6000 Oral Abstract Session

Phase 3 randomized trial (KEYNOTE-630) of adjuvant pembrolizumab (pembro) versus placebo (pbo) for high-risk locally advanced cutaneous squamous cell carcinoma (LA cSCC) following surgery and radiation (RT).

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Background: Patients with high-risk LA cSCC are standardly treated with surgical resection followed by postoperative RT. Up to 30% of pts experience recurrence and/or metastasis. PD-1 inhibitors including pembro are approved in the US for recurrent/metastatic or LA cSCC not curable by surgery or radiation. We present results from the randomized, double-blind, phase 3 KEYNOTE-630 trial (NCT03833167) that evaluated the efficacy and safety of the addition of adjuvant pembro for participants (pts) with high-risk LA cSCC. **Methods:** Adults with histologically confirmed LA cSCC with ≥1 protocol-defined high-risk feature who underwent complete macroscropic resection and completed adjuvant RT ≥4 and ≤16 weeks from randomization were randomly assigned 1:1 to receive pembro 400 mg or placebo (pbo) IV Q6W for ≤9 cycles. The primary end point was recurrence-free survival (RFS), defined as the time from randomization to the first event of local or regional recurrence of index lesion, distant metastasis, or death due to any cause. Secondary end points included overall survival (OS) and safety. The data cutoff date was June 28, 2024. **Results:** A total of 450 pts were enrolled (n = 225 in each arm). All pts completed surgery and RT and 224 in each arm received ≥1 dose of adjuvant treatment. Median study follow-up was 28.6 mo (range, 2.0-62.5). The 24-mo RFS rate was 78.3% (95% CI, 71.5-83.7) for pembro vs 68.6% (95% CI, 61.1-75.0) for pbo (HR 0.76 [95% CI, 0.53-1.10] P = 0.07243, which did not cross the p-value boundary of 0.0160 for statistical significance). On subset RFS analysis, pts with extracapsular extension (HR 0.44; 95% CI, 0.24-0.79), pts aged ≥65 years (HR 0.61; 95% CI, 0.41-0.91), and non-smokers (HR 0.58; 95% CI, CI 0.37-0.90) appeared to benefit most from pembro. Locoregional recurrence occurred in 13.8% of pts receiving pembro vs 25.3% receiving pbo; distant metastasis in 4.4% vs 11.6% of pts; and new high-risk primary cSCC in 0% vs 2.7% of pts. The 24-mo OS rate was 87.3% (95% CI, 81.5-91.5) in the pembro arm vs 90.7% (95% CI, 85.2-94.3) in the pbo arm (HR 1.47 [95% CI, 0.87-2.48]). Treatment-related AEs (TRAEs) occurred in 63.8% of pts in the pembro arm and 41.1% in the pbo arm (grade 3-4 in 7.6% and 2.7%). No pts died due to TRAEs. TRAEs led to treatment discontinuation in 5.4% of pts in the pembro arm and in 1.3% in the pbo arm. **Conclusions:** Pembro did not provide significant benefit in the adjuvant setting for pts with resected, high-risk LA cSCC. The safety profile of adjuvant pembro was consistent with reports from similar studies and there were no treatment-related deaths. The study was stopped for futility as the benefit/risk profile did not support continuing the trial based on recommendations from the data monitoring committee. Clinical trial information: NCT03833167. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

6001 Oral Abstract Session

Phase 3 trial of adjuvant cemiplimab (cemi) versus placebo (pbo) for high-risk cutaneous squamous cell carcinoma (CSCC).

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Background: Cemiplimab is standard of care for treatment of patients (pts) with advanced (metastatic/unresectable) CSCC. There is no approved systemic treatment for pts with CSCC at high risk of recurrence after definitive local therapy. **Methods:** C-POST, a double-blind, multicenter, phase 3 study (NCT03969004), enrolled pts with local and/or regional CSCC, after surgery and post-operative radiation therapy, deemed to be at high risk of recurrence due to nodal (extracapsular extension with largest node ≥2 cm or ≥3 involved lymph nodes) and/or non-nodal (in-transit metastases, T4 lesion, perineural invasion, or locally recurrent tumor with ≥1 additional risk feature) criteria. Pts were randomized 1:1 to cemi 350mg or pbo every (Q) 3w for 12w, then cemi 700mg or pbo Q6W up to 36w (up to 48w total). Original protocol had cemi 350mg or pbo Q3W up to 48w. Crossover was allowed after disease recurrence. Primary endpoint was disease-free survival (DFS). Secondary endpoints included freedom from local-regional recurrence (FFLRR), freedom from distant recurrence (FFDR), overall survival (OS), and safety. Data cutoff for pre-specified interim analysis 1 (IA1; ~50% of final DFS events) was Oct 4, 2024. Per IDMC, the pre-specified threshold for DFS was crossed at IA1. **Results:** From Jun 2019 to Aug 2024, 415 pts (209/206 cemi/pbo) were randomized: median age, 71 yrs (range 33–95); 84% male; 83% head and neck primary; 58%/42% high-risk nodal/non-nodal categories. Median follow-up was 24 mos (range 2–64). DFS was superior with cemi vs pbo: hazard ratio (HR) 0.32 (95% CI 0.20–0.51); p<0.0001 (Table). Estimated 24-mo DFS was 87% (95% CI 80–92) for cemi and 64% (56–71) for pbo. Cemi improved FFLRR (HR 0.20; 95% CI 0.09–0.40) and FFDR (HR 0.35; 0.17–0.72) vs pbo. At IA1, OS HR for cemi vs pbo was 0.86 (95% CI 0.39–1.90). Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 23.9% and 14.2% and discontinuations due to TEAEs occurred in 9.8% and 1.5% of pts receiving cemi and pbo, respectively. In exploratory analyses, DFS benefits were observed in pts with tumoral PD-L1 ≥1% (HR 0.28; 95%CI 0.15–0.52; n=309) and <1% (HR 0.32; 0.12–0.86; n=85). **Conclusions:** Cemiplimab is the first systemic therapy to demonstrate a statistically significant and clinically meaningful reduction in disease recurrence as adjuvant therapy for high-risk CSCC, and has an acceptable safety profile in this setting. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

	Cemi n=209	Pbo n=206
Pts with DFS event, n (%)[a]	24 (12)	65 (32)
Disease recurrence	18 (9)	61 (30)
Death	6 (3)	4 (2)
DFS, mos, median (95% CI)[b]	NR (NE–NE)	49.4 (48.5–NE)
HR (95% CI)[c]	0.32 (0.20–0.51)	-
2-sided p-value[d]	< 0.0001	-
24-mo DFS, % (95% CI)[b]	87.1 (80.3–91.6)	64.1 (55.9–71.1)
24-mo FFLRR, % (95% CI)[b]	94.6 (89.1–97.3)	76.7 (69.1–82.6)
24-mo FFDR, % (95% CI)[b]	94.3 (89.0–97.1)	83.8 (76.3–89.0)

NE, not estimable; NR, not reached.
[a]Censored pts: 185 cemi; 141 pbo.
[b]Kaplan-Meier estimate.
[c]Stratified Cox model.
[d]Stratified log-rank test.

