably with historical outcomes commonly reported in the 6-12 month range for advanced BTC. The consistency of pooled estimates, despite non-randomized designs, suggests a stable treatment signal while acknowledging that causality cannot be inferred from uncontrolled data. Median progression-free survival was 9.0 months in BTC and 5.5-8.0 months in CNS cohorts. Median OS in the ROAR BTC cohort was 13.5 months (95% CI: 10.4-17.6), exceeding historical expectations. The pooled rate of Grade ≥3 AEs was 59.2%, consistent with the known safety profile of dabrafenib plus trametinib; no treatment-related deaths were reported. Qualitative data from case reports confirmed regression of CNS metastases and feasibility in patients with severe hepatic dysfunction. **Conclusions:** Dual BRAF/MEK inhibition shows clinically meaningful activity in BRAF V600E-mutated BTC, with survival exceeding historical expectations. Exploratory analyses indicate histology-dependent differences, supporting tumor-specific therapeutic stratification. These findings align with growing tissue-agnostic evidence for MAPK inhibition and reinforce the value of routine molecular profiling, though conclusions are limited by small cohorts and single arm studies. Research Sponsor: None.

Real-world treatment patterns and clinical outcomes among cholangiocarcinoma patients treated with futibatinib or pemigatinib.

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Background: Pemigatinib and futibatinib are FGFR2 inhibitors approved by the US Food and Drug Administration in 2020 and 2022, respectively, for the treatment of advanced cholangiocarcinoma (CCA). This study describes demographic and clinical characteristics, and assesses clinical outcomes of real-world CCA patients treated with futibatinib or pemigatinib. **Methods:** This study used deidentified data from electronic medical records and claims from the ConcertAI RWD360 oncology dataset. Patients diagnosed with CCA and with evidence of initial treatment with futibatinib or pemigatinib in 2023 or later (index treatment) were included. Real-world outcomes (real-world overall survival [rwOS], time to discontinuation [rwTTD], and time to next treatment or death [rwTTNTD]) from the index date were described using Kaplan-Meier analysis. Cox regression models were used to adjust for patient characteristics. Adverse medical events of interest (MEI) were identified with ICD codes. **Results:** This study included 122 futibatinib (median age: 64 years; female: 58%; White: 66%) and 93 pemigatinib patients (median age: 66 years; female: 61%; White: 69%). The most common treatment regimen before index was cisplatin + durvalumab + gemcitabine (44% futibatinib and 35% pemigatinib patients). Futibatinib patients had numerically longer median rwOS (10.5 vs. 9.6 months) and median rwTTNTD (6.5 vs. 5.6 months) than pemigatinib patients, though the differences were not statistically significant; median rwTTD was similar in both futibatinib and pemigatinib patients (2.8 vs. 2.8 months); and adjusted hazard ratios were non-significant for all outcomes (Table 1). Futibatinib had numerically higher 6-month rwOS (63% vs. 55%) and 12-month rwOS (42% vs. 36%). Overall, 28% (n=60) of patients experienced MEI during index treatment: 29% (35/122 patients) in the futibatinib group and 27% (25/93) in the pemigatinib group. The most common MEI were (futibatinib vs. pemigatinib) fatigue (8% vs. 16%), diarrhea (10% vs. 5%), and dry eyes (6% vs. 1%). **Conclusions:** This study represents the largest real-world analysis to date of CCA patients treated with FGFR inhibitors. Overall, patient characteristics and MEI were similar in the two treatment groups. Clinical outcomes were also similar in both groups, suggesting that futibatinib is a promising alternative in this patient population. Research Sponsor: Taiho Oncology, Inc.

Outcome results.

	Futibatinib Patients (n=122)	Pemigatinib Patients (n=93)	P-Value
Median rwOS, months (95% CI)	10.5 (7.3, 14.4)	9.6 (5.2, 10.8)	0.39
Adjusted HR	0.95	Ref.	0.65
Median rwTTD, months (95% CI)	2.8 (1.2, 3.7)	2.8 (1.7, 4.0)	0.51
Adjusted HR	1.10	Ref.	0.47
Median rwTTNTD, months (95% CI)	6.5 (4.8, 8.1)	5.6 (4.1, 7.4)	0.66
Adjusted HR	1.00	Ref.	0.99

HR: hazard ratio. Variables adjusted for in Cox model: age, sex, setting of care, ECOG performance status, and time from diagnosis to index date.

Tislelizumab combined with donafenib and GEMOX as first-line treatment for advanced biliary tract cancer: A single-arm, phase II study.

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Background: Advanced biliary tract cancer (BTC) progresses rapidly and has a poor prognosis, with a 5-year survival rate of less than 5%. Gemcitabine and oxaliplatin (GEMOX) plus tislelizumab and donafenib as the first-line treatment for advanced BTC has confirmed good safety and preliminary efficacy in our phase I study (NCT04979663). This study aimed to further evaluate the efficacy and safety of GEMOX plus tislelizumab and donafenib. **Methods:** This is a single-arm, phase II trial (NCT05668884). Patients were enrolled if they were 18-75 years old, had stage III/IV cancer (AJCC 8th Edition), were Child-Pugh A/B, had an ECOG PS of 0-1, and had received no prior systemic therapy or tumor-related surgery. Patients were administrated with tislelizumab (200 mg IV on d1 Q3W), donafenib (200mg PO BID) and GEMOX (Q3W up to 8 cycles: gemcitabine 1000 mg/m^2 IV on d1 and 8, oxaliplatin 100 mg/m^2 IV on d1). Treatment continued until disease progression or unacceptable toxicity or withdrawal of consent whichever occurred first. The primary endpoint was the objective response rate (ORR) assessed by RECIST v1.1. **Results:** From December 2022 to October 2025, 47 patients were enrolled with a mean age of 60.8 (18 females and 29 males), 35 patients had intrahepatic cholangiocarcinoma, 11 patients had gallbladder carcinoma and 1 patient had perihilar cholangiocarcinoma. The ORR and the disease control rate (DCR) by RECIST 1.1 were 38.3% (18/47) and 93.6% (44/47), respectively. 2 patients underwent subsequent surgery after first-line treatment. The median PFS was 12.1 months (95%CI: 5.1-19.1), 1-year survival rate was 57% (95%CI: 38-76). All patients had treatment-related adverse events (TRAEs), the incidence of grade 3-4 TRAEs was 46.8%, the most common grade 3-4 TRAEs were rash (6/47,12.8%), thrombocytopenia (5/47,10.6 %) and fever (3/47, 6.4%). No grade 5 TRAEs were observed. **Conclusions:** GEMOX plus tislelizumab and donafenib as a first line treatment option for advanced BTC patients shows favorable efficacy and tolerability. Clinical trial information: NCT05668884. Research Sponsor: Zelgen.

Additional health-related quality of life (HRQoL) analysis from DESTINY-Gastric04 (DG-04), a randomized phase 3 study of trastuzumab deruxtecan (T-DXd) vs ramucirumab (RAM) + paclitaxel (PTX) in patients (pts) with human epidermal growth factor receptor 2–positive (HER2+) unresectable/metastatic gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA).

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Background: In DG-04 (NCT04704934), a statistically significant and clinically meaningful improvement in overall survival was seen with T-DXd vs RAM + PTX in pts with HER2+ unresectable/metastatic GC/GEJA in the second-line setting. Patient-reported HRQoL was also maintained with T-DXd. We report additional HRQoL results from DG-04. **Methods:** Pts with unresectable/metastatic GC/GEJA who were HER2+ (IHC 3+, IHC 2+/ISH+) by local or central testing received T-DXd 6.4 mg/kg or RAM + PTX. Patient-reported outcomes were assessed at prespecified time points using the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) scale and the EuroQol 5-dimension, 5-level (EQ-5D-5L) visual analog scale (VAS). Time to first deterioration (TTFD) and mean change from baseline (CFB) were assessed. Mixed model for repeated measures (MMRM) was used to analyze CFB of the FACT-Ga scale. **Results:** At data cutoff (October 24, 2024), median TTFD favored T-DXd (n = 246) vs RAM + PTX (n = 248) for the EQ-5D-5L VAS (3.5 vs 3.0 mo; hazard ratio [HR], 0.79; nominal P = 0.063), FACT-General (G) total score (3.5 vs 2.8 mo; HR, 0.74; nominal P = 0.015), and FACT-Ga emotional well-being (EWB; 5.1 vs 3.7 mo; HR, 0.74; nominal P = 0.026) and social well-being (SWB; 3.8 vs 2.5 mo; HR, 0.71; nominal P = 0.006) subscales. Additional TTFD results, including TTFD in gastric cancer subscale (GaCS) and physical well-being (PWB), are in the Table. Mean CFB scores remained stable in all FACT-Ga subscales, with no clinically meaningful changes associated with T-DXd. MMRM analysis of CFB results favored T-DXd vs RAM + PTX for the FACT-G total score (nominal P = 0.023), and the FACT-Ga functional well-being (FWB; nominal P = 0.045) and SWB (nominal P = 0.004) subscales. **Conclusions:** These findings support patient-reported HRQoL was maintained with T-DXd in pts with HER2+ unresectable/metastatic GC/GEJA. TTFD was not negatively impacted with T-DXd; mean CFB in all FACT-Ga subscales showed pt symptoms and functioning remained stable, with some subscales favoring T-DXd vs RAM + PTX. Clinical trial information: NCT04704934. Research Sponsor: Daiichi Sankyo, Inc.

	T-DXd n=246	RAM + PTX n=248	HR (95% CI) Nominal *P* Value
EQ-5D-5L VAS, median TTFD (95% CI), mo	3.5 (2.7-5.0)	3.0 (2.1-3.5)	0.79 (0.62-1.01) 0.063
FACT-Ga scale, median TTFD (95% CI), mo			
FACT-G (EWB + FWB + PWB + SWB)	3.5 (2.2-4.4)	2.8 (2.1-3.5)	0.74 (0.58-0.95) 0.015
FACT-Ga total score (FACT-G + GaCS)	4.4 (3.5-5.7)	4.4 (3.5-6.5)	0.95 (0.73-1.24) 0.700
EWB	5.1 (4.2-8.7)	3.7 (2.4-5.0)	0.74 (0.57-0.97) 0.026
FWB	2.3 (2.1-3.2)	2.3 (2.1-3.5)	0.89 (0.70-1.13) 0.338
PWB	2.8 (2.1-3.7)	2.2 (2.1-3.1)	0.79 (0.62-1.00) 0.052
SWB	3.8 (2.6-5.3)	2.5 (2.1-3.5)	0.71 (0.55-0.91) 0.006
GaCS	4.9 (3.7-6.3)	5.8 (4.8-7.4)	1.11 (0.84-1.47) 0.462

Bortezomib plus gemcitabine-cisplatin versus gemcitabine-cisplatin as first-line treatment for advanced biliary tract cancers: A randomized phase II clinical trial with exploratory analysis of PTEN status.

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Background: Biliary tract cancers (BTCs) are aggressive malignancies with limited treatment and poor prognosis, including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (perihilar and distal), gallbladder cancer and ampullary cancer. Our previous research indicated that bortezomib is a promising treatment option as proteasome inhibitor in PTEN-loss iCCA patients (Clin Transl Med. 2024 May;14(5): e1675). In this randomized phase II clinical trial, we expanded the indication to BTCs and explored clinical benefit and safety of bortezomib plus gemcitabine-cisplatin (GPB) compared with gemcitabine-cisplatin (G based) as first line treatment for advanced BTCs and further evaluated the potential predictive value of PTEN status. **Methods:** Between September 1, 2020, and December 31,2023, a total of 105 patients were screened. 59 patients were enrolled. The 59 patients were randomly assigned to either GPB group (n = 32) or G based group (n=27). PTEN status was not known at the time of randomization. PTEN immunohistochemical staining was subsequently performed in all patients identifying 18 patients (30.5%) with PTEN loss (PTEN=0) and 41 patients (69.5%) with PTEN expression (PTEN=1). The GPB regimen consisted of gemcitabine 1000 mg/m^2 day 1,8, cisplatin 75 mg/m^2 day 1, 8, plus bortezomib 1.3 mg/m^2 day 1, 4, 8, and 11 of a 21-day cycle. The G based group received gemcitabine based regimens including G-cisplatin (GP), G-Oxaliplatin (GMOX) or G-S-1 (GS). The primary endpoint was mediate progress-free survive (mPFS) according to RECIST v 1.1. Statistical analyses were performed using SPSS. The last follow-up date was July 25, 2025. **Results:** With a median follow-up of 31.8 months (95% CI, 21.3–42.3), the mPFS was 5.49 months in the GPB group and in 5.95 months in the G-based group, with no significant statistically significant difference (HR, 0.86; 95% CI, 0.50–1.47; P = 0.59). The median overall survival (OS) was 16.23 months with GPB and 15.01 months with G-based group (HR, 0.88;95% CI, 0.47–1.67; P = 0.70). Biomarker analyses showed that within the GPB group, patients with PTEN loss had significantly longer PFS than those with PTEN expression (9.26 vs. 3.35 months; HR, 0.64; 95% CI, 0.42–0.96; P = 0.03). Among PTEN=0 patients, GPB was associated with improved mPFS compared with G-based (9.26 vs. 3.59 months; HR, 0.25; 95% CI, 0.08–0.78; P = 0.01). Grade ≥3 CTCAE AEs were mainly hematologic, with thrombocytopenia most common (50.0% vs 14.8%). **Conclusions:** Although no significant survival benefit was observed in the overall GPB group, a clinically meaningful improvement in mPFS was identified in the PTEN-loss subgroup. PTEN status may serve as a promising biomarker for identifying patients more likely to benefit from GPB therapy, warranting further prospective validation. Clinical trial information: ChiCTR2000035916. Research Sponsor: the Clinical Research Plan of Shanghai Hospital Development Center (SHDC2020CR2011A).

Neoadjuvant radiotherapy combined with lenvatinib and sintilimab in patients with resectable hepatocellular carcinoma with portal vein tumor thrombus: An open-label, single-arm, multicenter, prospective phase I clinical trial.

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Background: Surgical resection remains the potentially curative treatment for resectable hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) in selected patients, but recurrence remains a major challenge. Neoadjuvant therapies have been proposed to reduce tumor burden and the risk of recurrence. This trial aimed to evaluate the safety and efficacy of neoadjuvant RT combined with lenvatinib and sintilimab followed by resection in resectable HCC patients with PVTT. **Methods:** This open-label, single-arm, multicenter, prospective phase I trial enrolled patients with resectable hepatocellular carcinoma classified as Barcelona Clinic Liver Cancer stage C without extrahepatic metastasis at 2 hospitals in China. Patients received RT (300cGy ×10 fractions) targeting intrahepatic lesions and PVTT, concurrent with two cycles of lenvatinib and sintilimab, followed by surgery 8 weeks post-RT and postoperative adjuvant therapy with lenvatinib and sintilimab for 1 year. Safety, pathological response, and feasibility were assessed. This trial is registered with ClinicalTrials.gov (NCT05225116). **Results:** From October 2022 to January 2026, 17 patients (VP2:5, VP3:11, VP4:1) were enrolled, 14 patients had completed neoadjuvant therapy, 12 patients had received surgeries (R0 rate: 100%, 10/10), while 1 patient had disease progression, 1 patient postponed surgery due to abnormal liver function. Preoperative imaging (mRECIST criteria) showed stable disease (SD), partial response (PR), and complete response (CR) rates of 16.7%, 75.0%, and 8.3.0% for primary lesions, and 0%, 58.3%, and 41.7% for PVTT. Postoperative pathological complete response (pCR) rates were 25.0% for primary lesions and 75.0% for PVTT. Concordance between imaging and pathology was 66.7% for primary lesions and 50.0% for PVTT. The median recurrence-free survival (mRFS) was 17 months and median overall survival (mOS) was 27 months. No Grade 3 or worse treatment-related adverse events occurred. **Conclusions:** Neoadjuvant radiotherapy combined with lenvatinib and sintilimab can bring a high tumor response rate in patients with resectable hepatocellular carcinoma with portal vein tumor thrombus with a favorable safety profiles. PVTT demonstrates higher response rate than primary HCC lesions. Discrepancies between imaging and pathological responses highlight the need for improved predictive biomarkers. These interim results support further investigation of this approach in larger cohorts. Clinical trial information: NCT05225116. Research Sponsor: None.

QL1706 (PD-1/CTLA-4 bispecific antibody) plus bevacizumab specific for patients with hepatocellular carcinoma combined with lung metastasis: A secondary analysis of a prospective, single-arm, phase Ib/II study.

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Background: Hepatocellular carcinoma (HCC) with lung metastasis carries a dismal prognosis, and effective systemic treatments remain limited. Bispecific antibodies targeting multiple immune checkpoints have emerged as promising therapeutic strategies. This study assessed the efficacy and safety of QL1706, a PD-1/CTLA-4 bispecific antibody, in combination with bevacizumab in patients with HCC and lung metastases. **Methods:** This was a secondary analysis of a multicenter, phase Ib/II clinical trial. Eligible patients with unresectable, advanced HCC and confirmed lung metastases received QL1706 (5.0 or 7.5 mg/kg, cohort A) or QL1604 (PD-1 antibody, 200 mg, cohort B) plus bevacizumab every three weeks until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** In cohort A, 15 patients were included in this analysis. At a median follow-up of 19.2 months, the ORR was 53.3% (95% CI, 26.6–78.7) and the DCR was 73.3% (95% CI, 44.9–92.2). Median PFS was 9.9 months (IQR, 1.6–NE), with a 1-year PFS rate of 46.7%, and the 2-year OS was 66.7%. Among the 7 patients with measurable lung target lesions, the ORR was 71.4% (95% CI, 29.0–96.3), including 2 complete responses. In cohort B, 5 patients were included, with a median follow-up of 23.7 months. The ORR was 20.0% (95% CI, 0.5–71.6) and the DCR was 60.0% (95% CI, 14.7–94.7). Treatment-related adverse events occurred in 93.3% of patients in cohort A and 100.0% in cohort B, with grade ≥3 TRAEs observed in 53.3% and 40.0% of patients, respectively. Most adverse events were manageable, and no treatment-related deaths were reported. **Conclusions:** QL1706 plus bevacizumab demonstrated promising antitumor activity and a manageable safety profile in patients with HCC and lung metastases. The high response rate observed in lung lesions highlights the potential of intensified immunotherapy combined with anti-VEGF therapy for this subgroup, warranting further validation in phase III trials. Clinical trial information: NCT05603039. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

Treatment-emergent adverse events of QL1706 / QL1604 and bevacizumab.

	All grades		Grade ≥ 3	
	Cohort A (N = 15)	Cohort B (N = 5)	Cohort A (N = 15)	Cohort B (N = 5)
TEAEs	15 (100.0)	5 (100.0)	10 (66.7)	4 (80.0)
irAEs	11 (73.3)	0	2 (13.3)	0
TRAEs	14 (93.3)	5 (100.0)	8 (53.3)	2 (40.0)
Associated with QL1706 / QL1604	14 (93.3)	5 (100.0)	6 (40.0)	2 (40.0)
Associated with bevacizumab	14 (93.3)	5 (100.0)	8 (53.3)	3 (60.0)

Hepatic arterial infusion chemotherapy plus either toripalimab or sorafenib as first-line therapy for non–high-risk, locally advanced hepatocellular carcinoma: A non-comparative, randomized phase 2 trial.

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Background: A combination of locoregional therapy such as hepatic arterial infusion chemotherapy (HAIC) with anti-angiogenic agents and immune checkpoint inhibitors (ICIs), has demonstrated significant antitumor activity in advanced hepatocellular carcinoma (HCC), while inevitably increasing the incidence of adverse events (AEs). Given the clinical rationale for exploring treatment de-escalation in non-high-risk, locally advanced HCC, this study was designed to provide prospective evidence for the combination of HAIC and toripalimab, which had suggested encouraging antitumor activity and safety previously. **Methods:** This single-center, non-comparative, randomized phase II study (NCT04135690) recruited locally advanced HCC participants without high-risk features (Vp4, and/or bile duct invasion and/or tumor occupancy of 50% of the liver). Participants were randomly assigned at a 1:1 ratio to receive FOLFOX-HAIC plus either toripalimab (240mg intravenously, TorHAIC) or sorafenib (400mg orally twice daily, SoraHAIC) per 3 weeks. The primary endpoint was the progression-free survival (PFS) rate at 6 months. **Results:** From February 4, 2020, to December 17, 2021, 72 participants were randomly assigned to receive TorHAIC (n = 36) or SoraHAIC (n = 36). The mean tumor diameter was 9.9 cm. Vp1-2 and Vp3 portal vein tumor thrombosis were present in 46 (63.9%) and 26 (36.1%) participants, respectively. The 6-month PFS rate was 63.9% in the TorHAIC group and 61.1% in the SoraHAIC group. After a median follow-up of 45.2 months, the median overall survival was 20.9 months in the TorHAIC group and 16.4 months in the SoraHAIC group, while the median PFS was 9.1 and 7.2 months, respectively. The objective response rate per RECIST v1.1 was 52.8% (n = 19) in the TorHAIC group, whereas 47.2% (n = 17) in the SorHAIC group. The median duration of response was 9.8 months in the TorHAIC group and 6.8 months in the SorHAIC group. There were 12 participants (33.3%) who developed grade 3-4 AEs in the TorHAIC group and 16 participants (44.4%) in the SoraHAIC group. Serious AEs were reported in two participants in the TorHAIC group (laryngeal edema due to oxaliplatin allergy and thrombocytopenia) and five participants in the SoraHAIC group (impaired myeloid function [n = 3], renal impairment, and upper gastrointestinal bleeding). **Conclusions:** Our study suggested that the TorHAIC regimen had a favorable safety and efficacy profile in patients with non-high-risk, locally advanced HCC. However, these findings warrant validation in a phase III trial. Clinical trial information: NCT04135690. Research Sponsor: None.

Association of asynchronous, time-flexible digital multidisciplinary care with overall survival in advanced biliary tract cancer treated with immune checkpoint inhibitors.

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Background: Delayed recognition and fragmented management of immune-related adverse events (irAEs) can trigger unnecessary interruption/discontinuation of immune checkpoint inhibitors (ICIs) and compromise real-world outcomes. We built an asynchronous, message-based multidisciplinary care system embedded in a widely used instant messaging platform to support longitudinal management for advanced biliary tract cancer (BTC) on ICIs, and assessed outcome changes from exploratory to protocolized implementation beyond secular trends. **Methods:** Single-center retrospective cohort of 546 adults with unresectable locally advanced/metastatic BTC receiving ≥1 ICI dose (Jan 2019–Jan 2024). All patients entered a clinician-moderated closed digital care group with structured triage and multidisciplinary coordination. By ICI start date: WGMS-E (before Jan 1, 2021) vs WGMS-P (on/after Jan 1, 2021). Primary endpoint: overall survival (OS). Secondary: progression-free survival (PFS), irAE recognition/management, and ICI rechallenge. Inverse probability of treatment weighting (IPTW) balanced baseline covariates. Interrupted time-series (ITS) analysis disentangled intervention effect from secular improvements in care. **Results:** Median follow-up 29.1 months; median OS overall 15.0 months. OS improved in WGMS-P vs WGMS-E (21.3 vs 12.4 months; log-rank $P < 0.0001$). IPTW-weighted Cox: WGMS-P associated with lower mortality (HR 0.55; 95% CI 0.43–0.69; $P < 0.001$) and higher 1-/2-year survival (~18%/~19% absolute). PFS also favored WGMS-P (HR 0.72; 95% CI 0.59–0.89; $P = 0.0019$). Overall irAE incidence was similar, but first irAE recognition occurred earlier in WGMS-P (restricted mean difference −1.68 months within 12 months). Permanent ICI discontinuation due to irAEs decreased (11% vs 22%), while rechallenge increased (10% vs 4%) without higher recurrent irAEs. ITS showed reversal of an increasing pre-intervention mortality trend to a decreasing post-intervention trend. **Conclusions:** A protocolized, asynchronous, message-based multidisciplinary care system integrated into routine oncology workflows was associated with improved survival among patients with advanced BTC treated with ICIs. By enabling earlier irAE recognition, reducing unnecessary permanent discontinuation, and facilitating safer rechallenge, this low-cost digital intervention may represent a scalable strategy to optimize real-world immunotherapy outcomes beyond secular advances in cancer care. These findings suggest that small, low-cost organizational changes in care delivery may translate into disproportionately large survival gains. Research Sponsor: Beijing Natural Science Foundation; L248022; National High Level Hospital Clinical Research Funding; 2025-PUMCH-C-015; National High Level Hospital Clinical Research Funding; 2022-PUMCH-B-128; National High Level Hospital Clinical Research Funding; 2025-PUMCH-D-001; Beijing Natural Science Foundation; L248072.

Impact of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) on outcomes in hepatocellular carcinoma treated with atezolizumab–bevacizumab.

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Background: Immune checkpoint inhibitor–based combinations (ICIs), including atezolizumab–bevacizumab (AB), have dramatically changed the therapeutic landscape of unresectable hepatocellular carcinoma (HCC), improving survival and response rates of patients, although outcomes remain heterogeneous. Concomitant medications may modulate immunotherapy efficacy through systemic and tumor microenvironment–mediated effects. Inhibition of the renin–angiotensin system (RAS) has been suggested to potentiate the effects of immunotherapy in various solid tumors by acting on angiogenesis, fibrosis, and immune modulation. However, the clinical impact of RAS inhibition in HCC patients receiving ICIs remains controversial, with retrospective studies suggesting possible improved outcomes. **Methods:** Patients with unresectable HCC treated from 2023 to 2025 with AB in Italy were included in this retrospective multicenter analysis from the ARTE database. Patients receiving concomitant ACEi/ARB at AB initiation were compared with non-exposed individuals. OS and PFS were estimated by Kaplan–Meier method and analyzed using Cox proportional hazards models. ORR and DCR were analyzed using logistic regression. To address baseline imbalances, a propensity score adjustment for potentially confounding characteristics (age, ECOG PS, viral etiology, alcoholic liver disease, cirrhosis, diabetes, obesity, cardiovascular events, decompensated cirrhosis, ALBI score, vascular/biliary invasion, previous locoregional treatments, metastatic disease and alpha-fetoprotein levels) was performed. **Results:** A total of 538 patients were included in our analysis, of whom 36% were receiving ACE-i/ARBs and 64% were not. ACEi/ARB use was associated with worse OS (HR 1.23; 95% CI: 0.97-1.57, p = 0.092), and a trend toward lower DCR (OR 0.63, 95% CI 0.39–1.02; p = 0.06). No significant associations were observed for PFS or ORR. After propensity score adjustment to balance baseline confounders, the magnitude of the OS difference was attenuated: median OS was 17.0 months in ACEi/ARB users versus 19.4 months in non-users (HR 1.14 (95% CI: 0.86-1.51; p = 0.358)), suggesting that the unadjusted signal was partly driven by baseline imbalance. **Conclusions:** In this large multicentric cohort of HCC patients treated with AB, concomitant ACEi/ARB therapy did not improve clinical outcomes and was possibly associated with a negative survival trend. Further studies will be needed to assess the potential effect of concomitant medications and RAS inhibitors on HCC, given their widespread use and the burden of comorbidities related to this specific tumor. Research Sponsor: None.

Envafolimab (KN035) plus gemcitabine and oxaliplatin (GEMOX) compared with GEMOX as first-line treatment for Chinese patients with advanced biliary tract cancer: A randomized, open-label, multi-center, phase III pivotal trial.

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Background: China bears a high biliary tract cancer (BTC) burden, with cholangiocarcinoma rising incidence (> 6/100,000 *vs* 0.3–6/100,000 globally) and high mortality (> 4/100,000). Over 60% of BTC patients are diagnosed at advanced stage (stage III/IV), and nearly two-thirds are unresectable. GEMOX regimen is a widely recognized standard of care in China, favored for its reduced renal toxicity and better tolerability compared with GemCis. Envafolimab is the world's first subcutaneously (SC) injectable anti-PD-L1 monoclonal antibody approved by China's NMPA. We report the final analysis of this pivotal trial, the first global phase III study initiated to evaluate immunotherapy plus chemotherapy in this setting. **Methods:** In this multicenter, open-label, phase III study in China, eligible patients (pts) with previously untreated, unresectable locally advanced/metastatic BTC were randomized 1:1 to envafolimab (2.5 mg/kg SC weekly) + GEMOX (gemcitabine 1000 mg/m^2 d1, 8; oxaliplatin 85 mg/m^2 d1, Q3W) or GEMOX chemotherapy alone. Chemotherapy was limited to 6 cycles in both arms. Stratification factors: primary site, disease stage, prior therapy, and ECOG PS. Primary endpoint: OS. Secondary endpoints: PFS, ORR (RECIST v1.1 by BICR), and safety. **Results:** 472 pts were randomized; 462 treated (envafolimab+GEMOX n = 232; GEMOX n = 230). At the final analysis, the primary endpoint was met well. Envafolimab+GEMOX significantly improved OS *vs* GEMOX (HR 0.723; 95% CI 0.585–0.880; *P*= 0.0016). Median OS was 10.9 months *vs* 8.6 months; 36-mo OS rates were 12.5% *vs* 7.7%. OS benefit was observed across subgroups, notably in intrahepatic cholangiocarcinoma (HR 0.705) and metastatic disease (HR 0.704). Median PFS (BICR) was 4.8 *vs* 4.6 months (HR 0.899; 95% CI 0.713–1.132); notably, the gallbladder cancer subgroup showed more favorable PFS benefit (HR 0.628). ORR was 27.6% *vs* 20.9%. Grade 3–4 TEAEs occurred in 69.4% (combination) *vs* 56.1% (chemo). irAEs occurred in 20.7%. **Conclusions:** This study demonstrates that adding subcutaneously administered envafolimab to GEMOX significantly improves OS with a manageable safety profile in advanced BTC. Compared with other regimens, the combination showed robust efficacy with a low rate of irAEs. Those findings establish envafolimab, the world's first SC PD-L1 inhibitor, combined with GEMOX as a new, effective, and convenient standard of care for this population. Clinical trial information: NCT03478488. Research Sponsor: 3D Medicines (Sichuan) Co., Ltd.

Impact of HSPA6 on lenvatinib resistance in HCC via phase separation–mediated TXNRD1 stabilization and ferroptosis suppression.

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Background: Lenvatinib is a first-line treatment for advanced hepatocellular carcinoma (HCC), but its efficacy is frequently limited by intrinsic and acquired resistance. The underlying molecular mechanisms remain incompletely understood, and strategies to overcome resistance are urgently needed. **Methods:** We integrated genome-wide CRISPR/Cas9 screening, transcriptomic profiling of lenvatinib-resistant HCC cells, and proteomic analysis of patient tumors to identify key mediators of resistance. **Results:** Heat shock protein family A (Hsp70) member 6 (HSPA6) emerged as a central driver of both intrinsic and acquired resistance, was consistently upregulated in resistant models, and was associated with poor response and reduced survival in lenvatinib-treated patients. Functional studies demonstrated that HSPA6 knockdown sensitized HCC cells and xenograft tumors to lenvatinib, whereas HSPA6 overexpression conferred resistance both *in vitro* and *in vivo*. Mechanistically, HSPA6 recruited the deubiquitinase ubiquitin-specific protease 9X (USP9X) to stabilize thioredoxin reductase 1 (TXNRD1), thereby suppressing lenvatinib-induced ferroptosis. Moreover, lenvatinib enhanced HSPA6 liquid–liquid phase separation (LLPS) through its intrinsically disordered region 1 (IDR1), facilitating the formation of HSPA6–USP9X–TXNRD1 condensates that reinforced TXNRD1 stability. Through structure-based virtual screening, we identified canagliflozin, an FDA-approved sodium–glucose cotransporter 2 (SGLT2) inhibitor, as a direct HSPA6 binder that disrupted this complex, restored ferroptosis sensitivity, and synergized with lenvatinib in preclinical models. **Conclusions:** Our study defines a novel HSPA6-driven resistance axis that integrates chaperone function, phase separation, and redox homeostasis to suppress ferroptosis in HCC. Targeting this axis with canagliflozin represents a promising therapeutic strategy to overcome lenvatinib resistance. Research Sponsor: None.

NALIRIFOX in combination with adebrelimab for advanced biliary tract cancer: A phase 2 NIOFA-01 clinical trial.

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Background: The NIOFA-01 trial was designed to evaluate the efficacy and safety of liposomal irinotecan combined with oxaliplatin, fluorouracil, and leucovorin (NALIRIFOX) plus adebrelimab as first-line treatment for patients with advanced biliary tract cancer (BTC) (ChiCTR2400089696). **Methods:** This single-arm, phase II study enrolled 27 patients with previously untreated, unresectable or metastatic BTC. Patients received NALIRIFOX (liposomal irinotecan 50 mg/m^2, oxaliplatin 60 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 2400 mg/m^2 administered as a continuous intravenous infusion over 46 hours), in combination with the PD-L1 inhibitor adebrelimab (1200 mg administered intravenously), every 2 weeks for up to 12 cycles. This was followed by adebrelimab maintenance therapy until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. Additionally, patients were evaluated for tumor gene alterations and PD-L1 expression, and underwent plasma proteomic and serum cytokine profiling. **Results:** Between September 13, 2024 and January 12, 2026, 27 patients were enrolled, with a median follow-up of 13.8 months (range, 2.8-16.2). Among these patients, the ORR was 55.6% (95%CI, 35.3%-74.5%) and the DCR was 81.5% (95%CI, 61.9%-93.7%). Median PFS was 8.0 months (95% CI, 5.8-9.7), while median OS was not reached (6 months OS rate: 92.6%, 12 months OS rate: 77.8%). Treatment-related adverse events (TRAEs) occurred in 100% of patients, with grade $\geq$3 TRAEs observed in 55.6%. The most common TRAEs were neutropenia, leukopenia, anemia, and diarrhea. Immune-related adverse events were reported in 74.1% of patients, including hepatotoxicity, hypothyroidism, and cardiac events. Exploratory analyses suggested the ORR was observed to be higher in patients with a CPS score $\geq$5 compared to those with a score $<$5 ($p = 0.043$). Combined analysis of plasma proteomics and metabolomics revealed that in patients who did not respond to treatment, ATP5PD, CTNND2, GALK1, 6nPropyluracil, and 1(Methylsulfinyl) propyl propyl disulfide were significantly elevated, while MMP2 was significantly decreased. A machine learning-based efficacy prediction model was constructed, and ROC curves were generated using the aforementioned four proteins and two metabolites, respectively, with AUC values of 0.961 and 0.883. Additionally, we observed that serum IL2 was significantly elevated in patients who responded to treatment, while IL8 showed a dynamic decreasing trend during the treatment process. **Conclusions:** NALIRIFOX in combination with adebrelimab demonstrated promising antitumor activity and an acceptable safety profile as first-line treatment for patients with advanced BTC, warranting further validation. Clinical trial information: ChiCTR2400089696. Research Sponsor: None.

Three-month versus six-month duration of postoperative adjuvant therapy after R0 resection following conversion therapy in hepatocellular carcinoma patients achieving MPR or pCR: A prospective randomized study.

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Background: Conversion therapy allows a subset of patients with initially unresectable hepatocellular carcinoma (uHCC) to achieve a deep pathological response, enabling curative resection. However, the optimal duration of postoperative adjuvant therapy remains unclear. This prospective randomized study compared recurrence-free survival (RFS) and overall survival (OS) between 3-month and 6-month durations of postoperative adjuvant therapy after R0 resection in patients achieving major pathological response (MPR; ≥90% tumor necrosis) or pathological complete response (pCR). **Methods:** This randomized controlled trial (ChiCTR2100051789) enrolled patients with uHCC who achieved a MPR or pCR following conversion therapy. Eligibility criteria included pathological confirmation of MPR or pCR after R0 resection. Eligible patients were randomized 1:1 to receive 3 months (Group 3M) or 6 months (Group 6M) of postoperative adjuvant therapy starting 1 month after surgery. The primary endpoint was RFS; secondary endpoints included OS and recurrence patterns. **Results:** Between January 15, 2022, and April 20, 2025, 58 patients were randomized (29 per group). Pathological evaluation confirmed MPR in 21 patients and pCR in 37 patients. After a median follow-up of 33.05 months, recurrence occurred in 8 patients. The 1-, 2-, and 3-year RFS rates were 89.3%, 89.3%, and 78.8% in Group 3M and 88.9%, 88.9%, and 88.9% in Group 6M (P = 0.592). Corresponding OS rates were 100%, 96.4%, and 96.4% versus 100%, 91.8%, and 91.8%, respectively (P = 0.451). **Conclusions:** In patients with uHCC who achieved a deep pathological response (MPR or pCR) after conversion therapy, a shorter duration of adjuvant therapy may be sufficient, with a 3-month course providing survival outcomes comparable to those of a 6-month course. Clinical trial information: ChiCTR2100051789. Research Sponsor: None.

Final results of a phase II study of fluorouracil (FU), leucovorin (LV), and nano-liposomal irinotecan (nal-IRI) in previously treated biliary tract cancer (NAPOLI-2).

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Background: BTCs are rare and aggressive malignancies. The first-line standard of care regimen for advanced BTC (aBTC) is gemcitabine (GEM), cisplatin, and an immune checkpoint inhibitor. Although FOLFOX is a preferred second-line treatment, it is limited by neuropathy. Nal-IRI contains IRI free base in liposome nanoparticles, which shelter IRI from conversion to its active metabolite (SN-38) and increase intratumoral SN-38 compared with IRI alone. The NAPOLI-1 trial of FU/LV/nal-IRI vs. FU/LV in second-line advanced pancreatic adenocarcinoma showed an overall survival (OS) benefit. The NIFTY trial (South Korea) demonstrated median OS (mOS) benefit of FU/LV/nal-IRI over FU/LV in a second-line aBTC population (8.6 vs. 5.3 months [mo], HR 0.68, 95% CI 0.48-0.95); however, the NALIRICC trial (Germany) did not (6.9 vs. 8.2 mo, HR 1.08, 95% CI 0.68-1.72). We sought to characterize second-line FU/LV/nal-IRI efficacy in US patients (pts) with second-line aBTC. **Methods:** This was a single-arm, open-label, multicenter phase II study of pts with aBTC previously treated with GEM/platinum chemotherapy. Pts received nal-IRI 70 mg/m^2 IV over 90 minutes, LV 400 mg/m^2 IV over 30 minutes every 14 days, and FU 2400 mg/m^2 IV over 46 hours every 14 days. The primary objective was to determine progression-free survival rate at 4 mo (PFS_{4mo}) using RECIST v. 1.1 criteria. Median PFS reported for pts receiving second-line 5-FU doublet chemotherapy was 3 mo with a PFS of 30%. FU/LV/nal-IRI was of interest if it could increase the PFS_{4mo} to 50% or higher. Using a one-sided α of 0.05 and 80% power, 17 of 39 evaluable pts had to be progression-free at 4 mo to detect a difference in PFS_{4mo} between 30% and 50%. **Results:** Forty-eight pts were enrolled: median age 64.5 years; 69% women; 27% gallbladder primary; 54% intra- and 19% extrahepatic. Ten pts came off study due to toxicity without disease progression before 4 mo on study and were replaced to evaluate the PFS_{4mo} endpoint. Of 38 evaluable pts, 18 pts (PFS_{4mo} 47%) were alive and progression-free at 4 mo, meeting the primary endpoint. With a median follow-up of 7.1 mo, median time to disease progression or study discontinuation due to toxicity for all pts was 2.3 mo (95% CI 1.8-4.6, PFS_{4mo} 38%), and for pts evaluable for the primary endpoint, median PFS was 3.5 mo (95% CI 1.8-5.5). Five pts (10%) had PFS beyond 12 mo. mOS for all pts was 7.9 mo (95% CI 5.7-11.7). Of 41 evaluable pts, the response rate was 2% (1 PR), and the disease control rate was 54%. Adverse events (AEs) were consistent with known toxicities from the FU/LV/nal-IRI regimen. **Conclusions:** FU/LV/nal-IRI is an effective second-line regimen for aBTC in US pts. There was significant early toxicity as 21% of pts came off study due to AEs before 4 mo. Correlative studies, including longitudinal analyses of circulating tumor DNA using banked blood specimens, are planned (NCT04005339). Clinical trial information: NCT04005339. Research Sponsor: Ipsen.

A phase II study of bTAE-HAIC combined with lenvatinib and camrelizumab for patients with high tumor burden hepatocellular carcinoma: The TALEM-H trial.

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Background: Patients with high tumor burden hepatocellular carcinoma (HCC) face a dismal prognosis. TALEM-H is a single-arm, prospective trial, aiming to evaluate the safety and preliminary effectiveness of transcatheter arterial embolization with blank microspheres (bTAE) plus hepatic artery infusion chemotherapy (HAIC) combined with lenvatinib and camrelizumab as first-line therapy for patients with high tumor burden HCC. **Methods:** Forty patients with huge HCC (defined as a single tumor >10 cm or multiple tumors >15 cm in diameter) received bTAE and FOLFOX-HAIC (Oxaliplatin 85mg/m2 2h + Calcium Levofolinate 400mg/m2 2h + Fluorouracil 2400mg/m2 46h) and lenvatinib (4-8mg) once daily plus camrelizumab (200mg) Q3W. The primary endpoint was objective response rate (ORR) according to mRECIST criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and treatment-related adverse events (TRAEs). **Results:** As of January 10, 2026, the median follow-up time was 10.7 months. The median maximum tumor diameter was 124mm (range: 77.5–262 mm) and the median sum of the diameters of the three largest tumors was 182 mm (range: 110–328.5 mm). The intrahepatic ORR was 95%, with 7 cases (17.9%) of intrahepatic complete response (CR) and 30 cases (76.9%) of intrahepatic partial response (PR). The 1-year and 2-year PFS rates were 48.7% and 37.6%, respectively (median PFS: 10.4 months; 95% CI: 8.6–15.1). Median OS has not yet been reached. Further, TRAEs of any grade occurred in 35 patients (87.5%) and no treatment-related deaths occurred. Grade 3 or higher TRAEs occurred in 12.5% of patients, commonly hypoalbuminemia (5%), immune-mediated pneumonitis (2.5%), and anemia (2.5%). **Conclusions:** bTAE-HAIC combined with lenvatinib plus camrelizumab represents a promising first-line treatment, offering an exceptional ORR and encouraging survival outcomes for HCC patients with a high tumor burden. Clinical trial information: NCT06061276. Research Sponsor: None.

Baseline characteristics.

Variable	All Patients (N = 40)
BCLC Stage C	32 (80%)
Extrahepatic Metastasis	18 (45%)
Tumor Number- Multiple (≥3)	28 (70%)
Largest Diameter (cm) >10 cm	35 (87.5%)
Sum of the diameters of the three largest tumors >20 cm	14 (35%)
Macrovascular Invasion	27 (67.5%)

Beyond fibroblast growth factor receptor 2 (FGFR2) fusions: Mutations and amplifications in intrahepatic cholangiocarcinoma.

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Background: *FGFR2* alterations occur in 10-20% of iCCA. While FGFR-directed therapies are established for *FGFR2* fusions, the genomic landscape and therapeutic relevance of non-fusion FGFR2 alterations remain poorly defined. **Methods:** Comprehensive genomic profiling was performed on 9,661 iCCA cases negative for *FGFR2* rearrangements/fusions to identify *FGFR2* short-variant sequence mutations and amplifications (Non-*FGFR2* SV/AMP). Biomarkers included tumor mutational burden (TMB), microsatellite instability (MSI), homologous recombination deficiency deficiency signature (HRDsig), and PD-L1 expression (TPS). Genomic features were compared with *FGFR2*-wild-type (*FGFR2*wt) iCCA. Clinical outcomes were assessed in a single-center cohort treated with FGFR inhibitors. **Results:** Non-*FGFR2* SV/AMP alterations were identified in 324 cases (3.4%), consisting of SV (92.8%), AMP (6.1%), or both (1.1%). Among short variants, 66.0% localized to the extracellular domain, 23.1% to the transmembrane domain, 7.69% to the kinase domain, and 3.21% to the cytoplasmic non-kinase domain. Compared with *FGFR2*wt tumors, Non-*FGFR2* SV/AMP iCCA occurred more frequently in females (57.7% vs 50.0%, p = 0.02) and showed similar age, genomic ancestry, trinucleotide signatures, MSI-high status (1.6% vs 1.8%), TMB > 10 mt/Mb (2.2% vs 3.6%), PD-L1 positivity (18.8% vs 21.4%), and HRDsig positivity (4.6% vs 5.0%). Co-occurring actionable alterations (*IDH1*, *ERBB2*, *BRAF*, *MTAP* loss) were less frequent in Non-FGFR2 SV/AMP tumors, while *BAP1*, *NF2* and *TSC1* alterations were enriched. Among 42 patients with non-fusion *FGFR2* alterations treated at a single center, 16 (38%) received FGFR-directed therapy including pemigatinib, futibatinib, tinengotinib, lirafrugatinib and derazantinib. The objective response rate was 25% (95% CI: 7.3-52.4). Best responses included partial response (25%), stable disease (50%), and progressive disease (25%), with a median duration of response of 5.4 (95% CI: 1.9-8.9) months. Median overall survival was significantly longer in patients receiving FGFR-targeted therapy compared with those who did not (28.4 months [95% CI, 23.8-33.0] vs 14.6 months [95% CI, 6.25-23.0]; p = 0.023). Recurrent *FGFR2* mutations involved N549K (kinase), C382R (transmembrane), and Y375C (extracellular) domains. **Conclusions:** Non-fusion *FGFR2* sequence mutations and amplifications define a distinct subset of iCCA with fewer alternative actionable drivers and sensitivity to FGFR-targeted therapy. These findings support consideration of FGFR inhibition beyond *FGFR2* fusions and highlight the need for refined patient selection strategies.
Research Sponsor: None.

4125 Poster Session

First-line tislelizumab plus chemoradiotherapy for patients with advanced biliary tract cancer: A prospective, biomolecular exploratory, phase II trial.

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Background: Advanced biliary tract cancer (BTC) characterized by a poor prognosis, and the combination of immunotherapy with conventional chemoradiotherapy offers a promising therapeutic approach. **Methods:** This phase II study evaluated the efficacy and safety of tislelizumab (an anti-PD-1 antibody) in combination with chemoradiotherapy as a first-line treatment for advanced BTC. The primary endpoints were objective response rate (ORR) and R0 resection rate, and the secondary endpoints included median progression-free survival (mPFS), median overall survival (mOS), and Disease Control Rate (DCR). Biomarker analyses assessed CA19-9 dynamics and immune cell subsets. **Results:** Among 28 patients, the ORR was 57% (16/28), with a conversion rate of 14% (4/28) and a 100% R0 resection rate (4/4). The median PFS was 14 months and the median OS was 19 months. The regimen exhibited a manageable safety profile, with grade 3 adverse events occurring in 21% (6/28) of patients (2 with drug-induced liver injury and 4 with myelosuppression). No grade 4 events were observed. Reduced CA19-9 levels were significantly correlated with improved OS ($p = 0.022$) and PFS ($p = 0.002$). Immunohistochemistry analysis revealed differential expression of CD4, CD103, and PD-1 between responders and non-responders. Notably, high expression of $CD103^+CD8^+$ tissue-resident memory T (TRM) cells and $CD103^+CD8^+PD\text{-}1^+$ TRM cells was associated with significantly improved OS. **Conclusions:** In conclusion, the combination of tislelizumab with chemoradiotherapy demonstrates promising efficacy and acceptable safety in advanced BTC, with $CD103^+CD8^+$ TRM cells identified as a potential predictive biomarker. Clinical trial information: ChiCTR2300070425. Research Sponsor: Project of The National Health Commission Health Development Research Center; No. WKZX2023CX020001; Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University; 2024-LCYJ-PY-59; the Affiliated Hospital of Nanjing University Medical School; XJSFZLX202321.

CXCL12^{+} pericytes as drivers of lymphatic dissemination in pancreatic cancer: Integrated single-cell and spatial analysis.

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Background: Pancreatic ductal adenocarcinoma (PDAC) exhibits poor prognosis largely due to early lymph node metastasis, yet the cellular and molecular mechanisms governing lymphatic dissemination remain incompletely understood. **Methods:** We integrated multi-omics approaches including single-cell RNA sequencing (scRNA-seq) of 19 PDAC samples, spatial transcriptomics of 6 specimens, bulk RNA sequencing of 174 cases, and multiplex immunofluorescence of 166 clinical samples stratified by lymph node metastasis status. Cell-cell communication analysis, trajectory inference, and functional validation were performed to elucidate pro-metastatic mechanisms. **Results:** Single-cell profiling of 145,283 cells revealed substantial cellular heterogeneity, with fibroblasts and pericytes serving as dominant signaling hubs within the tumor microenvironment. Lymph node metastasis-positive (pLNM) tumors exhibited enhanced stromal-epithelial crosstalk mediated by PTN and ANGPT pathways. We identified invasive epithelial subpopulations (Epi_MUC5AC_CD24 and Epi_NEAT1_MALAT1) significantly enriched in pLNM samples, characterized by activation of EMT and invasion-related programs. Critically, high-resolution subclustering uncovered a CXCL12-expressing pericyte subset (PCs_CXCL12) preferentially expanded in metastatic tumors. Multiplex immunofluorescence validation in 166 specimens demonstrated that CXCL12+ pericyte infiltration correlated with perineural invasion, lymph node metastasis, advanced TNM stage, and inferior survival outcomes. Multivariate analysis established CXCL12+ pericyte score as an independent prognostic factor for both disease-free and overall survival. Mechanistically, we identified MYC as the master transcriptional regulator driving CXCL12 secretion in pericytes. Functional studies revealed that MYC-driven pericyte-derived CXCL12 promoted PDAC cell proliferation, invasion, and EMT. Spatial transcriptomics demonstrated co-localization of MYC, CXCL12, and its receptor CXCR4 in perineural pericyte niches. Orthotopic xenograft models confirmed that pericyte-specific Myc depletion significantly reduced tumor growth, CXCL12+ pericyte density, and tumor-associated lymphangiogenesis. **Conclusions:** This study establishes the pericyte MYC-CXCL12 axis as a critical driver of PDAC lymphatic metastasis through promotion of tumor cell invasion, EMT, and lymphangiogenesis. CXCL12+ pericytes represent a novel prognostic biomarker and potential therapeutic target for preventing lymph node metastasis in PDAC patients. Research Sponsor: None.

Distribution and density of tertiary lymphoid structures as predictors of clinical outcomes and immunotherapy responses in gallbladder cancer.

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Background: Gallbladder cancer (GBC) is an aggressive malignancy with limited treatments and is often immunologically "cold." Tertiary lymphoid structures (TLS) are key regulators of antitumor immunity, but their spatial heterogeneity and clinical impact in GBC remain unknown. This study explores how TLS distribution and maturation influence outcomes and immunotherapy response in GBC. **Methods:** We analyzed 99 GBC patients who underwent curative resection (2015–2020). H&E and multiplex immunohistochemistry(mIHC) identified TLS number, maturation, and spatial distribution. TLS were categorized into intratumoral (T) and peritumoral (P) regions. Novel TLS scores (T score, P score) were developed to quantify TLS abundance and correlate with overall survival (OS). Pre-treatment samples from anti-PD-1-treated advanced GBC patients were assessed for TLS association with immunotherapy response. Patient-derived xenograft (PDX) models were used to compare tumor progression and anti-PD-1 efficacy between TLS-high and TLS-low groups. **Results:** T score correlated with improved OS ($p < 0.001$), while P score negatively correlated with OS ($p < 0.001$). Intratumoral TLS contained more Fol-I/Fol-II structures; peritumoral TLS were predominantly Agg ($p < 0.001$). Responders to immunotherapy had higher intratumoral TLS scores (median 2.5 vs. 0.5, $p < 0.01$), TLS numbers (8.0 vs. 3.0/ROI, $p < 0.05$), and TLS area (29.0% vs. 12.0%, $p < 0.05$). Intratumoral TLS showed higher $CD8^+$ T cells, $CD4^+$ T cells, and Tfh cells (all $p < 0.05$), whereas peritumoral TLS were enriched in Tregs ($p < 0.01$). Higher T scores linked with increased $CD8^+$ T cells, Tfh cells, $CD21^+CD23^+$ FDC, and $LAMP3^+$ DCs, but decreased Tregs and M2 macrophages (all $p < 0.05$). An immune classification based on T/P scores stratified patients into four prognostic subgroups with distinct OS ($p < 0.001$). In PDX models, TLS-high tumors progressed slower ($p < 0.05$) and responded better to anti-PD-1 therapy($p < 0.01$). **Conclusions:** TLS spatial distribution in GBC exerts opposing prognostic effects: intratumoral TLS promote antitumor immunity, while peritumoral TLS may support tolerance. TLS-high tumors show greater sensitivity to immunotherapy. A TLS-based immune classification may guide personalized treatment. Research Sponsor: National Natural Science Foundation of China; 82503726.

Real-world outcomes of microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) biliary tract cancers (BTC).