6002 Oral Abstract Session

A phase II (Alliance/A091802) randomized trial of avelumab plus cetuximab vs. avelumab alone in advanced cutaneous squamous cell carcinoma (cSCC).

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Background: There is a need for continued improvement in outcomes with systemic therapy for advanced cSCC. Pre-clinical data suggest immunologic synergy between IgG1 mAb therapy targeting EGFR and PD-1:PD-(L)1 blockade. **Methods:** Alliance A091802 is a randomized phase II trial of avelumab (AV) (800 mg) plus cetuximab (C) (500 mg/m2) vs. AV alone every 2 weeks for up to 2 years (yrs). C was given for 1 yr in the AV+C arm. Crossover at progression to AV+C was allowed in the AV arm. Randomization was 1:1 and stratified by PD-L1 [+(>1%) vs. -] and HIV status (+ vs. -). Eligible patients (pts) had distant metastatic or unresectable locally advanced cSCC, anti-PD-1/PD-L1 mAb naive, no prior cetuximab in the advanced setting, ECOG PS 0-2, HIV+ if CD4 >200 and VL <200. Pts with CLL, immunosuppression, or active autoimmune diseases were excluded. The primary endpoint was progression-free survival (PFS) (Ho: Median=12 mo vs Ha: 21 mo or a 75% improvement, power of 80% with one-sided alpha 0.2, n=57, 37 PFS events required). Secondary endpoints were overall survival (OS), confirmed response rate (ORR), clinical benefit rate, and toxicity. After 31/37 events, an early unplanned analysis (along with sensitivity analyses) was performed because it became apparent that 37 events would not be reached. These results were submitted to the Alliance Data and Safety Monitoring Board, which recommended releasing the data. Data cutoff was 1/16/25. **Results:** 60 pts were enrolled between 2019-2023; 57 pts were evaluable. Median age was 72 yrs (41–93), 96.5% were white, 91.2% male, all HIV-; 75.4% PD-L1+. 84.2% were head/neck origin, 47.1% had distant metastasis, and there were no differences in baseline characteristics by arm. AV+C significantly improved PFS compared to AV [median 11.1 months (mo) (7.6–not reached (NR)) vs. 4.8 mo (2.8–NR) hazard ratio (HR) 0.53 95% CI (0.26–1.09), one-sided p=0.041]. The median OS of AV+C vs. AV was NR (25.2–NR) vs. 35.8 mo (18.6–NR) HR 0.77 (0.33–1.78) p=0.267. ORR was 31.0% in the AV+C arm and 21.4% in the AV arm. Treatment-related adverse events (TRAE) of any grade (G) occurred in 93% and 78.6%, respectively, and were G>3 in 48.3% and 21.5% of pts in the AV+C [most common G3 TRAEs were rash (20.7%) and infusion-related reaction (20.7%)] and AV arms, respectively. There were no G5 events. Outcomes after crossover and by PD-L1 status will be presented subsequently. **Conclusions:** Avelumab plus cetuximab significantly improved PFS vs. avelumab alone in advanced cSCC pts, without unexpected toxicity. Alliance A091802 supports a larger confirmatory study with combination cetuximab and PD-1:PD-(L)1 blockade. Support: U10CA180821, U10CA180882, U24CA196171; U10CA180868 (NRG Oncology); U10CA180888 (SWOG); https://acknowledgments.alliance-found.org. EMD Serono CrossRef Funder ID: 10.13039/100004755. Clinical trial information: NCT03944941. Research Sponsor: National Cancer Institute/NIH- Alliance for Clinical Trials in Oncology; EMD Serono.

LBA6003 **Oral Abstract Session**

PD-1 blockade with toripalimab incorporated into induction chemotherapy and radiotherapy with or without concurrent cisplatin in locoregionally advanced nasopharyngeal carcinoma (DIAMOND): A multicenter, non-inferiority, phase 3, randomized controlled trial.

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6004 Oral Abstract Session

Tagitanlimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC): Results from a randomized, double-blind, phase 3 study.

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Background: The addition of PD-1 inhibitor to gemcitabine and cisplatin (GP) showed promising activity as first-line therapy for R/M NPC. Here, we first report the PD-L1 inhibitor Tagitanlimab (KL-A167) plus GP compared with placebo plus GP in a randomized phase 3 study (KL167-III-08, NCT05294172). **Methods:** Eligible patients (pts) with previously untreated R/M NPC were in 2:1 ratio randomly assigned to receive tagitanlimab or placebo (1200 mg, D1) in combination with cisplatin (80 mg/m^2, D1) and gemcitabine (1000 mg/m^2, D1 and D8) every 3 weeks (Q3W) for up to 6 cycles followed by tagitanlimab or placebo monotherapy Q3W until disease progression, unacceptable toxicity, or withdrawal of consent. After disease progression, pts from the placebo arm could crossover to receive tagitanlimab monotherapy. The primary endpoint was progression-free survival (PFS) assessed by the blinded independent central review (BICR) according to RECIST version 1.1. **Results:** Between Jun 16, 2022, and May 27, 2023, 295 pts were assigned to tagitanlimab plus GP arm (n = 197) or placebo plus GP arm (n = 98). The median age was 52 years, and 79.7% were male. As of Feb 4, 2024, 47.2% of pts in tagitanlimab plus GP arm vs 23.5% of pts in placebo plus GP arm were still on treatment, 36.7% of pts in placebo plus GP arm were crossed to receive tagitanlimab monotherapy after disease progression. The median follow-up time was 11.7 months. The PFS per BICR was met at the prespecified interim analysis with a 53% reduction in risk of progression or death (HR 0.47; 95% CI, 0.33 to 0.66; one-sided P $<$0.0001). The median PFS was not reached (95% CI, 10.9-NE) in tagitanlimab plus GP arm and 7.9 months (95% CI, 6.9-8.3) in placebo plus GP arm; the 12-month PFS rate was 56.7% vs 26.7%. The objective response rate (ORR) per BICR was 81.7% (95% CI, 75.6-86.9) in tagitanlimab plus GP arm and 74.5% (95% CI, 64.7-82.8) in placebo plus GP arm, with a median duration of response (DoR) of 11.7 months (95% CI, 8.2-NE) and 5.8 months (95% CI, 5.6-6.9; HR 0.48, 95% CI, 0.32-0.70), respectively. The overall survival (OS) benefit was observed in tagitanlimab plus GP arm vs placebo plus GP arm (median OS not reached for either arm; HR 0.62, 95% CI 0.32-1.22). The most common $\geq$ grade 3 treatment-related adverse events (tagitanlimab plus GP arm vs placebo plus GP arm) were neutrophil count decreased (57.9% vs 49.0%), white blood cell count decreased (52.8% vs 46.9%), and anemia (38.6% vs 40.8%). **Conclusions:** The addition of tagitanlimab to GP demonstrated superior PFS efficacy compared to GP alone, supporting that tagitanlimab, as a PD-L1 inhibitor, could be the new standard of treatment for pts with R/M NPC in the first-line setting. The safety profile of tagitanlimab combined with GP was manageable and consistent with previous reports, with no new safety signals identified. Clinical trial information: NCT05294172. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