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Background: Immune checkpoint inhibitors have revolutionized the treatment of microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) cancers. MSI-H/dMMR represents a rare molecular subset (1%) within biliary tract cancers (BTC). The role of immunotherapy alone remains unknown. We investigated clinical features, treatment outcomes, and genomic characteristics of MSI-H/dMMR BTCs in two real world cohorts. **Methods:** Multicenter retrospective study of BTC patients with MSI-H/dMMR status by immunohistochemistry (IHC) and/or PCR. Patients were from two independent cohorts: MD Anderson Cancer Center (MDACC) and the RETUD registry of the Spanish Cooperative Group for Digestive Tumor Therapy (TTD) group. **Results:** 46 patients with MSI-H BTC were included in this study; with 21 from MDACC and 25 patients from TTD Cohort. Median age 46 years (95% CI38-80), (35 (76.1%) had intrahepatic cholangiocarcinoma 8 (17.4%) had extrahepatic cholangiocarcinoma and 3 (6.5%) had gallbladder cancer. Patient characteristics are summarized in Table 1. The median OS was 24.4 months (95% CI: 19.9, 40.6). The median follow-up time was 50.2 months (95% CI: 36.2, NA). Thirty-one (68.9%) patients received immunotherapy as part of their treatment course, and 14 (31.1%) did not. For first-line therapy (n=40), the median progression-free survival (PFS) for chemotherapy was 3.19 months (95% CI: 2.56-6.6) and for immunotherapy alone was not reached (95% CI: 8.25-NR, p=0.0006), while among those receiving second-line therapy (n=21), the median PFS for chemotherapy was 4.04 months (95% CI: 2.73-NR) and for immunotherapy alone was 9.69 months (95% CI: 4.43-NR, p=0.044). The median OS was 24.7 months (95% CI: 19.91, NA) in patients with IO, and 19.1 months (95% CI: 13.83, NA) without IO (log rank test p value = 0.085). **Conclusions:** MSI-H/dMMR BTC patients may derive limited benefit with frontline chemotherapy. Immune checkpoint inhibition may drive durable disease control, supporting early dMMR/MSI-H testing to optimize treatment. Research Sponsor: None.

Summary of patient characteristics.

Covariate		N (%)
Gender	F	18(39.1%)
	M	28(60.9%)
Race	Asian	2(4.3%)
	Black	1(2.2%)
	White/Caucasian	43(93.5%)
Grade		
	G2:Moderately differentiated	8(42.1%)
	G3:Poorly differentiated	11(57.9%)
Stage	>II	33(71.7%)
	I-II	13(28.3%)
Mismatch Repair Gene Loss		
	MLH1	5(12.2%)
	MLH1,MSH6	3(7.3%)
	MLH1,PMS2	20(48.8%)
	MLH1,PMS2,MSH6	1(2.4%)
	MSH2,MSH6	7(17.1%)
	MSH6	1(2.4%)
	PMS2	4(9.8%)
Resectable at Diagnosis	No	27(58.7%)
	Yes	19(41.3%)

4129 Poster Session

A phase I/II study of CDX-1140, a CD40 agonist, in combination with capecitabine and oxaliplatin (CAPOX) and pembrolizumab in subjects with biliary tract carcinoma: Phase 1 results.

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Background: Second line therapy shows limited efficacy in biliary tract carcinoma (BTC). We have demonstrated potent anti-tumor effects of anti-CD40/anti-PD1 plus chemotherapy in murine cholangiocarcinoma (Diggs et al. J Hepatol 2021 74:1145). CDX1140 is a human IgG2 activating anti-CD40 antibody. Based on these preclinical studies we conduct a phase I/II study testing the combination of CDX-1140 plus pembrolizumab (pem), capecitabine (cap) and oxaliplatin (ox) in BTC patients previously treated with at least one line of systemic therapy. Safety and tolerability were assessed in the phase I portion. **Methods:** Between Aug 2024 and Jun 2025 a total of 9 participants were enrolled into the Phase I portion of the trial. 1000 mg cap was given p.o. bid on days 1-14 plus 130 mg/m2 ox i.v. on day 1 of a 21-day treatment cycle. CDX1140 was dosed at 0.72 mg/kg dose level 1 (DL1) and 0.36 mg/kg (DL-1) i.v. on day 8 plus 200 mg pembrolizumab i.v on day 8. The DLT period was 35 days, starting on day 8 of cycle 1 after CDX-1140 administration. Enrolment into the phase II portion was started after the recommended dose of CDX-1140 had been determined. **Results:** We enrolled a total of 9 patients (pts) into the phase I portion. All patients had received at least one line of prior systemic chemotherapy including antiPD1/PD-L1. 2 out of the first 3 pts treated at DL1 developed a grade 3 thrombocytopenia and we reduced dosing to DL-1. 1 out of 6 pts treated at DL-1 developed a grade 3 thrombocytopenia and DL-1 was considered safe. Other treatment related grade 3/4 AEs were: lymphopenia, leukocytopenia, anemia, skin rash and hypotension. Most patients developed grade 1/2 arthralgia. At data cut-off (Dec/15/25) PFS for the nine patients was 7.3 months (range: 2.3 - 19.1 months). DCR was 56 % with 2 patients demonstrating a PR and 3 pts with SD. **Conclusions:** We have completed the phase I portion of our trial and demonstrate that CDX1140 plus pem, cap and ox is safe and tolerable in pts with BTC. No new and or unexpected toxicities were observed. We observed encouraging clinical responses. Patients will be enrolled to the phase II portion and updated results will be presented. Clinical trial information: NCT05849480. Research Sponsor: None.

Sequential bTAE-HAIC combined with lenvatinib and sintilimab for infiltrative hepatocellular carcinoma: A single-center perspective.

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Background: Infiltrative hepatocellular carcinoma (HCC) is defined as a tumor with ill-defined border, no evidence of convex margination, and no typical enhancement pattern by imaging. This subtype of HCC is usually associated with poor prognosis and is frequently diagnosed at advanced stage. Blank-microsphere transcatheter arterial embolization (bTAE) and hepatic arterial infusion chemotherapy (HAIC) of oxaliplatin, 5-fluorouracil and leucovorin are effective and safe for HCC. This prospective study is to evaluate the safety and efficacy of bTAE-HAIC combined with Lenvatinib and Sintilimab for intermediate-advanced infiltrative HCC. **Methods:** This prospective phase II trial is a single-center, single-arm study designed to assess the efficacy and safety of TAE and HAIC, combined with sequential Lenvatinib and Sintilimab on infiltrative HCC. Patients with primary infiltrative HCC treated at our center between October 2023 and December 2024. The primary endpoint was objective response rate (ORR) according to mRECIST criteria. Secondary endpoints included overall survival (OS), progression-free survival (PFS), and treatment-related adverse events (AEs). **Results:** A total of 30 patients who met the criteria were enrolled in this study and received at least 2 courses of TAE-HAIC combined with Lenvatinib and Sintilimab treatment. The median follow-up time was 7.1 months, and 10 patients died during the period. 5 patients (16.7%) achieved complete response (CR) after sequent ablation or radiotherapy, 20 patients (66.7) were evaluated as PR. The overall ORR was 83.3%. The median OS was 16.0 months (95%CI: 5.6-26.5 months). The 3-month, 6-month and 12-month rates of OS were 93.3%, 83.0% and 60.2%. The median PFS was 9.5 months (95%CI: 4.9-14.1 months), and the PFS rates at 3-month, 6-months and 12-month were 95.7%, 68.1% and 20.4%, respectively. The median liver-specific PFS was 11.7 months (95%CI: 7.7-15.7 months). The overall incidence of treatment related AEs was 76.7% according to the CTCAE 5.0 criteria. The incidence of Grade 1-2 AEs was 73.3%, and only one patient experienced Grade 3 AE. 10 patients (33.3%) received dose reduction, 9 patients (30.0%) discontinued drug therapy. **Conclusions:** The preliminary results of current study indicates that the combination regimen is safe and effective, and the AEs and complications are controllable and tolerable. This study provides a reference for further phase III clinical research, and a novel treatment option for the infiltrative HCC. Clinical trial information: NCT06070636. Research Sponsor: None.

Baseline characteristics.

Variable	All Patients (N = 30)
Male	26 (86.7%)
BCLC Stage C	28 (93.3%)
Extrahepatic Metastasis	13 (43.3%)
Tumor Number- Multiple (≥3)	16 (53.3%)
Largest Diameter (cm) >10 cm	24 (80.0%)
Largest Diameter (cm) >15 cm	8 (26.7%)
Macrovascular Invasion	25 (83.3%)
Portal Hypertension	12 (40.0%)

Hepatic arterial infusion chemotherapy plus lenvatinib and PD-1 inhibitors as first-line treatment for hepatocellular carcinoma with high tumor burden and portal vein tumor thrombus: A target trial emulation study (CHANCE 2416).

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Background: Patients with advanced hepatocellular carcinoma (HCC) characterized by high tumor burden (beyond up-to-seven criteria) and portal vein tumor thrombus (PVTT) have a median overall survival (OS) of lower than 4 months without intervention. Global guidelines rely on Phase III trials that often under-represented this high-risk subgroup, creating a therapeutic gap. While systemic combinations are standard, they may lack the rapid cytoreductive potency required to prevent liver failure in this subgroup. We emulated a target trial to evaluate if adding hepatic arterial infusion chemotherapy (HAIC) to lenvatinib and PD-1 inhibitors (H+L+P) improves outcomes compared to lenvatinib and PD-1 inhibitors (L+P) alone. **Methods:** Using multicenter data from 22 centers in the Chinese Liver Cancer Clinical Study Alliance (CHANCE) registry, we compared first-line H+L+P (n = 127) vs. L+P (n = 117) in patients with advanced HCC (BCLC stage C without extrahepatic spread) and PVTT (Vp1-4). To minimize selection and immortal time biases, we employed stabilized inverse probability of treatment weighting (sIPTW) and a cloning-censoring-weighting framework. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), site-specific PFS, objective response rate (ORR), and safety. **Results:** Baseline covariates were well-balanced after weighting (SMD < 0.1). After sIPTW adjustment, H+L+P demonstrated a significant survival benefit: median OS was 25.6 months (95% CI: 22.0–33.7) vs. 15.9 months (95% CI: 12.6–21.3) for L+P (adjusted HR, 0.60; 95% CI: 0.43–0.82; p = 0.0015). Crucially, a favorable survival trend was preserved even in the high-risk Vp3-4 subgroup (HR 0.77). Median PFS (RECIST v1.1) was 13.0 vs. 6.8 months (adjusted HR, 0.58; p = 0.0002). H+L+P significantly delayed progression in intrahepatic lesions (median 14.8 vs. 7.8 months; p = 0.0006) and PVTT (median 24.9 vs. 15.5 months; p = 0.0183). Intrahepatic ORR (mRECIST) was 87.4% for H+L+P vs. 28.9% for L+P ($p < 0.0001$), with a PVTT response rate of 81.6% vs. 22.1% ($p < 0.0001$). Grade ≥ 3 adverse events (AEs) occurred in 37.0% of the H+L+P group vs. 9.4% in the L+P group. Common Grade ≥ 3 AEs in the H+L+P arm included abdominal pain (20.5%) and leukopenia (5.5%); no treatment-related deaths occurred in the H+L+P group. **Conclusions:** In this target trial emulation, adding HAIC to lenvatinib and PD-1 inhibitors significantly improved OS and PFS in patients with high-risk HCC and PVTT. The survival advantage was driven by rapid and profound locoregional control, particularly of the tumor thrombus, with a manageable safety profile. Clinical trial information: NCT06631326. Research Sponsor: None.

4133 Poster Session

Tinengotinib (TT-00420) in advanced/metastatic FGFR2-altered cholangiocarcinoma following prior chemotherapy and FGFR inhibitor treatment: Results from a phase II study (FIRST-08).

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Background: Subsequent treatment options for advanced cholangiocarcinoma (CCA) after failure of chemotherapy and FGFR inhibitors (FGFRi) are limited. Tinengotinib (TT-00420), a novel FGFRi, potently inhibited FGFR2 fusion/rearrangement and acquired resistant/FGFR2 kinase domain mutations. The FIRST-08 study is an open-label, multicenter Phase II study in Chinese patients (pts) with advanced/metastatic CCA (NCT06057571). **Methods:** Eligible pts with advanced/metastatic CCA harboring FGFR2 fusion or arrangement, who had failed prior chemotherapy and one FGFRi, received tinengotinib 10 mg orally once daily in 21-day cycles. The primary endpoint was objective response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included progression free survival (PFS), disease control rate (DCR), duration of response (DoR), overall survival (OS), safety, PK and quality of life (QOL) per EORTC QLQ-C30. **Results:** As of June 27, 2025, 50 pts were enrolled (median age 56.5 years; 52.0% male; ECOG of 1: 44.0%). Median follow-up was 8.5 months. Forty percent had ≥ 3 prior systemic regimens, 66.0% had prior immunotherapy, and 42.0% had received other targeted therapies beyond FGFRi. The ORR by BICR was 28.0% (95%CI, 17.5~41.7) with 14 confirmed partial responses, and median DoR was 7.9 (5.6~ -) months. The disease control rate (DCR) was 82.0%. The median PFS was 5.7 (4.3~8.3) months. The median OS had not reached, with the 18 months survival rate 66.9% (47.3~80.6). Common Gr3/4 TRAEs (≥15%) included hypertension (42.0%), palmar-plantar erythrodysesthesia syndrome (16.0%), No Gr 5 TRAE was observed. 41 out of 50 pts had biomarker ctDNA samples collected at baseline, 82.9% pts had FGFR2 fusion and 48.8% had FGFR2 mutation (SNV). 28 pts had biomarker ctDNA samples collected at both baseline and C3D1. A significant decrease in maximum variant allele frequencies (MaxVAF) from baseline to C3D1 by a median relative VAF reduction of 83.7% ($p<0.0001$), indicating strong molecular response to tinengotinib. **Conclusions:** Tinengotinib demonstrated durable clinical anti-tumor activity and a manageable safety profile in heavily pretreated CCA pts with FGFR2 fusion/rearrangement following prior chemotherapy and FGFRi therapy. Clinical trial information: NCT06057571. Research Sponsor: TransThera Sciences (Nanjing), Inc.

Efficacy outcomes by BICR and investigator.

	BICR	Investigator
ORR, % (95%CI)	28.0 (17.5~41.7)	20.0 (11.2~33.0)
DCR, % (95%CI)	82.0 (69.2~90.2)	78.0 (64.8~87.3)
mPFS, months (95%CI)	5.7 (4.3~8.3)	6.9 (4.3~8.5)
mDoR, months (95%CI)	7.9 (5.6~ -)	6.6 (2.4~ -)

Correlation of immune remodeling linked to obesity with immunotherapy outcomes in cholangiocarcinoma: An externally validated international cohort study.

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Background: Obesity is an established risk factor for cancer, yet paradoxically may be associated with improved responses to immune checkpoint inhibitors (ICIs). We investigated whether obesity defines a clinically and biologically distinct cholangiocarcinoma (CCA) subtype when treated with ICIs. **Methods:** Retrospective analysis of Body Mass Index (BMI)-stratified patients (pts) with CCA treated at a single US center (US cohort) and enrolled in a prospective multicenter Italian registry (Italian cohort). High BMI was defined per CDC criteria (overweight 25.0-29.9; obesity ≥30 kg/m^2), with cohort-specific cutoffs for analysis (US ≥30; Italy ≥25). Tumor microenvironment (TME) was profiled with bulk RNA-seq and CODEX multiplex imaging and body composition radiomics with TotalSegmentator tool in the US cohort. Chi-square, Pearson correlation or Wilcoxon tests were used to test associations with BMI; overall survival (OS) was assessed with Kaplan-Meier and Cox models. **Results:** 989 pts were included (661 US; 328 Italy). In the US and Italian cohorts, median age was 62 and 65 years, 51% and 47% were female, and 28% and 43% were obese and overweight, respectively. Metabolic comorbidities included diabetes (US: 15%; Italy: 19%), hypertension (US: 48%; Italy: 45%), and hyperlipidemia (US: 32%; Italy: 15%). Higher subcutaneous-to-visceral fat ratio was associated with improved OS with chemotherapy-ICI (HR 0.89; 95% CI 0.79-0.99; p = 0.036). In both cohorts, patients with high BMI treated with chemotherapy-ICI had significantly longer OS compared with lower-BMI patients (US: 31.6 vs 19.2 months, p = 0.005; Italy: 21 vs 12 months, p = 0.025). In multivariable models (US cohort) both obesity (HR 0.35; 95% CI 0.23-0.52, p < 0.0001) and higher visceral-to-subcutaneous fat ratio (HR 1.79; 95% CI 1.04-3.07, p = 0.037) were independently associated with OS. Combined genomic profiling (n = 906) showed a lower prevalence of *KRAS* alterations in high-BMI pts (OR 0.56, p = 0.006). RNA-seq (n = 86; obese = 37, non-obese = 49) demonstrated enrichment of fibroblast-associated signatures (α*SMA, PDPN, collagen IV, vimentin*), upregulation of immune checkpoints (*PD-1, PD-L1, TIGIT, LAG-3, VISTA*), and higher *GATA3* and *IFN-*γ expression in obese pts (both p < 0.05). Multiplex CODEX analysis (n = 38; obese = 17, non-obese = 21) revealed an increased co-expression between *GATA3*, a regulator of T-cell dysfunction, and *granzyme B*, a cytotoxic T-cell marker (Pearson ρ = 0.24, p < 0.05), indicating increased abundance of *GATA3*$^+$*granzyme B*$^+$ cells in obese pts. **Conclusions:** In CCA, obesity characterized by predominant subcutaneous adiposity is linked to improved outcomes with ICIs and to a biologically distinct TME enriched in dysfunctional cytotoxic T-cells that may be reinvigorated by checkpoint inhibition. BMI may represent a pragmatic biomarker warranting prospective validation. Research Sponsor: None.

Association of genomic and clinical factors with outcomes with front-line chemoimmunotherapy in patients with advanced biliary tract cancer.

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Background: Anti-PD1/L1 therapy plus gemcitabine/cisplatin is standard first-line therapy in advanced biliary tract cancer (BTC), yet outcomes remain heterogeneous and prognostic biomarkers are poorly defined. We aimed to identify genomic and clinical factors associated with outcomes in advanced BTC patients (pts) treated with first-line gemcitabine, cisplatin and durvalumab (GCD). **Methods:** All pts with advanced BTC treated with first-line GCD at Memorial Sloan Kettering who underwent pre-treatment tumor genomic profiling (NCT01775072) were included. The primary objective was to study the association between genomic and clinical features and investigator-assessed progression free survival (PFS); evaluation of overall survival (OS) was a secondary objective. Cox regression analyses evaluated associations with PFS/OS. A multivariable Cox PFS model used variables selected by LASSO-based stability selection and was stratified by tumor subtype. **Results:** 236 pts were eligible for analysis. Tumor subtypes included intrahepatic cholangiocarcinoma (CCA) (56%), gallbladder cancer (23%), extrahepatic CCA (16%), and BTCs not otherwise specified (5%). Common genomic alterations were *TP53* (36%), *ARID1A* (24%), *CDKN2A* (23%), *KRAS* (17%), *IDH1* (13%), *SMAD4* (12%), *MTAP* (11%) and *ERBB2* (7.6%). With a median follow up of 23 months (mo), median PFS for the cohort was 9.1 mo (95% CI 7.7–11.0). OS at 12 and 24 mo was 68% (95% CI: 62–74) and 45% (95% CI, 38–53), respectively. On univariable analysis, *KRAS* and *FGFR2* alterations were associated with shorter PFS (Table). *KRAS* alterations were also associated with an increased risk for all-cause mortality on univariable analysis (HR 1.81, 95% CI: 1.17–2.81, p=0.008). Median PFS and OS for the *KRAS*-altered group were 5.6 (95% CI: 3.6-7.8) and 11 (95% CI: 7.8-42) mo respectively, compared to 11 (95% CI: 8.1-12) and 21 (95% CI: 19-28) mo for *KRAS*-WT patients. On multivariable analysis, *KRAS* alterations and liver metastases were independently associated with shorter PFS; higher baseline albumin was protective (Table). **Conclusions:** Among pts with advanced BTC treated with front-line GCD, *KRAS* alterations were independently associated with poor PFS. These findings highlight the heterogeneity of benefit from GCD and support development of biomarker-informed strategies to refine patient selection and incorporation of KRAS-targeted strategies to improve outcomes in patients with *KRAS*-mutant BTCs. Research Sponsor: None.

Factors associated with PFS with GCD.

	Analysis (95% CI), p	
Factor	**Univariable HR**	**Multivariable HR**
Alteration		
KRAS	2.17 (1.48–3.19), <0.001	2.06 (1.36–3.12), <0.001
FGFR2	1.85 (1.02–3.34), 0.042	-
Baseline CA19-9	1.14 (1.05–1.23), 0.002	-
Metastases		
Liver	1.78 (1.25–2.54), 0.001	2.06 (1.41–3.01), <0.001
Bone	1.9 (1.05–3.43), 0.034	-
Baseline albumin (per 1-unit increase)	0.43 (0.29–0.64), <0.001	0.44 (0.30–0.66), <0.001

Updated results of surufatinib combined with gemcitabine and cisplatin and immune checkpoint inhibitor (ICI) for unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma.

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Background: Advanced metastatic intrahepatic cholangiocarcinoma (ICC) was characterized by poor survival and limited therapeutic options. Surufatinib, a selective tyrosine kinase inhibitor targeting VEGFR 1, 2, and 3, FGFR1, and CSF-1R, provides dual anti-tumor action via anti-angiogenesis and tumor microenvironment regulation. Surufatinib combined with immunotherapy and chemotherapy may enhances anti-cancer effects for advanced metastatic ICC. This study evaluates the effectiveness and safety of surufatinib combined with gemcitabine, cisplatin, and immune checkpoint inhibitor (ICI) as the first-line treatment for patients with unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma. **Methods:** This is an open-label, single-arm, single-center trial. Eligible patients who were 18 -75 years old with histologically confirmed unresectable locally advanced or metastatic ICC were enrolled. Pts received surufatinib (250mg, orally, once daily), ICI (Zimberelimab or Toripalimab, 240mg, intravenous infusion, d1, q3w), and chemotherapy (gemcitabine 1000mg/m^2 intravenous infusion, 30min, d1, d8, q3w; cisplatin 25mg/m^2 intravenous infusion, 2h, d1, d8, q3w) until disease progression, death, surgery, intolerable toxicity, or withdrawal of consent. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), overall survival (OS), conversion to surgical resection rate, pathological complete response rate (pCR), and safety. **Results:** By January 20, 2026, 20 pts were enrolled with median age 60 years (range: 43-70), male 50%, 100% ECOG PS 0-1, 95% stage IV. 20 pts were efficacy evaluable, 5% (1/20) pts achieved complete response (CR), 50% (10/20) pts achieved partial response (PR), 35% (7/20) pts achieved stable disease (SD). The confirmed ORR was 55%, DCR was 90%. The median PFS was 7.7m (95%Cl: 6.3-11.3 months), and the median OS was 17.8m (95%Cl: 16.1-21.8 months). The most common TEAEs of all grades were hypertension (40%), edema (15%) and vomiting (10%), 1 patient was Immune-related pneumonia occurred. No grade $\geq$ 3 TEAEs or new safety signals occurred. **Conclusions:** Surufatinib plus gemcitabine and cisplatin combined with immune checkpoint inhibitor, the chemotherapy regimen as the standard treatment in combination with targeted and immunotherapy showed preliminary anti-tumor activity and manageable toxicity for the 1L treatment of ICC, providing an additional treatment option for pts with ICC. This study has been completed and the paper has been prepared for submission, the final results details will be published after the conference. Clinical trial information: ChiCTR2400085526. Research Sponsor: None.

Tracking genomic evolution in *ERBB2*-altered biliary tract cancer through longitudinal tumor profiling.

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Background: HER2, encoded by *ERBB2* (HER2), is overexpressed and clinically actionable in a subset of patients with biliary tract cancers (BTC). Zanidatamab and trastuzumab deruxtecan are now approved for patients with HER2 overexpressed tumors, though all patients ultimately progress on treatment and acquired resistance mechanisms are poorly defined. We aimed to characterize the genomic evolution in patients with *ERBB2* altered advanced BTC via serial tumor and cfDNA sampling during systemic therapy. **Methods:** Patients with *ERBB2* altered BTC were extracted of Memorial Sloan Kettering Cancer Center (MSK)'s prospectively maintained institutional genomic profiling protocol (NCT01775072). Eligibility required ≥2 molecular profiles obtained during systemic therapy. Tumor sequencing was performed using MSK-IMPACT (tissue-based NGS) and/or MSK-ACCESS (ctDNA NGS). Paired samples could include tissue and/or ctDNA. Clinical data were annotated, and longitudinal molecular profiles were analysed to assess temporal changes in *ERBB2* status. **Results:** Among 1628 patients with BTC in the institutional database, 122 (7.5%) had *ERBB2* altered tumors. Of these, 26 patients had ≥2 molecular samples available for longitudinal analysis. Five were excluded due to incomplete clinical and/or molecular data, leaving 21 eligible patients [Median age at diagnosis, 63 years (range 38–76), gallbladder cancer (n = 12, 57%), intrahepatic cholangiocarcinoma (n = 6, 29%), and extrahepatic cholangiocarcinoma (n = 3, 14%)]. At baseline, *ERBB2* alteration patterns included *ERBB2* amplification in 15 patients (71.4%), single nucleotide variants (SNV) in 2 patients (9.5%), and concurrent amplification and SNVs in 3 patients (14.3%). The most common co-occurring alterations involved *TP53* (67%), *SMAD4* (19%), *CDKN2A* (19%), and *SMAD4* (19%). Over the course of systemic treatment [Median number of treatment lines, 3.5 (range 1-6), 71% patients received HER2 directed therapy (n = 15) at any line], loss of *ERBB2* amplification at last available molecular sampling was observed in 7 patients (46%) and gain in 1 patient. Longitudinal profiling also demonstrated acquisition of additional alterations in receptor tyrosine kinase (RTK) pathways, including *MAPK* genes in 19% patients and *MET* alterations in 4.7%. Among the 15 patients who received HER2-directed therapy, *MAPK* alterations were observed in 4 (25%) and *MET* alterations in 1 (6%) at progression. **Conclusions:** *ERBB2* alterations in BTC evolve over time with frequent loss of amplification and emergence of RTK pathway alterations during systemic therapy. Acknowledging limitations of small sample size as well utilization of both cfDNA and tumor profiling, these findings highlight the genomic heterogeneity of *ERBB2* altered BTC and support the potential value of longitudinal profiling to better understand mechanisms of resistance and help inform treatment sequencing. Research Sponsor: None.

Homologous recombination signature (HRDsig) in clinically advanced gallbladder adenocarcinoma (CAGAC): A genomic landscape study.

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Background: CAGAC is an aggressive malignancy with poor prognosis where chemotherapy and immunotherapy provide a limited benefit. There have been clinical trials investigating the benefit of PARP inhibitors in biliary tract cancers. HRDsig positivity in other types of cancer have shown to predict sensitivity to PARP inhibitors. We explored the genomic characteristics of CAGAC patients according to the HRDsig status using a large real-world genomic dataset. **Methods:** Comprehensive genomic profiling was performed on 2,423 cases of CAGAC to assess all types of genomic alterations (GA), including base substitutions, short insertions and deletions, copy number changes, rearrangements, and fusions. Microsatellite instability (MSI) status, tumor mutational burden (TMB), genomic ancestry, and trinucleotide signatures were determined from the sequencing data. PD-L1 was determined with the DAKO 22C3 IHC assay. HRDsig status was determined by measuring large scale copy number changes and DNA repair errors. Patients were grouped into HRDsig positive (HRDsig+) and negative (HRDsig-) based on results. Genes with GA $\geq$5% in either population were included in the analysis. **Results:** Among 2,423 total cases, 152 (6.3%) were HRDsig+. Between MRDsig+ and MRDsig-, there was no significant difference in gender (female 76.3% vs 69.1%, p = 0.061), age (median 66.5 vs 68.0 yrs; p = 0.065), genomic ancestry (EUR 67.6% vs 63.7%, p = 1.0), MSI-H status (0.0% vs 1.3%, p = 0.468), PD-L1 expression (Low 34.0% vs 23.4%, p = 0.529. High 1.9% vs 5.4%, p = 0.946). Median GA per tumor was the same between groups (median 5 vs 5, p = 0.723), but the proportion of TMB$\geq$10 mut/Mbp were higher in HRDsig+ (12.5% vs 4.7%, p = 0.001). HRDsig+ had more frequent alterations in BRCA1 (9.2% vs 1.4%, p $<$ 0.001), BRCA2 (21.7% vs 1.9%; p $<$ 0.001), PALB2 (11.2% vs 0.4%; p $<$ 0.001), NF1 (9.9% vs 4.4%; p = 0.018), PIK3R1 (5.9% vs 2.5%; p = 0.05), and PTEN (11.8% vs 5.3%; p = 0.015). HRDsig- had more frequent alterations in ERBB2 (5.9% vs 19.0%, p $<$ 0.001), KRAS (5.9% vs 14.9%, p = 0.007), and MDM2 (3.3% vs 9.4%, p = 0.024). **Conclusions:** HRDsig positivity comprised approximately 6% of all CAGAC cases. HRDsig+ were associated with a higher proportion of mutations related to homologous recombination repair (HRR) genes and mTOR pathway, whereas HRDsig- demonstrated a higher proportion of common driver mutations such as ERBB2 and KRAS. Notably, there were cases with discordant HRDsig and HRR mutation status, which may be attributed to factors such as epigenetic alterations or mono-allelic alterations. These cases may represent the role of HRDsig complementing HRR mutation status and potentially have clinical implications in predicting response to PARP inhibitors. Research Sponsor: None.

Multi-cohort validation of a multi-analyte liquid biopsy test for early-stage pancreatic cancer detection.

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Background: Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate below 12%, largely due to diagnosis at advanced, noncurative stages. Earlier detection could significantly improve survival outcomes; however, current approaches, including imaging and blood based assays lack sufficient sensitivity and specificity. Liquid biopsy methods that combine genomic, epigenomic, and glycan-based biomarkers may improve the detection accuracy by integrating a multi-analyte approach. We developed an improved prediction model for the Avantect Pancreatic Cancer Test (Avantect) using 5-hydroxymethylcytosine (5hmC) profiling, whole-genome based fragmentomics, together with genotyping and haplotype data, and CA19-9 biomarker levels. **Methods:** We employed a training cohort consisting of 162 PDAC cases and 983 noncancer controls. Cell-free DNA was analyzed using 5hmC profiling, low-pass whole-genome sequencing (WGS), and genotyping, alongside matched plasma CA19-9 measurements. A logistic regression model integrating 5hmC features, fragment size metrics, haplotype information, and CA19-9 levels was constructed and locked at a specificity of 97.75%. Performance was evaluated in two independent validation cohorts consisting of 1,445 individuals (259 PDAC; 1,186 noncancer participants) and 173 individuals (67 PDAC and 106 non-cancers). Sensitivity, specificity, and 95% confidence intervals (CIs) were computed. **Results:** In an independent validation cohort of 1,445 individuals with various high-risk features including type 2 diabetes, family history, and genetic predisposition, Avantect achieved an overall sensitivity of 82.6% (95% CI: 77.45%-87.04%) and an early stage (stage I-II) sensitivity of 76.8% (n=138; 95% CI: 68.87%-83.57%). A second validation cohort of 173 individuals, enriched for new onset type 2 diabetes, was evaluated and showed a sensitivity of 74.6% (95% CI: 62.51%-84.47%). Specificity in both cohorts remained high at 97.5% (95% CI: 96.41%-98.29%) and 98.1% (95% CI: 93.33%-99.77%) respectively, consistent with the pre-specified rate of 97.75%. Test specificity was further evaluated in a cohort comprising other cancer types, including breast, colorectal, lung, liver, prostate, ovarian, bladder, and kidney cancers, revealing a consistent high specificity of 97.70 (0.05% reduction). **Conclusions:** The multi-analyte model shows strong and robust performance across multiple independent cohorts detecting PDAC at high specificity. By integrating orthogonal biological signals, through the incorporation of epigenomic, genomic, and glycan biomarkers, the Avantect Pancreatic Cancer Test showed an improved PDAC detection to provide a tool that could significantly improve survival for patients with pancreatic cancer. Research Sponsor: None.

Sequencing in the post-immunotherapy era: Does second-line tyrosine kinase inhibitor choice impact survival and safety in advanced HCC?

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Background: IMbrave150 trial established atezolizumab/bevacizumab as first line (1L) treatment for advanced hepatocellular carcinoma (HCC) in 2020. Current guidelines for second line (2L) therapy in advanced HCC rely on pre-immunotherapy (IO) trials (Lenvatinib, REFLECT trial and Cabozantinib, CELESTIAL trial). We investigated whether Lenvatinib (potent FGFR 1–4 inhibitor) offers superior efficacy over Cabozantinib (MET/AXL inhibitor with minimal FGFR activity) in post-IO setting by targeting the FGF-driven angiogenic escape pathways. **Methods:** Using TriNetX global network, we identified advanced HCC patients who received 1L atezolizumab/bevacizumab followed by 2L Lenvatinib (n=436) or Cabozantinib (n=115) within 6 months. 1:1 propensity score matching (PSM) balanced demographics, liver function, viral hepatitis, alcohol-related disorders, chronic liver diseases and key comorbidities. Outcomes include 1-year overall survival (OS), hepatic decompensation, cardiovascular (CV) outcomes and 90-day healthcare utilization, GI toxicity and acute renal failure (ARF). Each cohort was analyzed for 1 year competing risk of transition to third line (3L) systemic therapy vs. death vs. hospice. **Results:** Baseline characteristics were balanced except for lower pre-existing hypertension in Lenvatinib cohort (64% vs 74%; p=0.02). Post matching (n=110/arm), Lenvatinib showed significantly higher 1-year overall survival (OS). Safety analysis revealed significantly higher rates of new onset hepatic decompensation and a trend toward increased acute healthcare utilization with Cabozantinib. Renal, GI, and CV outcomes were comparable between cohorts. Lenvatinib arm had lower competing risk of mortality and higher cumulative incidence of receiving 3L therapy. **Conclusions:** In the real-world post-IO setting, Lenvatinib conferred significant 1-year survival benefit with superior hepatic safety profile compared to Cabozantinib. Cabozantinib exhibited higher rates of new hepatic decompensation and a trend toward increased healthcare resource utilization. Beyond a favorable pharmacoeconomic profile, results suggest superior sustained clinical benefit while preserving eligibility for 3L therapy. Given sample size constraints, these hypothesis-generating signals warrant validation in larger, multi-institutional cohorts. Research Sponsor: None.

Key clinical outcomes.

Outcome	Lenvatinib	Cabozantinib	HR/ RR (95% CI)	p-value
Median OS (months)	10.2	8.3		
1 year OS	47.1%	31.9%	0.65 (0.45, 0.95)	0.026
Hepatic decompensation	22.1%	37.5%	0.59 (0.34, 1.01)	0.046
CV outcomes	18.2%	16.4%	1.11 (0.62, 1.98)	0.72
90-day outcomes				
Healthcare utilization	37.3%	50.0%	0.75 (0.55, 1.01)	0.057
ARF	12.7%	13.6%	0.93 (0.47, 1.84)	0.84
GI events	25.5%	23.6%	1.08 (0.68, 1.71)	0.75
1 year Competing risks				
Death	36.1%	48.7%		
3L therapy	30.7%	27.9%		
Probability of being event-free	32.6%	23.4%		

Global insights into survival outcomes and unmet therapeutic needs in *KRAS*-mutant gallbladder cancer: A comprehensive federated network analysis.

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Background: Gallbladder cancer (GBC) is an aggressive malignancy with limited systemic options and poor survival. KRAS targeted therapeutic are emerging across solid tumors, yet their prognostic relevance in GBC remains poorly defined. We evaluated the real-world impact of KRAS mutations on survival in patient with advanced gallbladder cancer utilizing a large, federated health data network. **Methods:** A retrospective cohort study was performed using the TriNetX Global Collaborative Network. Adults (≥18y) with GBC were grouped by genomic testing into KRAS-mutant (KRAS*MT*) or KRAS-wild type (KRAS*WT*). Propensity-score matching (PSM) was performed 1:1 adjusting for demographics and comorbidities, yielding 604 patients per cohort. Outcomes were assessed from 1 to 1825 days after index diagnosis. The primary endpoint was overall survival (OS). Kaplan-Meier (KM) estimates, log-rank testing, and hazard ratios (HR) were generated. **Results:** After PSM, median follow-up was 358.5 (11,7 months) vs 491 (16.1 months) days for KRAS*WT* and KRAS*MT* cohorts, respectively. Death occurred in 214 (35.4%) KRAS*WT* vs 305 (50.5%) KRAS*MT* patients (risk difference −15.1%, 95% CI −20.6 to −9.5; $p < 0.001$). Median OS was 1326 days (43.5 months) for KRAS*WT* vs 694 days (22.8 months) for KRAS*MT* patients, with survival probability at end of time window of 48.74% vs 32.49%. Kaplan-Meier survival analysis demonstrated significantly worse OS in the KRAS*MT* cohort (log-rank $\chi^2 = 10.76$; $p = 0.001$). Hazard ratio favored KRAS*WT* (HR 0.747; 95% CI 0.627–0.890; $p = 0.011$), indicating 34% higher mortality in KRAS*MT* patients. **Conclusions:** In this large real-world PSM analysis, KRAS mutations conferred poor prognosis in GBC patients with significantly higher mortality and shorter survival. These differences highlight pivotal clinical implications amid the growing role of KRAS-targeted therapeutics. Ensuring expanded trial access, including early-line KRAS-targeted therapies, is necessary to reach this rare and clinically fragile patient population. Research Sponsor: None.

A phase 1b/2 study of AK130 (TIGIT/TGF-β bispecific fusion protein) combined with ivonescimab in advanced biliary tract cancer (BTC).

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Background: Chemotherapy (chemo) combined with or without PD-(L)1 inhibition is the standard first-line treatment for advanced BTC. After first-line treatment fails, patients (pts) lacking targetable genetic alterations (FGFR2, IDH1, or HER2 etc.) have limited options. For the majority, chemo (FOLFOX as the preferred regimen) is the default but suboptimal option. To date, the therapeutic potential of multi-target ICIs and anti-angiogenesis combination in the post-line regimen of BTC remains unexplored and constitutes a significant clinical demand. Additionally, early preclinical and clinical evidences support the combination blockade of TIGIT, TGF-β and PD-(L)1 plus anti-VEGF therapy in several solid tumors. AK130 is a TIGIT/TGF-β bispecific fusion protein. Ivonescimab, the first approved PD-1/VEGF bispecific antibody, has demonstrated promising efficacy in solid tumors, including BTC. Here, we aim to evaluate the efficacy and safety of AK130 plus ivonescimab in post-line BTC and the primary results from phase 1b is reported. **Methods:** This was an open-label, multi-center phase 1b/2 study. Pts who had progressed on prior chemo combined with or without a PD-(L)1 inhibitor were enrolled and treated with AK130 and ivonescimab. Phase 1b included dose escalation and expansion parts. In the escalation part, escalating doses of AK130 (10, 30, 45 mg/kg Q3W) were administered using a "3+3+3" design, with ivonescimab at 20 mg/kg Q3W (previously approved dose by NMPA). Dose-limiting toxicities (DLTs) were assessed. Based on safety profile, the expansion proceeded at selected doses, with up to 15 evaluable pts per dose. The primary endpoint of phase 1b was the incidence of AEs and DLTs. The secondary endpoint was ORR. **Results:** As of Jan 2026, a total of 23 pts was enrolled. 12 pts were enrolled in dose escalation across 3 dose levels (10, 30, 45 mg/kg AK130 Q3W; n = 3, 3, 6). No DLTs were observed, and no maximum tolerated dose (MTD) was established. All pts in the 10 mg/kg and 30 mg/kg groups experienced stable disease (SD). The 45mg/kg group was further expanded to 17 pts, including 15 pts that progressed on prior PD-(L)1 inhibition plus chemo.15 pts from 45mg/kg group were efficacy-evaluable with an ORR of 20.0% (3/15) and a DCR of 73.3% (11/15). 87.5% of the SD pts (7/8) reached shrinkage from baseline. 40.0% pts (6/15) had only one time evaluation and are continuing to be followed. Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 39.1% (9/23) pts. The most common TRAEs were anemia and atopic dermatitis, each reported in 2 pts (8.7%). AK130 45 mg/kg Q3W is planned as the recommended phase 2 dose (RP2D), whose safety and efficacy will be further evaluated in phase 2. **Conclusions:** AK130 plus ivonescimab demonstrated potential anti-tumor activity with a manageable safety profile as a post-line option for advanced BTC, supporting its further development in this setting. Clinical trial information: NCT06938321. Research Sponsor: Akeso Biopharma, Inc.

Peritumoral stiffness as a novel noninvasive biomarker: Predicting TACE response in intermediate-stage hepatocellular carcinoma via 2D-shear wave elastography.

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Background: Intermediate-stage hepatocellular carcinoma (HCC) demonstrates considerable biological and clinical heterogeneity, making it challenging to predict treatment response to transcatheter arterial chemoembolization (TACE). This multicenter retrospective study evaluated the association between preoperative tissue stiffness measurements obtained by 2D-shear wave elastography (2D-SWE) and TACE outcomes in intermediate-stage HCC, aiming to identify an optimal peritumoral stiffness cutoff value for prognostic stratification and clinical decision-making. **Methods:** A total of 115 patients with intermediate-stage HCC were enrolled. Preoperative 2D-SWE was performed to measure stiffness of the tumor (TSWE), peritumoral tissue (PSWE), and background liver parenchyma (LSWE). Cox proportional hazards regression and Kaplan-Meier analyses were conducted to determine whether 2D-SWE-derived stiffness parameters independently predicted TACE efficacy. Immunohistochemical staining, immunofluorescence, and RNA sequencing were performed to characterize the biological features of peritumoral tissue associated with varying PSWE values. **Results:** Mean stiffness values demonstrated a progressive gradient from liver parenchyma (LSWE: 13.0 kPa) through peritumoral tissue (PSWE: 18.9 kPa) to tumor tissue (TSWE: 25.6 kPa). Univariate and multivariate analyses identified primary tumor size and PSWE as independent prognostic factors for both overall survival (OS) and time to progression (TTP). A PSWE cutoff of 19.04 kPa achieved the highest discriminatory performance for predicting objective response rate (ORR) and disease control rate (DCR) (AUROC = 0.691 and 0.695, respectively). Patients with low PSWE demonstrated significantly superior OS (26.0 vs 17.5 months, P = 0.008) and TTP (11.6 vs 9.5 months, P = 0.026) compared to those with high PSWE. RNA sequencing revealed 778 differentially expressed genes enriched in angiogenesis and fibrosis-related pathways. Notably, patients with elevated PSWE exhibited enhanced stromal activation and angiogenesis in peritumoral regions, including increased collagen deposition, α-SMA, COL-I, VEGF expression, and CD31+ microvessel density, correlating with inferior TACE response. **Conclusions:** Preoperative peritumoral stiffness measured by 2D-SWE serves as a promising noninvasive prognostic biomarker for intermediate-stage HCC patients undergoing TACE, offering valuable insights for personalized treatment stratification. Research Sponsor: None.

Yttrium-90 SIRT plus atezolizumab/bevacizumab in unresectable huge HCC (>10 cm): A multicenter retrospective study.

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Background: Huge hepatocellular carcinoma ((huge HCC, ≥ 10 cm)) has poor prognosis with limited systemic therapy efficacy. We evaluated Y-90 selective internal radiation therapy (SIRT) combined with atezolizumab plus bevacizumab (Atezo/Bev) in this population. **Methods:** This retrospective multicenter study enrolled 21 patients with unresectable huge HCC (maximum diameter >10 cm) treated with Y-90 SIRT plus Atezo/Bev from January 2023 to July 2025. Eligibility criteria included Child-Pugh class A/B, ECOG performance status 0/1, and completion of ≥2 treatment cycles. The primary endpoint was ORR assessed by mRECIST. Secondary endpoints: PFS, OS, and safety (CTCAE v5.0). **Results:** Among the patients median tumor diameter 116.2 mm (IQR 105.6-131.9); >15 cm 14.3%; BCLC C 76.2%; PVTT 76.2%; extrahepatic metastasis 23.8%. The objective response rate (ORR) was 61.9% (13/21), including 6 (28.6%) complete responses (CR) and 7 (33.3%) partial responses (PR). The disease control rate (DCR) was 76.2% (16/21), with 3 (14.3%) stable disease (SD) and 5 (23.8%) progressive disease (PD). Median follow-up 11.0 months (IQR 7.1-25.0). Respectively, the median OS was not reached, at data cutoff, the 6- and 12-month PFS rates were 65.1% and 27.1%, respectively. The 6-, 12-, and 24-month OS rates were 76.2%, 57.5%, and 49.3%. Radiological responders (CR/PR) showed reduced progression risk (HR 0.46; 95% CI 0.16-1.32) and death risk (HR 0.41; 95% CI 0.11-1.49) vs non-responders. Nonrim APHE correlated with improved survival (median OS: 18.0 vs 8.0 months; HR 0.54). Grade ≥3 treatment-related adverse events occurred in 14.3% (3/21): pneumonia (n=2), hepatic encephalopathy (n=1). No treatment-related deaths. **Conclusions:** In this cohort, Y-90 SIRT plus Atezo/Bev achieved 61.9% ORR with manageable toxicity. These findings warrant prospective trials. Research Sponsor: None.

Baseline characteristics and clinical outcomes (N=21).

Characteristic	Value
Age, median (range), years	53 (28–76)
Male sex, n (%)	18 (85.7)
ECOG performance status 0/1, n (%)	16 (76.2) / 5 (23.8)
Etiology HBV/Alcohol/Unknown, n (%)	18 (85.7) / 1 (4.8) / 2 (9.5)
Tumor diameter, median (IQR), mm	116.2 (105.6–131.9)
Tumor >15 cm, n (%)	3 (14.3)
BCLC stage A/B/C, n (%)	4 (19.0) / 1 (4.8) / 16 (76.2)
Child-Pugh A/B, n (%)	17 (81.0) / 4 (19.0)
Portal vein tumor thrombus, n (%)	17 (81.0)
Extrahepatic metastasis, n (%)	5 (23.8)
AFP >400 ng/mL, n (%)	10 (47.6)
Complete responses (CR)	6 (28.6%)
Partial responses (PR)	7 (33.3%)
Stable disease(SD)	3 (14.3%)
Progressive disease (PD)	5 (23.8%)
Objective response rate (ORR)	61.9% (13/21)
Disease control rate (DCR)	76.2% (16/21)
Median follow-up, months	11.0(IQR 7.1-25.0)
6- and 12-month PFS rates	65.1% and 27.1%
6-, 12-, and 24-month OS rates	76.2%, 57.5%, and 49.3%
Grade ≥3 TARE	14.3% (3/21)

TARE: treatment-related adverse events.

4145 Poster Session

Time-toxicity of first-line systemic therapy for hepatocellular carcinoma in clinical practice.

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Background: Combination immunotherapy has become a standard first-line systemic treatment for hepatocellular carcinoma (HCC). While efficacy outcomes have been well described, the treatment-related time burden experienced by patients, including frequent hospital visits and admissions, has not been sufficiently evaluated in real-world clinical practice. Aims: To evaluate time toxicity as a patient-centered measure of treatment burden and to identify baseline factors associated with high time toxicity in patients receiving first-line combination immunotherapy for HCC. **Methods:** This retrospective observational study included patients with HCC who received first-line combination immunotherapy (atezolizumab + bevacizumab or durvalumab + tremelimumab) at our institution by April 2025. The observational period was defined as the treatment duration plus 28 days. Time toxicity (TT) was calculated as the proportion of days requiring hospital contacts, including scheduled visits, management of adverse events, and hospital admissions. High time toxicity (hTT) was defined as TT ≥20%, representing a clinically meaningful high treatment burden. Factors associated with hTT were examined using multivariate logistic regression analysis. **Results:** A total of 126 patients were included, with a median age of 74 years (IQR 67–81). The median observational period was 178 days (IQR 75-287), the median total hospital contacts was 20 days (IQR 13-30) and the median inpatient days was 7 days (IQR 4-14). Moreover, the median TT was 11.8% (IQR 9.1–17.9) and 23.0% of all patients experienced hTT. In multivariate analysis, impaired liver function (mALBI grade 2b–3; OR 7.17, 95% CI 2.60–19.80) and AFP ≥100 ng/mL (OR 3.03, 95% CI 1.20–7.67) were independently associated with hTT. **Conclusions:** Patients with impaired liver function and elevated AFP levels experienced a significantly higher treatment-related time burden during first-line combination immunotherapy for HCC. Assessment of time toxicity may provide clinically meaningful information to support shared decision-making, particularly in elderly or vulnerable patient populations. Research Sponsor: None.

Transcriptomic profiling in advanced hepatocellular carcinoma to identify biomarkers for immunotherapy response and mechanisms of acquired resistance.

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Background: Immune checkpoint inhibitors (ICI) are the standard of care for advanced HCC, yet validated biomarkers for response and mechanisms of acquired resistance remain undefined. We utilized transcriptomic profiling to identify predictive mRNA expression signatures and characterize evolution of the tumor microenvironment (TME) under therapeutic pressure. **Methods:** RNA-sequencing was performed on 35 HCC samples, comprising a cohort of 20 patients (16 pre-treatment + 4 treatment-naive tumors) and an independent cohort of 11 post-progression tumors (Post-IO). Patients received first-line atezolizumab/bevacizumab (n = 9), durvalumab/tremelimumab (n = 4), or nivolumab/ipilimumab (n = 3). 29 validated immune and stromal gene signatures were quantified (Bagaev, Cancer Cell 2021). Differential expression was assessed using Welch's t-test and permutation testing. Survival outcomes were correlated with gene signatures using Cox regression and Kaplan-Meier estimation. **Results:** Comparison of the pre-IO exposure (n = 20) vs post-IO (n = 11) cohorts revealed significant TME remodeling. Acquired resistance was driven by the evolution of a "hypovascular immune desert," characterized by statistical downregulation of antigen presentation (MHC-II, P = 0.04) and angiogenesis (P = 0.04). Regarding baseline prediction to universal IO regimen (all 3 regimens), high tumor proliferation rate (HR 4.79, P = 0.007; mPFS 2.6 vs 10.0 m), Th2 signature (HR 22.5, P = 0.01), and Treg traffic (HR 15.6, P = 0.01) strongly correlating with inferior outcomes; high macrophage/DC traffic predicted favorable outcomes (HR 0.18, P = 0.04; mPFS 7.4 vs 3.4 m). Distinct from these universal IO predictors, we utilized permutation testing to differentiate regimen-specific signals, identifying higher myeloid cell traffic (P = 0.007) and higher angiogenesis (P = 0.02) at baseline as unique biomarkers of response exclusively in anti-CTLA4 regimens. Transcriptomic profiles of post-transplant recurrences (n = 4) were statistically indistinguishable from the pre-IO cohort. **Conclusions:** Advanced unresectable HCC shows distinct tumor states linked to immunotherapy benefit versus early resistance, and these states evolve with treatment. Our findings support a biology-driven framework for predicting response, understanding resistance, and prioritizing rational combination strategies to improve durable disease control. Research Sponsor: None.

Comprehensive genomic profiling to identify molecular determinants of efficacy of IDH1 inhibition in intrahepatic cholangiocarcinoma.

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Background: Ivosidenib (IVO) in *IDH1*-mutant iCCA yields modest mPFS (2.7 m) with heterogenous responses. Molecular features driving this variability remain undefined. We sought to identify determinants of therapeutic efficacy via comprehensive analyses of co-occurring genomic alterations and oncogenic pathway activation. **Methods:** We analyzed 93 *IDH1*-mutant iCCA cases (MD Anderson n=59, Moffitt n=23, Yonsei n=11) treated with IVO (n=78), IDH305 (n=15). We stratified patients (pts) into 3 groups based on co-occurring alterations: EC (Epigenetic/Chromatin remodeling: BAP1/ARID1A/PBRM1), PMF (Proliferative/Mitogenic signaling: PI3K/MAPK/FGFR), ACT (Amplified cyclins/CDKN2A-B/TP53), yielding 4 groups: G1 (EC-intact/low-oncogenic: EC+/PMF-/ACT-), G2 (signaling-driven: EC+/PMF+), G3 (cell-cycle-deregulated: EC+/ACT+), and G4 (EC-deficient: EC-). Cox models assessed group-specific treatment effects; TME characterization utilized 29 mRNA gene signatures (Bagaev, Cancer Cell 2021) (n=31) and paired pre/post-progression biopsies (n=4). **Results:** Survival analysis (n=93) revealed distinct stratification ($p<0.0001$): G1, the longest mPFS (11.4 m), significantly superior to G4 (3.5 m) and G3 (1.8 m). G1 had superior durability (12-m PFS 46.5%) over G2 and G4 (23.9%, 14.6%); G3 progressed rapidly (6-m 0%). G3 outcomes suggest that ACT co-mutations confer poor prognosis regardless of epigenetic context (HR 6.85, P=0.004). Transcriptomic analysis identified G1 as "inflamed-suppressed" (highest angiogenesis/Treg); G4 was "proliferative-inflammatory" (highest M1-macrophage/Ki67, p=0.04). Paired longitudinal analysis (n=4) identified genomic bypass via acquired kinase drivers (eg, *NTRK1* amplification) and stromal adaptation with dense fibrotic remodeling. Radiographic hyperprogression on IVO (Kato criteria) was observed in 2 pts in G3 harboring *CDKN2A* loss. **Conclusions:** Co-occurring genomic alterations may serve as prognostic markers in *IDH1*-mutant iCCA, suggesting distinct trajectories of response and resistance to IDH1 inhibition. This molecular classification could guide clinical decision-making by identifying pts likely to benefit from monotherapy vs pts requiring combination strategies to overcome intrinsic resistance. Research Sponsor: None.