LBA6005 **Oral Abstract Session**

Becotatug vedotin vs. chemotherapy in pre-heavily treated advanced nasopharyngeal carcinoma: A randomized, controlled, multicenter, open-label study.

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6006 Oral Abstract Session

SHR-A1811 in HER2-expressing salivary gland cancers: Preliminary efficacy and safety results.

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Background: Salivary gland cancer (SGC) is a rare and heterogeneous malignancy with limited treatment options in advanced stages. Overexpression of human epidermal growth factor receptor 2 (HER2) is linked to aggressive histological subtypes and poor prognosis in SGC, making HER2 a promising target for precision therapy. This study evaluates the efficacy and safety of SHR-A1811, a HER2-targeted antibody-drug conjugate (HER2-ADC), in patients with advanced SGC through a molecular subtype-guided approach (NCT05924256). **Methods:** Patients with advanced SGC were stratified into four arms based on genetic subtypes. This analysis focuses on Arm 1 (HER2 overexpression: IHC 3+ or IHC 2+/ISH+) and Arm 4 (HER2-low: IHC 1+ or IHC 2+/ISH-). In Arm 1, patients received SHR-A1811 at 4.8 mg/kg IV on Day 1 of a 21-day cycle. In Arm 4, patients received 4.8 mg/kg or 5.6 mg/kg (if tolerated). The study followed Simon's two-stage design, with the primary endpoint of 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:** As of January 1, 2025, 33 patients were enrolled (baseline characteristics in Table 1). In Arm 1 (21 evaluable patients), the ORR was 85.7%, and the DCR was 100%. In Arm 4 (10 evaluable patients), the ORR was 30.0%, and the DCR was 100%. After a median follow-up of 9.9 months (range: 1.2–16.6) for Arm 1 and 6.0 months (range: 4.7–9.2) for Arm 4, neither median OS nor PFS was reached. Only one patient in Arm 4 experienced disease progression. Treatment-related adverse events (TRAEs) occurred in 32 patients (97%). The most common grade 3/4 TRAEs included neutropenia (36%), leukopenia (15%), anemia (12%), and lymphopenia (12%). Two patients (6%) experienced treatment-related serious adverse events (SAEs), and one patient (3%) developed grade 1 interstitial lung disease. No patient discontinued treatment due to TRAEs, and no treatment-related deaths were reported. **Conclusions:** SHR-A1811 demonstrated promising efficacy in both HER2-positive and HER2-low advanced salivary gland cancers, achieving high ORRs and DCRs with an acceptable toxicity profile. Clinical trial information: NCT05924256. Research Sponsor: None.

Baseline characteristics.

	Arm 1 (N=23)	Arm 4 (N=10)
Age (years), Median (range)	58 (26-75)	56 (36-66)
Male : Female	16:7	8:2
HER2 status, n (%)	IHC 3+, 19 (83) IHC 2+/ISH+, 4(17)	IHC 1+, 8(80) IHC 2+/ISH-, 2(20)
Histology		
Salivary duct carcinoma, n (%)	12 (52)	1 (10)
Carcinoma ex pleomorphic adenoma, n (%)	3 (13)	2 (20)
Adenoid cystic carcinoma, n (%)	0	2 (20)
Others, n (%)	8 (35)	5 (50)
Prior treated for patients, n (%)	16 (70)	9(90)
Prior systemic therapy lines, Median (range)	0 (0-3)	1 (0-7)
Anti-HER2 treatment, n (%)	5 (22)	0

6007 Oral Abstract Session

Darolutamide plus goserelin for androgen receptor-positive salivary gland cancers: Results of phase 2 study (DISCOVARY).

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Background: No standard treatment exists for unresectable locally advanced (LA) or recurrent/metastatic (R/M) salivary gland cancer (SGC). Previous findings suggest that combined androgen blockade (CAB) provides promising clinical activity in patients with androgen receptor (AR)-positive SGC. However, no AR-targeted drug is currently approved for SGC. This multicenter phase 2 study investigated two approaches in patients with unresectable LA or R/M SGC: darolutamide monotherapy followed by the combination of darolutamide and goserelin. In the monotherapy phase, darolutamide showed an objective response rate (ORR) of 20.8% as determined by independent central review (ICR) with tolerable toxicity (ASCO 2023). We now report the results from the combination phase. **Methods:** Eligible patients had histologically confirmed AR-positive LA or R/M SGC, ECOG performance status (PS) 0–2, adequate organ function, and no local therapy options. Patients received darolutamide orally at 1,200mg daily, combined with goserelin at 3.6 mg every four weeks. The primary endpoint was ORR by ICR in patients verified to have AR positivity through central assessment. Secondary endpoints included clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety profiles. **Results:** Between Sep 2022 and Aug 2023, 33 patients were enrolled in the combination phase. Median age was 63 years; 26 were male; ECOG PS 0/1/2 in 28/4/1. Histology included salivary duct carcinoma (n=32) or adenocarcinoma not otherwise specified (n=1). Prior treatment included surgery (n=23), radiotherapy (n=21), and chemotherapy (n=15). The ORR by ICR was 45.2% (14/31; 95% CI, 27.3–64.0), meeting the primary endpoint. CBR was 51.6% (95% CI, 33.1–69.8), and DCR was 64.5% (95% CI, 45.4–80.8). At a median follow-up of 13.7 months, the median PFS was 13.1 months (95% CI, 2.0– not calculable [NC]). Thirteen patients continued treatment at the data cutoff (August 9, 2024). Median OS was not reached (95% CI, 20.0–NC), and 12 months OS rate was 87%(95% CI, 68.9–94.9). Treatment was generally well tolerated, with six patients (18.2%) experiencing grade 3 adverse events. **Conclusions:** This is the first prospective CAB trial in SGC which has met its primary endpoint. Darolutamide plus goserelin demonstrated clinically meaningful efficacy and a favorable safety profile, suggesting it may be a compelling option before initiating chemotherapy, which can significantly diminish a patient's quality of life. Clinical trial information: NCT05694819. Research Sponsor: Bayer.