	G1 EC+ / PMF- / ACT-	G2 EC+ / PMF+	G3 EC+ / ACT+	G4 EC-
N (%)	28 (30%)	19 (20%)	5 (5%)	41 (44%)
mPFS (95% CI)	11.4 mo (6.2-NR)	5.6 mo (3.7-9.2)	1.8 mo (0.9-3.5)	3.5 mo (2.1-5.8)
3-M Rate	80.9% (66.3-95.5)	88.9% (74.8-100)	20.0% (0.0-55.1)	59.5% (44.5-74.5)
6-M Rate	72.4% (55.8-89.0)	47.9% (25.4-70.4)	0.0% (0.0-0.0)	23.4% (10.4-36.4)
12-M Rate	46.5% (28.0-65.0)	23.9% (4.7-43.1)	0.0% (0.0-0.0)	14.6% (3.8-25.4)
Hazard Ratio	Reference (1.0)	2.15 (p=0.03)	6.85 (p=0.004)	2.94 (p=0.002)
TME Phenotype	Angiogenesis / Treg-High	Fibrotic (CAF-High)	Senescent / Dormant	Proliferative / M1-High

Effectiveness and safety of IBI310 combined with sintilimab versus sorafenib in the first-line treatment of advanced hepatocellular carcinoma (aHCC): A randomized, open-label, controlled, multicenter phase III clinical study.

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Background: Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 have demonstrated efficacy in aHCC. Despite improved outcomes with PD-1/PD-L1 inhibitor-based regimens, prognosis remains poor and there is a continued unmet need for alternative therapies with long-term survival benefits. This study aimed to evaluate the effectiveness and safety of IBI310 (anti-CTLA-4 antibody) combined with sintilimab (anti-PD-1 antibody) in the first-line treatment of aHCC. **Methods:** Pts were randomized in a 2:1 ratio to IBI310+sintilimab group or sorafenib group. The experimental group received IBI310 3mg/kg intravenously (IV) and sintilimab 200 mg IV on day 1 of every 3 weeks. The control group received sorafenib 400 mg orally twice daily (BID) continuously until disease progression, intolerable toxicity, death or other protocol-specified discontinuation criteria. During the study, the IBI310 dose was adjusted to 1 mg/kg every 6 weeks. Primary end points included overall survival (OS) and objective response rate (ORR)assessed by the independent radiology review committee (IRRC) per RECIST v1.1. Secondary endpoint included progression-free survival (PFS), disease control rate (DCR), safety, etc. **Results:** As of August 2022, 344 patients were enrolled and allocated to Group 1 (G1, IBI310 3mg/kg + sintilimab, n=84), Group 2 (G2, modified-dose IBI310 1mg/kg + sintilimab, n=145) and Group 3 (G3, sorafenib, n=115). Overall, PFS and ORR improved with IBI310+sintilimab vs Sorafenib. The median OS in the primary endpoint was 44.0 months(G1), 36.1 months(G2) and 22.9 months(G3), respectively. Confirmed ORRs were significantly higher in the combination therapy groups (G1: 41.7%; G2: 22.1%) versus the control group (2.6%). Median PFS of three groups were 13.5 months(G1), 6.1 months(G2) and 2.8 months(G3), respectively. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 60.7% (G1), 34.7% (G2), and 35.1% (G3) of patients. **Conclusions:** Compared with sorafenib group, combination treatment of IBI310 + sintilimab as first-line treatment demonstrated survival benefits and a manageable safety profile in aHCC. Clinical trial information: NCT04720716. Research Sponsor: None.

Survival data.

	IBI310(3mg/kg)+Sintilimab (N=84)	IBI310(1mg/kg)+Sintilimab (N=145)	Sorafenib (N=115)
mOS, m	44.0	36.1	22.9
Confirmed ORR, n(%)	35(41.7)	32(22.1)	3(2.6)
mPFS, m	13.5	6.1	2.8

Yttrium-90 SIRT followed by lenvatinib plus sintilimab for unresectable intermediate-to-advanced hepatocellular carcinoma: Phase II SIRLENS-90 trial.

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Background: Selective internal radiation therapy (SIRT) with yttrium-90 microspheres is an established locoregional therapy for unresectable hepatocellular carcinoma (HCC) and may induce immunogenic modulation, providing a rationale for PD-(L)1 blockade combinations. However, outcomes with SIRT–PD-(L)1 doublets suggest room for improvement. Lenvatinib has biological plausibility to augment radiation- and immunotherapy-mediated effects via VEGFR/FGFR pathway inhibition. We evaluated the efficacy and safety of sequential SIRT followed by lenvatinib plus sintilimab and explored serum protein biomarkers for outcome stratification. **Methods:** SIRLENS-90 (NCT05992584) is a single-center, open-label, single-arm phase II trial in unresectable BCLC B/C HCC (ECOG 0–1, Child–Pugh 5–7) suitable for SIRT after mapping and ^{99m}Tc-MAA simulation. Patients received yttrium-90 resin SIRT (partition-model dosimetry) followed 3–7 days later by lenvatinib (8/12 mg daily) plus sintilimab (200 mg IV Q3W). Primary endpoint: PFS by mRECIST. Secondary endpoints: PFS by RECIST v1.1, OS, ORR, DCR, and safety (CTCAE v5.0). Exploratory Olink proteomics and LASSO-penalized Cox modeling derived a baseline risk score. **Results:** Thirty patients were treated (mean age 57 years [(SD 9.9], 93% male, 87% HBV-related; 43% BCLC B, 57% BCLC C; 43% macrovascular invasion; 53% bilobar disease; 37% extrahepatic metastases; mean max tumor diameter 9.6 cm [SD 3.8; range 3.2–16.1]). Median follow-up was 23.4 months. Median PFS was 15.8 mo (95% CI 8.3–20.7) by mRECIST (6-, 12-, and 18-mo rates: 77%, 53%, 40%) and 17.0 mo (95% CI 8.3–20.7) by RECIST v1.1. Median OS was not reached (12-, 18-, and 24-mo OS rates: 83%, 73%, 68%). ORR was 83% (95% CI 65–94) by mRECIST and 60% (95% CI 41–77) by RECIST v1.1; DCR was 90% (95% CI 74–98) by both. Intrahepatic ORR was 93% (95% CI 78–99) by mRECIST. Grade 3–4 treatment-related AEs occurred in 47%, with treatment-related SAEs in 10% and no treatment-related deaths. A baseline risk score incorporating IL-5 (protective), CXCL11 (adverse), extrahepatic metastasis, and bilobar disease stratified PFS (log-rank P= 0.001) and OS (P= 0.02), with optimism-corrected C-index 0.758 (for PFS). **Conclusions:** Yttrium-90 SIRT followed by lenvatinib plus sintilimab demonstrated encouraging activity with manageable toxicity in unresectable intermediate-to-advanced HCC. The cytokine-integrated baseline risk score is hypothesis-generating and warrants external validation. Clinical trial information: NCT05992584. Research Sponsor: China Zhongguancun Precision Medicine Science and Technology Foundation.

Tumor microenvironment phenotypes and survival in fibrolamellar carcinoma: An exploratory study.

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Background: Fibrolamellar carcinoma (FLC) is a very rare liver cancer affecting children, adolescents, and young adults. FLC is characterized by a robust immune tumor microenvironment (TME), but the clinical relevance of TME phenotypes is unknown. **Methods:** This de-identified study was approved by the Genetic Alliance Organization Institutional Review Board (IRB #IRB00003999). Subjects consented under *XCELSIOR: A Patient-Centric Platform Study for Precision Oncology* (NCT03793088). From this database, FLC TMEs were classified using the BostonGene framework into immune–stromal subtypes: fibrotic (F), immune desert (ID), immune-enriched fibrotic (IE-F), and immune-enriched non-fibrotic (IE-NF), and further dichotomized into immune-active (IE-F, IE-NF) and immune-cold (F, ID) groups. Associations were assessed using chi-square and non-parametric tests. Overall survival (OS) and time to first progression (TTP1) were evaluated using Kaplan–Meier methods and log-rank tests. **Results:** Forty-seven subjects (21 females, mean age 20.7 years) were included. TME subtype distribution was: F 46.8%, ID 17.0%, IE-F 21.3%, and IE-NF 14.9%. TME phenotypes were not associated with sex (p = 0.15) or age at diagnosis (p = 0.81). During a median follow-up of 3.7 years, 20 deaths (42.6%) occurred. Median overall survival (OS) for the entire cohort was 75.1 months. Median OS by TME subtype were: F 58.8 months, ID not-reached, IE-F 54.6 months, and IE-NF 75.1 months. Median OS was 86.0 months in the immune-cold group and 54.6 months in the immune-active group (log-rank p = 0.69). **Conclusions:** In this preliminary analysis with uncompleted dataset of FLC, immune–cold TME phenotypes were not significantly associated with overall survival, although trends toward improved outcomes were observed in immune-active subtypes. These findings should be interpreted as hypothesis-generating due to small numbers. Larger data are needed to clarify the prognostic role of the TME in FLC. Research Sponsor: None.

Tumor microenvironment subtypes and clinical outcomes in fibrolamellar carcinoma.

TME group	N (%)	Female (n, %)	Median age (years, IQR)	Deaths (n, %)	Median OS (months, 95% CI)
Fibrotic (F)	22 (46.8)	12 (57.1)	20.2 (17.2–23.8)	12 (60.0)	58.8 (43.1–74.5)
Immune Desert (ID)	8 (17.0)	5 (23.8)	20.1 (17.2–27.7)	1 (5.0)	Not reached
Immune-cold (F + ID)	*30 (63.8)*	*17 (81.0)*	*20.2 (17.3–23.8)*	*13 (65.0)*	*86.0 (43.0–129.0)*
Immune-Enriched Fibrotic (IE-F)	10 (21.3)	3 (14.3)	16.1 (12.1–28.1)	4 (20.0)	54.6 (41.1–68.2)
Immune-Enriched Non-Fibrotic (IE-NF)	7 (14.9)	1 (4.8)	18.9 (17.7–23.6)	3 (15.0)	75.1 (36.6–113.6)
Immune-active (IE-F + IE-NF)	*17 (36.2)*	*4 (19.0)*	*18.7 (13.8–25.0)*	*7 (35.0)*	*54.6 (26.2–83.1)*
Total	47 (100.0)	21 (100.0)	20.1 (16.7–23.6)	20 (42.6)	75.1 (43.4–106.8)

Abbreviations: TME, tumor microenvironment; IQR, interquartile range; OS: overall survival, CI: confidence interval.
Note: Percentages are calculated within columns.

Characteristics of *SMAD4* alterations in an immune-cold genomic subtype of biliary tract cancers in the Indian population.

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Background: Biliary tract cancers (BTCs), comprising gallbladder cancer (GBC) and cholangiocarcinoma (CCA), are rare but highly aggressive malignancies with limited therapeutic options. While genomic profiling has identified actionable alterations in BTC, data from the Indian population remain underexplored. We characterized the mutational and pathway landscape of BTCs in Indian patients and identified subtype-specific and immune-relevant genomic features. **Methods:** We retrospectively analyzed 154 BTC tumors, including 69 CCA and 85 GBC cases, using data from targeted next-generation sequencing panels. Somatic single-nucleotide variants, copy-number variations (CNVs), and gene fusions in oncogenic and tumor suppressor genes were curated. Pathway enrichment analysis (Hallmark MSigDB database ($p < 0.05$)), and mutual exclusivity/co-occurrence testing (gene pairs selected based on Benjamini-Hochberg-corrected q-values < 0.05.) were performed to identify biologically relevant genomic signatures. Genomic alterations were correlated with PD-L1 status when available. **Results:** *TP53* was the most frequently mutated gene (53%), followed by *KRAS* (18%), *ARID1A* (9%), *IDH1* (7%), and *PIK3CA* (7%). Recurrent amplifications were observed in *MYC* (12%) and *ERBB2* (9%). Pathway enrichment analysis revealed significant dysregulation in the PI3K-AKT-mTOR, Notch, and Wnt/β-catenin signaling pathways (p-value <0.05). *IDH1* mutations were predominantly observed in CCA, supporting a clinically actionable subgroup amenable to IDH1-targeted therapy, whereas *ERBB2* alterations were enriched in GBC, identifying *HER2* as a key therapeutic target in this subtype. Importantly, PD-L1-negative tumors showed a higher frequency of *SMAD4* mutations (Fisher's exact test, p = 0.71), implicating disruption of TGF-β signaling in immune evasion and reduced tumor immune activation. **Conclusions:** This comprehensive genomic analysis of BTC from the Indian population delineates distinct molecular landscape between GBC and CCA. The subtype-specific actionable alterations, including *IDH1* mutations in CCA and *ERBB2* alterations in GBC, highlights clinically relevant opportunities for precision therapy. *SMAD4* alterations are associated with an immune-cold, poorly immunogenic tumor subtype in BTCs and warrant further investigation as a predictive biomarker for patient stratification in immunotherapy-based treatment strategies. These findings support the utility of molecular stratification in BTC and provide a rationale for integrating targeted and immunotherapy-based approached in Indian patients. Research Sponsor: None.

Envafolimab combined with lenvatinib and gemcitabine plus cisplatin in advanced biliary tract cancer as first-line treatment: A multicenter, single-arm, open-label, phase II study (ENLIGHTEN study).

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Background: The prognosis of advanced biliary tract cancer (BTC) remains unsatisfactory despite the use of first-line gemcitabine and cisplatin in combination with PD-1/PD-L1 inhibitors. Lenvatinib (LEN), an anti-angiogenic multi-kinase inhibitor, has recently demonstrated promising antitumor activity in various tumors. This study aimed to determine the efficacy and safety of envafolimab (PD-L1 inhibitor) and LEN in combination with gemcitabine and cisplatin as first-line treatment in advanced BTCs. **Methods:** This investigator-initiated, multicenter, single-arm, phase 2 trial enrolled patients with advanced BTCs from three centers. A Simon's two-stage optimal design was employed: if 4 or more patients achieved partial responses (PR) among the first 10 patients in stage 1, enrollment would expand to a total of 39 patients. The therapy would be considered promising if 15 or more patients achieved PR in total. Including a 10% dropout allowance, the total sample size was set at 43. All patients received subcutaneous envafolimab (400mg, day 1, Q3W) and LEN (8 mg, orally once daily) combined with gemcitabine (1000mg/m2, iv. drip, days 1, 8, Q3W) plus cisplatin (25mg/m2, iv. drip, days 1, 8, Q3W) up for 6-8 cycles, followed by maintenance envafolimab and LEN until disease progression (PD) or unacceptable toxicity. The primary endpoint was objective response rate (ORR) assessed per RECIST 1.1. Secondary endpoints included overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. **Results:** A total of 43 patients were enrolled in this study from October 2022 to July 2025. However, one patient withdrew consent due to personal reasons after completing one cycle of therapy and was therefore considered off-study. Forty-two patients were included in the final analysis, with a median age of 57 years (range, 29-73). The ORR and DCR were 42.9% (95% CI, 27.7%-59%) and 88.1% (95% CI, 74.4%-96%), respectively. The observed outcomes were 18 patients (42.9%) with a partial response (PR), 19 (45.2%) with stable disease (SD), and 5 (11.9%) with PD, which met the predefined threshold for a positive study endpoint. The median follow-up time, estimated by the reverse Kaplan-Meier method, was 21.5 months (range, 18.7-29.1). The median PFS was 8.8 months (95% CI, 8.0-14.1), and the median OS was 15.9 months (95% CI, 13.4-not reached). The most common grade 3/4 treatment-related adverse events (TRAEs) were platelet decreased (n = 9, 20.9%) and neutropenia (n = 7, 16.3%). No treatment-related deaths occurred. **Conclusions:** In summary, our study demonstrates that the quadruplet regimen of envafolimab, lenvatinib, gemcitabine, and cisplatin demonstrates promising efficacy and well-tolerated first-line therapy for advanced BTC. Clinical trial information: NCT05410197. Research Sponsor: State Key Program of National Natural Science Foundation of China; 82130083; National Natural Science Foundation of China; 82173191; National Natural Science Foundation of China; 82372914; Key Area Research and Development Program of Guangdong Province; 2023B1111020007; Science and Technology Program of Guangzhou, China; 202206080016.

Cyclin amplification in biliary tract cancer: Integrated profiling to evaluate immune exclusion, drug sensitivity, and prognosis.

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Background: The impact of cell cycle regulator amplifications on the tumor microenvironment (TME) and clinical outcomes in biliary tract cancer (BTC) remains undefined in the chemo-immunotherapy era. This study characterizes the genomic, transcriptomic, and clinical landscape of cyclin-amplified BTC (CCNE/CCND family). **Methods:** We analyzed 263 BTC patients (pts) via comprehensive genomic/transcriptomic sequencing. Cohorts were stratified into Cyclin-Amplified (Amp, N = 71, Copy Number $\geq$6) and non-amplified Control (Ctrl, N = 192). We compared demographics, DNA co-alterations, and survival (Kaplan-Meier/Log-Rank). Transcriptomic profiling utilized 29 established gene signatures (Bagaev et al, Cancer Cell 2021) quantifying immune cell infiltration and stromal features. Differential gene expression assessed markers of chemotherapy resistance. **Results:** Cyclin amplification defined a distinct subgroup characterized by younger age (median 56 vs 65 years, $p < 0.001$). The Amp cohort (N = 71) consisted of CCNE1 (N = 30), CCND1/2/3 (N = 29/2/7), and CCNE1/D1 co-amplification (N = 3). Amp pts had significantly inferior overall survival (OS) compared to Ctrl (median 21.2 vs 28.3 m, p = 0.009). In stage 3-4 disease, Amp pts demonstrated worse OS (19.2 vs 25.5 m, p = 0.035). While adding immunotherapy (IO) to chemotherapy significantly improved OS in the control group (36.1 vs 23.0 m, p = 0.001), it provided no OS benefit in the Amplified group (median 19.2 m [Chemo+IO] vs 24.1 m [Chemo only], p = 0.80). Amp tumors exhibited high genomic instability, dominated by TP53 (67%), IRS2 (13%), ARID1A (11%), KRAS (11%), and ATM (11%) mutations. Frequent co-amplifications included FGF19/4 (35%), MYC (23%), ERBB2 (19%), EGFR (16%), and MET (16%). Transcriptomic profiling revealed a profound "immune desert" phenotype in Amp tumors, characterized by widespread depletion of adaptive and innate immunity: B-cells ($p < 0.001$), NK cells (p = 0.002), T-cells (p = 0.008), and Th1/Th2 signatures ($p < 0.01$) were significantly downregulated compared to Ctrl. Amp tumors exhibited intrinsic chemotherapy resistance via upregulation of gemcitabine targets (RRM1, p = 0.04) and platinum efflux pumps (ABCC2, p = 0.04), alongside a trend toward increased tumor proliferation (p = 0.053). **Conclusions:** Cyclin amplification identifies a biologically distinct, aggressive BTC subtype characterized by intrinsic resistance mechanisms to standard chemo-immunotherapy. This resistance is driven by a profound "immune desert" microenvironment limiting immunotherapy efficacy and the upregulation of genes associated with chemotherapy resistance. Comprehensive genomic profiling in this subgroup provides prognostic context and reveals a landscape of frequent co-occurring actionable drivers, highlighting the complex biological underpinnings of this high-risk population. Research Sponsor: None.

Tumor microenvironment modulation by losartan in advanced gallbladder cancer (GBC): Results and genomic correlates from the phase 2 LAST study.

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Background: Advanced gallbladder cancer (GBC) carries a dismal prognosis, with a real-world median overall survival (OS) of 6.8 months. We hypothesized that adding losartan to standard chemotherapy could improve outcomes by modulating the fibrotic tumor microenvironment (TME). **Methods:** This was a single-arm phase II study conducted at two academic centers between July 2022 and April 2024. Adult patients with histologically confirmed, unresectable or metastatic gallbladder cancer or cholangiocarcinoma received six cycles of gemcitabine and cisplatin with concurrent oral losartan. The primary endpoint was overall survival (OS). Exploratory analysis by whole-exome sequencing (WES) was done on 18 patients. **Results:** Thirty patients were enrolled. Clinical characteristics are depicted in Table. Median OS was 10.3 months (range 0.5–38.7), with 6-month and 12-month OS rates of 68% and 36%, respectively. Median PFS was 5 months. An objective response was observed in 88% of patients, including five complete responses. Patients with ECOG performance status 2 and those with cholelithiasis had inferior survival. Losartan was well tolerated. Genomic analysis revealed a clear discretion between cohorts (median PFS >, <=6 months). Responders exhibited a "TME-favorable" signature, characterized by genes associated with anti-inflammatory properties, regulated angiogenesis, and cellular stress response. This group was uniquely enriched for variants in *ATRX, CHEK2, DNMT3A, EZH2, IDH1, SMARCA4*, and *TSC2.* Conversely, non-responders (NR) showed a pro-inflammatory profile and oncogenic mutations in the angiogenesis pathway (*AKT2, BRAF, MET, NRAS, SMAD4*), potentially mediating resistance to losartan-induced vascular normalization. Both groups shared core GBC drivers, including *TP53, KRAS, ARID1A*, and *ERBB2.* **Conclusions:** Losartan improves survival in GBC patients with a specific molecular buildup. The presence of anti-inflammatory genomic signatures and specific variants like *SMARCA4* and *ATRX* may serve as predictive biomarkers for TME-targeted therapy, whereas pro-inflammatory profiles and primary angiogenesis mutations identify a resistant phenotype. Clinical trial information: CTRI/2023/02/049523. Research Sponsor: INHS ASVINI.

Baseline clinical features (n=30).

Clinical features	n	%
Age in years		
Median (range)	59 (31-75)	
Gender		
Male	11	36
Female	19	64
ECOG PS*		
1	21	70
2	9	30
Gallstones	12	41
Cholecystectomy	10	34
Jaundice at baseline		
Present	8	26
Absent	22	74
Site	26	87
Gallbladder	1	3
Cholangiocarcinoma	3	10
Intra-hepatic		
Extra-hepatic distal CBD**		
Weight in Kgs		
Mean (range)	58 (41-82)	
History of weight loss present	15	52
Co-morbidities		
Diabetes mellitus	7	23
Hypertension	8	26
Hypothyroidism	1	3
Angiotensin receptor blocker		
Losartan	28	94
Telmisartan	2	6
ERBB2 positive	2	6
Received Trastuzumab	2	100
Immunotherapy (Durvalumab)	5	17

*PS: Performance status, **CBD: Common bile duct.

4155 Poster Session

Optimizing biliary drainage in malignant biliary obstruction: A systematic review and meta-analysis of transpapillary versus suprapapillary stent positioning.

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Background: Malignant biliary obstruction causes significant morbidity and poor survival with 5-year survival rates below 10%. Effective biliary drainage is essential to relieve cholestasis, prevent infection, and improve quality of life. Endoscopic stenting is a standard intervention, but the optimal stent position remains unclear. Placement of a stent across the duodenal papilla can lead to duodeno-biliary reflux, subsequent stent dysfunction, while suprapapillary placement may reduce reflux and improve stent patency. We performed a systematic review and meta-analysis to compare the clinical outcomes of trans-papillary versus suprapapillary biliary stent placement in patients with malignant biliary obstruction. **Methods:** We conducted a comprehensive search of major electronic databases to identify studies comparing suprapapillary and transpapillary biliary stent placement. All relevant studies published up to November 2025 were considered. The clinical outcomes assessed included stent occlusion, stent patency, post-ERCP pancreatitis, cholangitis, and overall adverse events. Meta-analysis was performed, and the choice of a fixed-effects or random-effects model was determined based on the presence of heterogeneity across studies. **Results:** A total of 14 studies, including randomized controlled trials and retrospective cohort studies, encompassing 1,169 patients, compared suprapapillary with transpapillary biliary stent placement. Suprapapillary stenting was associated with a significantly lower risk of post-ERCP pancreatitis (OR 0.23, 95% CI 0.11–0.49; I^2 = 0%). Stent occlusion demonstrated a non-significant trend favoring suprapapillary placement (OR 0.68, 95% CI 0.46–1.01; I^2 = 46%). Stent patency duration was longer with transpapillary stents (SMD 0.66, 95% CI 0.27–1.05). Rates of cholangitis were similar between groups (OR 0.86, 95% CI 0.54–1.38). Overall, adverse events were significantly lower with suprapapillary stenting (OR 0.67, 95% CI 0.47–0.94; I^2 = 25%). **Conclusions:** Suprapapillary biliary stent placement appears to be safer than transpapillary stenting, with lower rates of post-ERCP pancreatitis and overall adverse events while still providing effective biliary drainage. However, its superiority over transpapillary placement in terms of stent occlusion and stent patency remains uncertain. These findings highlight the potential advantages of suprapapillary stenting but underscore the need for further large-scale randomized controlled trials before it can be established as the standard of care. Research Sponsor: None.

Knowledge distillation–enabled ResNet framework for hepatocellular carcinoma diagnosis on multiphase CT: Toward scalable global deployment.

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Background: Hepatocellular carcinoma (HCC) accounts for 85–90% of primary liver cancers and remains a leading cause of cancer-related mortality worldwide. Early and accurate imaging-based diagnosis is critical for staging, treatment selection, and survival. Multiphase contrast-enhanced CT is widely used for HCC detection, yet diagnostic accuracy varies due to lesion heterogeneity and radiologist workload. Deep learning models demonstrate high performance but are computationally intensive, limiting deployment in resource-constrained settings. Knowledge distillation enables transfer of diagnostic capability from large teacher models to lightweight student networks while preserving accuracy. We evaluated a ResNet-based distillation framework for efficient HCC diagnosis using multiphase CT imaging. **Methods:** We analyzed a curated dataset of 140 pathologically confirmed HCC cases, comprising arterial, portal venous, and delayed-phase CT images annotated by two expert radiologists independently . A high-capacity ResNet152 teacher model was trained to detect and localize HCC lesions using hierarchical residual feature learning across multiphase inputs. A compact ResNet18 student model was trained via temperature-scaled knowledge distillation using soft probability targets and regularized cross-entropy loss. Performance was evaluated using accuracy, sensitivity, specificity, F1 score, and AUROC. Computational efficiency and inference latency were assessed to determine real-world deployment feasibility. **Results:** The ResNet152 teacher achieved robust diagnostic performance ($>$ 97% accuracy) for HCC detection across lesion sizes and locations. The distilled ResNet18 preserved near-teacher accuracy, achieving AUROC exceeding 0.93 with balanced sensitivity and specificity ($>$ 93%). Knowledge distillation reduced model parameters by over 80% and substantially lowered inference time, enabling real-time execution on standard clinical hardware. Performance remained consistent across lesion diameter and hepatic segment subgroups, comparable to expert radiologist assessment **Conclusions:** Knowledge distillation enables a lightweight ResNet18 model to retain near–ResNet152 diagnostic performance for HCC detection on multiphase CT while markedly reducing computational requirements. This scalable framework addresses key barriers to AI adoption in oncology imaging and supports global deployment of AI-assisted HCC diagnosis. Prospective multicenter validation is warranted to assess clinical impact on early detection and treatment planning. Research Sponsor: None.

Correlative analysis of phase II trial of olaparib and durvalumab in patients with *IDH*-mutated cholangiocarcinoma.

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Background: *IDH1/2* mutations occur in ~25% of cholangiocarcinomas (CCAs). Preclinical studies suggest synergy between PARP inhibition and PD-L1 blockade. We previously conducted a phase II trial of olaparib plus durvalumab in advanced *IDH*-mutant CCA. We report matched baseline tissue and serial cell-free DNA (cfDNA)-based correlative analysis of pts samples. The primary objective was to develop a cfDNA methylome signature as a non-invasive biomarker. **Methods:** This single-arm, open-label phase II study (NCT03991832) enrolled patients with unresectable/metastatic *IDH*-mutant CCA and ≤2 prior lines of systemic therapy. Patients received olaparib 300 mg orally twice daily and durvalumab 1500 mg IV every 4 weeks. Blood samples were collected at baseline and monthly while on treatment for planned correlatives to examine R2HG, S2HG, and artemin levels using HPLC (High-Performance Liquid Chromatography). Cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) was performed on pts cfDNA samples and case-matched *IDH*-wildtype pts. Formalin-fixed, paraffin-embedded blocks of baseline tumor biopsies were used for multispectral fluorescent IHC (FL-IHC) using a 6-marker panel composed of pan-cytokeratin, CD4, CD8, CD163, PD-L1, and CD68. **Results:** Ten patients were enrolled (median age 63.5 y; 50% female; 90% received prior platinum). Median treatment duration was 1.95 mo (range 1.8–13.5). No complete or partial responses were observed. DCR was 30% (3 patients with stable disease); one patient remained on therapy for 13.5 mo before progression. Median PFS was 1.97 mo (95% CI 1.73–3.93). HPLC from baseline plasma showed lower baseline artemin levels correlated with stable disease (p=0.038), while R2HG/S2HG ratios showed no association with outcome. FL-IHC showed enriched immune cell populations, specifically $CD4^+$ T cells (p=0.0032) and a trend for $CD68^+$ macrophages (p=0.062), in the tumor stroma compared with tumor core. 54 plasma samples (from 8 patients) were profiled with cfMeDIP-seq along with 8 *IDH*-wildtype controls. Using top 100 differentially methylated regions, the circulating tumour DNA methylome exhibited a highly specific signature, accurately discriminating *IDH*-mutant and *IDH*-wildtype CCA regardless of treatment status. The specific differentially methylated gene pathways between groups were comprehensively examined in both on-treatment and baseline plasma samples. **Conclusions:** Advanced *IDH*-mutant CCA harbors an immune-excluded phenotype, which may underlie primary resistance to immunotherapy. Plasma cfDNA methylome signature can accurately discriminate CCA with *IDH* mutations. Clinical trial information: NCT03991832. Research Sponsor: None.

The molecular landscape and clinical nomogram of cholangiocarcinoma harboring ESCAT I alterations.

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Background: Cholangiocarcinoma (CCA) is the second most common primary liver cancer, with rising global incidence and mortality. Despite molecular advances, most patients present with advanced disease unsuitable for curative resection, resulting in poor prognosis. ESCAT I alterations, including FGFR2 fusions, IDH1/IDH2 mutations, BRAF V600E, HER2 amplification, MSI-high, and NTRK fusions, represent validated therapeutic targets with FDA/EMA-approved treatments, occurring in 25% of CCAs. Here, we analyze genomic and transcriptomic data to characterize the molecular landscape and develop an OS nomogram for CCA patients with ESCAT I alterations. **Methods:** In this retrospective study, we analyzed publicly available data from 1928 CCA patients, enrolled in participating institutions between 2012 and 2022, sourced from the cBioPortal for Cancer Genomics. We investigated frequencies of ESCAT I alterations, copy number alterations, mRNA expression, clinicopathological factors, and OS. Transcriptomic profiling and pathway enrichment analysis identified survival-associated genes. A nomogram integrating clinical, pathological, and molecular features was constructed and validated for OS prediction. **Results:** Genomic analysis of 1,845 CCA samples revealed revealed *IDH1* mutations (12%), *FGFR2* fusions (8%), HER2 amplification (6%), *BRAF*V600E (4%), MSI-high (4%), *NTRK1/2/3* fusions (3.4%) and *IDH2* mutations (2%). Notably, ESCAT I alterations were associated with inferior OS (log-rank P = 0.009; mOS altered vs wild-type 33.84 vs 24.31 months). Transcriptomic and GSEA profiling linked these alterations to dysregulation of oncogenic pathways, including DNA damage repair, cell cycle regulation, epithelial-mesenchymal transition, and immune pathways. The prognostic nomogram incorporated age, stage, differentiation, ESCAT I subtype, and top 5 most significantly identified transcriptomic signatures. **Conclusions:** This study provides comprehensive molecular characterization of ESCAT I-altered CCA, revealing distinct genomic and transcriptomic profiles associated with specific alterations and oncogenic pathway dysregulation. The validated nomogram offers a practical tool for personalized OS prediction, potentially guiding treatment selection, surveillance intensity, and clinical trial stratification. These findings emphasize the importance of routine molecular profiling in CCA and support precision medicine integration to improve outcomes and target therapy resistance mechanisms in this population. Research Sponsor: None.

First-line GemCis ± immunotherapy vs FGFR inhibition in ctDNA-detected *FGFR2* fusion–positive advanced cholangiocarcinoma: A real-world analysis.

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Background: Advanced cholangiocarcinoma (aCCA) carries a poor prognosis. Approximately 40% of aCCA harbor targetable biomarkers; however, standard first-line (1L) therapy is gemcitabine-cisplatin (GemCis) ± immune checkpoint inhibitors (ICI), regardless of genomic status. Emerging data suggest that oncogene-driven molecular subsets of aCCA may exhibit reduced sensitivity to ICI, raising questions about the benefit of adding ICI to chemotherapy in genomically defined populations. Therefore, we compared outcomes for aCCA pts with ctDNA-detected *FGFR2* fusions (*FGFR2+*) treated with targeted therapy vs. GemCis ± ICI. **Methods:** Real-world data was sourced from InfinityAI Data Library, a database combining de-identified genomic information from Guardant360 (Guardant Health, Palo Alto, CA) and clinical data from administrative claims. aCCA pts with an *FGFR2* fusion detected prior to 1L therapy between Sept. 2018 and June 2025 were analyzed. Outcomes were assessed via real-world time to treatment discontinuation (rwTTD), real-world time to next treatment (rwTTNT) and real-world overall survival (rwOS) in months with 95% confidence intervals. Log-rank tests were used to compare Kaplan-Meier survival curves. **Results:** 149 *FGFR2+* aCCA pts with treatment and outcomes data were identified. 18.1% (27) were treated with GemCis, 45.6% with GemCis + ICI (68), and 19.5% (29) with FGFRi. *FGFR2+* pts treated with 1L FGFRi had improved rwTTD, rwTTNT, and rwOS compared to GemCis and GemCis + ICI, with significantly improved rwTTD in those treated with FGFRi vs GemCis + ICI (Table 1). Based on these data, the addition of ICI to GemCis was not associated with improved outcomes in *FGFR2+* pts. **Conclusions:** Real-world outcomes in ctDNA-detected *FGFR2+* aCCA did not improve with addition of ICI to 1L GemCis. In contrast, 1L FGFRi was associated with longer treatment duration and delayed need for subsequent therapy. These findings suggest standard chemo-immunotherapy may not be optimal for all biomarker-defined aCCA subgroups and support the use of ctDNA testing to inform biomarker-drive 1L treatment selection abd sequncing strategies, warranting prospective validation. Research Sponsor: None.

Outcomes in FGFR2+ pts by 1L therapy.

	rrwTTD	rrwTTNT	rrwOS
FGFRi vs GemCis	9.1 (4.9-11.5) vs 4.2 (2.3-6.2) HR=0.68, p=0.22	20.8 (8.3-20.8) vs 13.8 (5.6-30.3) HR=0.64, p=0.33	NR (16.9-NR) vs 17.5 (10.3-28.4) HR=0.48, p=0.16
FGFRi vs GemCis + ICI	9.1 (4.9-11.5) vs 5.2 (3.9-7.8) HR=0.62, p=0.03	20.8 (8.3-20.8) vs 8.9 (7.9-NR) HR=0.51, p=0.06	NR (16.2-NR) vs 20.9 (10.7-NR) HR=0.43, p=0.11
GemCis vs GemCis + ICI	4.2 (2.3-6.2) vs 5.2 (3.9-7.8) HR=0.91, p=0.91	13.8 (5.6-30.3) vs 8.9 (7.9-NR) HR=0.8, p=0.61	17.5 (10.3-28.4) vs 20.9 (10.7-NR) HR=0.89, p=0.69

Durvalumab or pembrolizumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy for advanced cholangiocarcinoma: A meta-analysis.

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Background: Cholangiocarcinoma (CCA) is a rare, aggressive malignancy of the bile duct epithelium with rising incidence and mortality. Curative surgery is feasible in few cases; for unresectable or metastatic disease, systemic therapy is standard. Gemcitabine plus cisplatin (GemCis) has been the first-line backbone, but phase 3 trials (TOPAZ-1 and KEYNOTE-966) demonstrated overall survival (OS) benefit with added immune checkpoint inhibitors (durvalumab or pembrolizumab). This systematic review and meta-analysis evaluates the efficacy and safety of immunotherapy (IO) plus GemCis versus GemCis alone in advanced CCA. **Methods:** We systematically searched PubMed, Embase, Scopus, and Google Scholar for English-language studies (2009–2025) including randomized controlled trials (RCTs) and cohort studies of first-line GemCis alone or with durvalumab or pembrolizumab in unresectable/metastatic CCA. Primary endpoint: OS. Secondary: progression-free survival (PFS) and grade 3-4 adverse events (AEs) per CTCAE. Kaplan-Meier curves were digitized, and individual patient data reconstructed using IPD tools for pooled estimates. Random-effects models generated hazard ratios (HRs) and pooled medians; heterogeneity assessed via I^2. **Results:** We included 3,703 patients from TOPAZ-1, KEYNOTE-966, ABC-01/02, and six cohort studies: 1,737 on GemCis alone, 1,433 on GemCis + durvalumab, and 533 on GemCis + pembrolizumab. In the full meta-analysis, GemCis + durvalumab showed the best outcomes (median OS 14.1 months, PFS 7.38 months) versus GemCis + pembrolizumab (OS 12.8 months, PFS 6.62 months) and GemCis alone (OS 9.27 months, PFS 5.81 months). Restricting to RCTs only, IO + GemCis improved OS versus GemCis alone (median 12.82 vs. 11.1 months; HR 0.78, 95% CI 0.71–0.86, $p<0.001$), with no significant PFS difference ($p=0.20$). Grade 3-4 AEs were infrequent across arms; thrombocytopenia was higher with pembrolizumab ($p=0.0002$), but other severe toxicities were comparable. **Conclusions:** Adding immunotherapy to GemCis significantly enhances survival in unresectable/metastatic CCA, with durvalumab + GemCis providing the most pronounced benefit in this pooled analysis incorporating RCTs and real-world cohorts. Regimens were well-tolerated with manageable toxicity. These findings reinforce chemoimmunotherapy as first-line standard and highlight potential differential efficacy between PD-L1 and PD-1 inhibitors warranting further study. Research Sponsor: None.

Real-world analysis of epigenomic molecular tumor-type prediction for biliary tract cancer in CUP.

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Background: Biliary cancers (BTC) are often diagnosed at advanced stages and can present as metastatic liver tumors, making determination of the primary site difficult, leading to frequent cancer of unknown primary (CUP) designations. Conventional histopathology or imaging may misclassify tumor origin, yet accurate distinction is essential because therapies differ for BTC and CUP. A novel liquid biopsy (LB) molecular tumor type (MTT) classifier using epigenomic signatures predicts tumor origin across 14 solid tumors with graded confidence. This study evaluated concordance, genomic features, and real-world outcomes of high-confidence MTT-BTC predictions in patients (pts) with BTC or CUP using the Infinity AI, a clinical-genomics and epigenomics database. **Methods:** Guardant360 LB results showing high-confidence (>80%) MTT predictions for BTC in pts with BTC or CUP listed on the test requisition form (TRF) were identified. Infinity AI links de-identified clinical, genomic, epigenomic, and administrative claims The LB assay interrogated >700 genes and thousands of methylation regions. First-line (1L) therapies were categorized as chemotherapy (chemo), immunotherapy (IO), or chemo-IO. Real-world time to treatment discontinuation (rwTTD) and time to next treatment (rwTTNT) were compared between TRF-BTC and TRF-CUP cohorts using log-rank tests. **Results:** Among pts with high-confidence MTT-BTC predictions (TRF-BTC n=410; TRF-CUP n=56), MTT accuracy for TRF-BTC was 51.7%. Female proportion was 58% (TRF-BTC) and 64% (TRF-CUP), respectively. Median ages for TRF-BTC and TRF-CUP pts were 68 years, respectively. The most frequent oncogenic mutations in TRF-BTC were *TP53* (34), *ARID1A* (8), *KRAS* (7), and *IDH1* (6); none had *FGFR2* . In TRF-CUP, common mutations included *TP53* (3), *ARID1A* (2), and *IDH2* (2). For TRF-BTC pts, rwTTD was longer with 1L IO+chemo vs IO or chemo alone (7.9 vs 4.3 vs 3.4 mo; p<0.0001). TRF-CUP pts showed similar, but non-significant trends. rwTTNT was longer for TRF-BTC pts receiving IO (p=0.00026) and trended higher for TRF-CUP (p=0.069). **Conclusions:** Guardant360 LB epigenomic–based MTT classifier consistently predicted biliary origin in pts labeled as BTC and in a subset labeled as CUP, with broadly concordant genomic features and real-world treatment patterns. CUP pts with high-confidence MTT-BTC predictions demonstrated outcomes that approximated those of TRF-BTC, supporting biologic similarity and suggesting that some CUP cases may represent occult BTC. These findings support consideration of MTT as a tool to refine uncertain diagnoses, guide BTC-aligned therapy selection (including targetable alterations), and improve clinical trial matching. Larger cohorts with longer follow-up and prospective validation are needed to define the impact of MTT-guided management on patient outcomes. Research Sponsor: None.

An immune-related pathologic response score as a predictor of survival after immune checkpoint inhibitor–based conversion therapy in hepatocellular carcinoma.

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Background: Immune checkpoint inhibitor (ICI) based conversion therapy is increasingly utilized in the management of initially unresectable hepatocellular carcinoma (HCC). However, the clinical significance of immune-related pathologic response (irPR) features remain poorly understood in HCC. **Methods:** We enrolled 217 HCC patients undergoing ICI-based conversion therapy followed by curative-intent resection and assigned them to discovery and validation cohorts (2:1). Thirteen immune-related pathological response (irPR) features—tumor-infiltrating lymphocytes, tertiary lymphoid structures, lymphoid aggregates, plasma cell infiltration, granulomas, neutrophils, foamy macrophages, cholesterol clefts, hemosiderin-laden macrophages, giant cells, neovascularization, necrosis, and mature fibrosis—were assessed on H&E-stained tumor bed sections. To explore differences in the tumor microenvironment, bulk mRNA sequencing was performed on FFPE samples from patients in the discovery cohort. **Results:** In the discovery cohort, four irPR features (tumor-infiltrating lymphocytes, lymphoid aggregates, neutrophils, and foamy macrophages) were integrated to construct the immunotherapeutic response score (ITRS), classifying patients as ITRSlow (0–1) or ITRShigh (2–4). $ITRS^{low}$ patients showed significantly improved OS (HR = 4.17; 95% CI 1.64–10.60; P = 0.003) and RFS (HR = 2.07; 95% CI 1.32–3.23; P = 0.001), with longer median RFS (32.3 vs 8.5 months). ITRS remained independently associated with OS (HR = 2.81; 95% CI 1.06–7.43; P = 0.038) and RFS (HR = 2.10; 95% CI 1.32–3.33; P = 0.002) and was validated in an independent cohort. FFPE transcriptomic profiling (n = 41) showed that $ITRS^{low}$ tumors were immune-inflamed, with enrichment of immune-related GO/KEGG pathways and globally higher immune/stromal infiltration (higher ESTIMATE immune/stromal scores, lower tumor purity; all $P < 0.001$). Unsupervised clustering identified hot/cold states, with hot tumors enriched in $ITRS^{low}$ (65.4% vs 13.3%, P = 0.003); $CD8^+$ T-cell infiltration was higher across MCPcounter/CIBERSORT/TIMER and was accompanied by stronger antigen presentation (MHC-II gene sets) and increased $CD8^+$ T-cell activation/cytotoxicity as well as exhaustion signatures (all $P < 0.05$), supporting an immune-active microenvironment linked to favorable outcomes. **Conclusions:** An irPR feature–based ITRS robustly predicts both OS and RFS in HCC patients following ICT. The ITRS is readily applicable in routine diagnostic pathology practice and provides novel insights into the biological mechanisms underlying immunotherapy resistance. Research Sponsor: National Natural Science Foundation of China; 82488101; National Natural Science Foundation of China; 82341027; National Natural Science Foundation of China; 82072715; National Natural Science Foundation of China; 82500694.

Comparative outcomes of first-line atezolizumab plus bevacizumab (A+B) and durvalumab plus tremelimumab (D+T) in hepatocellular carcinoma (HCC).

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Background: Standard first-line systemic therapy for hepatocellular carcinoma involves immune checkpoint inhibitors, including A+B and the STRIDE regimen consisting of D+T. However, there is limited data comparing outcomes of patients receiving these two regimens. We aimed to compare the survival and safety profiles of patients receiving A+B versus D+T as first-line systemic therapy for advanced HCC in a propensity score matched analysis. **Methods:** We performed a retrospective cohort study using data from TriNetX, a healthcare database of over 150 million patients in the United States. We identified adult patients with a history of HCC and included those who received A+B or D+T as first line treatment. Propensity score matching (PSM) was conducted, matching for patient demographics (age, sex, race), clinical history (alcohol use, ascites, esophageal varices, viral hepatitis), and laboratory parameters [platelets, albumin, bilirubin, INR, alpha-1-fetoprotein (AFP)]. Median overall survival (mOS) and relevant patient safety events were compared between those who received A+B or D+T. **Results:** We identified 2,762 patients who had HCC who were treated with A+B or D+T, of which 2,030 patients received A+B and 723 patients received D+T. Compared to patients in the A+B cohort, those who received D+T were more often older (68.5 vs 66.9 years, standardized mean difference (SMD) = 0.17), had lower platelet counts (186.4 vs 198.6, SMD = 0.11), had higher prevalence of ascites (33.1% vs 20.3%, SMD = 0.29), and alcohol use (23.8% vs 18.8%, SMD = 0.12). After PSM, 723 patients were included in survival analyses, with all variables adequately balanced except for albumin, which was higher in the A+B group (3.6 vs 3.5, SMD = 0.19). At 90 days after starting therapy, D+T was associated with higher incidence of immune-mediated colitis [5.3% vs 2.6%, odds ratio (OR) 2.1; 95% confidence interval (CI), 1.2-3.7], and a higher risk of hospitalization [35.4% vs 27.9%, OR 1.4; 95% CI, 1.1-1.8]. At 6 months, the risk of hypertension and proteinuria was higher in the A+B cohort [21.9% vs 13.7%, OR 0.57; 95% CI, 0.34-0.95], which persisted at 1 year [28.1% vs 16.5%, OR 0.51; 95% CI, 0.32-0.81]. There was no significant difference in mOS between those receiving A+B or D+T [18.3 months vs 22.8 months, hazard ratio (HR) 0.94; 95% CI, 0.79-1.1]. **Conclusions:** In patients with advanced HCC who received A+B or D+T as first-line systemic therapy, we found that A+B was associated with higher risk of hypertension and proteinuria, while D+T was associated with a higher risk of immune-mediated colitis and hospitalization. No significant difference in mOS was observed between the cohorts. These findings suggest that safety profiles, rather than survival differences, may be used to guide optimal first-line treatment regimens. Prospective studies are warranted to further assess differences in patient outcomes. Research Sponsor: None.

DEB-TACE combined with apatinib and camrelizumab as second-line therapy for unresectable intrahepatic cholangiocarcinoma: A prospective, single-arm, phase II study.

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Background: This study aimed to evaluate the efficacy and safety of drug-eluting bead transarterial chemoembolization (DEB-TACE) combined with Apatinib and Camrelizumab as second-line therapy for unresectable intrahepatic cholangiocarcinoma (ICC). **Methods:** This is a prospective, single-arm, phase II study. Eligible patients were those with unresectable ICC who had progressed after first-line gemcitabine-containing chemotherapy. These patients received DEB-TACE combined with Apatinib and Camrelizumab therapy. The primary endpoints were to assess the objective response rate (ORR) and disease control rate (DCR) in accordance with both Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 and modified RECIST (mRECIST) criteria. Secondary objectives included measuring progression-free survival (PFS), overall survival (OS), and safety profiles. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. **Results:** Twenty patients participated in this study. The ORR was 65% (95% confidence interval [CI]: 40.8%–84.6%) per mRECIST and 25% (95% CI: 8.7%–49.1%) per RECIST V1.1. The DCR was 95% (95% CI: 74%–99%) per mRECIST and 85% (95% CI: 62.1%–96.8%) per RECIST V1.1. The median PFS was 7.7 (95% CI: 5.5–9.8) months. The median OS was 13.2 (95% CI: 3.1–23.3) months. Treatment-related adverse events (TRAEs) occurred in all 20 (100%) patients. The most common TRAEs included decreased lymphocyte count, hypertension, and abdominal pain, with grade ≥3 TRAEs manageable via appropriate interventions. **Conclusions:** DEB-TACE combined with Apatinib and Camrelizumab as second-line therapy for unresectable ICC demonstrated promising efficacy and an acceptable safety profile, providing a viable treatment option for patients with unresectable ICC progressing after first-line gemcitabine-containing chemotherapy. Clinical trial information: NCT04834674. Research Sponsor: None.

Outcomes of combined HCC-cholangiocarcinoma with adjuvant chemotherapy: An NCDB cohort.

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Background: Combined (or mixed) hepatocellular carcinoma-cholangiocarcinomas (cHCC-CCA) are rare liver tumors that are associated with poor prognosis. Patients (pts) presenting with limited disease are candidates for curative intent surgery. However, the role of adjuvant chemotherapy is not established. **Methods:** This retrospective review was based on the National Cancer Data Base (NCDB) participant user file (PUF) from 2014 to 2022. Patients were identified using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography (C22.0–22.1) and histology code 8180 for cHCC-CCA. Adjuvant chemotherapy was defined as chemotherapy administered on or after 6 weeks from surgery. Patients who had neoadjuvant chemo were excluded. Analytical stage variable captures data from pathological stage, and if pathological stage is missing, then clinical stage is captured. Pathological stage data were available only for 13% of pts. Hence, analytical stage was used with about 31% data available. Frequency and proportions were reported for categorical variables. Median overall survival (mOS) and corresponding 95% confidence intervals were reported using Kaplan-Meier (KM) estimates. Cox's proportional hazard model was used to report the adjusted and unadjusted analysis of OS. Hazard ratio (HR) and 95% confidence intervals were reported. All statistical analysis were performed using SAS version 9.4 software. Analysis of the NCDB PUF is exempt from IRB review. **Results:** 2815 pts with cHCC-CCA were identified, of which 2174 pts data were used for final analysis. 394 (18.1%) pts received adjuvant chemotherapy and 1780 (81.9%) did not receive any chemotherapy. 90% were above age 50 years; 76.2% were Caucasians and 67.7% were Male. Of those who received adjuvant chemotherapy, 162 (41.1%) received chemotherapy as single agent and 203 (51.5%) received chemotherapy as multiple agents. Among 668 data on analytic stage, 28.3% were stage 1, 36.8% were stage 2, 20.9% were stage 3 and 14.1% were stage 4. LVI data was also available for 549 patients. Of these, 38.1% had LVI present. Adjuvant chemotherapy was associated with improved OS compared to no chemotherapy (HR = 0.87 (95% CI: 0.77 – 0.99) p = 0.0296) in the entire population. Adjusted OS analysis for adjuvant chemotherapy with analytical stage showed significant survival benefit with adjuvant chemotherapy (HR = 0.73 (9%% CI: 0.56 – 0.96), p = 0.0261). Further adjustment for LVI was not performed due to large missing data. **Conclusions:** Adjuvant chemotherapy is not currently a standard for pts with cHCC-CCA after curative intent surgery. However, it appears to be associated with improved survival. Prospective studies evaluating the role of adjuvant therapy in this pt population are needed. Research Sponsor: None.

Performance of a multi-cancer early detection test (MCED) for detecting small hepatocellular carcinoma (HCC) in a screening population.

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Background: Early diagnosis of small HCC (defined as single nodule ≤ 3 cm) is crucial, as it represents the optimal window for curative treatments. Abdominal ultrasound with alpha-fetoprotein (AFP) is recommended for HCC surveillance in high-risk population. However, traditional modality detects only ~63% of small HCC, resulting in most HCC being diagnosed at advanced stages. Genie-Seq, a cfDNA-based MCED assay, covers 5 high-mortality cancers including HCC. Here, we report preliminary results evaluating the performance of Genie-Seq for small HCC in an asymptomatic screening population. **Methods:** Participants aged 40-74 years with no clinical suspicion of cancer were enrolled in a prospective, interventional study. All participants underwent Genie-Seq testing and standard-of-care (SOC) screenings according to the China Guidelines for Cancer Screening, including abdominal ultrasound and AFP. Genie-Seq detects cancer signals and localizes tissue-of-origin (TOO) simultaneously. Further HCC-focused diagnostic workup was performed per physician's discretion if: 1) suspicious findings on HCC screening, or 2) positive MCED results with liver as the top-predicted TOO. Diagnostic outcomes were reviewed for cancer status, TOO prediction accuracy, and stage. **Results:** As of December 2025, 1210 participants completed MCED testing and HCC screening. Nine participants were suspected of HCC and underwent further evaluation, with definitive diagnosis achieved in 7. Of these, 4 were confirmed as HCC (3 small HCCs, 1 stage II), 1 had synchronous gastric and colorectal cancers, and 2 had benign hepatic lesions. Genie-Seq identified all HCC cases with 100% TOO prediction accuracy, including 2 that were missed or initially misdiagnosed by traditional imaging. Patient 885 was exclusively identified by MCED, as no nodule was detected by ultrasound. Patient 888 had atypical features on contrast-enhanced CT/Gd-EOB-DTPA MRI (initial suspicion of inflammatory pseudotumor), and Genie-Seq positivity prompted contrast-enhanced ultrasound, leading to definitive diagnosis of small HCC. **Conclusions:** Genie-Seq exhibits excellent performance for small HCC detection in screening population, supporting it as a complementary tool to conventional preventive care and potentially improving curable HCC detection. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co. Ltd.

Diagnostic outcomes of participants achieved diagnostic resolution.

Participants	Suspicious Lesions Detected by Ultrasound	AFP (ng/ml)[1]	MCED Results	Diagnosis	Tumor Stage (AJCC)
0108	Yes	2.96	Negative	Hepatic cysts	
0572	Yes	4.25	Negative	Hepatic cavernous hemangioma	
0640	No	2.6	Positive	Multiple primary cancers	Gastric cancer: IIB Colorectal cancer: I
0723	Yes	58.55	Positive	HCC	II
0885	No	8.16	Positive	HCC	IA
0888	Yes	42.53	Positive	HCC	IB
0971	Yes	9.11	Positive	HCC	IA

[1]AFP levels of < 7 ng/mL were defined as normal.

Phase I/II, first-in-human study of yttrium-90 carbon microspheres in patients with unresectable hepatocellular carcinoma: Safety and early efficacy profiles.

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Background: Yttrium-90 microsphere selective internal radiation therapy (Y-90 SIRT) plays a significant role in the treatment of unresectable hepatocellular carcinoma. The phase I clinical study evaluated the safety and efficacy of Y-90 Carbon Microspheres Injection in patients with unresectable hepatocellular carcinoma. **Methods:** This multicenter, single-arm, prospective study was conducted across eight centers in China. It enrolled all eligible patients with uHCC who underwent radioembolization between 2023 and 2024. Eligibility criteria included unresectable hepatocellular carcinoma, Child-Pugh A cirrhosis, and an Eastern Cooperative Oncology Group performance status of 0-1. The primary endpoints included the incidence of adverse events and serious adverse events post-infusion, and the objective response rate in the treated area at first assessment according to mRECIST criteria. Among the 40 enrolled patients, 40.0% had an ECOG status of 0. According to China Liver Cancer Staging (CNLC), there were 12 cases (30.0%) in stage Ia, 9 cases (22.5%) in stage Ib, 6 cases (15.0%) in stage IIa, 4 cases (10.0%) in stage IIb, and 9 cases (22.5%) in stage IIIa of liver cancer. The median tumor size was 55.36 mm (range: 11.2–141.2). **Results:** All subjects received radioembolization as primary treatment, with a median tumor target absorbed dose of 450 Gy (range: 196.5 Gy-2000 Gy). According to the SPECT/CT results after treatment with NRT6003 injection, the median tumor absorbed dose was 429.93 Gy (range: 197.1 Gy-2827.7 Gy). As of February 21, 2025, the median follow-up of 9.5 months, a total of 221 treatment-related adverse events were reported, including 16 events of grade ≥3 and 2 serious adverse events (Upper abdominal pain, gastrointestinal bleeding). The best overall objective response rates were 92.5% (37/40) for whole-body and 97.5% (39/40) for local responses. The confirmed objective response rates were 82.5% (33/40) for whole-body and 85% (34/40) for local assessments. Six patients were re evaluated for surgical treatment due to tumor shrinkage. **Conclusions:** In this multicenter Y-90 SIRT study, treatment with Y-90 Carbon Microspheres demonstrated a favorable safety and efficacy were observed in the treatment of unresectable HCC, providing a highly promising treatment option. Clinical trial information: NCT06310590. Research Sponsor: None.

Lanreotide for advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in a Korean population: A multicenter prospective observational study (AIM-NETs).

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Background: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of malignancies. Somatostatin analogues (SSAs) are the standard of care for patients with unresectable or metastatic well-differentiated G1/G2 GEP-NETs. However, most pivotal data including the CLARINET trial were derived from Western cohorts. We prospectively evaluated the efficacy and safety of lanreotide in a real-world Korean cohort to bridge this geographic data gap. **Methods:** AIM-NETs is a prospective, observational, multicenter study of patients with unresectable or metastatic GEP-NETs treated with lanreotide. Patients received lanreotide 120 mg deep SC every 4 weeks (dose reduction to 90 mg permitted). Tumor response evaluation was done every 8 to 12 weeks according to the RECIST v1.1. The primary endpoint was the 2-year progression-free survival (PFS) rate. Secondary endpoints included median PFS and overall survival (OS), and safety. **Results:** Between Feb 2021 and Feb 2023, 71 patients were enrolled in five tertiary referral cancer centers in Korea. Median age was 59 years (range 25-82); 53.5% (n = 38) were male. Primary sites included pancreas (n = 40, 56.3%), rectum (8, 11.3%), colon (3, 4.2%) and stomach (3, 4.2%). Only two patients (2.8%) had functioning tumors. Tumor grades were G1 (n = 20, 28.2%), G2 (50, 70.4%) and G3 (1, 1.4%). The 2-year PFS rate was 50.6% (95% CI, 38.2%-63.0%) and median PFS was 26.0 months (95% CI, 15.2-32.7). The 2-year OS rate was 89.9% (82.9%-97.0%); median OS was not reached. The objective response rate was 23.5% (95% CI, 14.1%-35.4%). Higher tumor grade was significantly associated with worse PFS ($p < 0.0001$) and OS ($p < 0.0001$). High somatostatin receptor expression (Krenning score of 3 or higher on baseline Ga-68 DOTATOC scan) did not significantly correlate with PFS ($p = 0.358$) or OS ($p = 0.199$). No new safety signal of lanreotide were identified. **Conclusions:** Lanreotide provides robust disease control and a manageable safety profile in Asian patients with advanced GEP-NETs. The observed efficacy, including a favorable ORR, supports lanreotide as a standard of care in this population, aligning with previous clinical trial outcomes. Clinical trial information: NCT04696042. Research Sponsor: Ipsen.

Quality of life in patients with gastroenteropancreatic neuroendocrine tumors receiving ^{177}Lu-edotreotide or everolimus: Results from the COMPETE study.

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Background: The Phase 3 COMPETE trial demonstrated a significant treatment effect in favor of ^{177}Lu-edotreotide over everolimus in patients with Grade 1/2, well-differentiated, gastroenteropancreatic neuroendocrine tumors; ^{177}Lu-edotreotide significantly improved progression-free survival (primary endpoint) and objective response rate (secondary endpoint) compared to everolimus. Nowadays, treatment choice also considers the impact of therapy on patients' quality of life (QoL); here, we present QoL results from the COMPETE trial. **Methods:** The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and EORTC QLQ-gastrointestinal neuroendocrine tumors (GI.NET) were completed by patients at baseline, each month during the first year, and every 3 months thereafter until disease progression or end of study. Mean change from baseline, duration of maximum health-related quality of life (HRQoL) improvement (until deterioration), and time to deterioration were calculated. Between-group comparisons were conducted using repeated measure analysis with factors for treatment, randomization stratification factors, visit, baseline value, and treatment-by-visit interaction; all HRQoL analyses were prespecified and exploratory. **Results:** Based on repeated measure analysis, mean change from baseline was in favor of ^{177}Lu-edotreotide: overall mean change (95% confidence interval [CI]) in global health score was 0.9 (-2.7, 4.4) in the ^{177}Lu-edotreotide arm vs -9.9 (-13.9, -6.0) in the everolimus arm (nominal $p<0.0001$) (positive change corresponds to improvement). Time to deterioration in global health status/QoL was longer in the ^{177}Lu-edotreotide arm vs the everolimus arm (Table 1). Similar trends were observed in the EORTC QLQ-C30 and EORTC QLQ-GI.NET subdomains. In the ^{177}Lu-edotreotide arm, 90/207 (43.5%) participants had a clinically meaningful improvement (≥10 points) in global HRQoL score, vs 31/102 (30.4%) participants in the everolimus arm. Among these participants, the median duration of improvement was 22.0 (95%CI: 10.1, not evaluable [NE]) vs 10.2 (95%CI: 3.3, NE) months in the ^{177}Lu-edotreotide and everolimus arm, respectively. **Conclusions:** Consistent with the overall COMPETE outcomes, this analysis demonstrated clinically meaningful and durable HRQoL benefits for ^{177}Lu-edotreotide compared with everolimus. Clinical trial information: NCT03049189. Research Sponsor: None.

Time to deterioration in global health status/QoL (≥10 points).

Parameter / Statistics	^{177}Lu-edotreotide (N=207)	Everolimus (N=102)
Patients with ≥10 points deterioration, n (%)	114 (55.1)	78 (76.5)
Median, months (95% CI)[a]	10.251 (7.359, 15.901)	2.267 (2.004, 3.253)
Nominal stratified p-value[b]	<0.0001	
Stratified hazard ratio (95% CI)	0.392 (0.292, 0.527)	

[a]Estimated via Kaplan-Meier method.
[b]Derived from a two-sided test between the two groups.

Organotropic and genomic characterization of pancreatic neuroendocrine carcinoma.

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Background: Pancreatic neuroendocrine carcinoma (PNEC) is a rare, aggressive malignancy. Neuroendocrine carcinomas (NEC) of other primary sites, such as small cell lung cancer (SCLC), have a propensity to metastasize to the brain. Incidence of brain metastases in PNEC is poorly characterized, and most staging recommendations for extrapulmonary NEC do not include routine brain imaging. We evaluated the incidence of brain metastases in PNEC, identified factors associated with brain metastases, and characterized the genomic profile of PNEC. **Methods:** We reviewed the genomic profile of patients with PNEC, pancreatic ductal adenocarcinoma (PDAC), SCLC, and pulmonary large cell neuroendocrine carcinoma (LCNEC), who underwent next generation sequencing (NGS) at Memorial Sloan Kettering Cancer Center (MSKCC). We queried the Surveillance, Epidemiology, and End Results (SEER) database to identify all cases of metastatic PDAC and small cell or large cell PNEC diagnosed 2010-2022. We performed multivariable logistic regression to identify demographic and clinical factors associated with brain metastases. We used chi-squared testing to compare metastatic site frequency between tumor types. **Results:** The SEER query identified 412 cases of metastatic PNEC and 60,668 cases of metastatic PDAC with documented site of metastasis at diagnosis. Compared to PDAC, PNEC had higher rates of metastasis to the brain (8% vs 0.8%, $p<0.001$), bone (16% vs 9%, $p<0.001$), and distant lymph nodes (15% vs 8%, $p<0.001$) but lower rates to the lung (19% vs 25%, $p=0.03$). The incidence of liver metastases was similar in both tumor types (88% vs 87%). Within the PNEC cohort, lung metastasis was positively associated with brain metastasis (odds ratio [OR] 5.4, 95% confidence interval [CI] 2.4-12.5, $p<0.001$), but liver metastasis was negatively associated with brain metastasis (OR 0.2, 95% CI 0.1-0.5, $p<0.001$). The presence of brain metastases did not impact overall survival. Twenty eight patients with PNEC underwent NGS at MSKCC, including 12 with mixed ductal-neuroendocrine carcinoma or mixed acinar-neuroendocrine carcinoma. TP53 alterations were common (>50%) in all tumor types. RB1 alterations were seen frequently in SCLC (78%), PNEC (54%), and LCNEC (24%), but not in PDAC (2%). KRAS alterations were highly prevalent in PDAC (84%), uncommon in SCLC (3%), and with intermediate frequency in PNEC (36%). **Conclusions:** We found a high incidence of brain metastasis in PNEC, especially in patients with lung metastases, supporting neuroimaging in many patients with this disease. The strong association between lung and brain metastases is also noted in breast cancer, possibly explained by sequential seeding or shared features driving organotropism to these organs. PNEC demonstrated genomic features of both PDAC and SCLC. More research is needed to determine how these genomic features can inform management practices in individual patients. Research Sponsor: None.

4173 Poster Session

Cohort-level safety and efficacy results for [^{212}Pb]VMT-α-NET in advanced somatostatin receptor subtype 2 (SSTR2+)–expressing neuroendocrine tumors (NETs): Cohorts 1–3.

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Background: [^{212}Pb]VMT-α-NET is an alpha-particle radiation-delivering agent targeted to somatostatin receptor type 2 (SSTR2)-expressing tumors. Here, we present safety and efficacy results from the dose-finding phase 1/2a clinical trial (NCT05636618). **Methods:** This phase 1/2a dose-escalation study uses a Bayesian algorithm to identify an optimal dose of [^{212}Pb]VMT-α-NET for participants with advanced, well-differentiated NETs expressing SSTR2. Eligible participants must have unresectable or metastatic disease, documented radiologic progression following at least one prior systemic treatment, and evidence of SSTR2 expression (Krenning Score ^{3}2) in ≥1 lesion confirmed on an FDA-approved somatostatin receptor PET scan. Patients previously treated with systemic peptide receptor radionuclide therapy (PRRT) are excluded from enrollment. During the dose-finding phase, participants may receive up to four administrations of [^{212}Pb]VMT-α-NET at their assigned dose level, and they are monitored for dose-limiting toxicities (DLTs) for 42 days and safety throughout the study. Efficacy is evaluated by investigators according to RECIST criteria v1.1. Dosimetry is included as a supportive analysis. **Results:** As of the 10-Dec-2025 data cut-off (DCO), 56 participants had been enrolled across Cohorts 1, 2, and 3 and received at least one dose of [^{212}Pb]VMT-α-NET: 2 participants in Cohort 1 (2.5 mCi), 46 in Cohort 2 (5 mCi), and 8 in Cohort 3 (6 mCi). No dose-limiting toxicities, grade 5 adverse events, treatment-related discontinuations, serious renal events, dysphagia, or clinically meaningful treatment-related myelosuppression were observed. The median follow-up for all treated participants was 40 weeks (range 6–97). Efficacy has been summarized in this abstract for 25 participants (2 in Cohort 1 and 23 in Cohort 2). Nineteen of these 25 participants remained progression-free at the time of the DCO, with a median efficacy follow-up of 49 weeks (range 6–97). In Cohort 2, investigators observed RECIST v1.1 objective responses in 9 of 23 participants (39%), including 8 confirmed responses. Both participants in Cohort 1 continued to exhibit stable disease after two years of follow-up. Updated safety for all participants and updated efficacy for participants with sufficient maturity beyond the 25 summarized here will be presented at the congress. **Conclusions:** Treatment with [^{212}Pb]VMT-α-NET continues to demonstrate a favorable safety profile across all treated participants (n = 56) and shows signs of sustained efficacy at the 2.5 mCi and 5 mCi dose levels. The therapy has been well-tolerated with no observed dose-limiting toxicities or serious treatment-related adverse outcomes. Based on these encouraging safety and efficacy findings, the study is ongoing, and enrollment into Cohort 3 (6 mCi) remains active. Clinical trial information: NCT05636618. Research Sponsor: None.

DISCO update: Diagnostic performance of ^{64}Cu-SARTATE compared to ^{68}Ga-DOTATATE in patients with known or suspected neuroendocrine tumors.

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Background: Diagnostic imaging is critical in the management of neuroendocrine tumors (NETs). ^{64}Cu-SARTATE may provide advantages over existing imaging agents due to its longer half-life and sarcophagine chelator, with a potential to accurately detect additional disease in NETs. **Methods:** This multi-center Phase II study assessed the safety and efficacy of ^{64}Cu-SARTATE (200 MBq) in participants with known or suspected gastroenteropancreatic (GEP)-NETs (NCT04438304). (SARTATE; at 4 ± 1 h and 20 ± 4 h post-injection) were assessed by two independent blinded central readers, and . Discordant lesions (only present on either DOTATATE or SARTATE PET/CT) were subsequently evaluated by an independent assessor against a standard of truth (SOT; biopsy and/or follow-up conventional imaging). The per-lesion sensitivity (SE) for discordant lesions was calculated for both SARTATE and DOTATATE (SE=proportion of true positive foci / [true positive foci + false negative foci]). Lesion detection rate (DR) was calculated for a composite (best-case scenario) lesion detection across both SARTATE time points and for DOTATATE (DR= total number of lesions detected on scan / total number of lesions on scan pair). Values express the averages across readers and both PET/CT time points (for SARTATE). **Results:** 45 participants were enrolled and received SARTATE (41 known and 4 suspected NETs). Most had stage 3 or 4 disease. The mean number of foci detected by SARTATE was 441 vs. 227 by DOTATATE. A total of 238 discordant foci were identified in 34 participants; 223 of these were detected by SARTATE alone and 15 by DOTATATE alone. For the 122 discordant foci with evaluable SOT, the difference in SE for SARTATE vs. DOTATATE was statistically significant 94.7% [95% CI 65.1, 99.5] for SARTATE vs. 5.4% [95% CI 0.5, 34.9] for DOTATATE; $p<0.001$). The lesion DR was 97.2% [95% CI 75.9, 99.5] for SARTATE and 44.4% [95% CI 32.3, 57.5] for DOTATATE. The liver had the highest number of foci detected by both tracers (352 foci on SARTATE vs. 180 on DOTATATE) among all regions. Seven (15.6%) participants experienced 9 SARTATE-related AEs; 8 were Grade 1 and one was Grade 2, with most resolving within 2 days. **Conclusions:** ^{64}Cu-SARTATE was found to be safe and well-tolerated in patients with GEP-NETs. SARTATE lesion detection was higher than that of DOTATATE, with the liver having the highest number of lesions identified. SARTATE was able to detect additional true positive lesions compared to DOTATATE. The enhanced diagnostic performance offered by SARTATE, especially in key organs affected by GEP-NETs, may have important clinical implications to inform treatment decisions. A phase III study of ^{64}Cu-SARTATE in NETs is being planned. Clinical trial information: NCT04438304. Research Sponsor: None.

4175 Poster Session

Genomic and biomarker landscape of MTAP deficiency in gastrointestinal cancers.

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Background: Genomic loss of *MTAP* and *CDKN2A* is frequently observed across cancers, with ongoing development of MTA-selective PRMT5 inhibitors aiming to achieve synthetic lethality in the setting of MTAP loss. However, the biomarker landscape of patients with gastrointestinal (GI) cancers and MTAP deficiency remains poorly defined, and whether subsets of GI cancers harbor non-genomic mechanisms of MTAP deficiency remains unknown. **Methods:** All GI cancer samples sequenced with MSK-IMPACT v7, a DNA-based next generation sequencing (NGS) panel with coverage for *MTAP*/*CDKN2A* were queried. *MTAP* and *CDKN2A* deletions (del) were defined by low read counts in coverage-based copy number analyses. Genomic and pathologic analyses were completed in tumors with high *MTAP* del prevalence: esophagogastric cancers (EGC), pancreatic adenocarcinoma (PDAC), pancreatic neuroendocrine tumors (PanNETs), and biliary tract cancers (BTCs). MTAP immunohistochemistry (IHC) was completed on PDAC, PanNET, small bowel NET, and BTC samples to investigate prevalence of MTAP protein loss. **Results:** Among 8346 GI cancer samples, *MTAP* del was identified in 456 (5.5%), co-occurring with *CDKN2A* del in 98.8% of cases, with 79.8% confirmed homozygous del by FACETS, and was associated with higher tumor purity compared to *MTAP*-intact samples ($p < 0.001$). *MTAP* del prevalence was 14.4% in esophageal squamous cell carcinoma (SCC), 5.9% in esophagogastric adenocarcinoma (EGA), 12.4% in PDAC, 7.4% in PanNET (grade 1 [G1]: 3.4%, G2: 4.3%, G3: 19.4%), 0% in small bowel NET, 10.2% in BTCs (including 11.5% in intrahepatic cholangiocarcinoma [iCCA]), and 0.7% in colorectal cancer. *MTAP* del was associated with wild-type (WT) *KRAS* amplifications (amp) in EGC, *KRAS G12V* and WT *KRAS* amp in PDAC, and *KRAS* mutations and *FGFR2* fusions in iCCA. Among EGA, PDAC, and BTCs, *MTAP* del tumors were associated with higher fractions of genome altered ($p < 0.001$ for each) and rates of whole genome duplication ($p < 0.001$ for each). Among 463 samples profiled by MTAP IHC, MTAP deficiency was found in 29/93 (31%) PDAC, 3/33 (11%) BTC, 15/60 (25%) PanNETs, and 196/277 (71%) small bowel NETs. Analysis of MTAP deficiency and activity of standard systemic therapies, as well as metabolomic and epigenomic profiling of MTAP-deficient GI cancers are ongoing and will be presented. **Conclusions:** *MTAP* genomic del are recurrently identified across GI cancers, most notably in esophageal SCC, PDAC, G3 pancreatic NETs, and iCCA. *MTAP* del are associated with distinct genomic drivers across GI cancers and markers of chromosomal instability more broadly. We found evidence of discrepancy between MTAP loss by NGS and IHC across multiple GI cancers, most notably small bowel NETs, which demonstrate frequent MTAP IHC deficiency in complete absence of genomic loss, suggesting non-genomic mechanisms of MTAP silencing. These observations may help define the role for therapies targeting MTAP deficiency in GI cancers. Research Sponsor: U.S. National Institutes of Health.

A multicenter single-arm study of induction EC/EP plus camrelizumab followed by maintenance camrelizumab plus apatinib in treatment-naive advanced or metastatic extrapulmonary neuroendocrine carcinoma.

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Background: Extrapulmonary neuroendocrine carcinoma (EP-NEC) is a poorly differentiated and highly aggressive malignancy with poor prognosis. Platinum (cisplatin or carboplatin) plus etoposide (EC/EP) remains the standard first-line regimen. However, clinical outcomes are suboptimal, highlighting the need for more effective strategies. Camrelizumab is a programmed cell death-1 (PD-1) inhibitor, and apatinib is a vascular endothelial growth factor receptor-2 (VEGFR2) inhibitor. Both have demonstrated antitumor activity in multiple solid tumors. Therefore, we investigated a sequential regimen consisting of induction EC/EP plus camrelizumab followed by maintenance camrelizumab plus apatinib in treatment-naive patients with advanced or metastatic EP-NEC. **Methods:** This multicenter, single-arm trial enrolled patients with previously untreated advanced or metastatic EP-NEC. Patients received 4–6 cycles of induction therapy with cisplatin (25 mg/m^2 iv, d1-3, q3w) or carboplatin (AUC = 5 iv, d1, q3w) plus etoposide (100 mg/m^2 iv, d1-3, q3w) in combination with camrelizumab (200 mg iv, d1, q3w). Patients without disease progression received maintenance camrelizumab (200 mg iv, q3w) plus apatinib (250 mg, qd) until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. Tumor response was assessed every 6 weeks per RECIST v1.1. The trial is registered on ClinicalTrials.gov, NCT05142865. **Results:** As of January 2026, 30 patients were enrolled (median age of 59.5 years, range 30–73), and all 30 patients were evaluable for efficacy. The ORR was 66.7% and the DCR was 83.3%. Median PFS was 9.87 months (95% CI, 6.23–NA). Median OS was not reached, and the 1-year OS rate was 74.6%. All patients experienced adverse events (AEs), with grade ≥3 AEs observed in 43.3% (13/30). Grade ≥3 AEs were mainly hematologic toxicities, including anemia (13.3%), neutropenia (13.3%) and thrombocytopenia (13.3%). Common non-hematologic AEs included elevated transaminases (43.3%), mainly grade 1–2, with grade ≥3 events in 10.0%. **Conclusions:** Induction EC/EP plus camrelizumab followed by maintenance camrelizumab plus apatinib showed encouraging activity and manageable safety in treatment-naive advanced or metastatic EP-NEC. Further studies are warranted to confirm these findings. Clinical trial information: NCT05142865. Research Sponsor: Natural Science Foundation of Hubei Province of China; No. 2023AFB1059.

Postoperative pancreatic fistula after resection of pancreatic neuroendocrine tumors: Incidence, predictors, and clinical impact.

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Background: Postoperative pancreatic fistula (POPF) remain a major source of morbidity after pancreatic surgery. Data specific to pancreatic neuroendocrine tumors (pNETs) are limited, although these neoplasms differ biologically and surgically from pancreatic adenocarcinoma, potentially influencing POPF risk and outcomes. This study evaluated the incidence, predictors, and clinical impact of POPF in a well-characterized cohort of patients undergoing resection for pNETs. **Methods:** All patients who underwent resection for histologically confirmed pNETs between 2010-2019 at a tertiary center were retrospectively analyzed. Clinicopathological parameters and surgical procedures were assessed for association with POPF occurrence and severity according to the International Study Group on Pancreatic Fistula (ISGPF) criteria. Statistical analyses included χ^2, Fisher's exact, Spearman correlation tests, and multivariable regression analysis; significance was defined as $\alpha = 0.05$. **Results:** Among 106 patients (44% female, mean age 61 ($\pm$ 13.5) years), 85% received a formal pancreatic resection, 15% an atypical resection. More than half (53%) of pNETs were located in the pancreatic tail. The majority (64%) of tumors were G1, only 4% G3, with 72% of diseases in early stages UICC I or II. 12% of pNETs were functional and exclusively insulinomas. 53 patients (50%) developed a POPF, predominantly Grade B (60%), followed by Grade A (34%) and Grade C (6%). No surgery- or POPF-related mortality was observed. POPFs were most frequent after distal pancreatectomy for tail lesions (60% vs. 23% body vs. 17% head; p = 0.065), and in functional pNETs (77% vs. 46% in non-functional pNETs; p = 0.072). Distant metastases were inversely associated with POPF (M0 54% vs. M1 28%; p = 0.043). A nonsignificant trend toward higher POPF rates was observed after atypical resections (73% vs. 48%; p = 0.095). Higher POPF grade was associated with female sex (p = 0.016), and tumor proliferation index (p = 0.046); female sex remained independently associated with POPF grade in multivariable regression analysis (beta = 0.334, p = 0.044). Patients with POPF exhibited lower long-term mortality during follow-up (8% vs. 29%; p = 0.009) and lower mean preoperative chromogranin A levels (82.8 ng/mL vs. 167.8 ng/mL; p = 0.038). **Conclusions:** POPF occurred in half of all pNET resections, most commonly of Grade B severity. Tumor location, functionality, and absence of metastases were associated with higher POPF risk, and female sex with higher grade POPF. The association of POPF with lower long-term mortality likely mirrors the favorable tumor biology and localized disease profile of patients selected for curative surgery. This underscores the long-term oncological benefit of surgical resection in pNETs and provides relevant insights for postoperative risk stratification and perioperative management. Research Sponsor: None.

Efficacy and safety of cabozantinib (CABO) in advanced neuroendocrine tumors (NET) according to hormone functional status: Subgroup analysis of phase 3 CABINET trial (Alliance A021602).

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Background: In the CABINET trial, CABO significantly prolonged progression-free survival (PFS) compared to placebo (PB) in patients (pts) with advanced, previously treated extrapancreatic NET (epNET) or pancreatic NET (pNET) (Chan et al., NEJM, 2025). Here we report outcomes according to functional status based on NET hormone secretion. **Methods:** Pts with locally advanced or metastatic epNET or pNET were randomized 2:1 in separate cohorts to receive CABO 60 mg daily vs PB. Eligibility included progression by RECIST within 12 months (mo) before registration, ≥ 1 prior systemic therapy not including somatostatin analogs (SSA). Pts with functional NET due to hormone secretion and non-functional NET were included. In this post hoc subgroup analysis, we analyzed PFS by blinded independent central review and adverse events for pts receiving CABO vs PB based on functional status. Cox regression models were used with stratification on primary tumor site (epNET vs pNET). Subset analyses to evaluate treatment arm differences were conducted in pts with functional and non-functional tumors. Due to small numbers, separate results for those with unknown functional status are not included. **Results:** Of the total 298 pts enrolled in both cohorts, 74 had a functional NET (CABO, n = 47; PB, n = 27); 179 had a non-functional NET (CABO, n = 123; PB, n = 56); 45 had unknown functional status (CABO, n = 28; PB, n = 17). For functional NET, primary tumor sites were GI tract (n = 50; 68%), pancreas (n = 15; 20%), unknown (n = 4; 5%), lung (n = 3; 4%), and thymus (n = 2; 3%). Secreted hormones that were reported included serotonin (55%), somatostatin (18%), gastrin (16%), glucagon (4%), insulin (4%), ACTH (1%), and vasoactive intestinal peptide (1%). For non-functional NET, primary tumor sites were pancreas (n = 75; 42%), GI tract (n = 42; 23%), lung (n = 30; 17%), unknown (n = 17; 9%), thymus (n = 8; 4%), and other (n = 7; 4%). Concurrent SSA was received by 91% and 53% of pts with functional and non-functional NET, respectively. In both subgroups, CABO was associated with improved PFS compared to PB (for functional NET: stratified hazard ratio [sHR], 0.40; 95% confidence interval [CI]: 0.20-0.82, P = 0.012; for non-functional NET: sHR, 0.26; 95% CI: 0.17-0.41, $P < 0.001$). The most frequent grade 3/4 adverse events (AEs) attributed to CABO vs PB in pts with functional NET included hypertension (21% vs 11%), diarrhea (9% vs 11%), and fatigue (2% vs 15%); in pts with non-functional NET, grade 3/4 AEs included hypertension (21% vs 4%) and fatigue (18% vs 4%). **Conclusions:** Subset analyses of the CABINET trial suggest that CABO is an effective treatment option for pts with functional and non-functional epNET or pNET. Efficacy and safety results for pts with functional or non-functional NET treated with CABO are consistent with results for the entire trial. Clinical trial information: NCT03375320. Research Sponsor: National Cancer Institute; U10CA180821, U10CA180882; U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG Oncology); U10CA180888 (SWOG); 5U24CA180803 (IROC). https://acknowledgments.alliancefound.org.; Exelixis, Inc.

Immune microenvironment signatures as prognostic biomarkers in gastro-enteropancreatic neuroendocrine carcinoma (GEP-NEC).

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Background: GEP-NEC is an aggressive malignancy with rising incidence and limited therapeutic options. While immune checkpoint inhibitors (ICIs) have become standard of care in small cell lung cancer (SCLC), their role in GEP-NEC remains undefined. Characterizing immune cell signatures in the tumor microenvironment (TME) across different NEC histologies may help identify prognostic biomarkers and guide immunotherapy strategies. **Methods:** We included 4863 NEC tumors that underwent DNA (592-gene panel, whole exome) and RNA (whole transcriptome) sequencing at Caris Life Sciences. Composition of the TME was estimated from bulk RNA sequencing using QuanTIseq method. Overall survival (OS) and IO-associated OS (IO-OS) were derived from insurance claims and calculated from date of tumor biopsy (OS) or IO initiation (IO-OS) to last contact using Kaplan-Meier estimates and Cox proportional hazards models. Statistical significance was determined by Fishers Exact, Chi-square and Mann-Whitney U test with adjustments for multiple comparisons ($P< 0.05$). **Results:** The cohort was comprised of small cell (SCNEC, n = 2320), large cell (LCNEC, 618), high-grade NEC (HGNEC, 414) and NEC not otherwise specified (NOS, 1511). Primary sites included lung (2642), pancreas (459), non-pancreatic GI (931) and other sites (831). SCNEC had lower Treg, M1 or M2 macrophage and neutrophils, and higher CD4+ T-, NK-, B- and dendritic-cell infiltration than other histologies, suggesting more lymphocyte-driven immune milieu with reduced myeloid-driven suppression. Compared with lung NEC, GEP-NEC demonstrated a more immunosuppressive TME, characterized by lower NK-, B- and dendritic-cell infiltration and higher Treg, M1/M2 macrophage and neutrophils—most pronounced in non-pancreatic GI primaries. Pancreatic NEC had reduced dendritic cells in LCNEC, HGNEC and NOS subtypes and higher neutrophils in HGNEC and NOS. Elevated B-cell infiltration was associated with improved OS in SCNEC of non-pancreatic GI (HR 0.56, 95%CI 0.37-0.85, $P= 0.032$) and lung (HR 0.81, 0.72-0.90, $P= 0.001$) origin. High M2 macrophage and NK-cell scores were associated with prolonged OS in NOS of non-pancreatic GI (M2: HR 0.35, 0.28-0.45, $P< 0.001$; NK: HR 0.32, 0.26-0.41, $P< 0.001$) and pancreas (M2: HR 0.46, 0.33-0.62, $P< 0.001$; NK: HR 0.64, 0.48-0.84, $P= 0.010$) origin. Among patients receiving ICIs (n = 1811, 910 with SCLC), only higher B-cell infiltration was associated with improved IO-OS in SCLC (HR 0.79, 0.68-0.92, $P= 0.029$); data was insufficient to analyze IO-OS for other histologic and anatomic subgroups. **Conclusions:** GEP-NEC exhibits a distinct and relatively immunosuppressive TME compared with lung NEC. B-cell, NK-cell, and macrophage signatures are prognostic across GEP-NEC subtypes. These findings support further evaluation of immune-based stratification and biomarker-driven therapeutic development in GEP-NEC. Research Sponsor: None.

Therapy-related myeloid neoplasms after radioligand therapy in neuroendocrine tumors: A multicenter real-world analysis.

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Background: Therapy-related myeloid neoplasms (t-MNs), including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), represent a rare but serious long-term hematological toxicity associated with radioligand therapy (RLT). Real-world data on the incidence of t-MNs and associated risk factors following RLT in are limited. We sought to investigate the incidence and risk factors of t-MN in patients with NETs treated with 177Lu-Dotatate. **Methods:** We conducted a multicenter retrospective cohort study using the TriNetX research network. Adult patients with NETs who received 177Lu-Dotatate were identified, with first administration defined as the index date. The primary outcome was development of t-MNs (incident MDS or AML) with a 12-month latency period after target treatment. Incidence was calculated and Cox proportional hazards models were used to evaluate associations between baseline covariates and t-MN risk. Covariates included age, sex, race, primary tumor site (small bowel, colon, pancreas, lung), liver and bone metastases, prior alkylating chemotherapy (temozolomide exposure), chronic kidney disease (CKD), and nicotine or alcohol dependence. Treatment pathways were assessed for 177Lu-Dotatate re-treatment and temozolomide. **Results:** A total of 1,811 patients met inclusion criteria. Mean age at index was 65.4 ± 10.9 years; 977 (54.0%) were male, and 1,503 (83.0%) were White. Median follow-up duration was 20.5 months. Following 177Lu-Dotatate, 37 of 1,807 patients (2.05%) developed MDS, and 15 of 1,804 patients (0.83%) developed AML, with an overall incidence of t-MNs 2.88% (52/1,804). At baseline, mean age (67.1 ± 9.3 vs 65.4 ± 11.0 years, p=0.27) and sex (males 42.0% vs 54.2%, p=0.14) were comparable between patients who did and did not develop t-MNs. On multivariable Cox proportional analysis, higher age at index (HR 1.03; 95% CI 1.01–1.07; p=0.048) and baseline CKD (HR 2.69; 95% CI 1.32–5.49; p=0.006) were independently associated with increased risk of t-MNs. Sex, race, primary tumor site, presence of liver or bone metastases, alkylating chemotherapy exposure, and nicotine or alcohol dependence were not significantly associated with t-MN risk. Evaluation of treatment pathways demonstrated similar 177Lu-Dotatate re-treatment rates (2.33% vs 2.77%, p=1.0), and comparable receipt of temozolomide for ≥12 months (18.6% vs 16.4%, p=0.66) between groups that did and did not develop t-MNs, respectively. **Conclusions:** In this large real-world cohort of NET patients treated with 177Lu-Dotatate, t-MNs were uncommon but clinically significant. Older age and CKD were associated with increased risk, whereas repeat 177Lu-Dotatate and alkylating chemotherapy exposure were not associated with increased t-MN incidence. These findings may inform risk stratification, patient counseling, and long-term hematologic surveillance following 177Lu-Dotatate.
Research Sponsor: None.

Germline pathogenic/likely pathogenic (P/LP) variants in epithelial neuroendocrine neoplasms: The case for universal germline genetic testing.

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Background: Current National Comprehensive Cancer Network (NCCN) guidelines for germline testing in neuroendocrine neoplasms (NENs) rely on organ-specific, syndrome-driven algorithms that may not adequately capture hereditary risk. We sought to analyze prevalence of P/LP germline variants in epithelial NENs and investigate relevant associations. **Methods:** Germline genetic testing results were analyzed from 3,611 probands. Cohort 1 included 3,409 patients identified by ICD-10 code C7A (2015–2025), and Cohort 2 included 201 consecutively curated patients with pathology information (2019–2021). Patients with paraganglioma, pheochromocytoma, or medullary thyroid carcinoma were excluded. Except 59 single-gene tests, multigene panels included a mean of 67 and 62 genes in Cohorts 1 and 2, respectively. Data were classified as P/LP, variant of uncertain significance (VUS), or negative. Comparisons of variant classification frequencies between cohorts were performed using chi-square or Fisher's exact tests. Multivariable logistic regression evaluated clinical and demographic predictors of P/LP variant detection, with results reported as likelihood ratios (LR) and two-sided p-values (< 0.05 considered significant). **Results:** Among all 3,611 probands, mean age was 56 years in Cohort 1 and 53 years in Cohort 2, with females comprising 63% and 71%, respectively. VUS and negative results differed between cohorts (VUS 21.9% vs 32.9%, $p = 0.002$; negative 67.4% vs 55.0%, $p < 0.001$), while P/LP rates were similar (10.6% vs 12.1%, $p = 1.0$), permitting pooled analysis. Overall, 387 patients (10.7%) harbored P/LP variants, with 399 P/LP variants identified across 49 genes. Sixty percent of P/LP variants were accounted for by *CHEK2*, *MEN1*, *BRCA2*, *ATM*, *FH*, *HOXB13*, *PALB2*, and *BRCA1*. Clinically actionable variants per NCCN guidelines were identified in 348 patients (9.6%). Among 479 probands with curated family history, meeting NCCN criteria for multigene testing or having a family history of NEN was not predictive of P/LP detection. Logistic regression demonstrated that male sex was a significant predictor of P/LP variants (LR = 4.538, $p = 0.03$), while age at NEN diagnosis and primary NEN site were not predictive, nor were the interaction terms significant. **Conclusions:** In this 10-year, multicohort study of patients at a commercial laboratory, more than one in ten patients with epithelial NENs harbored a germline P/LP variant, frequently outside classic hereditary NEN syndromes and inadequately predicted by NCCN criteria, family history, age, or tumor site. These findings suggest that current germline testing frameworks may miss clinically relevant hereditary cancer risk. Broader approaches to germline testing in these patients may be needed to improve identification of hereditary cancer risk and enable personalized prevention and surveillance strategies. Research Sponsor: None.

Cabozantinib in high-grade neuroendocrine neoplasms.

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Background: High grade neuroendocrine neoplasms (HG-NENs) are treated with platinum doublets mirroring guidelines for small cell lung cancer (SCLC) but recurrences are common and salvage options are limited in efficacy. Cabozantinib (CABO), an inhibitor of VEGFR, MET, and TAM kinases (TYRO3, AXL, and MER) was approved by the FDA for treatment of well differentiated (WD) NENs of both pancreatic and extrapancreatic origins based on the CABINET study (Chan, NEJM 2025). However, its efficacy in the whole spectrum of HG-NEN patients including poorly differentiated disease (PDD) has not been prospectively explored. **Methods:** This was a single institution, Phase II study of CABO in patients with HG-NENs who had progressed on at least one prior treatment. Key inclusion/exclusion criteria were NENs of any origin except SCLC, high grade by Ki-67 of $>$ 20% or histology consensus, ECOG of $<$ = 1, appropriate hematological parameters and no history of bleeding or active cardiac disease. CABO was given orally starting at 60 mg po daily in 3-week cycles. The primary endpoint of this study was overall response rate (ORR). Secondary endpoints included progression free survival (PFS) and overall survival (OS). A Simon optimal 2-stage design tested the null hypothesis that the true ORR is $<$ = 1% at the type I error rate of 5%, resulting in projected enrollment of up to 32 total patients. Toxicities were graded according to CTCAE v5.0 and response was evaluated according to RECIST v1. **Results:** All patients have been accrued, with 4/32 patients still on treatment. Median age at diagnosis was 62 years and male to female ratio was 1.46. Origin of tumor was GI in 68.8% of the cases, the rest being thoracic (6.3%), prostate (6.3%) cervical (6.3%) head/neck (3.1%) and unknown (9.4%). Median Ki-67 was 55%, 11 patients had Ki-67 $>$ 70%. Histology was WD-HG in 40% of patients and PDD in 60%. Two patients had mixed PDD/other components (MiNEN). Median PFS in evaluable patients was 4.01 months [95% CI 1.61 to 9.30] and mOS was 9.89 mo [95% CI 6.73 to 18.96]. Three patients so far (9.3%) have had partial response as best response (PDD-colon, WD-pancreas and PDD-cervical) while 19/32 (59.4%) patients have had stable disease as best response so far (disease control rate 68.8%). Five (15.6%) patients have received more than 10 treatment cycles. The three longest treated patients had WD-pancreas (23 and 17 cycles) and PDD-unknown (12 cycles). One patient had eventual resection of a metastatic site and is currently without evidence of disease. Three patients withdrew from the trial because of toxicities (shortness of breath, GI bleeding, thromboembolism). Twenty-six patients have expired. **Conclusions:** CABO monotherapy showed efficacy in some HG-NEN patients with not just WD but also the very aggressive PDD histology. No new side effects to the ones previously described for this agent were noted. Supported by Exelixis and a Siteman investment program grant. Clinical trial information: NCT04412629. Research Sponsor: Exelixis; The Foundation for Barnes-Jewish Hospital (BJHF); GR0033156.

Insurance, hospital, and racial disparities in surgical treatment and mortality among patients with neuroendocrine tumors: A national analysis.

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Background: Neuroendocrine tumors (NETs) are the second most common gastrointestinal malignancy with increasing incidence. Surgical resection remains curative, yet population-level disparities data are lacking. We examined insurance, hospital, and racial disparities in NET surgical treatment and outcomes. **Methods:** Using the National Inpatient Sample (2019-2022), we identified NET hospitalizations (ICD-10: C7A, C7B, C25.4, C4A). Outcomes were surgical resection and in-hospital mortality. Multivariable logistic regression estimated adjusted odds ratios (aOR) by insurance, hospital type, and race, controlling for demographics, tumor site, and metastatic status. **Results:** Among 198,955 NET hospitalizations (mean age 64.9 years; 52.7% metastatic), surgical resection was 35.3% and mortality 5.2%. Medicaid (aOR 0.58, 0.56-0.60) and Medicare (aOR 0.64, 0.63-0.66) patients had significantly lower surgery odds versus private insurance ($p<0.001$). In localized disease, surgery rates were 58.9% (Private) vs 36.9% (Medicare). Rural patients had 50% lower surgery odds (aOR 0.50, 0.48-0.53) and 47% higher mortality (aOR 1.47, 1.34-1.61) versus urban teaching hospitals. Black patients had 19% lower surgery odds (aOR 0.81, 0.78-0.83) and 18% higher mortality (aOR 1.18, 1.11-1.25) versus White patients. **Conclusions:** This largest national NET analysis reveals profound multilevel disparities: Medicaid/Medicare patients are 36-42% less likely to receive surgery, rural patients face 50% lower surgical access with 47% higher mortality, and Black patients experience significant treatment and survival inequities. Findings support targeted interventions including insurance coverage expansion, rural referral networks, and equity-focused initiatives. Research Sponsor: None.

Multilevel disparities in surgical resection and mortality among patients with neuroendocrine tumors.

Disparity Type	Comparison	N	Surgery Rate	Mortality	aOR (Surgery)	aOR (Mortality)	95% CI	P-value	Key Finding
Overall Cohort	—	198,955	35.3%	5.2%	—	—	—	—	Mean age 64.9y; 52.7% metastatic
INSURANCE DISPARITIES									
Insurance	Medicare vs Private	—	29.9% vs 45.3%	—	0.64	0.90	0.63-0.66 / 0.84-0.95	<0.001	36% lower surgery odds
Insurance	Medicaid vs Private	—	—	—	0.58	1.26	0.56-0.60 / 1.16-1.37	<0.001	42% lower surgery; 26% higher mortality
HOSPITAL DISPARITIES									
Hospital	Rural vs Urban Teaching	—	—	7.0% vs 4.9%	0.50	1.47	0.48-0.53 / 1.34-1.61	<0.001	50% lower surgery; 47% higher mortality
RACIAL DISPARITIES									
Race	Black vs White	—	—	—	0.81	1.18	0.78-0.83 / 1.11-1.25	<0.001	19% lower surgery; 18% higher mortality
Localized NETs	Private vs Medicare	87,100	58.9% vs 36.9%	1.7% vs 3.6%	—	—	—	—	22-point surgery gap

Circulating tumor deoxyribonucleic acid (DNA) and treatment outcomes of gastroesophageal cancer: A systematic review and meta-analysis.

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Background: Gastroesophageal tumors are some of the most highly prevalent cancers worldwide. Despite the high prevalence and advancement in treatments, they represent a major cause of cancer-related deaths. Thus, advancement in gastroesophageal cancer treatment and post-treatment monitoring are imperative in improving disease prognosis. In this study, we aimed to investigate the association between pre- or post-treatment plasma circulating tumor deoxyribonucleic acid (ctDNA) and post-treatment outcomes. **Methods:** We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus on October 30, 2025 using ctDNA and gastroesophageal cancer as the keywords along with their related MeSH terms. Studies were included if they investigated the association between the detection of pre- or post-treatment plasma ctDNA and disease outcomes among patients with esophageal or gastric cancer. Our exposure of interest was the detection of pre- or post-treatment ctDNA in plasma while the outcomes of interest were tumor recurrence and tumor progression. The odds ratio (OR) and its 95% confidence interval (95%CI) were the effect measures of choice in the analysis. **Results:** We included a total of 1,897 patients with gastric or esophageal cancer from 21 prospective or retrospective cohorts. Our analysis revealed that pre-treatment detection of ctDNA in the plasma was associated with higher odds of tumor recurrence (OR=4.37; 95%CI: 1.20-15.92) and progression (OR=4.80; 95%CI: 2.51-9.18). These results were consistent in the subgroup analysis among patients with esophageal cancer while they lost their significance among patients with gastric cancer and among good quality studies (Newcastle Ottawa Scale>5). Moreover, the detection of post-treatment ctDNA was associated with higher odds of tumor recurrence (OR=6.14; 95%CI: 3.79-9.94) and progression (OR=8.28; 95%CI: 5.03-13.64). These results were consistent in the subgroup analysis of patients with esophageal cancer, gastric cancer and among good quality studies. **Conclusions:** Our results highlight that detection of pre-treatment but more so post-treatment ctDNA is associated with post-treatment cancer outcomes. Our results emphasize the potential use of ctDNA as a valuable tool for detection of early gastroesophageal cancer recurrence and post-treatment progression.
Research Sponsor: None.

Evaluation of clinical success and adverse events with endoscopic ultrasound-guided biliary drainage (EUS-BD) compared to percutaneous transhepatic biliary drainage (PTBD) after failed ERCP in malignant biliary obstruction: A systematic review and meta-analysis.

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Background: ERCP fails to achieve biliary decompression in ~3–10% of malignant biliary obstruction cases. Rescue drainage is typically performed using percutaneous transhepatic biliary drainage (PTBD) or endoscopic ultrasound–guided biliary drainage (EUS-BD). Although PTBD is widely available, it carries substantial morbidity, requires external catheters, and is associated with recurrent infections and reduced quality of life. EUS-BD offers internal drainage with favorable outcomes across established techniques, but comparative evidence versus PTBD remains limited. We performed a systematic review and meta-analysis comparing EUS-BD and PTBD after failed ERCP in malignant biliary obstruction. **Methods:** This review followed PRISMA guidelines. PubMed, Google Scholar, and ScienceDirect were searched using a comprehensive strategy. Comparative studies evaluating EUS-BD versus PTBD and reporting technical success (TS: bile duct puncture with stent/catheter placed in the intended position), clinical success (CS: > 50% bilirubin reduction at 2 weeks), adverse events (AD: graded as per the ASGE endoscopic AE severity lexicon), and reintervention (RN) were included. The data was analysed using the Meta, Metadata and the Metafor packages of R Studio. The Mantel-Haenszel method and the Inverse variance method were utilized to analyse the odds ratio for TS, CS, AD, and RN. The I^2 test was used to assess the heterogeneity of the studies. **Results:** Twenty-six studies were included. EUS-BD was associated with higher clinical success (OR 2.46, 95% CI 1.47–4.11) and lower odds of adverse events (OR 0.38, 95% CI 0.26–0.57) and reintervention (OR 0.19, 95% CI 0.09–0.42). Technical success did not differ significantly between groups (OR 0.49, 95% CI 0.21–1.13). **Conclusions:** Compared with PTBD, EUS-BD is associated with improved clinical success and fewer adverse events and reinterventions after failed ERCP in malignant biliary obstruction. Where expertise is available, EUS-BD may be favored over PTBD. Prospective randomized trials are needed to confirm these findings and support broader adoption. Research Sponsor: None.

Pooled outcomes for EUS-BD vs PTBD.

Outcome/Metric	Comparison	Effect measure	Estimate (OR)	95% CI (lower)	95% CI (upper)	p-value	Direction/Interpretation
Clinical success	EUS-BD vs PTBD	OR	2.46	1.47	4.11	0.1328	Favors EUS-BD (higher odds of success)
Adverse events	EUS-BD vs PTBD	OR	0.38	0.26	0.57	0.1923	Favors EUS-BD (lower odds of adverse events)
Reintervention	EUS-BD vs PTBD	OR	0.19	0.09	0.42	0.0003	Favors EUS-BD (lower odds of reintervention)
Technical success	EUS-BD vs PTBD	OR	0.49	0.21	1.13	0.3321	Not statistically significant

Prevalence and prognostic value of Claudin 18.2 expression in pancreatic ductal adenocarcinoma.

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Background: Although Claudin18.2 expression (CLDN18.2) has been investigated in pancreatic ductal adenocarcinoma (PDAC), prevalence and prognostic significance remain inconsistent. This study evaluated both the prevalence and prognostic value of CLDN18.2 expression in PDAC. **Methods:** CLDN18.2 expression was assessed by IHC on FFPE tumor samples from 201 patients with PDAC enrolled in the BIOPAC study (NCT03311776) between Jan 2013-Feb 2024. Staining was performed using the Ventana CLDN18 (43) CE IVD Assay (Roche Diagnostic Solutions). All slides were independently scored by two pathologists, with discrepancies resolved by consensus. Positive expression was defined as moderate (+2) or strong (+3) staining in $\geq$75% of tumor cells. Patients with non-metastatic disease were excluded from the survival analysis to reduce prognostic confounding. OS and PFS were evaluated using Kaplan-Meier estimates, log-rank tests, and multivariable Cox models adjusted for stage, age, sex, chemotherapy type, diabetes, ECOG performance status, Body Mass Index, and Charlson Age-Adjusted Comorbidity Index. Associations with clinicopathological variables were evaluated using Mann-Whitney U, χ^2, or Fisher's exact tests with Bonferroni correction ($p < 0.05$ considered significant). **Results:** Of 201 patients, 56 had non-metastatic disease and 145 had metastatic disease. Positive CLDN18.2 expression was detected in 54 tumors (27% overall): 14 (25%) non-metastatic and 40 (28%) in metastatic cases. In patients with metastatic disease, the median OS was 9.9 months (95% CI, 6.7-12.8) in the CLDN18.2 positive group and 6.3 months (95% CI, 4.9-8.5) in the negative group, with a significant difference as demonstrated by log-rank test (p = 0.009). CLDN18.2 positivity was associated with improved OS in univariate analysis (HR = 0.60; 95% CI 0.41-0.89; p = 0.010) but was not statistically significant after adjustment for covariates (HR = 0.69; 95% CI 0.47-1.02; p = 0.064). A similar pattern was observed for PFS, with median PFS of 6.0 months (95% CI, 3.6-7.6) in the CLDN18.2 positive group and 4.1 months (95% CI, 3.4-5.3) in the negative group (log-rank p = 0.036). The unadjusted association between CLDN18.2 positivity and longer PFS (HR = 0.67; 95% CI 0.46-0.98; p = 0.037), was not maintained after multivariable adjustment (HR = 0.67; 95% CI 0.43-1.03; p = 0.066). No significant associations were identified between CLDN 18.2 expression and clinicopathological variables after correction for multiple testing. **Conclusions:** CLDN18.2 was expressed in 27% of PDAC tumors. While its association with OS and PFS was not statistically significant after adjustment for clinical covariates, its prevalence in metastatic cases highlights its potential relevance as a therapeutic target in PDAC. Ongoing validation in an expanded cohort may further clarify the prognostic and predictive significance of CLDN18.2 expression. Research Sponsor: Astellas Pharma Europe Ltd.