6008 Oral Abstract Session

Neoadjuvant pembrolizumab in combination with dabrafenib and trametinib (DTP) for *BRAF* V600E-mutated anaplastic thyroid cancer (*BRAF*m-ATC): A multicenter phase 2 trial.

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Background: ATC patients present with advanced, often surgically unresectable disease with historically dismal prognosis. Median PFS and OS of DT without pembrolizumab were 6.7 and 13.5 months, respectively, in the ROAR trial. Neoadjuvant DTP achieved locoregional control without radical surgery in a retrospective series of *BRAF*m-ATC patients, providing rationale to evaluate efficacy and safety in a phase 2 prospective trial. **Methods:** In this single-arm multicenter phase 2 trial, patients with *BRAF*m-ATC stage IVB/IVC were enrolled in 5 US centers. Following a 3-6 week run-in with D (150 mg BID) and T (2 mg daily), P (200 mg Q3W) was added, with restaging every three (21-day) cycles. Post-operatively, patients continued P (or DTP) with radiotherapy or transitioned directly to adjuvant DTP (up to 26 cycles). Primary endpoints included R0/R1 resection rate (historically 5%) and overall survival (OS). Secondary endpoints included RECIST 1.1 response after DTP and progression-free survival (PFS). **Results:** Between 9/2021-1/2025, 42 patients were enrolled; 36 are included in the current analysis (3 not evaluable, 3 pending surgery) (Table). Patients received median 4 (range: 2-7) neoadjuvant DTP cycles, with 26 (72%) achieving radiographic PR/CR. 30 patients (83%) had surgery after neoadjuvant DTP, achieving R0/R1 resection in 29/30 (97%). Mean surgical morbidity score (0-4 scale, 4=unresectable) improved from 3.3 to 1.6 after DTP ($p<0.01$). Complete ATC pathologic response occurred in 20/30 patients (67%), while 10/30 (33%) had residual ATC in the surgical specimen. Postoperatively, 11/30 (37%) received adjuvant neck radiation, and 28/36 (78%) completed a median of 11 (range: 1-26) adjuvant DTP cycles. With median follow up 18 months, 15/36 (42%) patients died. Median OS was 20 months (95% CI: 12.6-NR); 1- and 2-year OS were 71% and 48%. Complete pathologic responders had better 2-year OS than those with residual ATC (69% vs. 22%, p=0.02). Median PFS was 13.9 months (95% CI, 7.5-NR); 1- and 2-year PFS were 57% and 36%. Grade 5 adverse events occurred in 8 patients (22%), including one possible (duodenal perforation), one probable (kidney injury with sepsis), and 6 unlikely/unrelated treatment-related deaths. **Conclusions:** Neoadjuvant DTP enables surgical resection in *BRAF*m-ATC compared with historical controls, and leads to improved PFS and OS. This approach should now be considered a standard of care for *BRAF*m-ATC. Clinical trial information: NCT04675710. Research Sponsor: Merck; Gateway for Cancer Research; G-20-1200; MD Anderson Petrick Philanthropy.

	Total N=36
Age (y), median (range)	67 (46-86)
Stage IVB/IVC, n (%)	15 (42%)/21 (58%)
Best RECIST response neoadjuvant phase, n (%)	
CR	2 (6%)
PR	24 (67%)
SD	6 (17%)
PD	4 (11%)
Percent change target lesion diameter, mean (95% CI)	-44% (-54%, -34%)
Surgical morbidity score change, mean (95% CI)	-1.7 (-2.1, -1.3)

6009 Clinical Science Symposium

Risk-adapted therapy guided by human papillomavirus (HPV) circulating tumor DNA in patients with HPV-positive oropharyngeal cancer (ReACT 1.0).

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Background: Human papillomavirus-positive oropharyngeal cancer (HPV+ OPC) has favorable outcomes with platinum-based concurrent chemoradiation (CRT), but long-term toxicity can be significant. Various treatment de-intensification strategies have been explored to maintain survival and mitigate treatment-related morbidity. We present the first study using tumor tissue modified viral (TTMV)-HPV DNA in real-time to stratify non-surgical patients (pts) to receive de-intensified, curative-intent CRT. **Methods:** This phase 2 two-cohort, clinical trial (NCT04900623) enrolled pts with AJCC 2017 8th ed. stage I-III (no fixed nodes) HPV+ OPC treated with CRT if they had detectable TTMV-HPV DNA (type 16) pre-treatment (pre-tx). Pts were assigned to the low-risk (LR) arm with T0-3 N0-2 disease, a ≤10 pack-year smoking history, and any detectable HPV DNA result pre-tx. Pts were assigned to the intermediate-risk (IR) arm with T4 disease or a >10 pack-year smoking history if they had a pre-tx HPV DNA score of >200. LR arm pts received de-intensified CRT (54-66 Gy with reduced dose platinum or RT alone). IR arm pts who cleared their pre-tx HPV DNA by >95% were also de-intensified; those ≤200 pre-tx or who failed to clear received standard 70 Gy CRT with up to 300 mg/m^2 cisplatin. Primary endpoint was 2-year progression-free survival (PFS) among all de-intensified LR and IR pts. Group-sequential testing for non-inferiority (NI) was performed Q4 months after the first 40 pts completed >6 months of follow-up. Interim analyses (IAs) were declared NI if the 2-year PFS lower CI bound was >80% among de-escalated LR/IR pts (Bootstrap approach; alpha 0.05). Secondary endpoints: safety, overall survival, distant metastasis-free survival, quality of life (QoL) metrics, and exploratory radiomic data. **Results:** From 7/2021 to 5/2024, 138 pts screened, 71 accrued (cohort 1). Most were male (62, 87%) and white (70, 99%) with a median age of 63 (range: 46-80). Forty-four (62%) were assigned to the LR arm (23% had N2 disease) with a median pre-tx HPV DNA of 439 (range: 6-221995). Twenty-seven (38%) pts were assigned to the IR arm (33% T4, 78% smokers) with a median pre-tx HPV DNA of 2346 (range: 207-84971). Among the 27 IR pts, 18 (67%) had >95% DNA clearance and were de-escalated. At a median follow-up of 14 months, the 2-year PFS estimate at IA2 was 92% (95%CI, 85-100) among 62 de-escalated LR/IR pts including 18 (29%) T4/smokers and 15 (24%) with N2 disease. Two distant and 2 locoregional plus distant failures occurred; with no isolated locoregional failures. QoL data is forthcoming; 1 patient died from disease. Cohort 2 explores further de-escalation and is ongoing. **Conclusions:** Using HPV DNA-guided CRT de-intensification we achieved our primary endpoint and report a favorable 2-year PFS >90%, which included T4 pts and smokers. HPV DNA as a biomarker to guide de-intensification warrants further study. Clinical trial information: NCT04900623. Research Sponsor: Dana-Farber Cancer Institute.

Dynamic circulating tumor DNA-driven, risk-adapted systematic therapy in nasopharyngeal carcinoma: The EP-STAR trial.

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Background: Circulating tumor-derived Epstein-Barr virus (EBV) DNA (ctDNA) during treatment has been established as a biomarker in nasopharyngeal carcinoma (NPC). However, how this information would facilitate individualized management remains unknown. We designed EP-STAR, a multicentre, phase II, adaptive trial to investigate whether the dynamic on-treatment ctDNA-driven, risk-adapted treatment strategy improved survival for NPC patients. **Methods:** Locoregionally advanced NPC (stage III-IVA) with detectable pretreatment EBV DNA (excluding T3N0 with EBV DNA<2000 copy/mL), who received gemcitabine plus cisplatin induction chemotherapy (IC) concurrently with longitudinal on-treatment EBV DNA monitoring were enrolled and classified into different ctDNA risk subgroups. Low-risk patients (EBV $DNA_{post\text{-}IC1\text{-}3}$=0) did not undergo treatment adaptation and continued standard therapy (chemoradiotherapy, CCRT) (No_adaptive_Arm-control). At-risk patients (intermediate/high-risk) underwent risk-based treatment adaptation (Adaptive population): intermediate-risk patients (EBV $DNA_{post\text{-}IC1}$>0, EBV $DNA_{post\text{-}IC3}$=0 or EBV $DNA_{post\text{-}IC1}$=0, EBV $DNA_{post\text{-}IC2}$>0, EBV $DNA_{post\text{-}IC3}$=0) started treatment intensification with addition of adjuvant metronomic capecitabine to CCRT (650 mg/m² orally twice daily) (Adaptive_Arm-I_cap); high-risk patients (EBV $DNA_{post\text{-}IC1}$>/=0, EBV $DNA_{post\text{-}IC3}$>0) started treatment intensification with addition of 12 cycles sintilimab to CCRT (anti-PD-1 drug, 200 mg intravenously every three weeks) (Adaptive_Arm-II_sin). Primary endpoint was failure-free survival (FFS) of adaptive population; co-primary endpoint was FFS of Adaptive_Arm-II. **Results:** A total of 142 patients were enrolled (58 in Adaptive_Arm-I, 52 in Adaptive_Arm-II, 32 in No_adaptive_Arm-control). Primary endpoint was met, 3-year FFS of adaptive population was 89.0% (88.4–89.6%) at a median follow-up of 41.5 months (Table 1). Data compared favorably with historic cohort of the similar populations but did not undergo adaptive therapy (3-year FFS: 74.7% [68.8–80.6%]), Table 1). Toxicity was manageable with grade 3-4 adverse events recorded in 56.1% and 59.6% patients in Adaptive_Arm-I/II during adaptive phase, respectively; no treatment-related death was observed. **Conclusions:** The ctDNA-driven, risk-adapted paradigm was highly likely to result in improved survival outcomes than conventional unchanging treatment strategy in NPC. Clinical trial information: NCT04072107. Research Sponsor: Major Research Plan of the National Natural Science Foundation of China; 92259202.

Summary of FFS in EP-STAR and the similar population in historic control.

	EP-STAR	Historic control (*Prospective, Cancer Cell, 2024*)
Recruitment year	2020-2021	2019-2021
3-year FFS		
Intermediate & high-risk patients with or without adaptive therapy	89.0% (88.4–89.6%)	74.7% (68.8–80.6%)
High-risk patients with or without adaptive therapy	86.5% (77.3–95.7%)	64.8% (55.0–74.6%)
Low-risk patients	93.8% (91.0–100.0%)	90.8% (85.9–95.7%)

6011 Clinical Science Symposium

REMATCH2201: A phase II study on reducing surgical margins in HPV-negative advanced HNSCC with neoadjuvant PD-1 inhibitor and AP chemotherapy.

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Background: The standard of care for resectable HNSCC includes extensive surgical margins to ensure complete oncologic resection, often at the expense of significant functional impairment. Recent advancements in neoadjuvant PD-1 inhibitors with chemotherapy, have shown potential in achieving substantial tumor regressions. This study posits that such neoadjuvant immunochemotherapy can allow for narrower surgical margins without compromising oncological outcomes, potentially preserving vital anatomical structures and function. **Methods:** This single-center, phase II clinical study (NCT05459415) enrolled 52 patients with operable, HPV-negative locally advanced HNSCC. Participants received three cycles of the AP chemotherapy regimen combined with 200 mg of the PD-1 inhibitor Penpulimab. Tumor response was assessed via MRI and laryngoscopy after the second cycle. Patients achieving greater than 50% reduction in tumor size were selected for conservative-margin surgical resection. Surgical Protocol: If imaging or endoscopy identifies residual tumor, margins will be expanded 5-10mm beyond the tumor edges to ensure clear margins, confirmed by intraoperative frozen section analysis by dual pathologists, ensuring maximal oncologic safety and functional preservation. For patients achieving CR, surgical planning relies on prior diagnostic imaging and endoscopic outcomes to guide precise resections of the larynx and hypopharynx. Post-surgical adjuvant treatment was based on final pathology results, including further immunotherapy for nine cycles. **Results:** Of the initial cohort, 50 patients were evaluable for response; the objective response rate (ORR) stood at 96%, and a pathologic complete response (pCR) was observed in 40.7% of patients. Forty-seven patients proceeded to surgery, all maintaining laryngeal function, and 91.5% underwent reduced-margin resection based on deep imaging response, with a pCR achieved in 44.2% of these cases. The study noted clinical adverse events, including three unrelated deaths and two instances of severe postoperative complications. The 12-month and 24-month Event-Free Survival (EFS) rates were calculated at 97.62% and 89.28% respectively. The overall survival (OS) rate at 24 months was 92.85%. **Conclusions:** The REMATCH2201 trial supports the feasibility of reduced-margin surgery in patients with HPV-negative advanced HNSCC following effective neoadjuvant immunochemotherapy, without increasing the risk of oncologic recurrence. This approach importantly spares critical functional anatomy, advocating for a paradigm shift in the surgical management of these tumors. Nevertheless, further research in a multi-center, randomized controlled trial setting is required to substantiate these findings and refine protocols for broader application in clinical practice. Clinical trial information: NCT05459415. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

6012 Rapid Oral Abstract Session

Neoadjuvant and adjuvant pembrolizumab plus standard of care (SOC) in resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): Exploratory efficacy analyses of the phase 3 KEYNOTE-689 study.