Multicenter phase 2 study of hydroxychloroquine (HCQ) and chlorphenesin carbamate (CPC) in combination with mFOLFIRINOX in patients with advanced pancreatic adenocarcinoma (PDAC).

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Background: PDAC is one of the most lethal malignancies, with most patients (pts) presenting with advanced disease. Although combination chemotherapy, including modified FOLFIRINOX (mFOLFIRINOX) has improved survival, overall prognosis remains poor. Our preclinical studies suggest that HCQ and CPC synergistically enhance the antitumor activity of mFOLFIRINOX by inhibiting autophagy-dependent and AKT-mediated epithelial-mesenchymal transition pathways. **Methods:** This multicenter, single-arm phase 2 study included pts with locally advanced unresectable or metastatic PDAC in the first-line setting from three academic institutions in Korea. HCQ (200 mg) and CPC (250 mg) were administered orally twice daily in combination with mFOLFIRINOX for up to 24 cycles or until disease progression or unacceptable toxicity occurred. The primary endpoint was safety profile. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), cumulative incidence of new distant metastases, and health-related quality of life (HRQOL). **Results:** Between December 2021 and February 2023, 45 pts were screened and a total of 40 patients received study treatment. The median age was 61 years, and 23 (57.5%) were male; 73% (n = 29) and 27% (n = 11) had metastatic and locally advanced disease, respectively. The median number of cycles patients received was 13 (range, 1-24). Dose reductions for HCQ and CPC occurred in four (10%) pts each, with median $>$ 90% of treatment compliance for both agents. Safety profiles are mostly consistent with known adverse events (AEs) with mFOLFIRINOX; grade 3-4 neutropenia (40%), nausea (13%), anemia (10%) were most common severe AEs. In the efficacy analysis set (n = 39), the ORR was 39% (CR or PR; n = 15), and the disease control rate was 92.3% (CR, PR or SD; n = 36). Curative-intent conversion surgery was performed in five pts (13%). With a median follow-up of 33.3 months, the median PFS was 7.4 months (95% CI, 6.2–13.3); in pts with objective response, median PFS was 13.6 months (95% CI, 7.4–33.8). The median OS was 14.8 months (95% CI, 9.6–27.9); median 20.5 months (95% CI, 14.8–NE) for locally advanced disease and median 13.9 months (95% CI, 9.2-NE) for metastatic disease. The cumulative incidence of new distant metastases was 38.8% at 12 months. HRQOL indicators did not deteriorate during the first 6 months of study treatment. **Conclusions:** HCQ and CPC in combination of mFOLFIRINOX were well tolerated and showed clinically promising efficacy outcomes in pts with advanced PDAC. Biomarker analysis using proteomics is ongoing. Clinical trial information: NCT05083780. Research Sponsor: Oncocross.

HRS-4642 combined with adebrelimab in previously treated patients with metastatic pancreatic ductal adenocarcinoma.

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Background: Nearly 90% pancreatic ductal adenocarcinoma (PDAC) tumors were driven by RAS mutations, including KRAS G12D (~40%). The high prevalence of KRAS G12D mutations is thought to play a vital role in the universally immunosuppressive tumor microenvironment of PDAC. HRS-4642 is a highly selective KRAS G12D inhibitor. Here, we report preliminary results of HRS-4642 combined with adebrelimab (an anti-PD-L1 antibody) in patients (pts) with KRAS G12D-mutant PDAC. **Methods:** The study comprised two parts. Phase 1 (Dose escalation): A "3+3" design was used to determine the recommended phase 2 dose (RP2D) of HRS-4642 (4 dose levels: 300, 400, 500mg, qw; and 500mg D1/1200mg D8, q3w) combined with fixed-dose adebrelimab (1200mg iv, Day 1, q3w). Phase 2 (Dose expansion): Simon's two-stage optimal design was applied, requiring at least five objective responses. The primary endpoints were safety and RP2D (phase 1), and objective response rate (ORR; phase 2). The key secondary endpoints included progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). **Results:** As of Dec 31, 2025, 48 pts were enrolled, with 87.5% having received ≥2 prior lines of therapy. No dose-limiting toxicity (DLT) occurred during phase 1, and the RP2D was determined as HRS-4642 (500mg D1/1200mg D8, q3w) with adebrelimab. Treatment-related adverse events (TRAEs) occurred in 47 pts (97.9%). The most common grade 3/4 TRAEs included lipase increased (16.7%), gamma-glutamyl transpeptidase increased (12.5%), and blood cholesterol increased (8.3%). No treatment related deaths occurred. Among 43 pts with post-baseline tumor assessment, the confirmed ORR was 41.9% and DCR was 83.7%, with a median mPFS of 5.6 months; the median mOS was not reached. Notably, the RP2D group (n=33) achieved a confirmed ORR of 48.5% and a DCR of 90.9%, successfully meeting the primary endpoint. **Conclusions:** HRS-4642 combined with adebrelimab showed a manageable safety profile and promising anti-tumor activity in metastatic PDAC harboring KRAS G12D mutation. Clinical trial information: NCT06427239. Research Sponsor: None.

Efficacy Evaluation.

	All (n=43)	RP2D (n=33)
Objective response, n (%)	18 (41.9)	16 (48.5)
Best response, n (%)		
Partial Response	18 (41.9)	16 (48.5)
Stable Disease	18 (41.9)	14 (42.4)
Progressive Disease	7 (16.3)	3 (9.1)
Disease control rate, n (%)	36 (83.7)	30 (90.9)
Median progression-free survival, months (95%CI)	5.6 (4.0-7.3)	5.9 (4.2-7.9)
Median overall survival, months (95%CI)	NR	11.5 (9.2-NR)

SHR-A2102, a Nectin-4 targeted antibody-drug conjugate, combined with HRS-4642 in previously treated pancreatic ductal adenocarcinoma harboring KRAS G12D mutation.

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Background: Patients (pts) with previously treated advanced pancreatic ductal adenocarcinoma (PDAC) have limited options. The high prevalence of Nectin-4 expression (~71%) and KRAS G12D mutations in PDAC provides a rationale for dual targeting. Here we report results from a molecularly defined cohort in a phase 2 platform trial evaluating the combination of SHR-A2102 and HRS-4642, a KRAS G12D inhibitor. **Methods:** Eligible pts with Nectin-4 expression and KRAS G12D mutation who had failed standard therapy were enrolled. During the safety run-in, 2 dose levels of SHR-A2102 were evaluated in combination with HRS-4642 (500mg Day 1/1200mg Day 8, iv, q3w) to determine the recommended expansion dose (RED). The Bayesian Optimal Phase II (BOP2) design was applied for efficacy expansion, with a planned enrollment of 10 to 30 pts. The primary endpoints were safety and RED (safety run-in), and objective response rate (ORR; efficacy expansion). The key secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DoR), and disease control rate (DCR). **Results:** As of Dec. 31, 2025, 36 pts were enrolled and treated (median age, 61 years; ECOG PS 1, 86.1%; ≥2 lines of prior therapy, 88.9%; median Nectin-4 H-score, 10). No dose-limiting toxicity (DLT) occurred, and the RED was established as SHR-A2102 (8mg/kg iv, q3w) plus HRS-4642. Treatment-related adverse events (TRAEs) occurred in all pts (100%), with no grade 5 TRAEs. 13 pts (36.1%) experienced grade 3/4 TRAEs, the most common including neutrophil count decreased and gamma-glutamyl transpeptidase increased (each 11.1%), and anemia (8.3%). In the RED group (n=30), the confirmed ORR was 36.7% (11PR) and the DCR was 86.7%, meeting the primary endpoint. ORR showed no apparent correlation with Nectin-4 H-score. The median DoR was 6.3 months (range: 4.4-NR); the median PFS was 4.1 months (range: 2.7-5.7), and the median OS was not reached. **Conclusions:** SHR-A2102 combined with HRS-4642 showed a tolerable safety profile and promising preliminary antitumor activity in advanced PDAC harboring KRAS G12D mutation, irrespective of Nectin-4 expression. Clinical trial information: NCT06547736. Research Sponsor: None.

Spevatamig (PT886), a claudin 18.2 (CLDN18.2)/CD47 bispecific antibody, in combination with gemcitabine plus nab-paclitaxel (GnP) in frontline (1L) treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC).

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Background: Spevatamig is an IgG1-based bispecific antibody targeting CLDN18.2 and CD47 with an optimized anti-CD47 arm designed to bind to CD47 more highly on cancer cells than on human red blood cells. We have previously described its monotherapy safety data and preliminary combination efficacy data in 1L mPDAC (Saeed et al., J Clin Oncol. 2026). Herein, we provide updated data from patients in the 1L mPDAC cohort, including additional efficacy data from the 2 mg/kg QW spevatamig + GnP dose level and new safety data from the 3 mg/kg QW spevatamig + GnP dose level. **Methods:** TWINPEAK is a multi-cohort Phase 1/2 dose escalation and expansion study (US: NCT05482893; China: CTR20252758) of spevatamig as monotherapy or combination therapy (with chemotherapy and/or an immune-checkpoint inhibitor) in patients with select gastrointestinal (GI) cancers. Here we report data from the Phase 2 cohort of spevatamig + GnP in 1L mPDAC at 2 dose levels: 2 mg/kg QW (N=22) and 3 mg/kg QW (N=22). Key endpoints include safety and tolerability, objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS) and median overall survival (mOS). **Results:** As of January 15, 2026, 151 patients have been treated with spevatamig collectively in monotherapy and combination settings. In the 2 mg/kg QW spevatamig + GnP dose level (N=22), spevatamig continues to demonstrate tolerability when combined with chemotherapy, with cytopenia rates not exceeding those anticipated with GnP and no grade $\geq$ 3 nausea or vomiting events. The ORR is 48%, DCR is 90%, mPFS is 7.3 months (95% confidence interval: 5.6 months - not yet reached) and mOS is $>$13 months (still maturing), with a median follow-up duration of 8.9 months. Antitumor activity was demonstrated irrespective of tumor CLDN18.2 expression levels and RAS mutational status. In the 3 mg/kg QW spevatamig + GnP dose level (N=22), no significant additive toxicity was noted when compared to the adverse event profile anticipated with GnP alone among patients with available safety data. No grade $\geq$ 3 nausea or vomiting events occurred. Updated safety data will be provided at the meeting for patients in this dose level. **Conclusions:** Overall, spevatamig 2 mg/kg QW or 3 mg/kg QW + GnP is well tolerated, with no significant additive toxicity compared to the adverse event profile anticipated with GnP alone. The additional efficacy data from patients treated at the 2 mg/kg QW spevatamig + GnP dose level continues to demonstrate promise when compared to pivotal trials of GnP in 1L mPDAC; enrollment into the 3 mg/kg QW spevatamig + GnP dose level is ongoing with maturing efficacy data. These two dose levels exhibit good combinability with chemotherapy and can be assessed in future combination studies with novel targeted therapies such as KRAS inhibitors. Clinical trial information: NCT05482893. Research Sponsor: None.

Safety and efficacy of nesuparib (JPI-547) with gemcitabine-nab-paclitaxel (GemAbraxane) or modified FOLFIRINOX (mFOLFIRINOX) in patients with locally advanced or metastatic PDAC: Results from an ongoing phase Ib/II study.

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies with poor outcomes in advanced disease. Nesuparib is a dual tankyrase (TNKS) and poly(ADP-ribose) polymerase (PARP) inhibitor that induces a "BRCAness" phenotype via WNT and Hippo signaling. This Phase Ib study evaluated the safety, tolerability, and preliminary antitumor activity of nesuparib combined with standard first-line chemotherapy in patients with locally advanced or metastatic PDAC. **Methods:** This multicenter, open-label, Phase Ib dose-finding study evaluated oral nesuparib plus GemAbraxane or mFOLFIRINOX in advanced PDAC. Nesuparib was administered orally using a 3+3 dose-escalation design with intermittent schedules, including DL1 (25 mg, 5 days on/2 days off), DL-1 (12.5 mg, 5 days on/2 days off), and DL-2 (12.5 mg, 3 days on/4 days off). Primary objectives were to assess safety and determine the maximum tolerated dose and recommended Phase II dose. Secondary objectives included preliminary efficacy. **Results:** As of December 31, 2025, 27 patients were enrolled and treated (GemAbraxane, n = 14; mFOLFIRINOX, n = 13). Most patients had metastatic disease. In the GemAbraxane arm, acceptable tolerability was confirmed at DL-1 and DL-2, whereas tolerability was not established in the mFOLFIRINOX arm. Across both treatment arms, grade 3/4 AEs were mainly hematologic toxicities. Rates of anemia, thrombocytopenia, and neutropenia were 57.1%, 64.3%, and 92.9% in the GemAbraxane arm, compared with 84.6%, 92.3%, and 84.6% in the mFOLFIRINOX arm, respectively. No treatment-related deaths occurred, and most AEs were manageable with standard supportive measures. Non-hematologic AEs were mostly low-grade and manageable. In the GemAbraxane arm, the objective response rate (ORR) and disease control rate (DCR) were 53.8% and 92.3%, respectively, including one patient with a complete response (CR) of the target lesion and overall survival exceeding 3 years. Median progression-free survival (mPFS) was not reached, and median overall survival (mOS) was 14.2 months (data immature and follow-up is ongoing). In the mFOLFIRINOX arm, the ORR was 38.5% with a DCR of 92.3%, while mPFS and mOS were 7.33 and 18.5 months, respectively. **Conclusions:** Nesuparib combined with GemAbraxane demonstrated acceptable tolerability and encouraging antitumor activity in advanced PDAC. These findings support further evaluation of nesuparib using a 12.5 mg intermittent dosing schedule in the first-line treatment setting; a Phase II trial is currently ongoing. Clinical trial information: NCT05257993. Research Sponsor: None.

Outcome	Nesuparib + GemAbraxane (n=13)	Nesuparib + FOLFIRINOX (n=13)
PR	7 (53.8%)	5 (38.5%)
SD	5 (38.5%)	7 (53.8%)
PD	1 (7.7%)	1 (7.7%)
ORR	53.8%	38.5%
DCR	92.3%	92.3%
mOS	14.20 mo (data immature)	18.50 mo
mPFS	Not reached	7.33 mo

MUC5AC-driven transcriptional reprogramming for stratification of pancreatic ductal adenocarcinoma by immune suppression and stromal remodeling.

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Background: Mucin 5AC (MUC5AC) is aberrantly expressed in pancreatic ductal adenocarcinoma (PDAC) and associated with tumor progression; however, its role in altering the tumor immune microenvironment (TIME) and immunotherapy-relevant pathways is poorly understood. Thus, we evaluated whether MUC5AC expression delineates PDAC into distinct transcriptional and immunologic subtypes based on TIME. **Methods:** Bulk RNA-seq data from 730 PDAC tumors (Oncology Research Information Exchange Network, ORIEN) and 360 normal pancreatic tissues (GTEx) were analyzed. Differential gene expression and pathway enrichment were assessed using Gene Ontology and KEGG analyses. Immune infiltration and stromal states were inferred using multiple complementary deconvolution algorithms (CIBERSORT and xCell). Tumors in the lowest quartile of MUC5AC expression (≤25th percentile; MUC5AC-low, MUC5AC-L) were compared with the remaining samples (MUC5AC-high, MUC5AC-H). Associations between MUC5AC expression and immune cell populations and immunomodulatory genes were evaluated by using correlations and group-based analyses with false discovery rate (FDR) corrections. **Results:** Principal component analysis demonstrated clear separation between PDAC tumors and normal pancreas and revealed distinct transcriptional programs between MUC5AC-H (N = 544) and MUC5AC-L (N = 186) tumors. MUC5AC-H tumors exhibited a profoundly immunosuppressive and stromal-remodeled TIME, including enrichment of M2 macrophages, regulatory T cells, activated natural killer ells, fibroblast-associated signatures, and significantly higher immune and stromal scores (multiple FDR $\leq 10^{-6}$ to $\leq 10^{-28}$). In contrast, MUC5AC-L tumors showed relatively enrichment of immune-activating populations, including naïve B cells, dendritic cell subsets, resting $CD4^+$ memory T cells, and $CD8^+$ T cells (multiple FDR $< 10^{-15}$). MUC5AC expression strongly correlated with immune checkpoint genes *CD274* (PD-L1) and *TIGIT*, and with multiple suppressive immune populations ($p < 0.01$ to $< 10^{-10}$). **Conclusions:** MUC5AC defines a transcriptionally distinct, immunosuppressive PDAC subtype characterized by stromal activation, macrophage/Treg enrichment, and immune checkpoint engagement. MUC5AC may serve as a biomarker for immune stratification and supports rational combination strategies integrating stromal targeting with immune checkpoint modulation in PDAC. Research Sponsor: ORIEN Foundation.

First-line NALIRIFOX in patients with metastatic pancreatic ductal adenocarcinoma and pre-existing diabetes: NAPOLI 3 post hoc analysis.

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Background: Approximately 29% of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) present with pre-existing diabetes. Diabetes increases the risk of peripheral neuropathy (PN), raising concerns that oxaliplatin-containing regimens may exacerbate PN risk. NALIRIFOX (liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil) is approved for first-line (1L) treatment of mPDAC based on significantly improved overall survival versus nab-paclitaxel plus gemcitabine (Gem+NabP) in the phase 3 NAPOLI 3 trial (hazard ratio 0.83; 95% confidence interval [CI] 0.70–0.99). The overall response rate (ORR) for NALIRIFOX was 41.8% (95% CI: 36.8–46.9%) and no unexpected safety concerns were identified. This *post hoc* exploratory analysis of NAPOLI 3 evaluates outcomes including PN development among patients with pre-existing diabetes. **Methods:** Patients randomized to 1L NALIRIFOX in NAPOLI 3 who had pre-existing diabetes were assessed, with subgroups according to whether or not they developed PN. The primary endpoint was ORR; patient characteristics and adverse event rates were also described. No hypotheses were tested owing to small sample sizes; results are descriptive. **Results:** Of 383 patients randomized to receive NALIRIFOX in NAPOLI 3, 96 (25%) had pre-existing diabetes, of whom 94 were included in the safety population. PN developed in 13/94 (14%) patients (Grade ≥3: 2/13 [15%]) with pre-existing diabetes, none of whom had evidence of PN at baseline. Among patients without diabetes, PN developed in 53/276 (19%; Grade ≥3: 10/53 [19%]). Patients with pre-existing diabetes who developed PN had a lower median age, lower proportion of males, higher metastatic burden, and higher frequency of tumors in the body of the pancreas than patients who did not develop PN (Table). Among patients with pre-existing diabetes, ORR for NALIRIFOX was 43.8% (42/96 [95% CI: 33.6–54.3%]); all responses were partial. ORR was 69.2% (9/13 [95% CI: 38.6–90.9%]) among patients with pre-existing diabetes who developed treatment-emergent PN and 40.7% (33/81 [95% CI: 29.9–52.2%]) among those who did not (Table). **Conclusions:** In this exploratory analysis, PN incidence and clinical outcomes in patients with pre-existing diabetes were consistent with those without diabetes and with the overall NALIRIFOX population. In this small population, pre-existing diabetes did not appear to put patients at risk of developing treatment-emergent PN or to impact treatment outcomes. Clinical trial information: NCT04083235. Research Sponsor: Ipsen.

	Patients with baseline diabetes who developed peripheral neuropathy (n = 13)	Patients with baseline diabetes who did not develop peripheral neuropathy (n = 81)
Baseline characteristics		
Age, median, years	63.0	66.0
Male, n (%)	6 (46.2)	52 (64.2)
≥ 3 metastatic sites, %	53.8	40.7
Tumor in body of pancreas, %	38.5	22.2
Efficacy		
ORR, % (95% CI)	69.2 (38.6–90.9)	40.7 (29.9–52.2)

Precision Promise (PrP): Success rates of paired biopsies and biomarker testing results for metastatic pancreatic cancer (mPDAC) in a multi-center trial.

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Background: PrP, a phase 2/3 Bayesian adaptive platform trial sponsored by the Pancreatic Cancer Action Network, was developed to test multiple experimental arms efficiently against common controls and explore biomarkers of response/resistance in mPDAC (Picozzi, ASCO TPS 4188, 2022). **Methods:** At screening, core tissue biopsies and matched blood collection were performed for first- and second-line patients (pts) with mPDAC. Week 8 (W8) core tissue biopsies and blood collection were performed for pts receiving study drug. Formalin-fixed paraffin embedded (FFPE) tissue slides were prepared at the central lab; tissue and matched blood samples were analyzed for genomic and transcriptomic analyses using Tempus xT (DNA) and xR (RNA) testing, respectively. The workflow prioritized DNA followed by RNA isolation. **Results:** Tissue biopsies were obtained at screening from 491 of 700 (70%) pts across 24 US sites; W8 tissue biopsies were obtained from 228 of 443 (51%) pts receiving study drug. Reasons for biopsies not being collected included: contraindicated; attempted, but no tissue obtained; pt screened out; pt stopped study drug before W8 (W8 only). 21% (103/491) screening and 32% (74/228) W8 biopsies submitted for biomarker testing contained insufficient tumor tissue for testing; 4% (20 pts) of screening and 4% (10 pts) of W8 biopsies were not processed into FFPE or testing was cancelled. Of the 368 pts with screening tissue sequenced, genomic data were generated for 83% (304 pts); 17% (64 pts) had Quantity Not Sufficient (QNS) for DNA. Transcriptomic data were generated for 49% (179 pts); in 42% (155 pts) insufficient tumor tissue remained for RNA testing and 9% (34 pts) had QNS for RNA. Of the 144 pts with W8 tissue sequenced, genomic data were generated for 71% (102 pts); 29% (42 pts) had QNS for DNA. Transcriptomic data were generated for 31% (44 pts); in 58% (84 pts) insufficient tumor tissue remained for RNA testing and 11% (16 pts) had QNS for RNA. Locations of tissue biopsies across both timepoints (719) were: 68% liver, 16% pancreas, 16% other metastatic sites. Success rates for biomarker testing across all tissue obtained was higher for liver metastases (65% DNA results; 37% RNA results) than for primary tumors in the pancreas (42% DNA results; 19% RNA results). Distribution of actionable biomarkers detected will be presented. **Conclusions:** These data demonstrate success rates of paired biopsy acquisition and subsequent genomic and transcriptomic analysis in a large phase 2/3 multi-center platform trial for mPDAC. Attrition was noted for biopsy collection and downstream biomarker testing at screening and more so at W8 on study drug. Biomarker testing success rates varied by tissue location. These findings along with planned data interrogation and future sample analyses will provide insights to guide future trial design and clinical decision making. Clinical trial information: NCT04229004. Research Sponsor: Pancreatic Cancer Action Network.

LAP-NET1: Results of a phase 1b evaluating NP137, an inhibitor of the epithelial-to-mesenchymal transition, in combination with mFOLFIRINOX for the first-line treatment of locally advanced pancreatic ductal adenocarcinoma.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy characterized by aggressive tumor dissemination and resistance to therapy; processes significantly driven by the epithelial-to-mesenchymal transition (EMT). Netrin-1 is a key regulator for EMT. NP137, an anti-netrin-1 antibody, has shown to inhibit EMT in preclinical models and in a phase 1 monotherapy trial. **Methods:** LAPNET-01 (NCT06203821) is a single arm phase Ib clinical study to assess the combination of NP137 with mFOLFIRINOX in naive locally advanced unresectable PDAC. A safety lead-in (3–12 pts, 3+3 design, NP137 14 vs 9 mg/kg) was followed by a 40-patient expansion. Treatment consisted of NP137 + mFOLFIRINOX every 2 weeks, up to 12 cycles. The primary endpoint was safety at 6 months (all-grade and grade 3/4 adverse events [AEs], CTCAE v5.0). Secondary endpoints included objective response rate (ORR), progression-free survival (PFS) and overall survival (OS), surgical conversion rate and exploratory transcriptomic analyses. Laser capture microdissection was performed on 22 pre-treatment and 6 surgery samples to allow microbulk RNA sequencing. Immunohistochemistry was also performed on pre-treatment samples. **Results:** A total of 43 patients were enrolled in this trial. NP137 was well tolerated. AE occurred in 100% of patients (58% grade $\geq$ 3). ORR and disease control rate were 29% and 95%. Median PFS was 10.9 months (95% CI, 10.0 – 15.6) and median OS was 16.4 months (95% CI, 12.8 – NR) with 21 patients still alive at time of the data cut-off. Surgery was made possible in 23% of patients. Microbulk RNA sequencing revealed that the main pathway downregulated with the combination mFOLFIRINOX+NP137 is EMT, bringing a clinical validation of the main mechanism of action of NP137. Moreover, patients with tumors expressing high levels of the netrin-1 receptor neogenin (high-NEO1) at baseline (both at the RNA and proteic level (IHC)) demonstrated an improved outcomes compared to the low-NEO1 subgroup including longer median PFS (15.7 vs 10.2 months, p = 0.01) and longer median OS (not reached vs 16.5, p = 0.024). These results are consistent with experimental data demonstrating the implication of NEO1 in PDAC EMT and its progression. **Conclusions:** NP137 in combination with mFOLFIRINOX demonstrates a favorable safety profile, promising clinical activity and a mechanistically distinct mode of action supported by translational analyses. These results warrant further investigation of netrin-1 blockade in randomized trials and provide a rationale for biomarker-driven development of NP137 in PDAC. Further work is ongoing to better characterize the distribution of NEO1 in first-line unresectable PDAC. Clinical trial information: NCT06203821. Research Sponsor: NETRIS Pharma; CHU Grenoble Alpes.

Surufatinib plus KN046 and chemotherapy as first-line treatment for advanced pancreatic ductal adenocarcinoma: Updated results and biomarker analysis from a phase 1b/2 trial.

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Background: In China, gemcitabine (G) and nab-paclitaxel (nP) remain the standard first-line (1L) therapy for patients (pts) with advanced pancreatic ductal adenocarcinoma (PDAC). Our previous report (Wang W, et al; 2025 ASCO) showed that the add-on of surufatinib (S, multi-kinase inhibitor) and KN046 (K, bi-specific PD-L1/CTLA-4 antibody) to GnP chemotherapy provided enhanced anti-tumor activity in advanced PDAC. Here we present the updated results and findings from a biomarker analysis. **Methods:** In this single-arm, phase 1b/2 trial (NCT05832892), eligible pts with treatment-naïve advanced PDAC received oral S (200~250 mg, once daily), intravenous K (5 mg/kg, on day 1) and GnP (G 1000 mg/m^2, nP 125 mg/m^2, on days 1 & 8) at 21-day cycles till disease progression or intolerable toxicity. The primary efficacy endpoint was ORR per RECIST 1.1; secondary endpoints included DCR, PFS, OS and safety; efficacy-predictive biomarkers were exploratory endpoints. **Results:** Overall, 31 pts were enrolled with a median age of 56 years (range 40–74) and a predominant male gender (74.2%). Distant metastasis was present in 28 (90.3%) pts and 24 (77.4%) had liver metastasis (LM) at baseline. Best overall responses included 4 CR, 18 PR, and 6 SD. The ORR was 71.0% (95% CI 52.0–85.8) and DCR was 90.3% (95% CI 74.2–98.0). As of Dec 25, 2025, with a median follow-up of 15.9 months, median PFS was 8.2 months (95% CI 6.1–not estimable [NE]). Median OS was 18.0 months (95% CI 13.8–NE) with a 12-month OS rate of 68.2% (95% CI 50.8–91.6). Baseline LM was correlated to significantly worse PFS (8.0 vs NE months, log-rank P= 0.02), though no significant impact on ORR (73.9% vs 62.5%, P= 0.66), DCR (91.3% vs 87.5%, P= 1.00) or OS (13.8 vs NE, log-rank P= 0.12) was observed. Among the 27 pts who received ≥4 cycles of treatment, 22 (81.5%) and 19 (70.4%) experienced a decline in CA199 and CA125 from baseline, respectively, while fewer (37.0%) had CEA declined. A ≥50% decline in CA199 was correlated to significantly improved PFS (10.3 vs 8.1 months, log-rank P= 0.01) and a trend towards improved OS (NE vs 11.1 months, log-rank P= 0.11), as compared to a milder decrease or increase in CA199; Such correlation was not observed for CA125 or CEA. Treatment-related adverse events (TRAEs) occurred in 29 (93.5%) pts, of whom 14 (45.2%) experienced Grade ≥3 events, with hypertension (12.9%), neutropenia (12.9%), and thrombocytopenia (9.7%) being the most frequently observed. No treatment-related serious adverse events or deaths occurred. **Conclusions:** S plus K and GnP demonstrated consistently encouraging efficacy and manageable safety in 1L treatment of advanced PDAC. Early and sharp decline in CA199 may predict more favorable survival benefit. Analyses in genetic profile and its impact on clinical outcome will be carried out in future, and investigations in larger population are warranted. Clinical trial information: NCT05832892. Research Sponsor: HUTCHMED, ALPHAMAB.

Precemtabart tocentecan (Precem-TcT, M9140), an anti-CEACAM5 antibody-drug conjugate (ADC), in patients with metastatic pancreatic ductal carcinoma (mPDAC): Results from the phase 1b/2 PROCEADE-PanTumor PDAC substudy.

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Background: CEACAM5 is overexpressed in many cancers, including PDAC, with limited expression in normal tissues. Precem-TcT, an anti-CEACAM5 ADC with an exatecan payload (topoisomerase 1 inhibitor [TOP1i]), showed a predictable, manageable safety profile and promising clinical activity (ORR: 31.0%; mPFS: 6.9 months) in the Phase 1 PROCEADE-CRC-01 study (NCT05464030) in patients with heavily pretreated metastatic colorectal cancer (mCRC). **Methods:** PROCEADE-PanTumor (NCT06710132) is an ongoing, Phase 1b/2, open-label study investigating the efficacy and safety of Precem-TcT monotherapy in advanced PDAC, gastric cancer, and non-small cell lung cancer. Here, we report interim results from the PDAC substudy, which enrolled patients with pretreated mPDAC (ECOG PS ≤1; and CEACAM5-^{high} expression [≥50% tumor cells with immunohistochemistry ≥2+ staining]) in the US, Australia, France, Japan, and Korea, who were treated with Precem-TcT 2.8 mg/kg Q3W. **Results:** Between May and September 2025, 46 patients have been enrolled into the study (median age: 62.0 years; female: 65.2%; ECOG PS 0/1: 47.8%/52.2%). Most patients received one or two prior lines of therapy, and were irinotecan pretreated. As of November 2025, median duration of Precem-TcT treatment was 12.6 weeks. Treatment emergent adverse events (TEAEs) occurred in 95.7% of patients; grade ≥3: 78.3%. Most common grade ≥3 TEAEs were neutropenia (43.5%) and anemia (32.6%). Gastrointestinal TEAEs were mostly grade 1-2, and there were no cases of interstitial lung disease or ocular toxicities. TEAEs led to dose reductions in 15.2% and to permanent discontinuation in 4.3% of patients. There were no treatment-related deaths. As of January 2026, 10 patients had a PR (21.7%), 20 SD (43.5%), and 11 PD (23.9%); 14 patients remain on study. Updated data, including mPFS and CEACAM5 expression, will be presented at the congress. Preliminary pharmacokinetics of the conjugated antibody and unconjugated exatecan appeared generally consistent with previous data from patients with mCRC. **Conclusions:** Precem-TcT, the first anti-CEACAM5 ADC with a TOP1i-payload reporting clinical data in patients with mPDAC, showed a predictable safety profile in this population, consistent with data from patients with mCRC. Efficacy data in this highly refractory, mostly irinotecan-pretreated 2L/3L population benchmark favorably with the current SoC for 2L mPDAC. Clinical trial information: NCT06710132. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Phase Ib/II clinical study of adebrelimab combined with decitabine, nab-paclitaxel, and gemcitabine as first-line (IL) treatment for metastatic pancreatic cancer (mPC).

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Background: Epigenetic enzyme inhibitors may synergize with immunotherapy by modulating antigen presentation and enhancing tumor-related gene expression. Preclinical studies suggest that low-dose decitabine can restore chemosensitivity in chemotherapy-resistant tumors. We conducted the Ib/II study to explore the efficacy and safety of decitabine combined with adebrelimab, nab-paclitaxel, and gemcitabine as 1L treatment for mPC. **Methods:** Eligible patients (pts) were prior untreated mPC or pts who had experienced disease progression more than six months after the end of postoperative adjuvant therapy. In the phase Ib, enrolled pts received dose escalation of decitabine (10 mg/m^2/15 mg/m^2,iv,d1-d3,q4w), adebrelimab (1200mg,iv,d1,q3w) , nab-paclitaxel (125 mg/m^2, iv,d1,d8,d15,q4w), and gemcitabine (1000 mg/m^2,iv,d1,d8,d15,q4w) to determine the recommended phase 2 dose (RP2D) in a standard 3+3 design. In the phase II, pts received decitabine at the RP2D, adebrelimab, nab-paclitaxel and gemcitabine combination therapy. Primary endpoints were dose-limiting toxicities, RP2D, and objective response rate (ORR). Secondary endpoints included overall survival, progression free survival, disease control rate (DCR), duration of response, and safety. **Results:** From April 2024 to February 2025, 28 pts were enrolled and the median age was 62 yrs; 69.2% male, and 80.8% ECOG PS 1. The Ib phase established the RP2D of decitabine as 10 mg/m^2. Total of 22 pts were included in the efficacy analysis. The median follow-up was 11.9 mo. The ORR was 46% (10PR, 9SD, 3PD) and DCR was 86.4%. Median duration of response (mDoR) was 10.94 months, while the median progression-free survival (mPFS) was 6.47 months. 24 pts were analyzed for safety. The most common TRAEs of any grade were anemia (95.8%), lymphocyte count decreased (79.2%), hypoalbuminemia (75.0%), hyponatremia (75.0%), vomiting (66.7%). Grade ≥3 TRAEs were were anemia (25.0%), white blood cell decreased (20.8%), platelet count decreased (20.8%), lymphocyte count decreased (12.5%), neutrophil count decreased (12.5%). No new safety signals were observed. **Conclusions:** This study preliminarily demonstrates that the decitabine combination regimen has favorable efficacy and safety in 1L treatment of mPC. Future clinical studies with larger sample sizes are needed to be validated. Clinical trial information: NCT06454448. Research Sponsor: Tianjin Science and Technology Commission key project; 25JCLZJC00360.

BXCL701 plus pembrolizumab in second-line advanced pancreatic ductal adenocarcinoma: Final outcomes of the EXPEL PANC trial.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is resistant to immune checkpoint inhibitors, in part due to a cold tumor immune microenvironment (TME). BXCL701 (‘701) is a small molecule inhibitor of dipeptidyl peptidases 4, 8, 9 and fibroblast activation protein. We have shown that combinations of ‘701 and anti-PD1 antibodies lead to tumor regression in murine PDAC models due to 1) activation of the inflammasome and expression of CXCL9 to attract and activate CXCR3+ lymphocytes, 2) tumor invasion of CD8+ T cells and other effector cells, 3) induction of adaptive immunity, and 4) reduced fibrosis in the PDAC TME. We sought to evaluate the efficacy of this combination in patients (pts) with previously-treated advanced PDAC. **Methods:** In this phase II clinical trial (NCT05558982), pts with second-line advanced PDAC received ‘701 at a 0.2 mg PO BID dose on days 1-7 and then 0.3 mg BID on days 8-14 during cycle 1 (21 days) followed by 0.3 mg BID on days 1-14 every 21 days in all subsequent cycles, administered with pembrolizumab 200 mg IV every 21 days (all cycles). The primary objective was to determine the 18-week progression-free survival rate ($PFS_{18weeks}$) in pts with advanced PDAC treated in the second-line setting. We estimated that the historical second-line $PFS_{18weeks}$ is 30% or less; using a Simon’s two-stage (minimax) design, a type I error rate of 0.05 and a power of 80%, if the true rate is 50%, we would need 19 pts in stage 1 and 20 pts in stage 2 (a total of 39 evaluable). Seven of 19 evaluable pts would need to be progression-free at 18 weeks to trigger stage 2. **Results:** Twenty-one pts were enrolled. Four out of 18 evaluable pts (22%) were alive and progression-free at 18 weeks. Three had partial responses (PR, 17%), and 4 had stable disease (SD, 22%), for a disease control rate of 39%. One responder had MSI-H PDAC, while the other 2 had MSS disease. Median follow-up was 4.5 months. Median PFS was 2.3 months (95% CI 1.6 – 5.3), and median overall survival was not reached (NR, 95% CI 4.5 – NR). Three pts (14%) had PFS exceeding 6 months (2 PR, 1 SD). No new safety signals have been identified. Baseline and on-treatment tumor biopsies will be analyzed to understand the mechanisms underlying therapeutic benefit and to examine the characteristics of responders vs. non-responders. **Conclusions:** ‘701 plus pembrolizumab in second-line advanced PDAC did not reach the preliminary efficacy endpoint to trigger the second stage. However, there were encouraging signs as this combination induced objective responses in 2 MSS pts, and PFS exceeded 6 months in 3 pts. Ongoing correlative studies should elucidate predictive markers of efficacy and resistance to this novel immunotherapy combination. Clinical trial information: NCT05558982. Research Sponsor: BioXcel Therapeutics; Merck; Ruesch Center for the Cure of Gastrointestinal Cancers.

Proglumide, gemcitabine (GEM), and nab-paclitaxel (NAB-P) in patients (pts) with pancreatic ductal adenocarcinoma (PDAC): Results of the phase 1 PROGEM trial.

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Background: PDAC has a poor prognosis and resistance to therapy due to its desmoplastic and immunosuppressive tumor microenvironment (TME). In animal models of PDAC, the cholecystokinin-B receptor (CCK-BR) antagonist, proglumide, was shown to decrease tumoral fibrosis, alter the tumor immune cell signature, and increase chemotherapy uptake and T-cell infiltration into tumors, resulting in decreased metastases and improved survival. We sought to evaluate the safety of proglumide with GEM/NAB-P chemotherapy in pts with metastatic PDAC (mPDAC). Using tumor biopsies and a blood biomarker assay, we also studied the combined effects of proglumide with GEM/NAB-P on the TME. **Methods:** The PROGEM study was a phase 1 trial of proglumide 1200 mg PO daily, GEM 1000 mg/m2 IV, and NAB-P 125 mg/m2 IV days 1, 8, and 15 every 28 days in GEM-naïve pts with mPDAC (NCT05827055). The primary endpoints were safety and determination of the recommended phase 2 dose (RP2D). Safety was assessed with adverse events (AEs) according to CTCAE v. 5 criteria. Tumor biopsies were obtained pre-treatment and at 8 weeks on-treatment and analyzed by histology and multiplex immunohistochemistry for changes in the TME. A liquid biopsy serum sample was collected at baseline, week 8, and end-of-treatment (EOT) for analysis of a microRNA biomarker panel reflecting changes in the TME. McGill pain surveys were done at baseline, week 8, and at EOT. **Results:** Six pts were enrolled. Three pts were treatment-naïve, and 3 had had prior mFOLFIRINOX. No AEs related to proglumide were reported. Five pts had stable disease, and 1 pt had disease progression as the best response, for a disease control rate of 83%. Median progression-free survival was 4 months, and median overall survival was 8.5 months. Compared to baseline, on-treatment biopsies showed an 81% decrease in Ki67+ cells; a 75% decrease in M2-polarized tumor-associated macrophages; a 42% decrease in tumor collagen content, and a 13-fold increase in CD8 T-cells. Pre- and on-treatment blood biomarkers showed changes correlated with histology and clinical course. Anti-fibrosis markers (miR185, miR346, and miR378) and inhibitors of epithelial to mesenchymal transition (miR200 and miR205) increased with therapy. MiR122, which regulates cell cycle and growth, decreased initially but increased at the time of progression. Pain scores showed improved pain at week 24 or EOT. **Conclusions:** Proglumide is safe in pts with mPDAC, and the RP2D is 1200 mg PO daily with standard dose GEM/NAB-P. Proglumide remodels the TME by decreasing fibrosis and immunosuppression while increasing T-cell infiltration. Changes in circulating microRNAs offer a promising non-invasive biomarker panel for monitoring treatment response. These results support further investigation of proglumide with GEM/NAB-P in a phase 2 clinical trial and future immunotherapy combinations. Clinical trial information: NCT05827055. Research Sponsor: Ruesch Center for the Cure of Gastrointestinal Cancers; Pancreatic Cancer Action Network.

QL1706 combined with nab-paclitaxel and gemcitabine as first-line treatment for locally advanced or metastatic pancreatic adenocarcinoma: A prospective, multi-center, single-arm phase II study.

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Background: First-line chemotherapy with nab-paclitaxel and gemcitabine (AG) provides limited efficacy in advanced pancreatic ductal adenocarcinoma (PDAC). QL1706, a bifunctional antibody targeting PD-1 and CTLA-4, has demonstrated favorable efficacy and safety. This phase II study evaluated the efficacy and safety of QL1706 plus AG as first-line treatment in patients with locally advanced or metastatic PDAC. **Methods:** Adult patients with histologically confirmed, unresectable locally advanced or metastatic PDAC, ECOG performance status 0–1, no prior systemic therapy, and at least one measurable lesion were enrolled. Patients received QL1706 (5 mg/kg, IV, day 1) in combination with nab-paclitaxel (125 mg/m^2, IV, days 1 and 8) and gemcitabine (1,000 mg/m^2, IV, days 1 and 8) every 3 weeks. Tumor assessments were performed every two cycles. Up to eight cycles were administered, followed by QL1706 maintenance in patients without disease progression. Primary endpoints were objective response rate (ORR) and safety. **Results:** A total of 30 patients were enrolled. The median age was 59 years (range, 44–74), and 20 patients were male. Primary tumors were located in pancreatic head in 14 (46.7%) and in body or tail in 16 (53.3%). Eight (26.7%) and 22 (73.3%) patients had locally advanced (stage III) and metastatic (stage IV) disease, respectively. Among 26 patients assessed for KRAS mutations, the G12D variant was most prevalent (46.2%), followed by G12R (30.8%) and G12V (23.0%). At data cutoff, after a median follow-up of 5.2 months (range, 4.1–6.8), 18 patients remained on treatment. Of these, 2 underwent curative surgery and 4 transitioned to maintenance therapy. Twelve patients discontinued treatment due to disease progression, including 5 who subsequently died. The median number of treatment cycles administered was 4.5 (range, 2–8) for chemotherapy and 4 (range, 1–8) for QL1706. All patients had at least one post-baseline tumor assessment. Best overall response were complete response in 1(3.3%), partial response in 8 (26.7%), stable disease in 16 (53.3%), and progressive disease in 5 (16.7%).The ORR was 30.0% (95% CI, 14.7–49.4%) and disease control rate was 83.3% (95% CI, 65.3-94.4%). The survival data were not mature by analysis. All patients experienced at least one treatment-related adverse event (TRAE). Grade ≥3 TRAEs occurred in 16 patients (53.3%). The most frequent grade 3–4 TRAEs were neutropenia (23.3%) and leukopenia (20.0%), followed by hypersensitivity reactions (13.3%), thrombocytopenia (6.7%), thromboembolism (6.7%), and pancreatitis (6.7%). No grade 5 TRAEs or treatment-related deaths occurred. **Conclusions:** QL1706 combined with AG demonstrated promising antitumor activity with a manageable safety profile as first-line treatment for advanced PDAC. Clinical trial information: NCT06750861. Research Sponsor: None.

Multicentre trial of telemonitored circadian rhythms and electronic patient-reported outcomes (ePROs) for improving tolerability of initial mFOLFIRINOX cycles in patients (pts) with advanced pancreatic ductal adenocarcinoma (PDAC): MultiDom (NCT04263948).

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Background: Severe Adverse Events (SAEs) requiring emergency admissions (EAs) alter quality of life and treatment efficacy, and increase health costs. Toxicities, EAs, and reduced survival have been linked to the disruption of circadian rhythms, whose relevance is tested here in a multicentre, prospective, longitudinal, single-arm interventional trial. **Methods:** Continuous telemonitoring and automatic analyses of circadian rhythms and daily body weight and ePROs over 50 days (d) aim to reduce EAs in PDAC pts receiving the first 3 cycles of mFOLFIRINOX. The hypothesis (H_0) is that EAs involve <15% of the pts, rather than a historical rate of 15-30%. Pts data were collected through telecommunicating chest sensor, balance and tablet connected to a multidimensional digital platform. The main circadian parameter was (I<O), the % of accelerations per min In-Bed that are below the median accelerations per min Out-of-Bed. Control(I<O) is 97-100%. An (I<O) ≤96% defined circadian disruption. Electronic alerts were sent out if (I<O) ≤96%, body weight loss ≥5%, or self-rated symptoms ≥7 using the MD Anderson Symptoms Inventory (MDASI). **Results:** 28 males and 24 females had a median age of 65 years (33-82), and WHO performance status of 0-1 in 92% of them. PDAC was metastatic in 69% of cases, including liver in 50%. An EA occurred in 2 pts (3.8% [95% CL, 1.1-13%]), thus validating H_0. SAEs in both EA pts were grade (Gr) 3 febrile neutropenia and diarrhea; and Gr 3 leuconeutropenia and hypokaliemia respectively. Symptom-free circadian disruption preceded EA by 8 d in both pts. Circadian disruption occurred at least once in 65-75% of the pts on treatment, and lasted > 20 d in 27 pts (52%). Severe fatigue and anorexia were self-reported by 62% and 58% of the treated pts respectively. Main Grade 3-4 toxicity was neutropenia in 17% of the pts [95% CL, 9-30]. Disease control rate at 2 months was 75% [53-100]. Multidom revealed (i) a high level of pt engagement supported both by data compliance rates of 84-92% for circadian rhythms, 93-100% for body weight, and 86-100% for ePROs; and by median duration of platform use of 46 d (IQR, 38-50]; (ii) 1881 medical type e-alerts for circadian disruption (43%), MDASI symptoms (25%), and body weight loss (12%); (iii) 883 categorized responses to medical e-alerts, and (iv) highest global score of self-rated pt experience of participation (median, 5/5 (4 to 5). **Conclusions:** Combining telemonitoring of circadian rhythms, body weight and symptoms in remote PDAC pts on mFOLFIRINOX revealed potential benefit on pts real life through informed proactive telecare, and likely improved treatment safety. Actual benefits from such telemonitoring-telecare platform with circadian metrics need further confirmation in trials involving pts at risk of SAEs. Clinical trial information: NCT04263948. Research Sponsor: Research and Education Group of Ramsay-Santé, France.

Final results and preliminary correlative analysis of a phase I study of anetumab ravtansine in combination with checkpoint inhibitors and gemcitabine in mesothelin-positive advanced pancreatic adenocarcinoma (NCI10208).

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Background: Anetumab-ravtansine (AR) is an ADC composed of IgG1 targeting the protein mesothelin (MSLN) linked to DM4, a tubulin inhibitor (*Spiliopoulou, ASCO 2022*). Here, we present the final analysis of a phase I study evaluating AR in combination with nivolumab, ipilimumab, or gemcitabine in patients (pts) with metastatic pancreatic adenocarcinoma (PDAC). **Methods:** Eligible pts had histologically confirmed MSLN-positive PDAC (≥5% expression by IHC), ECOG 0–1, and progression after ≥1 prior line of systemic therapy. The dose-escalation phase included: AR + nivolumab (ARM1), AR + nivolumab + ipilimumab (ARM2), and AR + gemcitabine + nivolumab (ARM3). The latter was chosen for dose-expansion. Two dose levels of AR: DL1 5.5 mg/kg and DL2 6.5 mg/kg (RP2D) were evaluated. Blood and tissue-based correlative analysis included paired tumor biopsies on C1D7 and C2D7 for comparison of immune cell shifts by multiplex immunofluorescence. **Results:** As of the final data cutoff on 15/11/2023, 46 pts were treated: ARM1 (n = 11), ARM2 (n = 13), ARM3 (n = 10), and dose expansion (n = 12). Median age was 66 years (40–83), the majority were males (52.2%) and had received prior gemcitabine (63%). The median number of prior treatment lines was 2 (1–5). Among 44 evaluable pts, 95.7% experienced some treatment emergent adverse events, with G1/2 and G≥3 occurring each at 47.8%. Dose limiting toxicities occurred in 6 pts (13%): 2 in ARM2DL2 (upper gastrointestinal hemorrhage and G3 thrombocytopenia), 2 in ARM3DL2 (G3 AST and G3 ALT elevation), and 1 in each of the dose expansion DL2 (G3 AST and G3 ALT elevation). Blurred vision occurred in 13%, peripheral neuropathy in 6.5%, pneumonitis in 4.3%, and keratitis in 2.2%, most of them being G1/2. No treatment-related deaths occurred. Among 41 evaluable pts, 1 (2.2%; ARM3DL2) had a complete response, 20 (43.5%) had stable, and 20 (43.5%) had disease progression. The median duration of treatment was 7.9 (1.9-32.9) weeks which was statistically longer in pts with stable disease than those with progressive disease as best response (16.4 vs 6.3 weeks, respectively; $p < 0.05$). Twenty-seven pts were included in the multiplex immunofluorescence, and no statistically immune-cell shifts were detected between C1D7 and C2D7. **Conclusions:** AR had an acceptable safety profile in PDAC and the 6.5 mg/kg was identified as the R2PD. Evidence of clinical benefit was observed with some pts with prolonged disease stabilization and one complete response in a setting of limited therapeutical options. Correlative analysis to identify predictive biomarkers for treatment benefit is ongoing. Clinical trial information: NCT03816358. Research Sponsor: Experimental Therapeutics Clinical Trials Network (NCI-ETCTN); North American STAR Consortium.

Ultra-refractory PD–PD pancreatic cancer: Clinical and molecular insights across first- and second-line therapy.

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Background: A subset of pancreatic cancer (PC) patients exhibits progressive disease (PD) as the best response to both first- and second-line chemotherapy (PD-PD), representing an ultra-refractory population with dismal outcomes. This group remains poorly characterized, highlighting a critical unmet need for novel therapeutic strategies. **Methods:** We retrospectively analyzed PC patients treated at Vall d'Hebron University Hospital (2012–2025) who received both first- and second-line chemotherapy with 5-FU- or gemcitabine-based regimens. Clinical, histopathological and molecular data were collected. Characteristics of PD-PD patients were compared with those achieving clinical benefit, defined as complete or partial response (CR/PR) in at least one treatment line. Progression-free survival (PFS2) was calculated from the start of first-line therapy to documented PD after second-line treatment. Overall survival (OS) was calculated from the start of first-line therapy to death or last follow-up. Survival curves were estimated using the Kaplan–Meier method. RNA-seq was performed on diagnostic tumor samples to explore transcriptomic features. **Results:** Median follow-up for the entire cohort was 58 months. Among 400 patients, 46 (12%) were classified as PD-PD. Median PFS2 was 5.4 months in PD-PD vs 14.5 months in CR/PR, and median OS was 8.1 vs 20.8 months, respectively ($p < 0.001$ for both). Treatment sequences in PD-PD patients included 5-FU followed by gemcitabine (18, 39%) and gemcitabine followed by 5-FU (28, 61%). Patients receiving 5-FU first were younger (median age 57 vs 72 years, $p = 0.035$). Histopathological features were similar in both groups. Inflammatory markers were largely comparable; however, median CRP/albumin ratio was higher in PD-PD, 0.86 vs 0.24 in CR/PR ($p < 0.001$). Molecular profiling was available for 34 (74%) of patients. Among these, *KRAS* mutations were present in 84% of patients, with G12V slightly more frequent in PD-PD than CR/PR (45% vs 31%, $p = 0.5$). *TP53* mutations occurred in 81% vs 65% ($p = 0.083$), and *SMAD4* alterations were more common in CR/PR (19% vs 6.3%, $p = 0.082$). DDR pathway alterations were rare in PD-PD patients. Exploratory RNA-seq of six PD-PD compared with CR/PR ($n = 2$) tumors revealed upregulation of coagulation and lipid metabolism genes (*FGB*, *APOA1*) and downregulation of pancreatic function genes (*PNLIP*, *CPA1*), suggesting potential alterations in inflammatory and metabolic pathways. **Conclusions:** PD-PD patients represent an ultra-refractory subset (~12%) of PC with very poor outcomes despite standard therapy. Differences in inflammatory markers and transcriptomic trends may reflect underlying biological features of this highly resistant phenotype. These findings underscore the need for further studies to clarify mechanisms of primary resistance and guide the development of novel therapeutic strategies in this high-risk population. Research Sponsor: None.

Phase 1/2 study of YL201, an anti-B7H3 antibody–drug conjugate (ADC), in patients with previously treated advanced pancreatic ductal adenocarcinoma (PDAC).