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Background: The addition of immune checkpoint inhibitors to neoadjuvant/adjuvant SOC has led to efficacy benefits across multiple tumor types. The randomized phase 3 KEYNOTE-689 study (NCT03765918) showed significantly improved event-free survival (EFS) with neoadjuvant/adjuvant pembrolizumab + SOC vs SOC alone for participants (pts) with resectable LA HNSCC independent of PD-L1 combined positive score (CPS ≥10 population: HR 0.66, 95% CI 0.49–0.88, *P*=.00217; CPS ≥1 population: HR 0.70, 95% CI 0.55–0.89, *P*=.00140; all pts: HR 0.73, 95% CI 0.58–0.92, *P*=.00411). We present exploratory efficacy endpoints for the intention-to-treat population of the study. **Methods:** Adults with SCC of the larynx/hypopharynx/oral cavity (stage III/IVA) or oropharynx (stage III/IVA p16− or stage III T4 N0-2 p16+) were randomized 1:1 to SOC (consisting of surgery + postoperative radiotherapy [PORT] ± concurrent cisplatin 100 mg/m^2 Q3W) with or without 2 cycles of neoadjuvant pembrolizumab, 3 cycles of pembrolizumab concurrent with PORT ± cisplatin and 12 cycles of adjuvant pembrolizumab (200 mg IV Q3W). The primary endpoint is EFS per RECIST 1.1 by blinded independent central review. Safety is a secondary endpoint. Prespecified exploratory efficacy endpoints include locoregional control (time from randomization to first locoregional radiographic progression or recurrence by imaging or biopsy), distant metastases-free survival (DMFS; time from randomization to first distant metastasis or death), and incidence of second head and neck or other cancers. **Results:** A total of 714 pts were randomized (363 to pembrolizumab + SOC, 351 to SOC). At first interim analysis (data cutoff date 25 Jul 2024), median follow-up was 38.3 mo (range, 9.0–66.5). In all pts, cumulative incidence of locoregional progression or recurrence at 36 mo was 13.4% with pembrolizumab + SOC and 14.3% with SOC. The HR for risk of a locoregional failure event with pembrolizumab + SOC vs SOC was 0.92 (95% CI 0.61–1.41). Median DMFS was 51.8 mo with pembrolizumab + SOC vs 35.7 mo with SOC (HR 0.71, 95% CI 0.56–0.90). Estimated DMFS rate at 36 mo was 59.1% vs 49.0%, respectively. Second head and neck or other cancers occurred in 9 (2.5%) and 18 pts (5.1%), respectively. Incidence of treatment-related adverse events was similar with pembrolizumab + SOC and SOC (any grade, 81.4% vs 81.9%; grade ≥3, 44.6% vs 42.9%). **Conclusions:** Among all pts with resectable LA HNSCC in KEYNOTE-689, DMFS results and incidence of second cancers favored the addition of neoadjuvant/adjuvant pembrolizumab to SOC surgery and (chemo)radiotherapy, consistent with the primary EFS results of the study. Locoregional control was similar between arms. No new safety signals for pembrolizumab were observed. Clinical trial information: NCT03765918. Research Sponsor: This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

6013 Rapid Oral Abstract Session

Long-term results of the randomized, phase 3 KEYNOTE-412 trial of pembrolizumab (pembro) or placebo (pbo) plus concurrent chemoradiotherapy (CRT) for unresected, locally advanced head and neck squamous cell carcinoma (LA HNSCC).

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Background: In the final efficacy analysis of the randomized, double-blind, phase 3 KEYNOTE-412 trial (NCT03040999), pembro + CRT did not significantly improve event-free survival (EFS) vs pbo + CRT (HR 0.83; 95% CI 0.68-1.03) in unresected LA HNSCC. We present results for KEYNOTE-412 with >2 yrs of additional follow-up. **Methods:** Adults with newly diagnosed high-risk unresected LA HNSCC (any T3-T4 [N0-N3] or any N2a-3 [T1-T4] larynx/hypopharynx/oral cavity/p16-negative oropharynx cancers and T4 or N3 p16-positive oropharynx cancer) were randomly assigned to receive CRT (70 Gy in 35 fractions + 3 cycles cisplatin 100 mg/m^2 Q3W) + 17 cycles of pembro 200 mg or pbo IV Q3W: first cycle 1 week prior to CRT, 2 cycles during CRT, then 14 cycles of maintenance. The primary end point was EFS assessed by blinded independent central review. The key secondary end point was overall survival (OS). Efficacy was analyzed in all randomly assigned pts (ITT population). Exploratory analyses included locoregional control (LRC), distant metastasis-free survival (DMFS), incidence of second malignancies in the ITT population, and efficacy in pts with PD-L1 CPS ≥1. **Results:** 402 pts were assigned to each arm; and 398 received ≥1 dose of study treatment in each arm. As of data cutoff date (August 21, 2024), median study follow-up was 74.4 mo (range, 63.7-88.1). EFS was longer with pembro vs pbo (HR 0.79; 95% CI 0.65-0.96). Overall, 186 (46.3%) and 217 (54.0%) EFS events occurred in the pembro and pbo arms, which represents an additional 15 events in the pembro arm and 25 in the pbo arm since the previous analysis. Full efficacy results for the ITT population are in the table. LRC HR was 0.80 (95% CI 0.57-1.14). Overall, 36 pts (9.0%) in the pembro arm and 45 (11.2%) in the pbo arm developed a secondary malignancy. In pts with PD-L1 CPS ≥1 (pembro, n = 339; pbo, n = 346), median EFS was 70.9 mo (95% CI 55.4-not reached [NR]) for the pembro arm and 48.3 mo (95% CI 26.8-66.8) for the pbo arm (HR 0.80; 95% CI 0.64-0.98); median OS was NR (NR; 95% CI NR-NR) for the pembro arm and NR (95% CI 70.0-NR) for the pbo arm (HR 0.84; 95% CI 0.66-1.06). The safety profile was consistent with previously reported adverse events at the time of the final analysis. **Conclusions:** At end of trial, with >2 yrs of additional follow-up, results showed a clinically meaningful EFS benefit with pembro + CRT versus pbo + CRT and no new safety signals in pts with LA HNSCC. Clinical trial information: NCT03040999. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Pembro + CRT (n = 402)	Pbo + CRT (n = 402)
EFS, median (95% CI), mo	71.8 (55.4-NR)	49.8 (26.8-66.2)
HR (95% CI)	0.79 (0.65-0.96)	
5-yr EFS rate, %	54.7	47.2
OS, median (95% CI), mo	NR (NR-NR)	NR (74.3-NR)
HR (95% CI)	0.86 (0.70-1.07)	
5-yr OS rate, %	64.4	59.8
DMFS, median (95% CI), mo	NR (68.9-NR)	64.3 (49.8-76.0)
HR (95% CI)	0.80 (0.65-0.98)	
5-yr DMFS rate, %	58.6	51.3

6014 Rapid Oral Abstract Session

A randomized, open-label, multicenter, blank-controlled, phase IV clinical trial of Biyan Qingdu Granula in attenuating acute nose and oral damage in patients undergoing radiotherapy for nasopharyngeal carcinoma.

Zhigang Liu, Zhiqiang Wang, Zunbei Wen, Xin Wu, Li Bai, Deming Xu, Huaming Lin, Haichao Lin, Jiemei Tan, Wei Wu, Weijun Zhang, Sufang Qiu, Yimin Liu, Haisheng Zhu, Xiaowen Zhang, Yanhua Xu, Dehua Wu, Junlin Yi, Yan Ruan, Yexiong Li, Biyan Qingdu Granula; Cancer Center, the tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University, Dongguan, China; Medical Oncology, Gaozhou People's Hospital, Maoming, Guangdong, China; West China Hospital of Sichuan University, Chengdu, China; HuiZhou Municipal Central Hospital, Huizhou, China; Zhanjiang Cancer Hospital, Zhanjiang, China; Maoming People's Hospital, Maoming, China; Yulin Red Cross Hospital, Yulin, China; Jiangmen Central Hospital, Jiangmen, China; Ganzhou Cancer Hospital, Ganzhou, China; Affiliated Cancer Hospital & Institute of Guangzhou Medical University, Guangzhou, China; Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, Fujian, China; Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; Department of Oncology, First People's Hospital of Yulin City, Yulin, China; The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Department of Oncology, JinZhou Central Hospital, Jingzhou, China; Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China; Department of Radiotherapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China

Background: This randomized, open-label, multicenter, blank-controlled, phase IV trial aimed to evaluate the efficacy and safety of Biyan Qingdu Granula (BQG) in attenuating acute radiation-induced nasal and oral injuries in nasopharyngeal carcinoma(NPC) patients receiving radiotherapy, and to explore the potential advantages and application values of BQG through comparison with conventional treatments. **Methods:** This trial was conducted at 30 hospitals in China between July 21st, 2022 and May 21st, 2024.This trial was registered with the Chinese Clinical Trial Registry, ChiCTR2200060900. A total of 1000 NPC patients with first-time radiotherapy or chemoradiotherapy for NPC were randomly assigned (1:3) to receive routine cure (the control group, n=250) or that with additional BQG (the treatment group, n=750). All patients received basic oral hygiene guidance, gargled the oral cavity with normal saline and flushed the nasal cavity with normal saline. The treatment group patients were instructed to take BQG twice daily from the initiation to the end of radiotherapy for 6 weeks. The primary end points were the incidence of nasopharyngeal secretion and the incidence of Oral Mucositis (OM). The second end points were the grade of nasal mucosal congestion, the Visual Analog Scale (VAS) score for sore throat pharyngeal pain, the grade of symptom in dry and burning throat, the incidence of nasal comorbidities, and the incidence of adverse events (AEs). **Results:** 731 patients in the treatment group and 250 patients in the control group completed the trial, baseline patient characteristics were similar. After six weeks, the incidence of severe nasopharyngeal secretion (grade middle or higher)in the treatment group was significantly lower as compared with the control group(12.4% vs 20.0%, P=0.0033). The incidence of severe OM (World Health Organization grade 3 or higher) was significantly lower in the treatment group than in the control group (12.3% vs 22.4%, P=0.0001). The intergroup rate difference and 95% CI of the incidence of OM between the two groups was -10.1% (-15.8%, -4.4%). The upper limit of the 95% CI was greater than -10%, so it could not be concluded that the experimental group was superior to the control group. However, compared with the control group, the treatment group showed a certain trend in reducing oral mucositis. The BQG group also remarkably reduced the incidence of severe VAS score for sore throat pharyngeal pain and the grade of symptom with dry and burning throat compared to the control group. The incidence of AEs were similar between the groups. **Conclusions:** BQG significantly attenuated the incidence of nasal secretions in NPC patients undergoing radiotherapy, improved pharyngeal pain and the symptoms with dryness and burning, with a good safety profile. Clinical trial information: ChiCTR2200060900. Research Sponsor: Supported by Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine Co., Ltd.

6015 Rapid Oral Abstract Session

Phase 2 open-label study of brentuximab vedotin (BV) + pembrolizumab (pembro) in patients (pts) with treatment (tx)-naive metastatic head and neck squamous cell carcinoma (HNSCC).

Cristina P. Rodriguez, Sylvia Lee, Graham Watson, Amanda Lynn Gillespie-Twardy, Douglas Earl Laux, Patrick J. Ward, Jeffrey Yorio, Omar Khaled Abughanimeh, J. Thaddeus Beck, Kevin Kim, Hailing Lu, Jason Berndt, Marya F. Chaney, Eeman Shaikh, Erin R. Alesi; Fred Hutchinson Cancer Center, Seattle, WA; US Oncology Network, The Woodlands, TX; University of Iowa Hospital and Clinics, Iowa City, IA; University of Nebraska Medical Center, Omaha, NE; Highlands Oncology, Springdale, AR; Pfizer Inc., New York, NY; Pfizer, Bothell, WA; Pfizer Inc., Bothell, WA; Merck & Co, Inc., Rahway, NJ; Virginia Commonwealth University Health System, Richmond, VA