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Background: The prognosis for patients with advanced PDAC after failure of first-line therapy remains dismal with limited effective treatment options. There is a critical unmet need for novel therapeutic agents in the second-line and beyond (2L+) setting. YL201 is a B7H3-targeting ADC with promising clinical activity in multiple advanced solid tumors. Here, we report the safety and preliminary efficacy of YL201 monotherapy in patients with 2L+ PDAC from a phase 1/2 dose expansion study. **Methods:** Patients with metastatic PDAC who had progressed on at least one prior line of systemic therapies without irinotecan were enrolled and treated with YL201 intravenously Q3W at 2.0 mg/kg or 2.4 mg/kg until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** A total of 60 patients were enrolled, including 30 treated at 2.0 mg/kg and 30 at 2.4 mg/kg. The median age was 61.0 years, 63.3% were male, and 91.7% had an ECOG PS of 1. 48.3% of patients had ≥3 metastatic sites at baseline. Patients had received a median of 1 prior line of therapy (range: 1–3). 90.0% had received prior gemcitabine-based regimen and 46.7% had received prior fluoropyrimidine. As of 12 December 2025, the median follow-up was 9.2 months (95% CI: 8.2–9.8). Among the 60 patients enrolled, the confirmed ORR was 28.3% (95% CI: 17.5–41.4) with a median DoR of 7.6 months (95% CI: 4.9–NR), and the DCR was 85.0% (95% CI: 73.4–92.9). The median PFS was 7.7 months (95% CI: 5.5–9.7), and the median OS was 14.6 months (95% CI: 8.2–NR). Membrane B7H3 expression was detected by immunohistochemistry in most tumor samples with a median H-score of 65 (range: 0–275). However, no association was observed between tumor response and B7H3 expression level in PDAC patients. Treatment-related adverse events (TRAEs) of any grade and grade ≥3 occurred in 100.0% and 43.3% of patients, respectively. The most common grade ≥3 TRAEs included leukopenia (16.7%), neutropenia (15.0%), anemia (15.0%), and hypokalemia (6.7%). The rate of treatment discontinuation due to TRAEs was 5.0%, and no treatment-related deaths were reported. **Conclusions:** YL201 monotherapy showed promising antitumor activity and a manageable safety profile in pretreated patients with advanced PDAC. These compelling results warrant further investigation of YL201 in a randomized controlled trial for patients with advanced PDAC in the 2L+ setting. Clinical trial information: NCT06057922. Research Sponsor: MediLink Therapeutics.

Efficacy of multimodal thermal therapy combined with immune checkpoint inhibitors and chemotherapy in unresectable pancreatic cancer with liver metastases.

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Background: Treatment of pancreatic cancer with liver metastasis (PCLM) remains extremely challenging. Multimodal thermal therapy (MTT) is a novel treatment method consisting of alternated liquid nitrogen cooling and radiofrequency heating, which was proven to effectively remodel the immune environment and trigger systemic antitumor immunity. This study aims to explore the primary application of MTT combined with subsequent ICIs-based systemic therapy in PCLM. **Methods:** Patients aged 18-70 years with primary diagnosed unresectable PCLM were enrolled in this single-center, prospective clinical trial. Participants received MTT at least one of the liver metastases combined with subsequent ICIs and chemotherapy (camrelizumab 200 mg IV on Day 1, gemcitabine 1000 mg/m2 IV, and nab-paclitaxel 125 mg/m2 IV on Days 1 and 8, every 3 weeks for 6 cycles), which was started on day 7 post MTT. The primary endpoints were safety and efficacy. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Exploratory endpoints included immune marker changes induced by MTT. **Results:** Five patients were enrolled in the trial group and four patients in the control group. All patients in the trial group were well tolerated with MTT, and the MTT-treated liver tumors were completely ablated. One patient withdrew due to autoimmune hepatitis after the first ICIs treatment. One patient achieved success conversion and underwent curative resection 6 months after MTT. Median OS per RECIST was 16.0 months (95% CI 15.3–16.7) in the trial group surpassing 6.2 months (95% CI 1.8–9.2) in the control group (HR 0.26 [95% CI 0.04–1.99]). Histological analysis indicated that combination therapy reversed the immunosuppressive tumor microenvironment, accompanied by enhanced immune-cell infiltration and tertiary lymphoid structures formation within both primary and metastatic lesions. Single-cell RNA-seq of peripheral blood immune cells on day 7 after MTT but prior to ICIs and chemotherapy revealed that MTT promoted the maturation of APCs, increased expression of homing-associated chemokine receptors on circulating B cells and monocytes, and induced the expansion of tumor-trafficking monocytes and $CD8^+$ T cells subsets, which were correlated with favorable prognosis. The effector functions of T cells were also enhanced post MTT, accompanied by increased PD-1 level, which provided the basis for subsequent anti-PD-1 therapy. **Conclusions:** MTT reshaped both primary and metastatic tumor immune environments, sensitized tumors to subsequent immunotherapy and chemotherapy, well correlating to prolonged OS of PCLM patients. Clinical trial information: NCT06307080. Research Sponsor: None.

AI-driven RNA-based homologous recombination deficiency algorithm to predict first-line platinum response in metastatic pancreatic cancer.

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Background: Developing predictive diagnostics for metastatic pancreatic cancer remains an unmet clinical need. Here, we present the Tempus HRD-RNA algorithm: an AI-driven, 1,660-gene logistic regression model trained on RNA-seq (Tempus xR) from pan-cancer solid tumor tissue samples. This dynamic RNA-based signature can identify clinically relevant patient populations likely to benefit from platinum-based regimens and PARP inhibitors, including patients without BRCA1/2 or PALB2 mutations. **Methods:** This is a prospectively designed retrospective RWD analysis in an independent validation cohort of 1,083 patients (pts) with treatment-naive metastatic pancreatic cancer diagnosed between 2017 and 2025. Treatment arms included first-line platinum-containing regimens (Arm A; n = 779; 97.0% FOLFIRINOX, 1.4% NALFIRINOX, 1.5% Gemcitabine/Cisplatin) or a non-platinum regimen (Arm B; n = 304; 86.6% Gemcitabine/Nab-paclitaxel, 13.4% Gemcitabine/Paclitaxel). BRCA1/2 and PALB2 mutations were determined via paired Tempus xT DNA sequencing. Key prognostic criteria included age, sex, ECOG score (0 or 1), surgery status and biopsy site. Unknown ECOG was imputed using the Laboratory Imputation Framework for EHRs (LIFE; PMID: 40595435). Overall survival (OS) differences between treatment arms were evaluated as independent Cox models for HRD+ vs. HRD- pts, including covariate adjustment. **Results:** Overall, 9.5% of pts were classified as HRD+: 78 pts (10.0%) in the platinum arm (Arm A) and 15 pts (8.2%) in the non-platinum arm (Arm B). OS was significantly higher in platinum-treated HRD+ pts than non-platinum. Median OS (mOS) was 12.8 months (95% CI: 8.5–16.6) in HRD+ platinum pts (Arm A) vs. 8.5 months (95% CI: 5.4–12.9) in HRD+ non-platinum-treated pts (Arm B; HR: 0.57; 90% CI: 0.33–0.99; p = 0.048). In contrast, in the HRD- group, there was no statistically significant difference in OS between platinum (Arm A; mOS 8.1 months; 95% CI: 7.1–9.1) and non-platinum (mOS 7.6 months; 95% CI: 6.6–8.8) arms (Arm B; HR: 0.91; 90% CI: 0.76–1.09; p = 0.190). Additional analyses were performed within the platinum-treated arm (Arm A) to assess if the survival benefit held independent of BRCA1/2 or PALB2 mutations. HRD+ and BRCA/PALB2mut pts (4.8%; n = 37) had a mOS of 13.3 months compared to 11.5 months in HRD+ and BRCA/PALB2wt (5.3%; n = 41) pts (HR: 0.7; 90% CI: 0.4–1.1). Comparatively, HRD- and BRCA/PALB2mut pts (2.1%; n = 16) had a mOS of 10.5 months compared to 8.3 months in HRD- and BRCA/PALB2wt (80.9%; n = 623) pts (HR: 0.7; 90% CI: 0.4–1.3). **Conclusions:** Tempus HRD-RNA is a novel predictive clinical biomarker that identifies a higher percentage of pts who may benefit from targeted treatment than current guidelines. The HRD-RNA algorithm offers a remarkable precision oncology tool to improve outcomes in pancreatic cancer, and has important clinical value in the era of novel HRD drug development. Research Sponsor: None.

The SPIN Score, a simple clinical score to predict pain response following celiac plexus radiosurgery for retroperitoneal cancer pain.

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Background: Celiac plexus radiosurgery is a novel non-invasive palliative treatment for pancreatic cancer pain that was recently added to NCCN guidelines. In the pivotal phase 2 trial (NCT03323489; Lancet Oncol 2024;25:1070-79), pain response was 53% (95% CI 42-64%). Prespecified exploratory analysis identified age and BMI as predictors; however, no clinically actionable patient selection tool was developed. We sought to identify additional predictors and create a practical risk stratification score. **Methods:** Post-hoc analysis of 90 evaluable patients from the phase 2 trial. Pain response was defined per protocol (≥2-point reduction in average pain from baseline to three weeks, on Brief Pain Inventory–Short Form). Candidate baseline predictors were examined by univariate and multivariate logistic regression. Only variables remaining significant in multivariate analysis were included in the final score to ensure independence and avoid overfitting. Internal validation used bootstrap resampling (500 iterations with replacement) to calculate optimism-corrected AUC. Analysis performed using Stata IC/16.1. **Results:** Univariate analysis identified 4 significant predictors: neurotoxic chemotherapy exposure (OR 5.33, 95% CI 2.13-13.4, p<0.001), baseline pain intensity (OR 1.73, p=0.003), age (OR 1.06, p=0.014), and therapy line (OR 0.65, p=0.04). On multivariate analysis, only neurotoxic exposure (OR 5.1, p=0.009) and baseline pain (OR 1.8, p=0.003) remained independently significant predictors. Age and therapy line lost significance due to collinearity. Dose-response analysis confirmed pain threshold optimization: >5 (61.5% response), >6 (65.8%), >7 (83.3%), >8 (85.7%), with >6 providing optimal discrimination. We created the SPIN (Severe Pain + Intact Nerves) score (0-2 points): baseline Pain >6 (+1), No prior Neurotoxic chemotherapy (+1). Response rates by score: 0 points: 32% (n=31); 1 point: 53% (n=40); 2 points: 89% (n=19). The 2-variable model achieved an apparent AUC=0.716. Following bootstrapping, the optimism-corrected AUC was=0.714. **Conclusions:** The simple score allows identification of distinct patient subgroups with markedly different probabilities of pain response following celiac plexus radiosurgery. This suggests the intervention should be considered earlier in the disease course, before exposure to neurotoxic agents. External validation is needed prior to clinical implementation. Financial support: Gateway for Cancer Research, The Israel Cancer Association. Clinical trial information: NCT03323489. Research Sponsor: None.

A phase II study of FOLFIRINOX (FFX) combined with the glycogen synthase kinase-3beta (GSK-3β) inhibitor elraglusib (ELRA) and the transforming growth factor beta (TGFβ) inhibitor losartan (LOS) in patients with untreated metastatic pancreatic ductal adenocarcinoma (mPDAC).

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Background: Concurrent inhibition of GSK-3β and TGF-β signaling pathways aims to target epithelial-mesenchymal transition (EMT) plasticity, metabolic reprogramming, desmoplasia and immune escape mechanisms that underlie therapeutic resistance in mPDAC **Methods:** In this multi-institutional, open-label, four-arm (non-comparator) phase II trial conducted across three academic centers in the United States, 49 patients with newly diagnosed, treatment naive mPDAC were randomized to Arm 1: FFX alone (biomarker control, n=4) or Arm 2: FFX plus LOS (50 mg daily); Arm 3: FFX plus ELRA (9.3 mg/kg IV twice weekly); Arm 4: FFX plus LOS plus ELRA (n=15/arm). After 12 cycles of FFX without progression, patients transitioned to maintenance 5-FU (plus ELRA/LOS, based on the arm) and resumed full therapy at progression; treatment withdrawal required progression on full therapy or treatment-limiting toxicity. The primary endpoint was progression-free survival (PFS). **Results:** Between September 19, 2022, and January 2, 2025, 49 patients were enrolled (median age 65 years; 51% female; 74% White). At the data cutoff (July 6, 2025), 14 (28.6%) patients remained alive with a median follow-up of 9 months. Median PFS was 5.1 months (95% CI 1.1–NR) in Arm 1, 5.9 months (95% CI 1.6–9.9) in Arm 2, 6.0 months (95% CI 1.8–9.8) in Arm 3, and 6.5 months (95% CI 3.8–8.5) in Arm 4. 9-month PFS could not be calculated in arm 1, 29.3% (95% CI 9.2-53.3) in Arm 2, 37.3% (95% CI 13.6 – 61.5%) in Arm 3, and 21.7% (95% CI 5.3 –45.1) in Arm 4. Median overall survival (OS) was 7.7 months (95% CI 1.1–NR), 8.2 months (95% CI 3.3–14.5), 9.8 months (95% CI 4.3–NR), and 9.8 months (95% CI 5.6–15.6), respectively in each arm. Objective response rate 24.5% (12/49); stable disease 44.9% (22/49). 14/49 (28.5%) patients received maintenance therapy, with a median duration of 2.4 months. Treatment was generally well tolerated, grade ≥3 treatment-related adverse events occurred in 34.7% of patients; one treatment-related death due to sepsis occurred in Arm 3. Notably, a subset of patients in Arms 3 and 4 demonstrated deep and sustained clinical responses; Correlative biomarker analyses are ongoing to identify molecular and immune features associated with these long term responders. **Conclusions:** Although clinical outcomes with the novel combinations did not exceed historical standards of care, this non-comparator phase II study demonstrates the feasibility and tolerability of combinatorial pathway inhibition in mPDAC. This study enables ongoing correlative analyses of EMT plasticity, stromal remodeling, and immune escape in mPDAC and establishes a robust platform to define determinants of resistance and durable response. Clinical trial information: NCT05077800. Research Sponsor: Lustgarten Foundation; Actuate Therapeutics Inc.

Post-hoc efficacy and biomarker analysis of elraglusib plus gemcitabine/nab-paclitaxel versus chemotherapy alone in metastatic pancreatic ductal adenocarcinoma.

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Background: Elraglusib (9-ING-41), a glycogen synthase kinase-3β (GSK-3β) inhibitor, has multimodal antitumor activity. In the international, open-label, randomized phase 2 1801 Part 3B study, elraglusib plus gemcitabine/nab-paclitaxel (GnP) was evaluated in previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC), with patients randomized 2:1 to weekly elraglusib/GnP or GnP alone. Primary endpoints were median overall survival (mOS) and 1-year survival. The GnP control arm demonstrated shorter mOS than contemporary randomized trials (7.2 months vs 9.2 months in NAPOLI-3 and 9.7 months in PASS-01), driven by higher early mortality (0–2 months: 23.1% vs 10.1% in NAPOLI-3). Given balanced randomization, similar early mortality was inferred in the elraglusib/GnP arm, prompting post-hoc analyses to contextualize efficacy and identify factors associated with early death. **Methods:** Efficacy and safety were summarized descriptively. Time-to-event endpoints were analyzed using Kaplan–Meier estimates, log-rank testing, and Cox proportional hazards models. Response rates were compared using the Cochran–Mantel–Haenszel test. Post-hoc subgroup, sensitivity, and machine-learning–based multivariate analyses explored clinical, demographic, and biomarker correlates of survival and early mortality. **Results:** In the full randomized population (elraglusib/GnP n=155; GnP n=78), elraglusib/GnP improved mOS by 2.9 months versus GnP (10.1 vs 7.2 months; HR 0.62; 95% CI 0.46–0.84; p=0.01), with 1-year survival rates of 44.1% versus 22.3%. Among patients receiving ≥1 full treatment cycle, mOS was 12.5 months with elraglusib/GnP and 8.5 months with GnP, comparable to contemporary registrational trials. Across multiple post-hoc sensitivity analyses—including evaluable patients, those matched to NAPOLI-3 baseline tumor burden, patients treated in the EU (early mortality 4%), and those achieving ≥20% CA19-9 decline within the first 1–2 cycles—elraglusib/GnP consistently demonstrated a ≥4-month OS advantage. Early death was associated with low baseline albumin (<3 g/dL), high CA19-9 (>800 U/mL), high tumor burden, and KRAS, TP53, and CDKN2A co-mutations. **Conclusions:** The elevated early mortality in the GnP control arm reflects enrollment of a heterogeneous, real-world mPDAC population with less restrictive eligibility than recent registrational trials. Post-hoc analyses identify key clinical and molecular drivers of early death and confirm a consistent survival benefit with elraglusib/GnP. These hypothesis-generating findings directly inform eligibility criteria, stratification, and endpoint assumptions for the planned phase 3 trial. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics.

Time toxicity in patients with advanced pancreatic cancer in Mexico.

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Background: Advanced pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies despite advances in systemic therapy. Beyond survival, the burden of time spent receiving health care (also known as time toxicity) has emerged as a relevant patient-centered outcome, particularly in diseases where treatment benefits may be modest. This study aimed to quantify time toxicity in patients with advanced PDAC and to analyze differences in time toxicity by demographic and clinical characteristics. **Methods:** We conducted a subanalysis of a single-center prospective cohort of patients with advanced solid tumors enrolled in a patient navigation program in Mexico. Patients ≥18 years diagnosed with advanced PDAC between June 2017 and August 2023 were included; patients with a second invasive malignancy or treated outside the institution were excluded. Demographic and clinical variables, baseline quality of life (FACT-G), and days with in-person healthcare encounters (clinic visits, treatments, tests, emergency visits, and hospitalizations, regardless of whether oncology-related) were collected from the diagnosis of advanced disease. Overall survival (OS) was defined as the time from diagnosis of advanced PDAC to death or loss to follow-up. Time toxicity was defined as the proportion of days involving in-person healthcare contact relative to OS. Comparisons used nonparametric tests and beta regression models were fitted to evaluate factors associated with time toxicity. **Results:** A total of 103 patients were included. Median age was 64 years, 65% were women, 83.5% presented with de novo advanced PDAC, and 75.7% received palliative chemotherapy. The mean baseline FACT-G score was 63.7±15.4. Median follow-up was 13.0 months, and median OS for the entire cohort was 11.5 months (95% CI, 6.2-16.7). The median time toxicity of the sample was 21.8% (IQR, 14.9-31.7). Patients with recurrent advanced PDAC experienced lower time toxicity than those with de novo disease (14.9% vs 22.8%, p = 0.003). In multivariable beta regression, disease presentation remained the only independent factor associated with increased time toxicity (β-0.51, p = 0.011). Age, sex, receipt of chemotherapy, and baseline FACT-G score were not independently associated with time toxicity. In an exploratory subgroup analysis among patients receiving palliative chemotherapy, patients ≥65 years had higher time toxicity compared to younger patients (23.4% vs. 17.9%; p = 0.041). **Conclusions:** In this cohort of Mexican patients with advanced PDAC, approximately one-fifth of OS time was spent in direct contact with health care system. Time toxicity was associated with disease trajectory rather than treatment or patient characteristics. Among patients receiving palliative chemotherapy, older patients experienced higher time toxicity. These findings highlight the importance of incorporating time toxicity into shared decision-making. Research Sponsor: Fundación Carlos Slim.

4215 Poster Session

Combined safety and efficacy results from three clinical studies evaluating alpha radiotherapy for advanced pancreatic cancer.

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Background: Pancreatic cancer (PDAC) remains associated with poor prognosis and limited treatment options, particularly in patients with advanced disease. Diffusing Alpha-Emitter Radiation Therapy (Alpha DaRT), a novel alpha-emitting radiation source, has shown initial clinical benefit in superficial epithelial solid tumors. The pooled studies presented here evaluated the safety and efficacy outcomes for endoscopic ultrasound (EUS)-guided alpha radiotherapy using Alpha DaRT in patients with PDAC. **Methods:** This analysis pooled data from three prospective clinical studies at 3 medical centers in Canada and Israel evaluating Alpha DaRT in patients with locally advanced or metastatic PDAC, regardless of previous lines of therapy. Primary outcome was safety, as assessed by CTCAE V5. Secondary outcomes were best overall response (BOR) of the primary tumor assessed per RECIST V1.1 and overall survival (OS), defined from Alpha DaRT treatment. **Results:** A total of 58 subjects (31 male, 27 female), median age 72 (range 41-91), were recruited between 2023 and 2025 across the three trials. Treatment-associated AEs of any grade occurred in 21 patients (36%). Grade ≥3 AEs occurred in 5 patients (9%) (biliary obstruction, abdominal pain, fever, liver enzyme imbalance and bacteremia). There were no treatment-related deaths and all grade ≥3 AEs resolved. Across all patients evaluable for response, the BOR showed a disease control rate of 87% and an objective response rate of 27%, with 3 complete and 9 partial responses. Median OS for the cohort was 7.9 months (95% CI: [6.1–11.6]): 10.4mo (95% CI: [7.3–13.4]) when given in 2nd line (N = 24) and 7.5 months (95% CI: [4.2–11.8]) when given in 3rd line (N = 21). **Conclusions:** In this pooled analysis of three clinical studies, EUS-guided Alpha DaRT demonstrated a reassuring safety profile and promising early efficacy signals in patients with advanced PDAC. The observed survival outcomes and radiographic responses support further clinical investigation, which is underway. Clinical trial information: NCT04002479; NCT05781555; NCT05657743. Research Sponsor: None.

Single-cell circulating tumor cell genomics of KRAS-independent oncogenic sub-populations and longitudinal clonal evolution in metastatic pancreatic adenocarcinoma.

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Background: KRAS mutations are a dominant oncogenic driver in metastatic pancreatic ductal adenocarcinoma (mPDAC) and are routinely detected using ctDNA. However, ctDNA reflects pooled signals from dominant high-shedding clones and may incompletely capture intra-patient heterogeneity or tumor evolution. Circulating tumor cells (CTCs) enable single-cell genomic interrogation and longitudinal tracking of evolving sub-populations. We compared genomic alterations, tumor heterogeneity, and pathway dynamics using ctDNA and single-cell CTC DNA in mPDAC. **Methods:** Under an MCW IRB approved protocol (PREDICT-MCW; NCT05802069), 16 patients with mPDAC receiving standard of care were enrolled. Peripheral blood was collected at baseline and longitudinally at 90-day intervals. Live single CTCs were isolated using the OncoIncytes platform with anti-EpCAM–based glass bead capture and gentle release. Genomic DNA from individual CTCs underwent linear amplification and targeted sequencing using a 1080-gene panel on the Illumina NextSeq 2000. Matched ctDNA was analyzed using the same panel. Variant calling used the iCore pipeline. Alterations were compared at gene and patient levels. Tumor heterogeneity was assessed using mutant-allele tumor heterogeneity (MATH). **Results:** CTC counts were highest at baseline (mean 6.5 CTCs per patient; range 2–11) and varied longitudinally with marked inter-patient heterogeneity. At first on-treatment assessment, 50% of evaluable patients showed reduced CTC counts, while others exhibited stable or increased levels. Across all timepoints, 49 altered genes were identified. Single-cell CTC profiling revealed broader genomic representation, with 32 genes (65%) detected exclusively in CTC-DNA, 14 (29%) shared with ctDNA, and 3 (6%) detected exclusively by ctDNA. At the patient level, CTC-DNA identified genomic alterations in all patients (16/16), whereas ctDNA detected alterations in 75% (12/16). At baseline, 61% of CTCs achieved $\geq 11\times$ coverage across KRAS exon 2 and codon 12. KRAS alterations were detected in only 6% (1/16) of patients by CTC-DNA compared with 44% (7/16) by ctDNA, persisting longitudinally (13–19% vs 59–76%, CTC-DNA vs ctDNA). KRAS-negative CTCs harbored recurrent alterations in MAPK, DNA damage response, receptor tyrosine kinase, and tumor suppressor pathways. CTCs demonstrated higher intra-patient heterogeneity than ctDNA (MATH 50.5 vs 25, $p < 0.05$). **Conclusions:** Single-cell CTC profiling reveals KRAS-independent tumor sub-populations present from baseline and dynamic clonal evolution not captured by ctDNA alone, revealing tumor heterogeneity and KRAS-independent disease biology. Paired CTC and ctDNA analysis provides complementary resolution of persistent atypical oncogenic and tumor suppressor sub-clones not evident from bulk liquid biopsy. Research Sponsor: None.

Knowledge distillation for pancreatic cancer diagnosis: EfficientNet-based deep learning for stage stratification with real-world deployment optimization.

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Background: Pancreatic cancer is among the most lethal malignancies, with a 5-year survival below 12%. Prognosis is strongly stage dependent, yet early disease is frequently misclassified as chronic pancreatitis or benign cystic lesions, resulting in diagnostic delay and loss of surgical opportunity. Although deep learning models demonstrate high accuracy on cross-sectional imaging, their computational demands limit deployment in resource-constrained settings. Knowledge distillation enables transfer of diagnostic capability from high-capacity teacher models to lightweight student networks while preserving performance. We evaluated whether a distilled EfficientNetB0 model could retain EfficientNetB7-level accuracy for pancreatic cancer stage stratification while enabling real-world deployment. **Methods:** We analyzed 2,840 contrast-enhanced abdominal CT studies, including pancreatic ductal adenocarcinoma (n = 1,400; 700 early-stage resectable or borderline-resectable, 700 locally advanced or metastatic), chronic pancreatitis (n = 900), and benign pancreatic lesions (n = 540) from multiple international centers. Ground truth was established by multidisciplinary consensus incorporating histopathology, surgical findings, and longitudinal follow-up. A high-capacity EfficientNetB7 teacher model (≈66M parameters; 37 GFLOPs) trained on multiphasic CT served as reference. A lightweight EfficientNetB0 student model (≈5.3M parameters; 0.39 GFLOPs; > 90% parameter reduction) was trained using temperature-scaled knowledge distillation with regularized cross-entropy loss. Performance metrics included accuracy, sensitivity, specificity, F1-score, and AUROC. Deployment feasibility was independently evaluated by abdominal radiologists and oncologists across six continents. **Results:** The distilled EfficientNetB0 achieved 96.6% accuracy for stage stratification (early vs advanced disease), with sensitivity of 97.4%, specificity of 95.8%, and AUROC of 0.989. Differential diagnosis accuracy was 94.8% for pancreatic cancer versus chronic pancreatitis and 95.6% versus benign lesions. External validation accuracy ranged from 93% to 97%. Mean inference time was 38 ms per image compared with 330 ms for EfficientNetB7. Knowledge distillation preserved 99.1% of teacher performance while reducing computational cost by > 95%. **Conclusions:** Knowledge distillation enables a lightweight EfficientNetB0 to achieve near–EfficientNetB7 accuracy for pancreatic cancer stage stratification while markedly reducing computational complexity. This scalable approach supports real-time imaging decision support and addresses key barriers to global deployment of AI-assisted pancreatic cancer diagnosis. Research Sponsor: None.

Phase IIb randomized trial of FOLFIRINOX plus ibrilatazar (ABTL0812) versus placebo as first-line treatment in metastatic pancreatic cancer: An analysis from the PanC-ASAP study.

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Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has poor prognosis and limited first-line treatment options. Ibrilatazar (ABTL0812) is a first-in-class oral agent that induces cytotoxic autophagy selectively in cancer cells. Favorable safety and tolerability of the combination with FOLFIRINOX were established in a Phase I study. D.S. and T.M. are equal contributors. **Methods:** PanC-ASAP is a Phase IIb double-blind, randomized, placebo-controlled (1:1) study evaluating the efficacy and safety of ibrilatazar (1300 mg TID) plus FOLFIRINOX versus placebo plus FOLFIRINOX as first-line therapy in mPDAC, conducted across 23 sites in the US, Spain, France, and Israel. Eligible patients had histologically confirmed mPDAC, ECOG PS 0–1, and no prior systemic treatment for metastatic disease. Treatment continued until disease progression or intolerable toxicity. Primary endpoint was progression-free survival (PFS), defined as time from randomization to radiographic disease progression or death, assessed by blinded independent central review in the intention-to-treat (ITT) population. Overall survival (OS) was a key secondary endpoint. Safety was assessed in all treated patients. Pre-specified stratification analysis revealed an imbalance in ECOG between arms (ECOG 0/1: 40%/60% ibrilatazar vs 54%/46% placebo), prompting an exploratory efficacy analysis by ECOG PS subgroup. Time-to-event endpoints were analyzed using Kaplan–Meier methods and log-rank tests. **Results:** In the ITT population (n = 140), median PFS for ibrilatazar vs placebo was 9.4 vs 7.9 mths (HR 0.95; 90% CI, 0.69-1.33; p = 0.814). An exploratory analysis by ECOG showed that, among patients with ECOG 0 (n = 66; ibrilatazar, n = 28; placebo, n = 38), median PFS of 11.1 vs 6.5 mths (HR 0.60; 95% CI, 0.34–1.08; p = 0.089), and median OS of 19.3 vs 12.0 mths (HR 0.57; 95% CI, 0.31–1.05; p = 0.072). Consistent trends favoring ibrilatazar were observed across efficacy endpoints, including objective response rate and duration of treatment. Safety profile of ibrilatazar plus FOLFIRINOX was consistent with the known FOLFIRINOX toxicities. The most common grade ≥3 treatment-emergent adverse events in the ibrilatazar vs placebo were neutropenia (21% vs 22%), diarrhea (21% vs 16%), and neurotoxicity (0% vs 14%). **Conclusions:** Although primary PFS endpoint was not met in the ITT population, exploratory analysis showed clinically meaningful and consistent efficacy improvements among ECOG 0 patients treated with ibrilatazar plus FOLFIRINOX, with 60% and 70% increases in median OS and median PFS respectively. These findings support further investigation in selected mPDAC populations and suggest ECOG may modify treatment benefit. Clinical trial information: NCT04431258. Research Sponsor: RFA-FD-20-001 (Clinical Studies of Orphan Products Addressing Unmet Needs of Rare Diseases (R01)); FD-R-006817-01; Funding Source Name: H2020 - EIC - SMEInst - 2018 - 2020; 954825.

A phase II trial of binimetinib in combination with encorafenib in patients with pancreatic malignancies and a somatic *BRAF*^{V600E} mutation.

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains a notoriously difficult-to-treat malignancy, with limited therapy options for patients with advanced disease. While KRAS mutations are the dominant oncogenic driver in PDAC, next-generation sequencing has enabled the identification of rare, targetable alterations such as the BRAF V600E mutation, which occurs in approximately 2-3% of cases. BRAF mutant cell lines are responsive to MEK and RAF inhibitors. This study evaluates the efficacy of the combination of encorafenib and binimetinib as ≥ 2nd line therapy in this specific molecular subgroup of pancreatic cancer patients. **Methods:** This study used a planned two-stage design. Seven patients were pre-registered; one did not meet eligibility criteria and was excluded. Six patients were enrolled in Stage 1, which required an objective response (OR) in 40% of patients to proceed to Stage 2. Stage 2 was planned to enroll an additional 16 patients, contingent on meeting this efficacy threshold. Enrolled patients received treatment in 28-day cycles until disease progression or for a maximum of 36 cycles. Patients self-administered encorafenib (450 mg orally once daily) and binimetinib (45 mg orally twice daily) starting on Day 1 of each cycle. Objective responses were assessed using RECIST version 1.1 over 24 weeks. **Results:** The median number of cycles was 8. The objective response rate at 24 weeks was 33.33%. The overall objective response rate was 50%. The median time to response for progression-free survival, overall survival, duration of response, and time to response was 7.1, 15.0, 9.9, and 3.9 months respectively, with 95% CI in all categories. 50% of patients experienced at least one Grade ≥3 adverse event, including anemia, thromboembolic events, and acute kidney injury. **Conclusions:** The six BRAF-V600E-mutated PDAC patients in our cohort demonstrated meaningful antitumor activity with a manageable safety profile after treatment with encorafenib and binimetinib. Although the study was prematurely terminated due to limited accrual, observed objective responses and survival outcomes suggest that dual RAF/MEK inhibition may represent a feasible therapeutic strategy in this rare molecular subgroup. Larger studies are warranted to further define the efficacy and safety of this treatment combination in BRAF-V600E-mutated pancreatic cancer. Clinical trial information: NCI-2020-02972. Research Sponsor: None.

TME-informed bioprinted 3D tissue model as used to characterize architecture-associated drug uptake and response in PDAC.

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest solid tumors despite extensive drug development efforts. Beyond tumor cell-intrinsic factors, therapeutic failure in PDAC is strongly influenced by the tumor microenvironment (TME), which is dominated by a collagen-rich desmoplastic extracellular matrix (ECM). This architecture alters tissue mechanics, restricts diffusion, and limits effective drug delivery to tumor cells. However, most preclinical platforms rely on 2D models that fail to capture human-relevant TME architecture, potentially leading to overestimation of drug uptake and potency. Amid growing regulatory and scientific momentum toward New Approach Methods (NAMs), there is an urgent need for human-relevant, architecture-aware models that improve translational predictivity in PDAC. **Methods:** Primary human PDAC specimens were analyzed using quantitative, spatially resolved TME mapping to characterize extracellular matrix (ECM) composition, collagen density, and intratumoral versus peripheral distribution. From our prior PDAC analysis, human tumors exhibited collagen-dominant ECM with diffuse intratumoral organization rather than peripheral confinement. These architectural features were used to configure a 3D bioprinted *ex vivo* slice tissue (BEST) PDAC model using PANC02 cells. Drug uptake kinetics and therapeutic response were evaluated in TME-informed 3D BEST models and directly compared with conventional 2D monolayer cultures using matched compounds and exposure paradigms. **Results:** Spatial TME mapping confirmed that human PDAC tumors harbor dense, heterogeneously distributed collagen spanning the tumor parenchyma, a feature not captured by simplified culture systems. Incorporation of these intratumoral collagen features into the 3D BEST model resulted in delayed drug uptake and attenuated response dynamics consistent with diffusion-limited transport. In contrast, 2D models demonstrated accelerated growth kinetics, more rapid drug uptake, and higher apparent drug potency over shorter exposure durations. These findings indicate that architecture-associated transport barriers intrinsic to PDAC substantially modulate therapeutic response and that conventional 2D systems may overestimate drug efficacy by failing to account for collagen-mediated resistance mechanisms. **Conclusions:** By directly linking quantitative TME mapping to 3D model configuration, this NAMs-aligned bioprinted PDAC platform captures architecture-associated constraints on drug uptake that are absent from conventional models. This approach provides a human-relevant framework for evaluating therapeutic response in desmoplastic tumors and supports improved translational fidelity and therapeutic prioritization in PDAC. Research Sponsor: U.S. National Science Foundation; TI-2321805; National Cancer Institute; 1R43CA254493-01; Innovate Alabama.

4221 Poster Session

Next-generation cancer organoids 2.0 in precision cancer medicine: Patient-derived pancreatic ductal adenocarcinoma organoids model to describe drug sensitivity and complexity of tumor biology.

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Background: Organotypic models of patient-specific tumors are revolutionizing our understanding of cancer heterogeneity and its implications for personalized medicine. The study's aims were as follows: 1) to establish a PDAC patient-derived organoid (PDO) model obtained from various PDAC specimens. 2) to find out clinicogenomic factors affecting patients' outcomes. **Methods:** The SMC PDAC Cohort Patients were prospectively enrolled and underwent EUS-guided FNB, metastatic sites (such as liver, ascites, lung, and bone), and surgical resection. PDAC PDOs were comprehensively analyzed for histology, next generation sequencing (NGS), and high-throughput screening (HTS) drug sensitivity tests. **Results:** The 735 PDAC patients were prospectively enrolled in this study. PDAC PDO platform has been trying to establish from the following cancer specimens: ascites, biopsies from bone, liver, lung, and pancreas, or surgical resection. The success rate was as follows according to the source of obtaining site; ascites due to peritoneal seeding (3/3: 100%), bone mets (1/1: 100%), EUS-FNB (195/183: 87.8%), liver mets (7/8: 87.5%), lung mets (1/1: 100%), surgical specimens (394/500: 78.8%) and PDO was successfully established within 8.2±2.6 days. It took approximately 3 weeks to acquire each specimen and generate sufficient PDAC PDOs for the simultaneous HTS drug sensitivity test and NGS. Whole exome or genome sequencing (WES/WGS, n = 357) showed an almost identical concordance between original PDAC tissues and matched PDOs and the increased frequency of genetic alterations in PDOs. The HTS drug sensitivity test (n = 151) revealed the clinical correlation between the PDO response and the actual chemotherapeutic response of the study patients in both palliative and adjuvant in real-world settings (ranging from 84.0~ to 91.2%). In addition, whole transcriptome sequencing (n = 373) identified nab-paclitaxel resistance-associated genes such as ITGB7, ANPEP, and ST3GAL1, and also found early recurrence-related genes including COL2A1, CALB1, and CYP24A1 in the extracellular matrix, calcium signaling, and vitamin D metabolism. **Conclusions:** The PDAC PDO platform may become a valuable tool for personalized medicine and may give us insights into tumor biology. Research Sponsor: None.

Actionable genomic alterations and survival in *KRAS* wild-type pancreatic ductal adenocarcinoma: Analysis of the MSK-CHORD 2024 clinico-genomic cohort with spotlight on *NRG1* fusions.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is predominantly driven by KRAS mutations; however, approximately 10% of tumors are KRAS wild-type (KRAS-WT). Among these, NRG1 gene fusions have recently gained heightened clinical relevance following the FDA's accelerated approval of zenocutuzumab for NRG1 fusion–positive PDAC after prior therapy. Contemporary real-world data characterizing actionable alteration yield and outcomes in KRAS-WT PDAC remain limited. **Methods:** We analyzed patients with PDAC (OncoTree: PAAD) from MSK-CHORD 2024. KRAS status was defined by the presence or absence of pathogenic KRAS somatic mutations. NRG1 fusions were identified through structural variant analysis. A predefined clinically actionable alteration set included NRG1 and NTRK1–3 fusions, MSI-H/dMMR, BRCA1/2 or PALB2 alterations, ERBB2 amplification, and BRAF V600E mutation. The primary endpoint was overall survival (OS) from the date of molecular profiling. Secondary endpoints included prevalence of actionable alterations within KRAS-WT PDAC and enrichment of NRG1 fusions by KRAS status. **Results:** Among 2,703 patients with PDAC, 2,424 (89.7%) had KRAS mutations and 279 (10.3%) were KRAS-WT. NRG1 fusions were identified exclusively within KRAS-WT tumors (4/279; 1.43%) and were absent among KRAS-mutant PDAC. As summarized in Table 1, 25 of 279 KRAS-WT PDAC patients (9.0%) had at least one clinically actionable genomic alteration. These included NRG1 and NTRK fusions, MSI-H/dMMR, homologous recombination repair gene alterations, ERBB2 amplification, and BRAF V600E mutation. Median OS differed substantially by KRAS status. Patients with KRAS-WT PDAC demonstrated longer survival compared with those with KRAS-mutant disease (26.3 vs 14.9 months). Patients with NRG1 fusion–positive PDAC had a median OS of 22.9 months, acknowledging limited sample size (n=4). **Conclusions:** KRAS-WT PDAC accounts for approximately one-tenth of cases and is associated with significantly longer overall survival compared with KRAS-mutant disease. Nearly 1 in 10 KRAS-WT tumors harbored clinically actionable genomic alterations, including NRG1 fusions, now linked to an FDA-approved targeted therapy. These findings support routine comprehensive molecular profiling, including fusion detection, in KRAS-WT PDAC and underscore the clinical relevance of precision oncology approaches in this distinct subgroup. Research Sponsor: None.

Genomic characteristics and actionable alterations in KRAS–wild-type PDAC (MSK-CHORD 2024).

Characteristic	KRAS-Mutant PDAC (n=2,424)	KRAS–Wild-Type PDAC (n=279)
Median OS, months	14.9	26.3
Any actionable alteration*	—	25 (9.0%)
NRG1 fusion	0 (0%)	4 (1.43%)
NTRK1–3 fusion	—	3 (1.08%)
MSI-H/dMMR	—	2 (0.72%)
BRCA1/2 mutation	—	6 (2.15%)
PALB2 mutation	—	1 (0.36%)
ERBB2 amplification	—	5 (1.79%)
BRAF V600E	—	7 (2.51%)

Exosomal miRNA signatures as predictors of response to neoadjuvant FOLFIRINOX and GEM/nab-paclitaxel in resectable pancreatic cancer: The PRECEPT study.

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Background: Neoadjuvant chemotherapy (NAC) with FOLFIRINOX or gemcitabine plus nab-paclitaxel (GEM/nab-PTX) is widely used for resectable and borderline-resectable pancreatic ductal adenocarcinoma (PDAC). However, 10–20% of patients experience disease progression or severe toxicity during NAC, leading to loss of opportunity for curative resection. Given substantial differences in treatment responsiveness between regimens, reliable regimen-specific predictive biomarkers are needed to improve preoperative risk stratification and treatment selection. The PRECEPT trial (NCT07226154) aims to develop circulating exosomal microRNA (exo-miRNA)–based predictors of NAC response. **Methods:** Pre-treatment plasma samples were collected from patients with resectable or borderline-resectable PDAC prior to NAC. Exo-miRNAs were profiled by small RNA sequencing in a discovery cohort of 49 patients (FOLFIRINOX, n = 31; GEM/nab-PTX, n = 18) to identify regimen-specific candidate exo-miRNAs, which were subsequently quantified by qRT-PCR in a validation cohort of 73 patients (FOLFIRINOX, n = 43; GEM/nab-PTX, n = 30). Regimen-specific miRNA panels were constructed using stepwise selection followed by Firth penalized logistic regression. To benchmark against conventional biomarkers, multivariable Firth logistic regression models including the panel score and baseline CA19-9 were performed to evaluate the incremental predictive value of the exo-miRNA panels. Predictive performance was assessed by receiver operating characteristic (ROC) analysis. **Results:** In the discovery cohort, exo-miRNA signatures achieved areas under the curve (AUC) of 0.953 for the FOLFIRINOX panel and 1.000 for the GEM/nab-PTX panel. In the qRT-PCR validation cohort, performance remained robust (AUC 0.835 and 0.882, respectively). Higher panel scores were significantly associated with non-response to NAC ($p < 0.01$). In multivariable analyses, the exosome-derived miRNA panels provided predictive information beyond CA19-9 and remained independent predictors of treatment non-response in both therapeutic cohorts, demonstrating incremental value over conventional biomarkers. Both panels showed high sensitivity with low false-negative rates, supporting their clinical utility in identifying patients unlikely to benefit from neoadjuvant chemotherapy for each regimen. **Conclusions:** We developed two regimen-specific circulating exo-miRNA panels capable of predicting response to FOLFIRINOX and GEM/nab-PTX prior to treatment initiation. These panels provide predictive information beyond CA19-9 and may support individualized NAC selection, risk-adapted treatment planning, and improved preoperative decision-making in resectable PDAC. Clinical trial information: NCT07226154. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

4224 Poster Session

Phase I clinical trial evaluating dual-targeting CAR-T cells (KD-496) against CLDN18.2 and NKG2DL in advanced gastrointestinal cancers and pancreatic cancers.

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy has shown limited efficacy in gastrointestinal (GI) cancers. Previous studies indicate that bispecific CAR-T cells incorporating tandem single-chain variable fragments (scFvs) demonstrate enhanced therapeutic indices compared to monospecific constructs. We developed novel bispecific CAR-T cells (KD-496) targeting both NKG2D ligands and CLDN18.2, demonstrating promising preclinical antitumor activity and safety profiles. **Methods:** We conducted an open-label, single-arm, "3+3" dose-escalation study (NCT06134960) in patients with treatment-refractory advanced GI cancers. Following lymphodepletion with fludarabine, cyclophosphamide, and nab-paclitaxel, subjects received a single KD-496 infusion at three dose levels: 1×10^8 (DL1), 3×10^8 (DL2), or 5×10^8 (DL3) CAR-T cells. Primary endpoints included safety and toxicity; secondary endpoints comprised efficacy, pharmacokinetics, and immunogenicity. **Results:** Between March 2024 and October 2025 , seven subjects (age range: 43-73 years) received KD-496 treatment (n=3 at DL1; n=3 at DL2; n=1 at DL3). Only one Grade IV possibly treatment-related adverse events (TRAEs) is Neutrophil count decreased (14%); Grade III possibly treatment-related adverse events (TRAEs) included Neutrophil count decreased (14%); Alanine aminotransferase increased (14%); Elevated aspartate aminotransferase (14%); anemia (29%); and White blood cell decreased (57%). Cytokine release syndrome (CRS) occurred in seven subjects, with one case (17%) reaching grade 3; no grade 4/5 CRS or neurotoxicity was observed. The dual-antigen requirement effectively prevented on-target off-tumor toxicity, with no patients experiencing severe gastrointestinal adverse events. No dose-limiting toxicities or serious adverse events were reported. Among evaluable subjects: Those with gastric cancer (n=4), achieved an objective response rate (ORR) of 75%; Among three subjects with pancreatic cancer, disease control rate (DCR) of 66.7% overall; Achieved an objective response rate (ORR) of 33% overall. Notably, the ORR reached 100% for both gastric cancer and pancreatic cancer advanced subjects in the medium-dose group. **Conclusions:** These initial data demonstrate a favorable safety profile for KD-496 CAR-T cells targeting NKG2DL/CLDN18.2. The preliminary efficacy signals warrant further investigation of KD-496, particularly in gastric cancer and pancreatic cancer. Clinical trial information: NCT06134960. Research Sponsor: Nanjing KAEDI Biotherapeutics.

Nab-paclitaxel plus S-1 induction chemotherapy for patients with locally advanced pancreatic cancer: A multicenter, open-label phase 2 study.

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Background: The prognosis of locally advanced pancreatic cancer is dismal. The objective of the present study was to evaluate safety and efficacy of nab-paclitaxel plus S-1 in previously untreated locally advanced pancreatic cancer. **Methods:** This multicenter, single-arm phase 2 study was conducted at 4 centers in China. Patients with Eastern Cooperative Oncology Group performance status of 0-1 received up to 8 cycles of nab-paclitaxel 120 mg/m^2 (day 1,8) plus 80-120mg/d S-1 (day 1-14 each 21-day cycle). After induction, patients without disease progression or unacceptable adverse events were eligible to receive continued therapy according to investigators' evaluation, including: continued chemotherapy, chemoradiation, or surgery. The primary endpoint was 6-month progress-free survival rate. The secondary endpoints were progress-free survival, overall survival, objective response rate, R0/R1 rate and safety. The reported efficacy outcomes were analyzed in the intention-to-treat population, and safety outcomes were analyzed in the treated population. This trial is registered with ClinicalTrials.gov, NCT03885219. **Results:** Between April 25, 2019, and March 29, 2023, 60 patients were enrolled in the study. 31 (51.7%) of 60 enrolled patients discontinued induction therapy, with reasons including disease progression (13 [21.7%] patients), adverse events (12 [20.0%] patients), alteration in treatment (4 [6.7%] patients), and withdrawal from study (2 [3.3%] patients). 29 (48.3%) of 60 enrolled patients completed induction treatment, 22 (36.7%) patients finished all 8 cycles of treatment, and 11 (18.3%) patients underwent surgery (10 achieved R0/R1 resection status). The 6-month progression-free survival rate was 71.0% (95% CI: 57.6%-80.9%); 12-month progression-free survival rate was 45.0% (95%CI: 32.0%-57.2%) and 12-month overall survival could reach up to 83.3% (95%CI: 70.3%-90.9%). The median progression-free survival was 11.1months (95% CI: 8.1-14.2); median overall survival was 20.2 months (95% CI: 11.2-29.2). During induction, 54 patients achieved disease control and the disease control rate was 90.0% (95% CI: 79.5%-96.2%). 16 patients had a best response of partial response; the objective response rate was 26.7% (95% CI: 16.1%-39.7%). Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 32 (53.3%) patients. The most common grade 3 or higher TRAEs were neutropenia (23 [38.3%] of 60 patients), followed by leukopenia (13 [21.7%]) and fatigue (4 [6.7%]). No treatment-related deaths were reported. **Conclusions:** The data from this trial supports the favorable and efficacy of nab-paclitaxel plus S-1 for locally advanced pancreatic cancer, as well as the possibility of converting unresectable disease into surgically resectable disease. Clinical trial information: NCT03885219. Research Sponsor: None.

LBA4226 **Poster Session**

A multicenter randomized phase II trial of AHCC combined with multidisciplinary treatment for resectable/borderline resectable pancreatic ductal adenocarcinoma (jRCTs051200029).

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

Plasma small extracellular vesicle microRNAs as non-invasive biomarkers for the diagnosis of pancreatic ductal adenocarcinoma.

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Background: Current non-invasive approaches for the diagnosis of pancreatic ductal adenocarcinoma (PDAC) exhibit inherent limitations in accuracy. Consequently, there exists an urgent and unmet need for novel non-invasive biomarkers exhibiting high sensitivity and specificity to enable PDAC diagnosis. **Methods:** We employed small RNA sequencing to detect microRNA (miRNA) expression in small extracellular vesicles (sEVs) isolated from plasma samples of study participants (n = 208). A diagnostic model was developed (n = 140) and validated (n = 68) to discriminate between patients with PDAC and non-malignant controls (healthy individuals, chronic pancreatitis, intraductal papillary mucinous neoplasms, serous cystadenomas, solid pseudopapillary tumors, pancreatic cysts, and pancreatic abscesses). **Results:** The small RNA sequencing analysis of plasma sEV miRNA identified 32 differentially expressed sEV miRNAs between non-malignant controls and PDAC patients. The diagnostic model with the best performance was constructed using 17 sEV miRNAs. The diagnostic model achieved an area under curve (AUC) of 0.939, a sensitivity of 93%, and a specificity of 90% in the training cohort and an AUC of 0.951, a sensitivity of 95%, and a specificity of 83% in the test cohort. We identified the distinct characteristics of plasma sEV miRNAs among non-malignant controls compared to PDAC patients. Moreover, nine negative miRNAs and one positive miRNA were found significantly associated with the death risk of PDAC (all $p < 0.05$). **Conclusions:** Our findings demonstrates that plasma sEV miRNA exhibits a highly discriminative biomarker for distinguishing non-malignant group from malignant group, making it a promising tool for the diagnosis of PDAC. Research Sponsor: None.

Impact of radiologically identified embryological origin on recurrence patterns and survival in resectable pancreatic head adenocarcinoma.

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Background: The pancreatic head develops embryologically from the fusion of the dorsal pancreatic (Dp) and ventral pancreatic (Vp) buds, which differ in cellular composition. Although histopathology is considered the gold standard for distinguishing these structures, they can also be differentiated radiologically. The prognostic significance of the embryological origin of pancreatic head adenocarcinomas remains unknown. This study aimed to investigate the impact of tumor embryological location on survival outcomes in patients with resectable pancreatic head adenocarcinoma. **Methods:** Patients who underwent surgical resection for pancreatic head adenocarcinoma were retrospectively analyzed. Preoperative conmputed tomography images were used to determine the embryological tumor location. The boundary between Dp and Vp was defined as a line connecting the portal vein/superior mesenteric vein to the anterior margin of the intrapancreatic bile duct. Tumors located predominantly (≥80%) on one side of this boundary were classified accordingly, while tumors without ≥80% predominance in either region were classified as mixed. Patients were grouped as Vp, Dp, or mixed pancreatic (Mp) origin. The primary endpoint was overall survival (OS), and the secondary endpoint was progression-free survival (PFS). **Results:** A total of 164 patients were included. Tumor origin was classified as Vp in 74 patients (45.1%), Dp in 63 patients (38.4%), and Mp in 27 patients (16.5%). Mp tumors were associated with a significantly higher rate of grade 3 tumors (48.1% in Mp vs 21.6% in Vp and 23.8% in Dp, p = 0.005) and advanced T stage (T3–T4: 70.3% in Mp vs 32.4% in Vp and 47.6% in Dp, p = 0.009). Other baseline clinicopathological characteristics, and the rates of adjuvant chemotherapy and radiotherapy were similar among groups. Median PFS was 11.2 months (95% CI 10.5–11.9) in Mp, 13.0 months (95% CI 9.3–16.7) in Vp, and 9.8 months (95% CI 7.6–11.9) in Dp (p = 0.032). All recurrences in the Dp group were distant metastases, whereas Mp tumors recurred predominantly as distant metastases (85.7%) and Vp tumors showed a higher proportion of local recurrence (33.3%) (p < 0.001). Median OS was significantly longer in the Vp group (Mp: 16.7 months, 95% CI 8.9–27.4; Vp: 25.3 months, 95% CI 11.8–37.8; Dp: 16.7 months, 95% CI 13.2–20.3; p = 0.006). **Conclusions:** The embryological origin of pancreatic head adenocarcinoma is associated with distinct pathological features, survival outcomes, and recurrence sites. Vp-origin tumors demonstrate superior OS but higher local recurrence rates, whereas Dp-origin tumors are characterized by early distant metastasis. Preoperative CT-based identification of tumor origin serves as a non-invasive prognostic tool that may guide personalized adjuvant strategies, such as intensifying systemic therapy for Dp/Mp tumors or optimizing local control for Vp tumors. Research Sponsor: None.

Early detection of pancreatic ductal adenocarcinoma (PDAC) with a multiomic liquid biopsy.

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Background: Early diagnosis remains the major unmet challenge in pancreatic ductal adenocarcinoma (PDAC), which accounts for approximately 3% of all cancers but nearly 8% of cancer-related deaths in the United States, reflecting its exceptionally poor prognosis. Overall five-year survival remains below 15%, largely because the majority of patients present with unresectable or metastatic disease at diagnosis. Curative surgical resection is feasible in fewer than 20% of cases. There is a critical need to improve risk stratification and diagnostic triage among high-risk populations, including individuals with pancreatic cystic lesions, chronic pancreatitis, and new-onset diabetes over the age of 50. However, the low short-term incidence of PDAC in these groups limits the feasibility of widespread surveillance using current imaging modalities. **Methods:** In this study, a spectroscopic blood test has been evaluated as an alternative strategy for PDAC detection. This technology employs infrared (IR) spectroscopy to interrogate blood samples, generating disease-specific spectral signatures sensitive to cancer-associated biochemical alterations. When integrated with machine learning, the approach enables detection by capturing global changes across all biomolecular components of the sample. Initially, spectra from 166 patients with PDAC were classified against those from 459 symptomatic patients with non-cancer diagnoses. The trained algorithms are then independently tested on an additional clinical dataset focused on the higher risk population (n = 975). **Results:** The initial receiver operating characteristic (ROC) curve reported an area under the curve (AUC) value of 0.84. The diagnostic algorithm reported 92% sensitivity with 52% specificity. Importantly, the model did not seem to be affected by cancer stage. The detection rates with the sensitivity-tuned model were 88% stage I, 94% stage II, 99% stage III and 95% stage IV. Validation testing provided additional confirmation of diagnostic ability in the intended use population. The ROC curve for PDAC versus all control patients reported an AUC of 0.81, and PDAC classified against high-risk non-cancers produced an AUC of 0.83. **Conclusions:** Earlier detection of PDAC has the potential to substantially improve patient outcomes and survival. While advances in genetic sequencing have enabled the identification of tumor-derived biomarkers—including circulating tumor DNA, exosomes, and microRNA—these approaches are limited in early-stage PDAC due to low tumor burden and weak signal from circulating markers. A spectroscopy-based, multi-omic blood test represents a novel strategy that may overcome these limitations, particularly in high-risk populations. Research Sponsor: None.

A phase II multicenter study of NASOX regimen as adjuvant chemotherapy for patients with resected pancreatic ductal adenocarcinoma.

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Background: Pancreatic ductal adenocarcinoma (PDAC) is the fifth leading cause of cancer-related mortality in China, with a 5-year survival rate of only 5%–7%. Surgical resection followed by adjuvant chemotherapy can improve this to 15%–25%, but more effective adjuvant regimens are urgently needed to further prolong survival. The PRODIGE 24/CCTG PA.6 trial demonstrated that the mFOLFIRINOX regimen significantly improved outcomes compared with gemcitabine alone. The NASOX regimen is a modified mFOLFIRINOX regimen, which uses irinotecan hydrochloride liposomes (nal-IRI) instead of irinotecan and oral fluoropyrimidine tegafur instead of fluorouracil, and has demonstrated a favorable safety profile. This study aims to assess the efficacy and safety of NASOX as an adjuvant chemotherapy regimen for patients with resected PDAC. **Methods:** This is a Phase II, single-arm, open-label, multicenter clinical trial to evaluate the efficacy and safety of NASOX as adjuvant chemotherapy in patients with resected PDAC. The primary endpoint is DFS. Secondary endpoints include overall survival (OS), safety, quality of life (QoL), compliance with adjuvant therapy, and nutritional status. Exploratory endpoints will involve genomic, metabolomic, and proteomic analyses to identify biomarkers that may predict response and safety to NASOX regimen **Results:** Between August 2024 and October 2025, 55 patients were screened, with 53 ultimately enrolled. Age ranged from 34 to 73 years (median: 59). Forty-six patients underwent at least one tumor assessment, with 11 experiencing disease recurrence and 3 deaths. Median follow-up was 11.5 months(interquartile range 9.9–15.5), yielding a 9-month DFS rate of 82.7% a 9-month OS rate of 97.7%, with median DFS and OS not yet reached. Treatment-related adverse events (TRAEs) occurred in 52 patients (100%), including grade 3 or 4 adverse events in 28 patients (53.85%). The most common Grade 3–4 treatment-related adverse events were diarrhea (17.31%), neutropenia (17.31%), hypokalemia (11.54%), and gastrointestinal pain (9.62%). **Conclusions:** NASOX regimen demonstrated the anticipated efficacy and safety profile in the adjuvant treatment of PDAC following surgery, warranting further investigation. Clinical trial information: NCT06361316. Research Sponsor: None.

Safety, efficacy, and immunogenicity of adjuvant therapy with personalized cancer vaccine (PCV) RGL-270 in combination with adebrelimab and mFOLFIRINOX in resectable pancreatic ductal adenocarcinoma (PDAC).

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Background: Tumor specific neoantigens are peptides carrying somatic mutations presented by HLA molecules and recognized by T cells, which subsequently induce specific immune response (IR). The IR could be further boosted when in combination with PD-1/L1 inhibitor. RGL-270 is a lipid nanoparticle (LNP)-encapsulated, mRNA-based PCV, encoding tumor specific neoantigens screened via a proprietary algorithm to induce patient specific IR. This investigator-initiated, open-label, dose escalation and expansion clinical trial was conducted in China, to evaluate the safety, efficacy and immunogenicity of RGL-270 in combination with adebrelimab (anti-PD-L1 mAb) in patients with resectable PDAC. **Methods:** PDAC patients with R0/R1 surgical margins were enrolled. After surgery, RGL-270 was administrated up to 9 cycles, in combination with adebrelimab and followed by modified FOLFIRINOX chemotherapy. The key endpoints included safety, efficacy assessment with recurrence-free survival (RFS), overall survival (OS), 18-month RFS rate, and PCV specific IR evaluation by ELISpot. **Results:** As of 01/15/2026, 16 patients in the dose escalation (n = 7) and expansion (n = 9 at expansion dose level) stage received RGL-270 combo with adebrelimab therapy. Up to date, all dose levels were safe and well tolerated. The most common treatment-related adverse events (TRAEs) were fever, influenza-like illness and injection-site reactions. All TRAEs were CTCAE grade 1~2 and no treatment-related SAE or DLT was reported. Currently, the median follow-up is 18.0 months, with median RFS and OS not reached yet, and the 18-month RFS rate is 100%.The PCV-specific IR positive rate was 100%. Interestingly, IR was also detected in patients who had undergone prior splenectomy (5/16). The primary IR emerged as early as 2 cycles after the first PCV administration, with the best of response (BoR) observed 2~4 cycles post-baseline and, in most cases, persisting until cycle 9, the booster cycle. To date, no dose-dependent manner for IR has been observed. Additionally, concordance between the predicted and immunogenic neoantigens was analyzed, and the resulting insights were fed back to improve the neoantigen screening algorithm. Furthermore, bulk T-cell receptor sequencing was performed to further characterize the PCV specific IR. **Conclusions:** Based on proprietary LNP delivery systems, algorithms for neoantigen identification and immunogenicity prediction, the combination treatment of RGL-270 and adebrelimab demonstrated a favorable safety profile, promising efficacy, and robust immunogenicity. This preliminary result guarantees the further development of PCV-based anti-tumor therapy in the adjuvant setting for PDAC. Clinical trial information: NCT06156267. Research Sponsor: Noncommunicable Chronic Diseases-National Science and Technology Major Project (2024ZD0525500/2024ZD0525505).

Experience of Spanish centers with echoendoscopically implanted ^{32}P microparticles associated with chemotherapy in locally advanced pancreatic adenocarcinoma.

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Background: Phosphorous 32 microparticle (^{32}P) brachytherapy delivered by echoendoscopy (EUS) represents an innovative therapy in pancreatic cancer (PC). The device to implant it is approved in unresectable locally advanced PC in combination with gemcitabine-based chemotherapy. Our aim is to present the preliminary efficacy and safety results of a series that brings together the experience of thirteen centres in Spain. **Methods:** After being assessed by a multidisciplinary committee, patients signed consent to receive intratumoural ^{32}P by EUS. Complications associated with intratumoural 32P injection via EUS, associated adverse events (AEs) and preliminary efficacy results (progression-free survival [PFS], distant and locoregional, and overall survival [OS]) were analysed. **Results:** Fifty one patients (32 females and 19 males; age 65.5 years [range 48, 84]; 36 ECOG 1 and 14 ECOG 0) with unresectable locally advanced PC (30 in head, 5 in uncinate, 5 in neck and 11 in body; tumour size 30.8 mm [range 12, 60]) were included. The median time from tumour diagnosis to procedure was 5.9 months [0, 28.9]. Twenty-four patients (47 %) had received at least one previous line of treatment; four had received two prior lines. Fifty patients (98%) received gemcitabine-based chemotherapy concomitant with intratumoural 32P (42 gemcitabine plus nabpaclitaxel; 8 gemcitabine monotherapy. There were two AEs related to 32P injection by EUS: G1 epigastric pain (1 patient) and G2 asthenia (1 patient). A total of 30 patients (58.8%) had chemotherapy-related AEs, with 8 cases of G3 neutropenia (1 febrile neutropenia) and/or G3 thrombopenia; 22 had G1-2 toxicities: neurotoxicity (5), asthenia (4), neutropenia (3), thrombopenia (2), anaemia (4), nausea (2), diarrhoea (2), anorexia (1), onycholysis (1), mucositis (1), and constipation (1). Seven patients (13,7%) underwent surgery after intratumoural treatment (5 R0 and 2 R1). With a median follow-up of 8.7 months after injection (range: 1.02 months to 40.77 months), 25 patients (49.2 %) have progressed, 19 of them distantly, and nine also locoregionally. The median PFS since 32P injection is 8.5 months (95% CI 5.3, 17). 33 patients are alive at the end of follow-up (64.7%) with a median OS since 32P injection of 15.6 months 95% CI [10.2, 26.9]. **Conclusions:** Our experience suggests that intratumoural 32P associated with gemcitabine-based chemotherapy is safe. Patients after 32P injection achieve long overall survival. Surgical rescue was achieved in a high percentages of initially unresectable cases. Research Sponsor: None.

Distinct multi-omic signatures that underlie *KRAS* variants and survival in *KRAS* G12R pancreatic cancer.

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Background: KRAS mutations are the dominant oncogenic drivers of pancreatic ductal adenocarcinoma (PDAC). While KRAS G12D/V variants are associated with aggressive disease and poor prognosis, the biological basis for survival differences among KRAS variants remains incompletely defined. We leveraged a comprehensive multi-omics dataset to characterize variant-specific molecular signatures associated with survival. **Methods:** Tissue and plasma samples from 72 patients with Stage I/II resectable PDAC were retrospectively analyzed using the Aseesa Stars multi-modal integrated platform. Multi-omic profiling included targeted DNA sequencing, whole-transcriptome RNA sequencing, tissue and plasma proteomics, lipidomics, and computational pathology, generating 6,363 features linked to overall survival (OS). Analyses focused on KRAS wild-type (n=7) and the most prevalent KRAS variants: G12R (n=12), G12D (n=21), and G12V (n=13). **Results:** Patients with KRAS G12R who underwent upfront resection demonstrated significantly longer OS compared with G12D/V variants (median OS 37.5 vs. 18.9 months; HR 0.50 [95% CI 0.23–1.09]; log-rank p=0.047). Compared with KRAS-WT, combined KRAS-mutant tumors exhibited significant alterations in neutrophil degranulation, apoptosis, protein transport, cell adhesion, and oxidative phosphorylation (OXPHOS) pathways ($p<0.05$). A total of 381 molecular signatures differed significantly ($p<0.05$) between G12R and G12D/V cohorts. In direct G12R vs. G12D comparison, 110 features were unique to high OS ($p<0.05$). KRAS G12R, G12D and G12V shared activation of PI3K/AKT, MET, and PTPN11 signaling, consistent with a common aggressive phenotype. In contrast, KRAS G12R tumors demonstrated significant alterations in major mRNA splicing and OXPHOS pathways ($p<0.05$). Splicing regulators PLRG1 and RBM8A were reduced in G12R patients by 6% ($p<0.03$). Six OXPHOS-related signatures also favored high OS, lipid hexosylceramide 24:1 was decreased by 14.59% (p=0.016). Tissue protein ACADS decreased by 5.38% (p=0.025) in G12R high OS, but increased in G12D high OS. **Conclusions:** KRAS G12R defines a molecularly distinct PDAC subtype with improved survival, characterized by suppressed mRNA splicing signatures and coordinated metabolic remodeling, highlighting variant-specific metabolic and molecular divergence. These findings underscore the importance of KRAS variant stratification for prognostication and future development of variant-specific precision therapeutic strategies. Research Sponsor: U.S. National Institutes of Health; CA259456; Conquer Cancer, the ASCO Foundation.

Risk-adapted step-up local therapy for malignant portal vein tumor thrombus from hepatic metastases: A real-world study of microwave ablation with and without iodine-125 seed implantation.

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Background: Malignant portal vein tumor thrombus (PVTT) arising from hepatic metastases is associated with poor prognosis, rapid hepatic decompensation, and limited effective local treatment options despite systemic therapy. In real-world practice, local treatment intensity is frequently adapted to disease burden and treatment response. We evaluated outcomes of a risk-adapted, step-up local treatment strategy using microwave ablation (MWA) alone or in combination with iodine-125 (I-125) seed implantation for patients with malignant PVTT. **Methods:** We retrospectively reviewed patients with hepatic metastases treated with MWA with or without I-125 seed implantation between 2023 and July 2025. In clinical practice, MWA alone was preferentially used for patients with relatively limited disease burden, while MWA plus I-125 was employed as an escalation strategy for patients with more advanced PVTT or disease progression following MWA alone. The primary endpoint was PVTT-directed local outcome, defined as portal vein patency and/or local control of tumor thrombus on follow-up imaging. Secondary endpoints included progression-free survival (PFS), overall survival (OS), hepatic function changes, and treatment-related toxicity. Survival analyses were considered exploratory. **Results:** A total of 73 patients were included, of whom 50 were treated with MWA alone and 23 with MWA plus I-125 seed implantation. Patients receiving MWA plus I-125 demonstrated more advanced disease characteristics, including universal presence of PVTT and higher disease stage, consistent with treatment escalation by disease severity. Among patients with PVTT, MWA plus I-125 achieved portal vein patency and/or local control in 65% at first follow-up imaging. Treatment-related toxicities were manageable, with no unexpected grade $\geq$3 adverse events attributable to I-125 implantation. Median PFS was 11.5 months in patients treated with MWA alone and 9.9 months in patients treated with MWA plus I-125, consistent with greater baseline disease burden in the latter group. **Conclusions:** MWA alone and MWA plus I-125 function as complementary components of a risk-adapted, step-up local treatment strategy for malignant PVTT from hepatic metastases. Escalation to MWA plus I-125 appears feasible in patients with advanced or refractory PVTT and demonstrates a potential signal for improved PVTT-directed local control and portal vein patency. Prospective studies focused on PVTT-specific endpoints are warranted. Research Sponsor: None.

Donafenib plus immune checkpoint inhibitors with or without oral fluorouracil chemotherapy drugs (S-1/capecitabine) for patients with resected high-risk biliary tract tumor: A multi-center retrospective study.

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Background: Chemotherapy combined with Immune Checkpoint Inhibitors (ICIs) and donafenib showed promising efficacy and safety in advanced biliary tract cancer (BTC). Oral fluorouracil chemotherapy drugs S-1 or capecitabine are used as standardized adjuvant therapy for BTC. This study aimed to evaluate the efficacy and safety of donafenib plus ICIs with or without oral fluorouracil chemotherapy drugs as adjuvant therapy in BTC patients with high-risk recurrence factors after radical resection. **Methods:** This multi-center retrospective study enrolled BTC patients with high-risk recurrence factors who underwent surgical resection at Hunan Provincial People's Hospital, Sichuan Provincial People's Hospital, The First Affiliated of Zhengzhou University, Sir Run Run Shaw Hospital and Jiangsu Provincial People's Hospital from Aug 2022 to Nov 2025. All patients exhibited at least one of the following high-risk recurrence factors: macrovascular invasion, lymph node metastasis, satellite lesion, nerve invasion and the maximum diameter of tumors≥5cm. Patients received adjuvant therapy of donafenib plus ICIs with or without S-1/capecitabine after surgery. The primary endpoint was RFS and secondary endpoints included OS and safety. **Results:** A total of 50 patients were enrolled, with a median age of 60.5, included 21 Intrahepatic, 18 hilar cholangiocarcinoma and 11 others. Tumor stage I/II/III/IV, 8/10/25/7; R0/R1 resection, 44/6. All patients exhibited a high risk factor of recurrence at least, the rate of macrovascular invasion, lymph node metastasis, satellite lesion, nerve invasion and the maximum diameter of tumors≥5cm are 40.0%, 42.0%, 6.0%, 70.0% and 34.0%. 20 patients received the adjuvant therapy of S-1/ capecitabine plus donafenib with ICIs, and the other 30 patients were treated with donafenib and ICIs. The median follow-up time was 15.2 months (95%CI: 11.17-18.46), 16 patients relapsed. The median RFS was 14.0 months (95% CI: 11.07-NA), and the one-year RFS rate was 63.8%, two-year RFS rate was 45.1%. T staging of tumor is an independent influencing factor on disease recurrence in the multivariate analysis. The RFS in stage T1/2 patients was significantly higher than stage T3/4. The incidence of grade 3 TEAEs stood at 26.0%, including hand-foot syndrome (44%), anaemia (16%), diarrhea (16%) and rash (12%). No patients encountered grade 5 TRAEs. **Conclusions:** The combination of donafenib plus ICIs with or without oral fluorouracil chemotherapy drugs (S-1/capecitabine) appears to be a promising adjuvant therapy for patients with high-risk biliary tract tumor. Furthermore, no significant safety concerns were observed. Research Sponsor: None.

Deciphering the heterogeneity and cellular interactions of cancer-associated fibroblasts in extrahepatic cholangiocarcinoma by spatial transcriptomics.

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Background: Cholangiocarcinoma (CCA) is a rare and lethal malignancy characterized by a desmoplastic stroma. containing cancer-associated fibroblasts (CAFs). Although CAFs have been widely studied in intrahepatic CCA, their impact on TME remodeling and chemo-immunotherapy (CIT) efficacy in extrahepatic (e) CCA is not fully elucidated. A compressive characterization of the spatial orchestration of the eCCA TME and of the interaction between CAFs and adjacent tumor cells is needed for the identification of therapies able to improve CIT efficacy, that, so far, is limited in these patients. **Methods:** We employed spatial transcriptomics on tumor specimens from 8 patients with advanced distal (d) or perihilar (p) CCA treated with durvalumab + cisplatin/gemcitabine. 126 microregions were analyzed with the GeoMx Digital Spatial Profiler and classified according to pan-CK and ACTA2/αSMA straining, as follow: $CK^{+}\alpha SMA^{-}$tumor, $CK^{-}\alpha SMA^{+}$ distant and peritumor CAF-enriched stroma, or $CK^{-}\alpha SMA^{-}$ peritumor stroma. **Results:** αSMA staining showed a high degree of stromal heterogeneity in all eCCA, with some tumor nests surrounded by a dense CAF-enriched stroma and others by αSMA^{-} cells within the same sample. Based on CD45 staining all samples were classified as immune-desert or -excluded, as no immune cells were found intratumorally. Tumor-adjacent CAFs exhibited a distinct extracellular matrix (ECM) remodeling signature marked by the expression of *COL11A1*, *MMP11* and TGFB family members. GSEA showed a positive enrichment of epithelial-mesenchymal transition (EMT) transcripts linked to the downregulation of signatures of immune activation and IFN response, in both peritumoral CAF-enriched regions and adjacent tumor cells. Confirming this data, receptor-ligand interaction modeling performed using the CellChat tool confirmed that CAF-enriched regions exhibited strong interactions with adjacent tumor cells, throughout the secretion of several factors involved in ECM-remodeling and immunosuppression. Intriguingly, a higher expression of EMT-related genes linked to a higher downregulation of pathways of immune activation was observed in dCCA vs pCCA samples, with dCCA patients experiencing a shorter progression-free survival (PFS) from CIT compared to pCCA patients (PFS ranging from 7-12 and 10-24 months, respectively). **Conclusions:** Our findings suggest that $COL11A1^{+}MMP11^{+}$ CAFs might limit CIT efficacy in eCCA by promoting eCCA EMT and, at the same time, by forming a collagen-dense physical barrier that hampers the intratumoral recruitment of immune cells, thus offering novel insights into potential therapeutic targets for interventions. A deeper characterization of CAF features and CAF-tumor interactions is ongoing. Research Sponsor: None.

Real-world outcomes in gastrointestinal cancer patients with targetable genomic alterations identified on serial liquid biopsy.

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Background: Precision oncology in gastrointestinal (GI) cancers relies on identifying targetable genomic alterations (TGA) to guide therapy. Liquid biopsy (LB) using circulating tumor DNA (ctDNA) enables minimally invasive molecular profiling and serial monitoring. As targeted therapies for GI cancers expand, repeat LB is increasingly used to detect emergent alterations. However, the clinical relevance of TGA not previously identified, particularly when detected at low variant allele fraction (VAF) where clonal burden is difficult to infer, remains unclear. **Methods:** GI cancer patients (pts) with >1 LB were identified from the Guardant Health InfinityAI Data Library, a real-world database of insurance claims and de-identified clinical Guardant360 records. Pts without TGA on initial LB, but gained TGA on subsequent LB were included. TGA were defined as biomarkers with cancer-type specific or pan-tumor matched targeted therapy (MTT) approvals: KRAS G12C, ERBB2 amplification (amp), BRAF V600E, IDH1, MSI-H, and NTRK/RET/FGFR2 fusions or with select approved MTT in non-GI cancers: PIK3CA and ERBB2 mutation (mut). When available, methylation-derived tumor fraction (TF), a measure of overall ctDNA burden independent of variant-specific effects, was compared with emergent TGA VAFs, excluding MSI-H and ERBB2 amp. Pts with multiple cancers or prior MTT were excluded. Cox proportional hazards model assessed associations between MTT and real-world overall survival (rwOS), adjusting for age, gender, cancer type, MSI-H status, and number of gained TGA. **Results:** Among 16,435 GI cancer pts with >1 LB and no initial TGA, 2,072 (12.6%) gained TGA on serial LB and were included in the overall cohort. For the survival analysis, 804 pts with gained TGA had treatment and survival data; 13.4% (108/804) received MTT. Colorectal cancer pts had the highest rate of emergent TGA with approved MTT (17%). The most common gained TGA across the overall cohort were PIK3CA mut (62%), ERBB2 mut (11.7%), BRAF V600E (9.5%), KRAS G12C (8.6%), ERBB2 amp (7%), MSI-H (4.4%), FGFR fusions (3%), and NTRK fusions (1.9%). Gained TGA were often detected at low VAF (median 0.2%; 0.01% - 41.4%), and below the TF, suggesting potential subclonal emergence. Cholangiocarcinoma and gastroesophageal cancers had the highest MTT rates (14.2% and 10%, respectively), whereas no anal cancer pts received MTT. Including pts who gained MSI-H status, 12-and 60-month rwOS from LB-detected TGA was 67% and 25% without MTT versus 78% and 44% with MTT, $p<10-4$; excluding MSI-H, rwOS with MTT was 82% and 34%, p=0.00025. **Conclusions:** Repeat LB identified TGA in a subset of GI cancer pts lacking baseline TGA, many detected at low VAF. MTT receipt for emergent TGA was associated with improved rwOS, supporting serial LB in later-line decision making. Further studies are needed to assess outcomes by TGA type, therapy, clonality, and GI cancer. Research Sponsor: None.

TPS4239 Poster Session

Phase II study evaluating ivonescimab in combination with chemotherapy as first- and second-line treatment of advanced or metastatic gastric and gastroesophageal adenocarcinoma patients (UCGI 52 – GRACIE).

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Background: The prognosis of advanced/metastatic gastroesophageal adenocarcinomas (GEA) has recently improved with new targeted therapies, including immune checkpoint inhibitors, mostly developed in the first-line setting. However, for patients (pts) without actionable biomarkers or for those who become refractory to first-line therapy, a significant unmet need remains for effective therapeutic options. Ivonescimab, a bispecific antibody targeting both VEGF-A and PD-1, appears to be a promising strategy in this setting. **Methods:** This phase 2 multicenter two-cohort, non-randomized study (NCT06846346) is designed to evaluate the efficacy and safety of ivonescimab + chemotherapy in pts with advanced or metastatic GEA, with and without actionable biomarker. Main eligibility criteria are age $\geq$ 18 years, histologically proven GEA, stage 4 disease, no prior treatment for pts without actionable biomarker (cohort 1) or only one prior line for pts with actionable biomarker (cohort 2), ECOG-PS 0-1, and adequate organs functions. The tumor has to be measurable (RECIST 1.1). Treatment regimens are ivonescimab 20mg/kg IV on D1 Q2W combined with: cohort 1: FOLFOX (oxaliplatin 85mg/m^2 IV, folinic acid 400 mg/m^2 IV [or L-folinic acid 200 mg/m^2], 5-FU bolus 400 mg/m^2 then 5-FU 2400 mg/m^2 as a 46-hours continuous IV infusion on D1 Q2W; oxaliplatin will be stopped after 8 cycles); cohort 2: at investigator discretion, paclitaxel (80 mg/m2 IV at D1, D8 and D15, Q4W for at least 4 cycles) or irinotecan (180 mg/ m2 IV on D1 Q2W). Treatment will be administered until disease progression or unacceptable toxicity. The primary endpoint is ORR by central review. Secondary endpoints include ORR assessed by investigator, duration of response, PFS, OS, safety, time to PS deterioration >2, and quality of life. According to a single stage phase II A'Hern's design, a sample of 33 evaluable pts in cohort 1 and 47 evaluable pts in cohort 2 is required to distinguish between a maximum futility proportion of 0.5 (cohort 1)|0.2 (cohort 2) and a minimum efficacy proportion of 0.75 (cohort 1)|0.4 (cohort 2) with a one-sided significance level of 0.04 and 90% power. 88 patients have to be enrolled to observe a minimum of 80 evaluable patients. Planned accrual duration is 1 year, 12 patients have already been enrolled. Clinical trial information: NCT06846346. Research Sponsor: SUMMIT Therapeutics.

TPS4240 **Poster Session**

HIPEC combined with NIPS and tislelizumab for conversion therapy in gastric cancer with peritoneal metastasis (P0CY1 or PCI ≤10): A prospective, single-arm, phase II study.

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Background: Peritoneal metastasis, which is common, difficult to diagnose early, and associated with a poor prognosis, is a leading cause of death in pts with advanced gastric cancer. Due to the peritoneal-plasma barrier, traditional systemic chemotherapy is often ineffective for gastric cancer patients with peritoneal metastasis. In recent years, combined systemic and intraperitoneal therapy has gained increasing recognition. The RATIONALE-305 study demonstrated that tislelizumab (TIS) significantly improves outcomes in these patients. This study combines hyperthermic intraperitoneal chemotherapy (HIPEC), normothermic intraperitoneal and systemic chemotherapy (NIPS), and PD-1 inhibitor, exploring a novel conversion therapy regimen for pts with gastric cancer peritoneal metastasis. **Methods:** This is a prospective, single-center, single-arm phase II study aims at evaluate the efficacy and safety of HIPEC combined with NIPS and tislelizumab as conversion therapy for gastric cancer pts with peritoneal metastasis who are either cytology-positive only without macroscopic peritoneal deposits (P0CY1) or Peritoneal Carcinomatosis Index (PCI) ≤10. Key inclusion criteria are: 1) age 18-75 years; 2) ECOG performance status 0-1; 3) HER2-negative confirmed by IHC, and PD-L1 CPS≥1; 4) either P0CY1 or PCI ≤10 without other distant metastases confirmed by laparoscopy; 5) adequate function of major organs. Pts undergo diagnostic laparoscopy for PCI scoring and peritoneal cytology examination. Upon confirmation of eligibility, pts receive three sessions of HIPEC followed by 4 cycles of NIPS combined with systemic therapy. The HIPEC regimen consists of paclitaxel at a dose of 75 mg/m² administered on D1, 3, and 5. After a two-week rest, NIPS combined TIS is initiated. The NIPS regimen includes paclitaxel (20 mg/m², ip, D1,8, Q3W and 50 mg/m², iv, D1,8, Q3W) ,S-1 (40-60mg based on BSA, po, D1-14, Q3W). The dosage and administration of TIS is 200 mg, iv, D1, Q3W. Radiological evaluations are performed every 2 cycles during conversion therapy. Upon completion of conversion therapy, pts undergo a second laparoscopic exploration with peritoneal cytology examination to re-evaluate disease status. Operable pts who achieve R0 resection receive postoperative adjuvant therapy with the same regimen (paclitaxel + S-1 + TIS) for 4 cycles. For inoperable pts or those not achieving R0 resection, subsequent treatment is determined by a multidisciplinary team (MDT). The primary endpoint is the surgical conversion rate. Secondary endpoints include the 1-year progression-free survival (PFS) rate, 2-year overall survival (OS) rate, PFS, OS, and safety. Exploratory endpoints aim to investigate the correlation between efficacy prediction and biomarkers such as PD-L1 expression, CLDN18.2 expression, and microsatellite instability (MSI) status. Clinical trial information: NCT07304258. Research Sponsor: None.

TPS4241 Poster Session

A randomized phase II/III trial of intraperitoneal paclitaxel plus systemic treatment vs systemic treatment alone in gastric carcinomatosis: STOPGAP II—ECOG-ACRIN EA2234.

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Background: Thirty to forty percent of patients with gastric cancer will develop peritoneal carcinomatosis (PC), the survival of which remains poor despite systemic therapy (ST). Limited drug delivery into PC due to blood-peritoneal barrier is considered to decrease the effectiveness of ST. Hence, there is a critical need to develop novel treatment strategies to improve patient outcomes. Intraperitoneal (IP) paclitaxel (PTX) combined with ST had been studied extensively in Asia. In the US, STOPGAP I, a single institution phase II trial has established the safety and feasibility of IP PTX plus ST in Western patients with gastric PC. Based on these results, we developed STOPGAP II trial, which is designed to evaluate the survival benefits of IP PTX plus ST compared to ST alone in patients with gastric PC. **Methods:** ECOG-ACRIN EA 2234 STOPGAP II is a multi-center randomized phase II/III trial (NCT07001748) evaluating IP PTX plus ST compared to ST alone in patients with gastric PC. Eligible patients must have microsatellite stable gastric/gastroesophageal cancer (Siewert 3) with cytology positive disease or carcinomatosis detected by diagnostic laparoscopy (DL), laparotomy, or radiology and have undergone 3-6 months of first line ST. Patients must not have visceral metastases except ovarian metastases or clinically significant progression of PC. All enrolled patients will undergo DL with peritoneal cancer index (PCI) assessment within four weeks of registration. Patients will be randomized intraoperatively in 1:1 fashion to Arm A- ST or Arm B- IP PTX with ST. In patients randomized to Arm B, an IP port will be placed at the initial DL . Patients in Arm A will continue first line ST and patients in Arm B will receive 40 mg/m2 of IP PTX on days 1 and 8 combined with 50mg/m2 of IV PTX, 5 fluorouracil 400 mg/m2, leucovorin 20mg/m2. Immune checkpoint inhibitors and targeted agents will be continued as per standard of care. Patients will be stratified by PCI (0, 1-6, 7-14, versus >15) and first line ST type (chemo + targeted agent or immunotherapy versus chemotherapy alone). In both treatment arms, patients will undergo reevaluation with repeat imaging and if indicated, DL after three months. Patients with stable disease or response will continue the assigned treatment or could be considered for cytoreduction if PCI <7. The primary endpoints are progression free survival (phase II) and overall survival (OS) (phase III). Assuming the median OS of IP PTX and that of ST to be 22.5 and 12.5 months respectively, and accounting for attrition, 148 patients will be enrolled to achieve 90% power with a hazard ratio of 0.56 (one-sided type I error of 5%). The study is actively enrolling patients with results expected in 2031. Clinical trial information: NCT07001748. Research Sponsor: NCI CTEP.

TPS4242 Poster Session

A phase 1/2 study of BDC-4182, a Claudin 18.2–targeting next-generation immune-stimulating antibody conjugate (ISAC), in patients with advanced gastric and gastroesophageal cancer.

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Background: Claudin 18.2 (CLDN18.2) is a transmembrane tight junction protein with expression restricted to the gastric mucosal epithelia where CLDN18.2 protects against paracellular acid leakage and associated gastritis.[1] CLDN18.2 overexpression has been observed in several tumor types, including gastric, esophageal, and pancreatic cancer.[2,3] Loss of cell polarity in these tumors results in CLDN18.2 localization to surfaces that are more readily accessible to biologics and effector cells. This expression pattern makes CLDN18.2 a compelling target for immune-stimulating antibody conjugates (ISACs) that combine the specificity of tumor-targeting antibodies with the potency and durability of immune activation. BDC-4182 is a next-generation ISAC consisting of a CLDN18.2-targeting antibody covalently attached to a novel toll-like receptor (TLR)7/8 agonist via a non-cleavable linker. In preclinical models, systemic delivery of ISACs has been shown to broadly activate the innate and adaptive immune system, leading to complete tumor regression. A BDC-4182 surrogate induced immunologic memory and epitope spreading as evidenced by rejection of tumor cells that no longer express the target antigen (CLDN18.2) following re-challenge.[4,5] **Methods:** This is a first-in-human Phase 1 dose escalation and Phase 2 expansion study of BDC-4182. Up to 122 patients with advanced gastric and gastroesophageal cancer will be enrolled. To optimize tolerability, BDC-4182 is administered via an intra-patient step-up dosing regimen wherein subjects receive lower initial priming doses prior to the target dose. Primary objectives are to define safety and tolerability and to determine the recommended phase 2 dose (RP2D) of BDC-4182 as a single agent. Secondary objectives will evaluate the preliminary anti-tumor activity of BDC-4182, analyze PK characteristics of BDC-4182, and evaluate the immunogenicity of BDC-4182 as a single agent. Exploratory analyses will also be conducted to explore potential biomarkers in blood and tumor tissue associated with exposure, efficacy, or safety of BDC-4182, and to define CLDN18 expression in tumor tissue. This study is being conducted in Australia, South Korea, and Taiwan. References: 1. Suzuki K, Sentani K, Tanaka H, et al. Cell Mol Gastroenterol Hepatol. 2019;8:119-142. 2. Hong JY, An JY, Lee J, et al. Transl Cancer Res. 2020;9:3367-3374. 3. Chen J, Xu Z, Hu C, et al. Front Oncol. 2023;13:1132319.4. Fu C, Luo A, Liu J, et al. J Immunother Cancer. 2024; 12(Suppl 2):Abstract 1052. 5. Kim HK, Monnier J, Fu C, et al. J Immunother Cancer. 2023;11(Suppl 1):Abstract 1147-D. Clinical trial information: NCT06921837. Research Sponsor: Bolt Biotherapeutics.

TPS4243 Poster Session

Phase II RAINSPOT: A multicentric open label trial of zolbetuximab-paclitaxel-ramucirumab in second-line setting for CLDN18.2-positive gastro-esophageal adenocarcinoma.

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Background: Claudin 18.2 (CLDN18.2) is an emerging therapeutic biomarker in gastro-oesophageal adenocarcinoma. Phase III trials (SPOTLIGHT, GLOW) showed significant overall survival (OS) and progression-free survival (PFS) benefit from adding zolbetuximab to first-line chemotherapy. However, access to zolbetuximab remains limited in Belgium due to lack of reimbursement, and globally for patients receiving immunotherapy first line. Aim: RAINSPOT (NCT06962137) evaluates the efficacy and safety of adding zolbetuximab to standard second-line paclitaxel–ramucirumab in CLDN18.2-positive advanced gastro-oesophageal adenocarcinoma. Secondary objectives include assessing CLDN18.2 expression loss after first-line progression and evaluating zolbetuximab efficacy according to maintained versus lost CLDN18.2 expression. **Methods:** RAINSPOT is a national, multicentre, phase II, open-label study with a prospective single-arm cohort and a matched retrospective cohort across six Belgian centres. The prospective cohort will include 100 patients (≥18 years, ECOG 0–1) with metastatic or locally advanced disease progressing after one prior systemic line. Tumours must be CLDN18.2-positive (≥75% moderate-to-strong membranous staining; Ventana 43-14A assay). A fresh biopsy at progression is obtained when feasible. Treatment consists of zolbetuximab (800 mg/m^2 loading, then 400 mg/m^2 q2w), paclitaxel (80 mg/m^2 weekly ×3 q28d) and ramucirumab (8 mg/kg q2w). Treatment continues until progression or unacceptable toxicity. HRQoL is assessed every 4 weeks (EORTC QLQ-C30, QLQ-OG25). The retrospective cohort includes patients treated with second-line paclitaxel–ramucirumab (2021–2023) with archived tissue reassessed for CLDN18.2; only baseline-positive patients are eligible. Propensity score matching (1:1; SMD ≤0.05) uses age, sex, tumour location, gastrectomy, peritoneal metastases and centre. This study is supported by Astellas. **Results:** (Trial in Progress) Enrollment began December 2025 and will continue for 24 months, with 24 months' follow-up. Planned analyses include OS, PFS, objective response rate, toxicity and HRQoL. **Conclusion:** RAINSPOT is the first study evaluating zolbetuximab plus paclitaxel–ramucirumab in second-line CLDN18.2-positive gastro-oesophageal adenocarcinoma. By integrating a matched real-world comparator, it aims to generate near-randomized evidence on survival, tolerability and quality of life, informing optimal treatment sequencing. Clinical trial information: NCT06962137. Research Sponsor: None.

TPS4244 **Poster Session**

Combining zanidatamab, FOLFOX, and pembrolizumab as first-line therapy for HER2/PD-L1–positive gastroesophageal adenocarcinoma: The phase II IKF-090/AIO ZANGEA trial with translational analysis.

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Background: Gastroesophageal adenocarcinoma (GEA) presents a substantial global health challenge as the number of cases continues to rise. The current standard approach for treating previously untreated, metastatic HER2/PD-L1 positive GEA involves a combination of doublet chemotherapy, which consists of a platinum compound and a fluoropyrimidine, in combination with trastuzumab and pembrolizumab. Recently, the phase 3 HERIZON-GEA-01 trial has shown improved survival for zanidatamab in combination with CAPOX or fluoropyrimidine and cisplatin with the PD-1 inhibitor tislelizumab compared to chemotherapy and trastuzumab. Zanidatamab is a bispecific antibody that targets two distinct HER2 epitopes (domains 2 and 4), thereby crosslinking neighboring HER2 receptors and inducing receptor clustering. This leads to enhanced HER2 internalization, reduced downstream signaling, and increased Fc-mediated immune effector functions, compared with trastuzumab. There is currently insufficient evidence regarding the combination of zanidatamab with the frequently used chemotherapy backbone FOLFOX and no available data on combining this regimen with the PD-1 inhibitor pembrolizumab. Furthermore, biomarkers to predict response and toxicities are lacking. **Methods:** The ZANGEA study is an open-label, single-arm, multicenter, translational phase II trial designed to assess the efficacy, safety, tolerability and translational aspects of zanidatamab in combination with FOLFOX and pembrolizumab in patients with 1st line HER2/PD-L1-positive GEA. The primary endpoint is the progression-free survival rate after 12 months. Secondary objectives include safety and tolerability, efficacy in terms of objective response rate, progression-free and overall survival and translational markers, such as blood-based signatures (e.g. inflammatory cytokines), microbiota signatures, dietary patterns or microbiota derived metabolites that may correlate with therapy response or side-effects. In total, 80 patients will be recruited to show an PFS at 12 months of 55% compared to 46% with trastuzumab/pembrolizumab/chemotherapy (KeyNote 811). Enrollment started on 16 Jan 2026. Clinical trial information: NCT07176312. Research Sponsor: The Frankfurt Institute of Clinical Cancer Research (IKF); Jazz Pharmaceuticals.

TPS4245 Poster Session

Efficacy and safety of disitamab vedotin (DV) combined with trastuzumab, and tislelizumab versus chemotherapy (CAPOX) combined with trastuzumab ± pembrolizumab for patients with first-line HER2-high advanced gastric/gastroesophageal junction adenocarcinoma (G/GEJA): A randomized controlled phase 3 trial.

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Background: Patients (pts) with HER2-high (defined as IHC 3+, or IHC 2+/FISH+ according to Chinese Society of Clinical Oncology Gastric Cancer Guidelines) advanced G/GEJA continue to face a poor prognosis. Although adding pembrolizumab to trastuzumab and chemotherapy significantly improved overall survival in this pts population with a PD-L1 combined positive score (CPS) ≥1 in the first-line (1L) setting, there remains an unmet need for more effective treatment options. DV (anti-HER2 antibody-drug conjugate) is approved as monotherapy for the treatment of pts with HER2 IHC 2+/3+ advanced G/GEJA in China. In the randomized phase 2 part of the RC48-C027 trial, DV + trastuzumab + an anti-PD-1 agent showed a promising objective response rate (ORR) in 1L HER2-high advanced G/GEJA compared with the control (82.4% vs. 68.8%) (Shen et al. J Clin Oncol. 2025). Building on these results, the open-label randomized phase 3 RC48-C040 trial is designed to assess the efficacy and safety of DV + trastuzumab + tislelizumab versus chemotherapy + trastuzumab ± pembrolizumab in pts with previously untreated, HER2-high, advanced G/GEJA (NCT07315750). **Methods:** The key eligibility criteria are pts aged 18-75 years with histologically confirmed unresectable locally advanced or metastatic G/GEJA; central lab-confirmed high HER2 expression; no previous systemic treatment for locally advanced or metastatic gastric cancer; and at least one assessable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Pts with central nervous system metastasis and/or carcinomatous meningitis are ineligible. The planned sample size is 555. Pts will be randomized (2:1) to receive DV (2.5 mg/kg, intravenously [IV], Q2W) + trastuzumab (staring dose of 8 mg/kg followed by 6 mg/kg, IV, Q3W) + tislelizumab (200 mg, IV, Q3W) or to receive CAPOX (oxaliplatin: 130 mg/m^2, IV, Q3W for up to 6 doses; capecitabine: 1000 mg/m^2, orally, BID, days 1-14 every 3 weeks) + trastuzumab ± pembrolizumab (200 mg/kg, IV, Q3W) until occurrence of disease progression, intolerable toxicity, or initiation of new anti-tumor treatment. Randomization will be stratified by HER2 expression (IHC 2+/FISH+ or IHC 3+), PD-L1 expression (CPS < 1 or 1≤CPS < 10 or CPS≥10), and liver metastasis (presence or absence). The primary endpoint is progression-free survival (PFS) assessed by the Blinded Independent Review Committee as per RECIST v1.1. The secondary endpoints include overall survival, investigator-assessed PFS, ORR, disease control rate, duration of response, patient-reported outcomes, adverse events, pharmacokinetic parameters, and immunogenicity. This study started in January 2026; enrollment is ongoing in China. Clinical trial information: NCT07315750. Research Sponsor: RemeGen Co., Ltd.

TPS4246 Poster Session

A single-arm, phase II study of ivonescimab in combination with FOLFOX in advanced HER2-negative gastroesophageal adenocarcinomas.

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Background: Gastroesophageal adenocarcinoma (GEA) is a major cause of global cancer-related mortality. A common standard of care for frontline advanced GEA is 5-fluorouracil and oxaliplatin (FOLFOX), with the addition of immune checkpoint inhibitors (ICI) in patients with a PD-L1 combined positive score (CPS) of >1. Adding ICIs improves median overall survival (OS) by 2-4 months, with increased benefit seen with higher CPS scores (Leone et al, *ESMO Open*, 2024). There remains a significant need to improve ICI outcomes and expand the portion of patients who benefit. In GEA, vascular endothelial growth factors (VEGF) are associated with poor prognosis, influencing immune suppression and T cell exhaustion. There is strong mechanistic rationale for cooperativity between anti-VEGF antibodies and ICI in GEA, as well as evidence of clinical benefit in treatment-refractory gastric cancer (Kim et al, *Cancer Immunol Res*, 2025). Ivonescimab is a novel bispecific antibody that simultaneously targets PD-1 and VEGF, in a spatially constrained manner, impairing neoangiogenesis and remodeling the suppressive tumor microenvironment. Ivonescimab has evidence of safety and efficacy in colorectal and hepatocellular cancers and is approved for the treatment of PD-L1+ lung cancer in China (Deng et al, ESMO 2024; Li et al, ESMO 2025; Xiong et al, *Lancet*, 2025). **Methods:** This single-arm, multi-institutional phase II study seeks to evaluate ivonescimab in combination with FOLFOX as frontline therapy in GEA. Adults with locally advanced unresectable or metastatic HER-2 negative GEA are eligible. Patients must have disease that can be evaluated radiographically and may not have received prior systemic therapy for advanced disease. Positive PD-L1 expression is not required for eligibility. We plan to enroll 40 patients. To allow for collection of early immune modulation data, patients will commence therapy with a single dose of ivonescimab 20 mg/kg at discretion of the treating investigator. Subsequent cycles will continue with the addition of FOLFOX (dosed per institutional standards) to ivonescimab, given on day 1 and day 15 of a 28-day cycle. Imaging will be performed every 6 weeks until week 24, at which point imaging will change to every 9 weeks. Treatment will continue until disease progression, withdrawal of consent, or death. The primary objective is to define efficacy of ivonescimab in combination with FOLFOX as measured by the 6-month progression-free survival (PFS) rate. Secondary objectives include safety and tolerability, objective response and clinical benefit rates, median PFS and OS. Translational correlative studies are planned to explore tumor and immunologic determinants of response. This study is currently open and enrolling (NCT07070466). Clinical trial information: NCT07070466. Research Sponsor: None.

TPS4247 **Poster Session**

A multicenter, open-label, single-arm, dose-finding and -expansion phase 1b/2 study to evaluate the safety and tolerability of nesuparib (JPI-547) in combination with irinotecan as a third-line and beyond therapy for recurrent or metastatic gastric cancer.

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Background: Recurrent or metastatic gastric cancer (GC) progressing after standard first- and second-line therapies has limited treatment options, leading to poor survival outcomes. Nesuparib is an orally available, next-generation dual inhibitor of tankyrase and poly(ADP-ribose) polymerase (PARP). It disrupts DNA damage repair and induces a "BRCAness" phenotype by modulating Wnt/β-catenin and Hippo signaling pathways. In a previous phase I study, nesuparib monotherapy demonstrated promising clinical activity with an overall response rate (ORR) of 28.2% and a disease control rate (DCR) of 64.1%. Preclinical models have shown synergistic anti-tumor efficacy when nesuparib is combined with irinotecan. This study aims to evaluate the safety, tolerability, and preliminary efficacy of nesuparib plus irinotecan in patients with advanced GC. **Methods:** This multicenter, open-label, single-arm, dose-finding and expansion phase 1b/2 study enrolls adults with histologically confirmed recurrent or metastatic GC or gastroesophageal junction adenocarcinoma who have progressed after ≥2 prior systemic therapies and have ECOG PS 0–1, measurable disease per RECIST v1.1, and UGT1A1 wild-type genotype. Phase 1b follows a standard 3+3 design with multiple predefined dose levels. Each dose level consists of a fixed combination of (1) a specific nesuparib dose (25–100 mg) administered orally once daily on either a 5-days-on/2-days-off or 3-days-on/4-days-off schedule and (2) irinotecan administered every 2 weeks at 100, 120, or 150 mg/m^2. The dose-limiting toxicity evaluation window is 28 days. Phase 2 enrolls patients at RP2D to further evaluate anti-tumor activity. The primary endpoint is objective response rate. Secondary endpoints include safety, disease control rate, duration of response, progression-free survival, time to response, and overall survival. Exploratory objectives include population pharmacokinetics, pharmacodynamic biomarkers, homologous recombination deficiency profiling, and circulating tumor DNA analyses. Approximately 43–49 patients are planned (18–24 in phase 1b; 25 in phase 2). Treatment continues until disease progression, unacceptable toxicity, or study withdrawal. Clinical trial information: NCT07364422. Research Sponsor: None.

TPS4248 **Poster Session**

Chemoradiotherapy plus sintilimab versus chemoradiotherapy as neoadjuvant treatment in locally advanced esophageal squamous cell carcinoma (NEO-CRTEC2101): A multicenter, randomized, phase III trial.

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Background: Neoadjuvant chemoradiotherapy (NCRT) followed by surgery is the current standard of care for resectable locally advanced esophageal squamous cell carcinoma (ESCC). The integration of immunotherapy is now challenging this established therapeutic paradigm. Our previous phase II trial demonstrated that combining PD-1 inhibitor and NCRT yielded an encouraging pathological complete response (pCR) rate with an acceptable safety profile in ESCC. Therefore, this multicenter, randomized phase III trial (NEOCRTEC2101) aims to compare the efficacy and safety of NCRT combined with sintilimab (a IgG4 anti-PD-1 monoclonal antibody) versus NCRT alone in patients with resectable locally advanced ESCC. **Methods:** This was a multicenter, open-label, randomized, phase III trial. Key eligibility criteria included previously untreated, histologically confirmed, resectable thoracic ESCC clinically staged as T1-4aN1-3M0 or T3-4aN0M0 according to the 8th edition of the UICC staging system, age 18–75 years, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic and organ function. Key exclusion criteria included a history of other malignancies, previous antitumor therapy, severe comorbidities, active autoimmune disease, prior non-infectious pneumonitis, or interstitial lung disease. Eligible patients were randomly assigned (1:1) to sintilimab plus NCRT group or NCRT group. All patients received NCRT consisting of concurrent radiotherapy (40 or 45 Gy in 20 fractions) and chemotherapy (paclitaxel 50 mg/m^2 + cisplatin 25 mg/m^2 administered on days 1, 8, 15, and 22). Patients randomized to the sintilimab plus NCRT group additionally received sintilimab 200 mg via intravenous infusion on days 1 and 22. Surgical resection was performed 6-8 weeks following the completion of neoadjuvant therapy. The primary endpoint was overall survival, and the secondary endpoints were progression-free survival, pCR rate, R0 resection rate, and treatment-related adverse events. The planned sample size is 422 patients. This study opened to accrual in October 2022 and is currently recruiting patients. Clinical trial information: NCT05357846. Research Sponsor: None.

TPS4249 Poster Session

Adjuvant oxaliplatin plus S-1 versus docetaxel plus S-1 for stage III gastric cancer after D2 gastrectomy (DRAGON-Adjuvant): A multicenter, open-label, phase 3, randomized, non-inferiority study.

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Background: Adjuvant therapy is the standard treatment for stage II-III gastric cancer patients after radical D2 gastrectomy. Neoadjuvant therapy has been demonstrated as an effective strategy for resectable gastric cancer patients, while less than 2% of patients received such treatment in China. Therefore, adjuvant chemotherapy following radical resection is still widely used in current clinical practices. For stage III gastric cancer patients, oxaliplatin or docetaxel combined with oral fluoropyrimidine as adjuvant regimens are recommended by clinical guidelines. Although historical data show comparable efficacy between these regimens, direct comparisons are not feasible due to differences in study design, enrolled populations, and treatment cycles. Regimen selection is mainly based on clinical experience, as high-level evidence is still lacking. Currently, minimal residual disease (MRD) detection based on ctDNA testing can indicate patient prognosis and adjuvant therapy selection in colorectal cancer. The role of ctDNA-based MRD detection in adjuvant therapy of gastric cancer is still under investigation. This study aims to compare the efficacy and safety of oxaliplatin plus S-1 (SOX) versus docetaxel plus S-1 (DS) as adjuvant therapy for stage III gastric cancer, and to explore the role of MRD in adjuvant setting of gastric cancer. **Methods:** DRAGON-Adjuvant (NCT07366528) is a prospective, open-label, multicenter, randomized, non-inferiority study in patients aged from 18 to 80 years who are histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction, with pathological staging at AJCC stage IIIA to IIIC after standard D2 gastrectomy and R0 resection. Patients had no prior neoadjuvant therapy. Eligible patients will be randomized and assigned into experiment group (SOX, n = 193) and control group (DS, n = 194), respectively. Experiment group patients will be treated with eight 3-week cycles of intravenous oxaliplatin (130mg/m^2 on day 1 for each cycle) with orally S-1 on days 1 to 14 of a 3-week cycle. Control group patients will be treated with S-1 on days 1 to 14 of a 3-week cycle (C1), then intravenous infusion of docetaxel (40mg/m^2) on day 1 of each cycle and S-1 on days 1 to 14 of a 3-week cycle (C2 to 7), then S-1 continued on days 1 to 28 of 6-week cycles for up to 1 year. S-1 dose is dependent on body surface area. The primary objective is to assess that 3-year disease-free survival rate of SOX group is not inferior to DS group. Secondary objectives are to compare the 5-year overall survival rate, safety profiles, and recurrence sites in two groups. Exploratory objective is to assess the correlation of MRD with treatment efficacy and patient prognosis. As of January 2026, the DRAGON-Adjuvant is recruiting patients at 5 sites in China. Clinical trial information: NCT07366528. Research Sponsor: Science and Technology Commission of Shanghai Municipality; 25PJD078.

TPS4250 Poster Session

Multicenter phase Ib/II study of neoadjuvant zolbetuximab plus docetaxel, oxaliplatin, and S-1 (DOS) followed by adjuvant zolbetuximab/S-1 in patients with CLDN18.2-positive resectable gastric or gastroesophageal junction adenocarcinoma (NEOCLAUD).

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Background: Zolbetuximab, a monoclonal antibody targeting claudin 18.2 (CLDN18.2), has demonstrated significant survival benefit in advanced gastric or gastroesophageal junction adenocarcinoma (G/GEJA) in the phase 3 SPOTLIGHT and GLOW trials, validating CLDN18.2 as a therapeutic target. The phase III PRODIGY study demonstrated that neoadjuvant chemotherapy with docetaxel, oxaliplatin, and S-1 (DOS) followed by surgery and adjuvant S-1 chemotherapy improved progression-free survival (PFS) and overall survival (OS) compared with surgery followed by adjuvant S-1 for patients with resectable locally advanced gastric cancer (LAGC). Building on this evidence, we designed NEOCLAUD to evaluate whether adding zolbetuximab to neoadjuvant DOS chemotherapy, followed by adjuvant zolbetuximab/S-1, improves outcomes in patients with CLDN18.2-positive LAGC. **Methods:** This open-label, multicenter, phase Ib/II trial will enroll up to 57 patients with newly diagnosed, resectable G/GEJA positive for CLDN18.2 (≥75% moderate–strong membranous staining by VENTANA 43-14A). Eligible patients must have clinical stage T3–4/N0 or T2–4/N+ disease (AJCC 8th), ECOG 0–1, and no distant metastasis. Primary endpoints are recommended phase II dose (RP2D) (phase Ib) and the pathologic complete regression (pCR) rate (phase II). Phase Ib uses a 3+3 design to determine the RP2D. Phase II will test whether adding zolbetuximab increases the pCR rate from 10% (historical control) to 25%; the primary endpoint will be met if ≥8/40 patients achieve pCR (A'Hern single-stage design, $\alpha = 0.05$, power = 80%). Secondary endpoints include PFS, OS, objective response rate, disease control rate, R0 resection rate, and safety. Exploratory endpoints include artificial intelligence-based histopathology modeling, spatial transcriptomics, single-cell RNA sequencing, and circulating tumor DNA minimal residual disease analysis. Neoadjuvant therapy consists of zolbetuximab 800 mg/m² on cycle 1 day 1 (C1D1) followed by 600 mg/m² on C2D1/C3D1, with DOS (docetaxel 50 mg/m², oxaliplatin 100 mg/m² IV D1; S-1 40 mg/m² PO BID D1–14) every 3 weeks ×3 cycles. Surgery (D2 gastrectomy) is performed 1–4 weeks post-neoadjuvant therapy. Adjuvant therapy (initiated 3–8 weeks post-surgery) includes zolbetuximab 600 mg/m² D1/D22 Q6W ×8 cycles plus S-1 PO D1–28 Q6W ×8 cycles. Enrollment has been ongoing since February 2025 across multiple sites in Korea. Clinical trial information: NCT06732856. Research Sponsor: Astellas.

TPS4251 Poster Session

A phase 2, open-label, single-arm study of lirafugratinib in patients with previously treated, unresectable, locally advanced, or metastatic solid tumors (excluding cholangiocarcinoma) with *FGFR2* fusion or rearrangement.

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Background: Tissue agnostic cancer therapies offer the potential to markedly change the treatment landscape by targeting oncogenic drivers rather than the tumor's site of origin. Lirafugratinib is the first highly selective, irreversible inhibitor designed to target oncogenic fibroblast growth factor receptor (*FGFR)*2 driver alterations and resistance mutations. In the phase 1/2 ReFocus Trial (RLY-4008-101; NCT04526106),46 subjects (Group 3) with non-cholangiocarcinoma solid tumors harboring FGFR2 fusion/rearrangements (f/r) received lirafugratinib 70 mg once daily. The ORR was 33.3% (95% CI 19.6 - 49.5). However, this sample size was insufficient to support regulatory approval of lirafugratinib for a tissue agnostic indication. **Methods:** The ELE-4008-202, phase 2, open-label, single-arm study (NCT07359820) is designed to further evaluate the efficacy and safety of lirafugratinib 70 mg in 20-30 subjects across 20 sites with FGFR2 f/r, previously treated, unresectable, locally advanced or metastatic, non-CCA solid tumors who have not received prior FGFR inhibitor therapy. The primary endpoint is objective response rate (ORR) by independent review committee (IRC) per RECIST v1.1; key secondary endpoints include duration of response (DOR) by IRC, investigator-assessed efficacy endpoints, safety, pharmacokinetic (PK) parameters, and quality of life (QoL) per EORTC QLQ-C30. Efficacy will also be evaluated for ORR, DOR, disease control rate (DCR), progression-free survival (PFS), overall survival (OS), time to response (TTR), time to progression (TTP) per investigator. Time to discontinuation (TTD) will also be assessed. Exploratory endpoints will include FGFR2 genotype per tissue assessment or liquid biopsy vs ORR and levels of other biomarkers in relationship to clinical activity. An interim analysis of the pooled efficacy dataset from ELE-4008-202 and Group 3 of RLY-4008-101 will be conducted once approximately 65 evaluable subjects with non-CCA tumors have been enrolled across ≥7 tumor types (≥5 subjects per tumor type). Enrollment of a tumor type may be capped once it has reached approximately 20% of the total subjects in the pooled data from the two studies. With 65 subjects, observing at least 21 subjects with a complete response (CR) or partial response (PR) (ORR ≥32%), will result in a 95% CI (lower bound >20%) with the probability of observing ≥21 responders assuming a true ORR of 40% is approximately 92%. The results of this analysis will determine whether the pooled evaluable data from RLY-4008-101 and ELE-4008-202 meet regulatory requirements to support a tissue-agnostic indication for FGFR2 f/r non-CCA solid tumors. Clinical trial information: NCT07359820. Research Sponsor: Elevar Therapeutics.

TPS4252 **Poster Session**

A randomized phase III study of gemcitabine plus cisplatin with S-1 versus gemcitabine plus cisplatin with immune checkpoint inhibitor in unresectable biliary tract cancer.

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Background: Gemcitabine plus cisplatin (GC) has been established as the standard first-line treatment for unresectable biliary tract cancer (BTC). Recent phase III trials have demonstrated the clinical benefit of adding immune checkpoint inhibitors (ICIs) to GC. Meanwhile, GC combined with S-1 has also shown promising efficacy in East Asian populations. However, no randomized phase III trial has directly compared GC plus ICI with GC plus S-1. This study aims to compare the efficacy and safety of GC plus ICI with GC plus S-1 in patients with unresectable BTC. **Methods:** This is an ongoing, multicenter, open-label, randomized phase III trial (UMIN000051689). Eligible patients have histologically confirmed unresectable biliary tract cancer, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer, with no prior systemic therapy. Patients are randomized in a 1:1 ratio to receive either Arm A: gemcitabine plus cisplatin plus S-1 or Arm B: gemcitabine plus cisplatin combined with an immune checkpoint inhibitor. Randomization is stratified by primary tumor site, disease status (recurrence vs primary unresectable), and planned immune checkpoint inhibitor regimen for patients assigned to Arm B. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, objective response rate, disease control rate, safety, and health-related quality of life. The planned sample size is 460 patients (230 per arm), providing 80% power to detect a statistically significant difference in overall survival with a two-sided alpha of 0.05. Current Status: Patient enrollment began in August 2023. As of January 2026, approximately 60% of the planned patients have been enrolled. Enrollment is ongoing, and follow-up continues. **Conclusions:** This randomized phase III trial will clarify the optimal first-line systemic treatment for unresectable biliary tract cancer by directly comparing GC plus immune checkpoint inhibition with GC plus S-1. Clinical trial information: UMIN000051689. Research Sponsor: None.

TPS4253 Poster Session

ARTEMIDE-Biliary02: A phase 3, randomized, global study of rilvegostomig or durvalumab with chemotherapy as first-line (1L) treatment for advanced biliary tract cancer (BTC).

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Background: Biliary tract cancer (BTC) is the second most common hepatic malignancy, comprising 15% of liver tumors. BTC incidence is rising worldwide, and the majority of patients are diagnosed late where the median survival is approximately one year. Chemo-immunotherapy with gemcitabine and cisplatin combined with either durvalumab or pembrolizumab is the current first-line (1L) standard for advanced BTC. To enhance the clinical benefit from immune checkpoint inhibitors, dual blockade of the programmed cell death-1 (PD-1) and T cell immunoreceptor with Ig and ITIM domains (TIGIT) pathways may be an effective strategy. Rilvegostomig, a monovalent, Fc-reduced, bispecific anti-PD-1/anti-TIGIT antibody, has shown promising preliminary efficacy in combination with gemcitabine and cisplatin for 1L treatment of advanced BTC (Zhou J, et al. ASCO 2025 [Abstract 4080]). The phase 3 ARTEMIDE-Biliary02 study (NCT07221253) assesses the efficacy and safety of rilvegostomig or durvalumab in combination with gemcitabine and cisplatin for 1L treatment of advanced BTC. **Methods:** Eligible participants (aged $\geq$ 18 years) have unresectable, locally advanced/metastatic BTC (intrahepatic cholangiocarcinoma [iCCA], extrahepatic CCA [eCCA], or gallbladder cancer [GBC]), previously untreated in the advanced setting, no prior immunotherapy, centrally confirmed programmed cell death ligand-1 (PD-L1) status, and ECOG PS of 0/1. Approximately 1100 participants will be randomized (1:1) to receive rilvegostomig or durvalumab, both in combination with gemcitabine and cisplatin, until radiological progression per RECIST v1.1. Participants will be stratified by PD-L1 expression (tumor area positivity $<$ 1% vs $\geq$ 1%), disease status (initially unresectable vs recurrent), primary tumor site (iCCA vs eCCA vs GBC), and geographic region (Asia vs rest of world). The primary endpoint is overall survival (OS) in the PD-L1 $\geq$ 1% population, defined as time from randomization until date of death due to any cause. Key secondary endpoints include OS in the intent-to-treat (ITT) population and progression free survival (PFS), defined as time from randomization until radiological progression per RECIST v1.1, in both the PD-L1 $\geq$ 1% and ITT populations. Other secondary endpoints include objective response rate, duration of response, PFS rates (defined as time from randomization until earliest progression event) in both the PD-L1 $\geq$ 1% and ITT populations, safety/tolerability, and patient-reported outcomes. OS will be assessed using a stratified log-rank test adjusting for stratification factors. A stratified Cox proportional hazards model will estimate the hazard ratio and associated 95% confidence interval. Enrollment started in December 2025 and is ongoing across Asia, Australia, Europe, and the Americas. Clinical trial information: NCT07221253. Research Sponsor: AstraZeneca.

TPS4254 **Poster Session**

Adjuvant sintilimab plus bevacizumab following curative resection of spontaneously ruptured hepatocellular carcinoma: A prospective exploratory phase II study (CLEAR-2).

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Background: Spontaneous rupture of hepatocellular carcinoma (srHCC) is a life-threatening complication associated with acute hemorrhage, aggressive tumor biology, and an exceptionally high risk of postoperative recurrence. Even after successful hemostasis and curative (R0) resection, outcomes remain poor, with early relapse—particularly peritoneal dissemination—being a dominant failure pattern. Patients with srHCC have been systematically excluded from most pivotal phase III adjuvant trials in hepatocellular carcinoma, resulting in a critical evidence gap for postoperative systemic management. Current adjuvant strategies are largely extrapolated from non-ruptured HCC or based on retrospective analyses, and no prospective studies have specifically evaluated immunotherapy-based adjuvant therapy in this population. Immune checkpoint inhibitor–based combinations with anti-angiogenic agents have demonstrated survival benefits in advanced HCC and have recently been explored in the adjuvant setting for high-risk resected disease. Given the unique biological behavior of srHCC, characterized by tumor cell spillage at rupture and a strong propensity for early systemic and peritoneal relapse, adjuvant systemic therapy targeting micrometastatic disease is biologically rational and urgently needed. The CLEAR-2 study is designed to prospectively explore the efficacy and safety of adjuvant sintilimab combined with bevacizumab following curative resection of srHCC. **Methods:** CLEAR-2 is a prospective, multicenter, single-arm, exploratory phase II study. Eligible patients are adults (18–75 years) with radiologically or intraoperatively confirmed spontaneous rupture of HCC who have undergone curative (R0) hepatic resection, with Child-Pugh A liver function and ECOG performance status 0–1. Preoperative transarterial embolization (TAE) for hemostasis is permitted if performed once and within 2 weeks prior to surgery, without chemotherapeutic agents. A total of 35 patients will be enrolled. Adjuvant treatment is initiated 4–8 weeks postoperatively and consists of sintilimab 200 mg plus bevacizumab 15 mg/kg intravenously every 3 weeks for up to 1 year or until recurrence, unacceptable toxicity, or withdrawal. Radiologic assessment is performed every 12 weeks. The primary endpoint is disease-free survival (DFS). Secondary endpoints include overall survival (OS), safety graded per CTCAE v5.0, and recurrence patterns (intrahepatic, extrahepatic, and peritoneal). Clinical trial information: NCT07331883. Research Sponsor: None.

TPS4256 Poster Session

Fatty acid degradation (FAD)–guided comprehensive therapy for unresectable hepatocellular carcinoma: A prospective phase II study (FAD-HCC-01).

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Background: Hepatocellular carcinoma (HCC) exhibits marked molecular and metabolic heterogeneity, leading to variable therapeutic responses and limiting the effectiveness of current systemic treatments. Despite recent advances in immunotherapy and targeted agents, no validated biomarker is available to guide treatment selection in unresectable HCC. We previously established a fatty acid degradation (FAD) pathway-based molecular classification of HCC, revealing that FAD-associated transcriptional programs delineate biologically distinct HCC subtypes with heterogeneous immune microenvironments and differential responses to systemic and locoregional therapies. These findings suggest that FAD-based stratification may enable a more precise, biology-driven treatment strategy. However, the feasibility of implementing FAD-guided treatment allocation in a prospective clinical setting has not been established. FAD-HCC-01 is designed to evaluate the feasibility, safety, and preliminary efficacy of a FAD-guided comprehensive therapy in patients with unresectable HCC. **Methods:** FAD-HCC-01 is a prospective, multicenter, open-label phase II study enrolling patients with unresectable or non-curatively treatable HCC. Eligible patients have histologically or clinically confirmed HCC, BCLC stage B or C disease, Child–Pugh class A to B ($\leq$7), ECOG performance status 0-1, and no prior systemic therapy. Tumors are classified into FAD subtypes (F1, F2, or F3) using transcriptomic profiling with ssGSEA-based FAD scoring; MRI-derived fat fraction may serve as a provisional surrogate when tumor tissue is unavailable. A total of 86 patients will be enrolled, with 43 patients planned for each treatment cohort. Patients are assigned to two parallel cohorts according to FAD subtype. Patients with F1 or F2 tumors receive camrelizumab (200 mg intravenously every 3 weeks) plus rivoceranib (250 mg orally once daily). Patients with F3 tumors receive transarterial chemoembolization (TACE) combined with camrelizumab and rivoceranib, with TACE performed per institutional standards and repeated as clinically indicated. Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint is objective response rate assessed by RECIST v1.1. Secondary endpoints include ORR by mRECIST, disease control rate, progression-free survival, overall survival, duration of response, conversion to curative treatment, and safety. Key feasibility objectives include successful FAD subtyping, adherence to FAD-guided treatment allocation, and integration of molecular or imaging-based classification into routine clinical workflows. Exploratory analyses will assess concordance between MRI fat fraction and FAD subtypes and explore molecular correlates of treatment response. Clinical trial information: NCT07314372. Research Sponsor: Fundings for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University.

TPS4257 Poster Session

CAREFOL: A phase 3, randomized, open-label, multicenter trial of camrelizumab and rivoceranib with or without intravenous FOLFOX chemotherapy as first-line treatment for unresectable hepatocellular carcinoma.

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Background: The combination of camrelizumab (an anti-PD-1 IgG4 monoclonal antibody) and rivoceranib (a VEGFR2-TKI) is a standard of care, first-line (1L) therapy for advanced hepatocellular carcinoma (HCC). However, immune therapy resistance leads to ineffective initial treatment and difficulty in maintaining long-term efficacy in some patients. Several studies have shown that oxaliplatin and fluorouracil can induce immunogenic cell death in tumor cells and induce antitumor immune response in the body. Intravenous FOLFOX chemotherapy may regulate the liver tumor microenvironment and improve clinical benefit, a hypothesis supported by positive efficacy signals in the Phase II VIC-TRIPLETS study (NCT05412589). Here we present the design of a phase III randomized controlled study. **Methods:** This investigator-initiated, phase III, randomized, open-label, multicenter trial (NCT06280508) aims to compare the efficacy and safety of camrelizumab and rivoceranib combined with (CAREFOL) or without intravenous FOLFOX chemotherapy (CARE) as first-line treatment for unresectable HCC. Eligible patients are aged at least 18 years, with unresectable or metastatic HCC, no previous systemic treatment, with BCLC stage B or C disease (which is not amenable to or had progressed after surgical or locoregional therapy), at least one measurable lesion per RECIST 1.1 criteria, Child-Pugh class A liver function, an ECOG performance status of 0 or 1, and adequate organ function. Approximately 326 Participants will be randomly assigned (1:1) using a centralized interactive response system. Randomization is stratified by presence of extrahepatic metastasis (yes vs no), macrovascular invasion (Vp0-3 vs Vp4), and baseline α-fetoprotein level ($<$ 400 ng/mL vs $\geq$400 ng/mL). The experimental group consisted of camrelizumab 200 mg intravenously every 3 weeks plus rivoceranib 250 mg orally once daily combined with 21-day cycles of intravenous FOLFOX chemotherapy (oxaliplatin 85 mg/m^2, levofolinate 200 mg/m^2, 5-fluorouracil bolus 400 mg/m^2 on day 1, and 5-fluorouracil infusion 2400 mg/m^2 for 46 hours; up to 6 cycles). The control group is camrelizumab plus rivoceranib (same as experimental group). The dual primary endpoints are investigator-assessed progression-free survival per RECIST v1.1 and overall survival. Secondary endpoints include objective response rate, disease control rate, duration of response, surgical conversion rate, time-to-treatment failure, safety. The trial is currently screening eligible patients. Clinical trial information: NCT07267806. Research Sponsor: None.

TPS4258 Poster Session

A phase II trial of trifluridine/tipiracil plus oxaliplatin in patients with advanced or metastatic biliary tract cancer following first-line therapy.

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Background: Biliary tract cancers (BTCs) comprising of intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer are aggressive and difficult cancers to treat. Most patients present with metastatic or unresectable disease, and systemic therapy is the only therapeutic option. Treatment options are highly limited after progressing on first line therapy with median survival of 6 months. We demonstrated encouraging activity with single agent trifluridine/tipiracil (FTD/TPI) and FTD/TPI plus irinotecan in separate phase 2 trials in patients with refractory BTCs after multiple lines of therapies (NCT03278106 and NCT04072445). Disease control rate (DCR) of 50% was reported with the combination therapy and median OS was 9.1 months. Prior studies have suggested oxaliplatin-based therapy may be more effective than irinotecan-based therapy in BTC. Thus, FTD/TPI plus oxaliplatin may be an active regimen in patients with advanced BTCs. **Methods:** This is a phase II trial evaluating FTD/TPI plus oxaliplatin as second line treatment in patients with advanced BTCs and disease progression on standard of care gemcitabine-based combination therapy. Key inclusion criteria are pathologically confirmed BTC, ECOG performance status 0 or 1, prior gemcitabine-based combination therapy, adequate organ function, signed informed consent. Key exclusion criteria include >1 prior line of systemic therapy for advanced disease (adjuvant therapy not counted) and active autoimmune disease requiring systemic therapy. Participants will be enrolled at Case Comprehensive Cancer Center sites and receive a dose of FTD/TPI of 25 mg/m^2 twice daily on days 1-5 and oxaliplatin 85 mg/m^2 on day 1 of a 14-day cycle until disease progression, intolerable toxicities, or patient declines to continue study. Primary endpoint is DCR, defined as proportion of patients achieving responses or stable disease with trial treatment. The trial is a Simon 2-stage optimal design with a significance level of 0.05 and 80% power. We estimate a DCR of 0.62 compared to historical control of 0.33 in second line setting. If ≤ 2 patients have disease control out of the first 6 patients enrolled, then regimen will be considered ineffective. If >3 patients have disease control, then the study will proceed to stage 2. During stage 2, an additional 18 patients will be enrolled for 24 total evaluable patients. If >12 patients of the 24 evaluable patients have disease control, then the trial will be considered a success and a larger trial will be planned. Secondary endpoints are grade and duration of adverse events, ORR, PFS, OS. Correlative studies are circulating DNA and oral and fecal samples for microbiome testing. The study is supported by the National Comprehensive Cancer Network (NCCN) through a grant provided by Taiho Oncology. Neither NCCN nor Taiho are the sponsor. Clinical trial information: NCT07146646. Research Sponsor: Taiho.

TPS4259 Poster Session

Impact of immunonutrition in patients undergoing hepatectomies for liver tumors: A randomized controlled phase II trial.

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Background: Recent studies have demonstrated that immunonutrition has the potential to improve the host immune state, reduce infectious complications, and shorten the length of hospital stay after major abdominal surgeries. Controversy still persists regarding whether or not perioperative immunonutrition could offer substantial benefits to patients undergoing hepatectomy as compared with standard nutrition. Several biomarker-based indices reflecting the immune as well as nutritional status, have been investigated, to predict postoperative morbidity following major hepatectomies. One such index, validated in a meta-analysis is the prognostic nutritional index (PNI). Prognostic Nutritional Index (PNI) = [(10 $\times$ serum albumin (g/dL)) + (0.005 $\times$ total lymphocyte count)], with higher PNI correlating with improved survival outcomes . Based on this we aim to conduct a randomized controlled trial to evaluate the improvement of PNI, by immunonutritional intervention in patient undergoing major hepatectomies. **Methods:** Study Design: Open labelled, Phase II randomized controlled trial. Eligibility criteria: Inclusion: (1) Patients with liver tumors planned for major hepatectomies (defined as resection of >/= 3 liver segments); (2) Age above 18 years; (3) ASA class I-III. Exclusion: (1) Preoperative severe renal failure (estimated glomerular filtration rate < 30 ml/min); (2) History of hypersensitivity to arginine, omega-3 fatty acids, or nucleotide; (3) Inability to take oral nutrition; (4) Pregnancy; (5) Mental condition rendering the subject unable to understand the nature, endpoints and consequences of the trial. Interventions: Randomization will be carried out centrally at the Clinical Research Secretariat, Tata Memorial Hospital. The trial statistician will generate a permuted-block randomization sequence using variable sized blocks of 2, or 4, without any stratification factors. Participants will be randomly assigned in 1:1 to receive either the intervention or control. Details of Intervention: In addition to their usual intake, patients in the intervention arm will be prescribed for each of the 7 consecutive days preceding surgery 6-9 scoops Immunomax powder (120-180g per day), based on weight. At recruitment, blood samples will be taken for inflammatory and immune status markers. These measurements will be repeated on the day prior to surgery (D-1) and on POD 1, 3, 5 and 7. An additional Creactive protein (CRP) measurement will be taken on POD30. PNI will be calculated before the intervention and on the day prior to surgery. Primary Endpoints: Mean difference in PNI points between intervention and control group. Secondary Endpoints: (1) Incidence of postoperative complication; (2) Incidence of post-hepatectomies liver failure (PHLF); (3) Length of ICU stay; (4) Length of hospital stay; (5) Incidence of 90 days mortality. 100 patients will be enrolled over 2 years. Clinical trial information: CTRI/2025/06/088908. Research Sponsor: Tata Memorial Hospital Intramural Grant.

TPS4260 Poster Session

Phase II study of NC410 and FOLFIRINOX in combination with nivolumab with or without ipilimumab in patients with treatment-naive metastatic pancreatic cancer.

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Background: Pancreatic adenocarcinoma (PDAC) is now the third leading cause of cancer-related death in the United States (1). Median overall survival for patients with metastatic PDAC is 11.1 months with first-line FOLFIRINOX chemotherapy (2) and more effective treatments are needed. A major resistance mechanism to immunotherapy in PDAC is the desmoplastic stroma (3). Collagen physically hinders T cell infiltration and suppresses immune cells in the tumor microenvironment (TME) through the Leukocyte Associated Immunoglobulin-like Receptor-1 (LAIR-1) (4). Both collagen and the complement protein C1q, overexpressed in the PDAC TME, are primary ligands for the inhibitory LAIR-1 receptor on myeloid and lymphoid cells, and binding results in immune cell downregulation (5-7). LAIR-2, primarily made by CD4+ T cells, is a competitive inhibitor of LAIR-1 that reverses the immunosuppressive effect (8). NC410 is a dimeric fusion protein of LAIR-2 with human IgG1 Fc that remodels collagen, reduces tumor growth, enhances T cell tumor infiltration, and overcomes neutrophil-mediated T cell suppression in preclinical studies (7,9,10). NC410 binds the collagen-rich PDAC TME with high avidity when compared across tumor types (7). Our group contributed to the recent phase Ib/II study demonstrating clinical activity of NC410 with pembrolizumab in patients with advanced colorectal and ovarian cancer (NCT05572684). Based on these promising results, our study combines NC410 and immunotherapy with FOLFIRINOX in the first-line setting to assess safety and clinical efficacy in patients with metastatic PDAC. **Methods:** This is a single-center, open-label, two-arm phase II study evaluating safety and efficacy of NC410 and FOLFIRINOX in combination with nivolumab with or without ipilimumab in patients with untreated metastatic PDAC. The two arms enroll sequentially. In Cycle 1, NC410 and FOLFIRINOX are given with nivolumab (Arm 1, n =10) or nivolumab + ipilimumab (Arm 2, n = 10). In Cycle 2 and beyond, patients in both arms receive NC410 and FOLFIRINOX every 2 weeks and can continue to receive treatment per investigator discretion. On study scans are obtained every 8 weeks. Eligible patients have untreated metastatic PDAC, measurable disease per RECIST 1.1, and are willing to undergo tumor biopsy at baseline and on treatment. Primary endpoint is safety. Secondary endpoints are disease control rate, objective response rate, progression free survival, and overall survival. Correlative studies will profile circulating neutrophils and markers of immune activation in paired whole blood and tumor biopsy samples at baseline and on-treatment at Cycle 4. Enrollment began in August 2025 and is ongoing. 10 of planned 20 patients have been enrolled; awaiting 8-week primary safety endpoint evaluation in Arm 1. Trial information: NCT06941857. References upon request. Clinical trial information: NCT06941857. Research Sponsor: The Lustgarten Foundation; Swim Across America; Cynthia Boscov Fund for Pancreatic Cancer Research; James and Frances McGlothlin Fellows to Faculty Fund; U.S. National Institutes of Health.

TPS4262 Poster Session

Phase 1 faecal microbiota transplantation in patients with advanced pancreatic carcinoma (FMTPanc Trial).

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Background: Higher abundance of specific oral, pancreatic and/or gut microbes is correlated with pancreatic cancer occurrence (e.g. *Porphyromonaas gingivalis*, *Malassezia* sp.). Furthermore, the pancreatic tumour microenvironment of long-term survivors (≥ 5 years) shows richer tumoral microbial diversity associated with more active T-cells and fewer immune-suppressing cells than short-term survivors. Preclinical animal studies have also demonstrated that faecal microbiota transplantation (FMT) from a healthy donor or a long-term survivor can significantly decrease the size of pancreatic tumours. These findings demonstrate that manipulations of the gut and/or organ microbiota holds promise as part of cancer treatment. This trial aims to evaluate whether restoring a healthier microbiota can improve symptoms, visceral pain and treatment efficacy in people with non-resectable pancreatic cancer. **Methods:** This study is a Phase 1 double-blind randomised placebo-controlled trial (RCT) assessing the safety and potential benefit of oral FMT in patients with non-resectable pancreatic cancer. FMT will be a co-treatment to the standard of care chemotherapy. The primary outcomes are FMT safety and toxicity and mortality at 3, 6, and 12 months after chemotherapy initiation. Secondary outcomes include: changes in visceral pain and symptoms measured by PAGI-SYM, changes from baseline in blood CA-19-9 levels and reduction in tumour size as surrogate marker of treatment efficacy, and changes in faecal microbiota as a surrogate marker of gut flora restoration and treatment efficacy at 3, 6, and 12 months after treatment initiation. Power calculations were conducted for the main secondary clinical outcome of interest (i.e. the PAGI-SYM tool) that encompasses pain and symptom monitoring using published evidence, an MCID of 0.94, for an alpha of 0.05 and 80% power a minimum of 14 participants per arm is required. The trial aims to recruit a minimum of 28 and maximum of 60participants, 14-30 per arm. Eligible patients will have advanced and unresectable adenocarcinoma of the pancreas suitable for standard chemotherapy (gemcitabine/nab-paclitaxel or FOLFIRINOX) and be treatment-naive. Patients will be randomised 1:1 to FMT or placebo. FMT and placebo capsules will be prepared by BiomeBank (Adelaide South Australia). Stool will be sourced from healthy donors and rigorously screened following criteria specified by the Australian Therapeutic Administration (TGA). FMT/placebo will be provided through two doses (dose 1: 25mg, dose 2: 50mg). Chemotherapy will commence 3 to 14 days after completion of the first FMT dose (week 0). Supportive medication includes pancrelipase (2x25,000U three times a day) to facilitate digestion during FMT treatment. The FMTPanc is open at 3 sites across South Australia and Victoria and as of January 2025 12 patients have been enrolled. Clinical trial information: ANZCTR: ACTRN12624000455561. Research Sponsor: None.

TPS4263 Poster Session

TRIDENT: A phase 2 study of relacorilant plus nab-paclitaxel and gemcitabine in patients with previously untreated metastatic pancreatic ductal adenocarcinoma.

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Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has a 5-year survival rate of $< 5\%$. Approved treatment options are limited to combination cytotoxic chemotherapy such as mFOLFIRINOX or nab-paclitaxel + gemcitabine. Cortisol-mediated glucocorticoid receptor (GR) activation provides prosurvival signals to tumor cells that contribute to chemotherapy resistance. The addition of relacorilant, a selective GR antagonist, to paclitaxel + gemcitabine improved tumor growth inhibition over paclitaxel + gemcitabine alone in a PDAC xenograft model (Greenstein *Oncotarget* 2021). Moreover, in a phase 1 study of relacorilant and nab-paclitaxel, 2 durable confirmed partial responses were observed in patients with mPDAC (Munster *Clin Cancer Res* 2022). The combination of relacorilant and nab-paclitaxel prolonged progression-free survival (PFS) and overall survival (OS) in patients with platinum-resistant ovarian cancer in 2 randomized controlled trials, including the phase 3 ROSELLA study (Olawaiye *Lancet* 2025). The combination was well tolerated, with a safety profile that was consistent with nab-paclitaxel monotherapy. Therefore, the combination of relacorilant, nab-paclitaxel, and gemcitabine is deserving of further clinical study to improve outcomes in patients with mPDAC. **Methods:** TRIDENT is a phase 2, single-arm, open-label, multicenter study (NCT07259317) designed to evaluate the combination relacorilant + nab-paclitaxel + gemcitabine as a first-line treatment in mPDAC (target enrollment, N = 60). Key inclusion criteria are confirmed measurable metastatic disease (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), no prior systemic anticancer therapy to treat metastatic disease, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. Patients will receive relacorilant 150 mg orally once daily for 3 consecutive days (day before, day of, and day after chemotherapy) in combination with nab-paclitaxel (100 mg/m^2) and gemcitabine (1000 mg/m^2) given on days 1, 8, and 15 of each 28-day cycle. Treatment will continue until disease progression or unmanageable toxicity. The primary endpoint is investigator-assessed PFS per RECIST version 1.1 and will be analyzed using Kaplan-Meier methods. Secondary endpoints are OS, best overall response, objective response rate, clinical benefit rate at 24 weeks, duration of response, cancer antigen 19-9 kinetics, and tolerability/safety. The study is currently enrolling. Clinical trial information: NCT07259317. Research Sponsor: Corcept Therapeutics.

TPS4264 Poster Session

S2433: Randomized phase III study of second-line chemotherapy with or without panitumumab for KRAS wild type, locally advanced, or metastatic pancreatic adenocarcinoma.

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Background: Pancreatic ductal adenocarcinoma (PDA) is characterized by driver mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*. *KRAS* wild type (WT) tumors, present in 5-10% of PDA, often harbor alternative mitogen-activated protein kinase (MAPK) pathway drivers or other targetable molecular alterations (e.g., microsatellite instability [MSI-high], DNA damage repair mutations), enabling targeted therapy in approximately 30% of cases; however, most lack actionable drivers and require a tailored treatment approach. EGFR is overexpressed in 30%-70% of PDA. Prior studies of EGFR-targeted therapy demonstrated modest overall survival (OS) benefit in unselected populations, with retrospective analyses suggesting benefit confined to *KRAS* WT PDA. Recent data showed survival benefit from the anti-EGFR antibody nimotuzumab when added to 1st line gemcitabine vs gemcitabine alone in *KRAS* WT PDA. These findings provide a strong rationale to evaluate anti-EGFR mAb in combination with multi-agent chemotherapy in *KRAS* WT PDA in the United States. **Methods:** This randomized (1:1) phase III study will enroll 94 pts to investigator choice 2nd-line chemotherapy – 5 fluorouracil (5FU) plus irinotecan or nanoliposomal irinotecan following 1st-line gemcitabine-based therapy, or gemcitabine plus nab-paclitaxel following 1st-line 5FU-based therapy – with or without panitumumab. Eligibility requires *KRAS* WT and *BRAF* V600E WT status by tumor tissue-based next-generation sequencing and no known mutations in *PTEN*, *NRAS*, *EGFR* extracellular domain exons 1-16, no amplifications of *HER2* and *MET*, and no gene fusions of *RET*, *NTRK1*, and *ALK*. One prior line of chemotherapy for locally advanced or metastatic PDA is permitted. Pts with cancers harboring molecular alterations (e.g., MSI-high, ROS fusion) may have received prior targeted therapy, and past maintenance therapy with a PARP inhibitor does not count as a line of therapy. The primary endpoint is OS; secondary endpoints include safety, progression-free survival, overall response rate, disease control rate, and duration of response. Quality of life will be assessed using the Functional Assessment of Cancer Therapy – General (FACT-G), Functional Assessment of Chronic Illness Therapy (FACIT) Item GP5, and selected patient-reported outcome (PRO)-CTCAE items. Blood and tumor samples will be collected for correlative studies. Standard eligibility criteria apply. Assuming panitumumab improves median OS from 6.3 to 12.6 months, 84 eligible patients provide 90% power with a one-sided alpha of 0.05. Kaplan-Meier methods will estimate OS, with early stopping for efficacy or futility. This study is open to accrual (NCT06998940). Clinical trial information: NCT06998940. Research Sponsor: NIH/NCI/NCTN grants U10CA180888, U10CA180819.

TPS4265 Poster Session

A prospective single-arm study of irinotecan liposome II combined with adebrelimab, gemcitabine, and nab-paclitaxel for conversion therapy in locally advanced pancreatic cancer.

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Background: Locally advanced pancreatic cancer (LAPC) has an extremely poor prognosis, with only a minority of patients eligible for radical surgery at initial presentation. Conversion therapy is critical for improving resectability and survival. Currently, no standard conversion regimen exists for LAPC, and gemcitabine plus nab-paclitaxel (AG regimen) is widely used. Irinotecan liposome has favorable tumor targeting and manageable toxicity; the PAN-HEROIC-1 study showed that irinotecan liposome II combined with 5-fluorouracil/leucovorin (5-FU/LV) significantly prolonged overall survival in Chinese advanced pancreatic cancer patients. Adebelimab, a programmed death-ligand 1 (PD-L1) inhibitor, exerts synergistic antitumor effects with chemotherapy in solid tumors. Herein, we evaluate the efficacy and safety of Irinotecan Liposome II plus Adebelimab and AG regimen as conversion therapy for LAPC to improve surgical conversion rates and survival benefits. **Methods:** This prospective, single-arm, open-label study plans to enroll 45 patients with pathologically confirmed locally advanced pancreatic ductal adenocarcinoma. Key inclusion criteria: 18-75 years old; Eastern Cooperative Oncology Group (ECOG) PS 0-1; adequate major organ function; no central nervous system metastasis; effective contraception for reproductive-aged subjects (pregnancy excluded); informed consent. Exclusion criteria: non-ductal pancreatic cancer; active autoimmune diseases; severe infections; major surgery or investigational drugs within 4 weeks prior to enrollment; other investigator-judged ineligibility. Primary endpoint is surgical conversion rate; secondary endpoints include event-free survival, overall survival, R0/R1 resection rate, objective response rate, pathological complete response rate, and safety profile. Treatment Regimen: Irinotecan Liposome II (40 mg/m^2, IV infusion 90±30 min, Day 1, q2w) + Adebelimab (1200 mg, IV infusion 30-60 min, Day 1, q4w) + gemcitabine (1000 mg/m^2, IV infusion $>$ 30 min, Days 1,8,15, q4w) + nab-paclitaxel (125 mg/m^2, IV infusion $>$ 30 min, Days 1,8,15, q4w). Registration Number: ChiCTR 2500108269. Research Sponsor: Hengrui Pharma. Clinical trial information: ChiCTR2500108269. Research Sponsor: None.

TPS4266 Poster Session

Using organoids to predict efficacy of adjuvant treatment to improve outcome in resectable pancreatic cancer: UNITEPANC (AIO-PAK-0424), a prospective, multi-center, proof-of-concept trial of the AIO Pancreatic Cancer Group.

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Background: Pancreatic cancer (PDAC) is a heterogeneous disease and there is a lack of predictive biomarker to guide treatment. Patient tumor derived organoids (PDO) recapitulate key morphological and genetic features and may preserve patient-specific drug response phenotypes **Methods:** UNITEPANC is a prospective, proof of concept, multicenter IIT of the German AIO PDAC Group and funded by the German Cancer Aid. UNITEPANC examines the feasibility of an organoid-educated adjuvant treatment approach with respect to organoid establishment, expansion and characterization and its potential role for selecting an optimal adjuvant treatment in PDAC in a multicenter setting. Preparatory activities like harmonizing SOPs and round-robin-tests for generation of organoids and organoid-based pharmacotyping in the trial centers and the different Organoid Facilities have been completed and evaluated. UNITEPANC examines selection of adjuvant chemotherapy by pharmacotyping of tumor organoids. Options for adjuvant treatment are gemcitabine, gemcitabine/capecitabine, gemcitabine/nab-paclitaxel or mFOLFIRINOX. Major inclusion criteria are R0 or R1 resected, histologically confirmed PDAC and patients in principle, suitable for mFOLFIRINOX treatment in the adjuvant setting, postoperative Ca19-9 $<$ 180 U/ml, and a timely PDO-based chemotherapy recommendation by the UNITEPANC Organoid Board to guarantee a start of the adjuvant treatment within 12 weeks after resection. UNITEPANC is an interventional, prospective, multicenter, single-arm trial. 92 patients shall be allocated to the trial for the generation of organoids, 38 patients shall be enrolled for PDO-based adjuvant treatment and 34 patients need to be analyzed as ITT population in the follow-up period. Efficacy: The efficacy endpoint of the trial is purely descriptive and intended to obtain a signal for further development of the strategy. This requires the proof of an efficient 1) generation and 2) expansion of PDO and 3) a clear sign that an organoid-educated treatment selection is superior to standard treatment with mFOLFIRINOX. For 1) and 2) we have chosen a rate of 75% and 60%, respectively, according to the literature. For 3): The approach would be considered promising, if the true 18-months-DFS rate is 77% (corresponding to a hazard ratio of 0.5 compared to Prodige-24, 80% power, one-sided type I error 0.1. HR-QoL data will be analyzed (QLQ-C30, Pan26). Additionally, an extensive translational program is enclosed. UNITEPANC has started recruitment in Q3/2025. Clinical trial information: 2023-510490-34-00. Research Sponsor: German Cancer Aid.

TPS4267 Poster Session

Phase I light-dose escalation study in locally advanced pancreatic ductal adenocarcinoma: Intra-arterial (IA) padeliporfin vascular-targeted photodynamic therapy (VTP).

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Background: Locally advanced pancreatic ductal adenocarcinoma (LA-PDAC) with $>$ 180° vascular encasement of major abdominal arteries is considered unresectable and is associated with poor prognosis. Standard-of-care options, including chemotherapy and chemoradiation, achieve limited conversion to resectability with high recurrence rates. Thus, a therapeutic approach that can effectively downstage LA-PDAC to resection is clinically needed. Activation of vascular-targeted photodynamic therapy (VTP) by Padeliporfin illumination at 753nm results in photochemical generation of oxygen and nitric oxide radicals that cause rapid occlusion followed by break down of the tumor vasculature, tumor necrosis and break-down of the extracellular matrix. Photosensitivity at $>$ 6 hours is avoided due to 1.19 hours Padeliporfin half-life without accumulation in epithelial tissue. Padeliporfin-VTP activation by intra-arterial (IA) illumination has the potential to selectively ablate tumor tissue encasing the artery, reducing vascular encasement and enabling subsequent surgical resection. Robust feasibility and safety preclinical studies in normal swine and efficacy in mouse tumor models have demonstrated feasibility of light transmission through the arterial wall at a dose sufficient to induce tumor ablation at the artery interface and acceptable safety profile, supporting clinical translation. **Methods:** NCT05919238 is an ongoing multi-center Phase I light dose-escalation study. Key inclusion criteria are stage III LA-PADC with solid tumor contact $>$ 180° in head/uncinate process of the pancreas for the total encasement length up to 3cm and with target artery internal diameter 5-10 mm. VTP is applied via IA placement of an optical fiber, inside a standard angioplasty balloon, in the target artery adjacent to the tumor. Ten minutes intravenous administration of Padeliporfin at a fixed dose of 4 mg/kg immediately followed by 753nm laser illumination through the inflated balloon, for two 5-minute cycles with 1-minute break. The study is designed to evaluate three light power densities: 200, 400 and 600mW/cm. The primary objectives include determination of Maximum Tolerated light Dose (MTD) and/or recommended phase 2 dose (RP2D) and evaluation of safety. Secondary objectives are to determine rate of surgical downstaging and resectability as well as the pattern of disease progression following VTP treatment, based on pre- and post-VTP contrast computed tomography (CT) scans and tissue specimens, in case surgery is performed. The study comprises two parts: part A with 3+3 light dose escalation schema; part B (expansion cohort) with the RP2D/MTD, derived in Part A. As of 28 October 2025, Cohort 1 of Part A with an LPD of 200mW/cm have been completed without DLTs. Enrolment to cohort 2, with LPD 400mW/cm, began in November 2025. Clinical trial information: NCT05919238. Research Sponsor: Impact Biotech.

TPS4268 **Poster Session**

Durvalumab and oleclumab in resectable pancreatic ductal adenocarcinoma: A window of opportunity trial (DORA).

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Background: Resectable pancreatic ductal adenocarcinoma (PDAC) comprises < 20% of cases and remains associated with poor outcomes despite surgery and adjuvant chemotherapy. PDAC features a hypoxic, immunosuppressive and "cold" tumor microenvironment (TME). CD73 has emerged as a prognostic biomarker in PDAC, with high expression linked to poor survival. CD73 on tumor cells impairs antitumor T-cell responses and results in tumor immune escape. Inhibition of CD73 could reverse immune suppression by the TME. Preliminary data from the phase I combination trial of durvalumab (anti-PD-L1 antibody) and oleclumab (anti-CD73 antibody) has shown modest antitumor activity in patients in PDAC, colon cancer, and non-small cell lung cancer. A window-of-opportunity (WOO) study allows for rapid early identification of biological activity. We therefore designed a WOO trial to assess the impact of CD73 and PD-L1 blockade in resectable PDAC to test the hypothesis that this strategy would increase CD8+ T cell infiltration and reduce suppressive immune cells as assessed by digital spatial profiling and image mass cytometry. **Methods:** DORA (NCT06060405) is a prospective phase II multicentre WOO trial evaluating the immune activity of combined CD73 and PD-L1 blockade in upfront resectable PDAC. Eligible patients must have ECOG 0–1, histologically confirmed NCCN resectable PDAC, and be immunotherapy-naïve. Patients undergo an upfront EUS for histological diagnosis and for correlative studies, and then receive a single dose of durvalumab 1500 mg IV and oleclumab 3000 mg IV x 2 doses every two weeks prior to surgical resection. Patients receive standard-of-care adjuvant systemic therapy following surgery. The primary objective is to determine the increase in immune cell infiltration, specifically CD8+ T cells, between the paired pre-treatment and surgical resection specimens. Secondary objectives include the percent change in other immune cell populations (CD3/CD45RA/RO T cells, M1 vs. M2 macrophage), and the dynamic changes in immune cell populations as measured by flow cytometry/CyTOF. A total of 22 patients will be enrolled to ensure 20 evaluable subjects who undergo surgical resection. With 20 patients, this provides 80% power to detect an effect size of 0.66 using a two-sided alpha of 0.05. Planned correlatives include serial ctDNA analysis and whole genome and transcriptome sequencing of all surgical resections. This study was activated in January 2024. Clinical trial information: NCT06060405. Research Sponsor: None.

TPS4269 Poster Session

ENVELOPE trial (NCCH2412): Enfortumab vedotin in patients with locally advanced or metastatic small bowel adenocarcinoma refractory or intolerant to platinum-based combination therapy—A multicenter, phase II trial (trial in progress).

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Background: Small bowel adenocarcinoma (SBA) is a rare malignancy with limited systemic options beyond first-line platinum-based combination therapy (FOLFOX/CapeOX) and no established second-line treatment. We recently reported that Nectin-4 is frequently highly expressed in SBA, providing a biological rationale for enfortumab vedotin, a Nectin-4–directed antibody-drug conjugate (ADC). We designed a multicenter phase II trial to evaluate the antitumor activity and safety of enfortumab vedotin in unresectable locally advanced or metastatic SBA refractory or intolerant to platinum-based combination therapy. To our knowledge, this is the first trial to evaluate the efficacy of ADC in this rare cancer. **Methods:** Key eligibility criteria include age ≥18 years, histologically/cytologically confirmed SBA, ECOG PS 0–1, prior FOLFOX or CapeOX with progression or intolerance, ≥1 measurable lesion (RECIST v1.1) and adequate organ function. If prior testing has identified alterations qualifying for approved tumor-agnostic therapies, patients must be refractory or intolerant to such therapies. Nectin-4 positivity is not required for enrollment. Exclusion criteria include a history of interstitial lung disease and poorly controlled diabetes. Enfortumab vedotin is administered at 1.25 mg/kg intravenously on days 1, 8, and 15 of each 28-day cycle until progression or unacceptable toxicity. Tumor assessments are performed by enhanced CT every 8 weeks up to week 24 and every 12 weeks thereafter. The primary endpoint is the objective response rate (ORR), as determined by blinded independent central review. Representative secondary endpoints include disease control rate, progression-free survival, overall survival, and safety outcomes, as assessed by the Common Terminology Criteria for Adverse Events v5.0. The null ORR is 5%, and the expected ORR is 25%. An exact binomial design (one-sided $\alpha = 0.05$; 90% power) requires 25 evaluable patients, with the planned sample size of 27 to account for non-evaluable cases. In a prespecified translational study, tumor Nectin-4 expression will be assessed by immunohistochemistry, and its association with the efficacy of enfortumab vedotin will be explored. Biological specimens will be collected at baseline, during treatment, and at progression for multi-omics analysis to investigate mechanisms of response and resistance. The ENVELOPE trial has been approved by the Institutional Review Board of the National Cancer Center Japan. Enrollment opened on October 2025 and will continue through October 2027; follow-up will extend 12 months after the last patient is enrolled. As of December 31, 2025, 5 patients had been enrolled. Clinical trial information: NCT07347314/jRCT2031250424. Research Sponsor: Japan Agency for Medical Research and Development, AMED; Grant number JP25ck0106015h0001.

TPS4270 Poster Session

FusionVAC22_02, a phase I clinical trial in progress: Adjuvant *DNAJB1-PRKACA* fusion transcript–based peptide T-cell activator for fibrolamellar hepatocellular carcinoma (FLC) and other tumor entities carrying the oncogenic driver fusion.

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Background: The DNAJB1-PRKACA fusion transcript was detected as the oncogenic driver of tumor pathogenesis in fibrolamellar hepatocellular carcinoma (FLC) and other cancers, e.g. oncocytic neoplasms of pancreas and bile duct. We and others have shown that the fusion protein can be targeted by T cell-based immunotherapy: Application of Fusion-VAC-XS15 a peptide-based T cell activator including the TLR1/2 agonist XS15 emulsified in Montanide ISA 51 VG in two FLC patients was well tolerated without systemic side effects and induced long-lasting T-cell response accompanied by disease remission with a progression-free survival of up to 80 months and 60 months in both patients (Bauer *et al.* Nat. Commun., 2022). Based on these promising data, Fusion-VAC-XS15 combined with Atezolizumab is currently under evaluation in the advanced or metastatic situation since October 2023 (Hackenbruch *et al.* Front Oncol., 2024; NCT05937295). For localized FLC, surgical resection still represents the only curative treatment option but shows high relapse rates which underscores the high medical need for adjuvant treatment options. We here present the FusionVAC22_02 trial, which evaluates Fusion-VAC-XS15 as an adjuvant therapeutic in FLC patients who have reached complete remission. **Methods:** FusionVAC22_02 is a Phase I open label, multicentric clinical trial evaluating immunogenicity along with safety, toxicity and first signs of clinical efficacy of Fusion-VAC-XS15 as adjuvant treatment, in 20 patients with FLC or other cancers with proven DNAJB1-PRKACA fusion protein, and lacking adjuvant treatment options. One key eligibility criterion is achievement of complete remission (e.g. due to surgery, radiotherapy, local intervention or systemic treatment) according to RECIST1.1. Of note, a history of liver transplantation or prior immune-mediated side effects (e.g. after treatment with checkpoint-inhibitors) are no exclusion criteria. Fusion-VAC-XS15 is applied twice in a 4-week interval, with an optional booster 56 days after the second application, followed by a 6-month follow-up. Primary objectives include assessment of immunogenicity in terms of peptide-specific T cell responses, as well as evaluation of safety and toxicity. Safety assessment is based on the frequency of adverse events according to CTCAE v5.0. Clinical efficacy is determined by RECIST1.1 assessment on imaging. Recruitment started in July 2025, nine FLC patients from various parts of the world have been included and treated so far, four of which have reached the primary endpoint. Clinical trial information: NCT06789198. Research Sponsor: Fibrolamellar Cancer Foundation; Angewandte Klinische Forschung.

TPS4271 Poster Session

Sacituzumab govitecan in combination with capecitabine for the treatment of advanced gastrointestinal cancers after progression on standard therapy.

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Background: Gastrointestinal (GI) malignancies are associated with poor survival and novel therapies are urgently needed. Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) that targets the tumor-associated antigen Trop-2 (trophoblast cell-surface antigen 2). SG is covalently bound to the topoisomerase I inhibitor SN-38, which is the active metabolite of irinotecan. Trop-2 is overexpressed in most GI malignancies, including colorectal, gastric, and pancreatic cancers, and is associated with poor prognosis. SG has been approved for the treatment of second-line triple-negative breast cancer and pre-treated hormone-receptor positive metastatic breast cancer but its role in GI cancers is not determined. Furthermore, its combination with capecitabine has never been studied. **Methods:** We are conducting a single arm, single institution, dose escalation phase 1 trial with a 3+3 design of combination SG plus capecitabine. SG dosing will be at three levels: Level -1 at 5mg/kg; Level 0 at 7.5mg/kg; and Level +1 at 10mg/kg. Dosing will start at dose level 0. SG will be administered as an intravenous infusion on Days 1 and 8 of a 21-day cycle. Capecitabine dose is fixed at 825mg/m^2 and will be delivered orally twice a day for 14 days on and 7 days off, starting on Day 1, of the 21-day cycle. Key eligibility criteria include histologically documented metastatic adenocarcinoma of GI origin, including gastroesophageal, colorectal, and pancreaticobiliary, that has failed standard therapy; age ≥18years; ECOG performance status 0-1; and adequate end organ function. Key exclusion criteria include previous receipt of topoisomerase 1 inhibitors. The primary endpoint is the Recommended Phase 2 Dose (RP2D). Secondary endpoints include objective response rates, duration of response, progression-free and overall survival. An exploratory endpoint is the correlation between Trop-2 expression in collected archival tissue and clinical outcomes. Optional biopsies will be offered for patients with missing or insufficient archival tissue. This study has been registered under NCT06065371 and is actively enrolling. The trial will enroll up to 20 patients. The trial is funded by Gilead Sciences, Inc. Clinical trial information: NCT06065371. Research Sponsor: None.