Background: BV, an antibody-drug conjugate (ADC) targeting CD30, is hypothesized to deplete T regulatory cells (Tregs) that express CD30 and resensitize tumors to anti–PD-1 therapy. SGN35-033 (NCT04609566) is an ongoing multicohort study evaluating the efficacy and safety of BV + pembro in pts with solid tumors; we report results for cohort 6 in tx-naive HNSCC with PD-L1 combined positive score (CPS) ≥1, where pembro has historically demonstrated ORR of 19% and mPFS of 3.2 months. **Methods:** Cohort 6 included pts with metastatic HNSCC with PD-L1 CPS ≥1 by local testing and no prior therapy for metastatic disease or exposure to a PD-1/PD-L1 inhibitor. Pts received BV 1.8 mg/kg + pembro 200 mg every 3 wks. The primary endpoint was confirmed ORR assessed by investigator per RECIST 1.1. Secondary endpoints included DOR, PFS, and safety. Exploratory endpoints included OS and biomarker analyses. A genAI tool (01/02/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** As of 10/25/24, 32 pts received ≥1 dose of BV + pembro. In all pts, the confirmed ORR was 34% (95% CI, 18.6-53.2), with median follow-up duration of 9.7 mo and median DOR not reached (95% CI, 3.9 mo-not estimable [NE]). BOR is in the Table. Responses were seen regardless of HPV status and across PD-L1 CPS ≥1 subgroups, with responses in 11 of 32 (34%) vs 9 of 25 (36%) in CPS ≥1 vs CPS ≥20, respectively. The KM estimate of DOR ≥6 mo was 89%. Median PFS was 7.2 mo (95% CI, 3.2 mo-NE); 6-mo PFS rate was 56%. Biomarker analyses of peripheral blood showed that Tregs expressed relatively higher CD30 vs other T cells. There was a trend of Treg depletion and increased T-cell proliferation and activation after BV + pembro. Observed PK of BV when combined with pembro in HNSCC was similar to that of BV monotherapy. All pts had ≥1 tx-emergent adverse event (TEAE); 24 pts (75%) had a grade ≥3 TEAE; 10 pts (31%) had tx-related grade ≥3 TEAEs. The most common tx-related grade ≥3 TEAEs were lymphocyte count decreased (13%), ALT increased, fatigue, neutropenia, and neutrophil count decreased (6% each). Tx-related serious TEAEs were reported in 2 pts (6%). No new safety signals were identified. **Conclusions:** BV + pembro demonstrated promising clinical efficacy with a safety profile consistent with each individual agent in pts with tx-naive metastatic HNSCC with PD-L1 CPS ≥1. Biomarker analyses support the hypothesized immunomodulatory mechanism of action of BV + pembro. These encouraging data are consistent with prior findings in PD-1–refractory NSCLC and melanoma and support continued investigation of CD30-directed ADCs + anti–PD-1 therapy in solid tumors. Clinical trial information: NCT04609566. Research Sponsor: Pfizer.

	n=32
BOR, n (%)[a]	
Complete response	1 (3)
Partial response (PR)	10 (31)
Stable disease	12 (38)
PD	5 (16)

[a]1 pt (3%) had unconfirmed PR at data cutoff; 3 pts (9%) discontinued tx with no postbaseline response assessment.

6016 Rapid Oral Abstract Session

Randomized phase I trial of adjuvant personalized cancer vaccine TG4050 in resected locally advanced (LA) head and neck squamous cell carcinoma (HNSCC) patients (pts).

Christophe Le Tourneau, Jean-Pierre Delord, Olivier Lantz, Emmanuelle Dochy, Maurizio Ceppi, Clémentine Spring-Giusti, Katell Bidet Huang, Berangere Bastien, Annette Tavernaro, Gisele Lacoste, Per Brattas, Allan Devanadera, Hugues Fontenelle, Oliver Baker, Andrea Meiser, Christian H.H Ottensmeier; Department of Drug Development and Innovation (D3i), Institut Curie, Paris-Saclay University, Paris, France; IUCT-Oncopole, Toulouse, France; Laboratoire d'Immunologie, Institut Curie, Paris, France; Transgene SA, Illkirch-Graffenstaden, France; NEC OncoImmunity, Oslo, Norway; NEC Corporation, Tokyo, Japan; NEC Laboratories Europe GmbH, Heidelberg, Germany; The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom

Background: Approximately one third of pts with resected LA HNSCC recur. T-cells targeting tumor specific mutations drive anti-tumor immune responses. TG4050 is a viral-based personalized cancer vaccine, encoding up to 30 tumor-specific DNA sequences bearing in-silico predicted class I and class II epitopes. We hypothesized that TG4050 prime an adaptive immune response against tumor antigens and prevent relapse in pts with resected LA HNSCC after treatment with curative intent (NCT04183166). **Methods:** The multicenter, open label, randomized, 2-arm Phase I trial evaluated TG4050 in LA HNSCC pts achieving complete remission following surgery and adjuvant radiotherapy +/- chemotherapy. Pts were randomized to receive (Arm A) weekly doses of TG4050 for 6 weeks followed by a maintenance period of one dose every 3 weeks for up to 20 doses or no vaccine (Arm B, vaccination at relapse in combination with SOC). Safety, efficacy and immunogenicity were evaluated. In selected pts, exploratory characterization of the T cell response was performed using tetramer staining, bulk and single-cell (sc)TCR sequencing. **Results:** 33 pts were randomized between January 2021 and April 2023, 17 pts to Arm A and 16 pts to Arm B. Median age was 61 years (26-79 years), tumor location was oral cavity in 24 pts (72.7%), hypopharynx and oropharynx in 4 pts (12.1%), respectively and larynx in one pt (3.0%). TG4050 was safe and well tolerated with only grade 1 or 2 treatment-related adverse events (AEs). The most frequently reported were injection site reactions. After a median follow-up of 28.5 months, all 16 pts receiving TG4050 in Arm A remained disease-free whereas 3 out of 16 pts in Arm B relapsed. Disease Free Survival (DFS) data at 24 months for all patients will be presented. Exploratory qualitative analyses of the neoantigen-specific T cell response by ELISpot were presented previously. In-depth characterization of the neoantigen-specific T cells including clonal expansion by TCR sequencing and longitudinal analysis by tetramer staining will be presented. **Conclusions:** TG4050 is safe and induces immune responses in pts with resected LA HNSCC. No relapse occurred in the vaccine arm as opposed to 19% in the control arm. With the evolution of the landscape, adjuvant anti-PD1 therapy may become standard in resected LA HNSCC. TG4050 warrants further evaluation in combination with anti-PD1 therapy in phase III trials. Clinical trial information: NCT04183166. Research Sponsor: None.

6017 Rapid Oral Abstract Session

Ficerafusp alfa with pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: Updated results from an expansion cohort of an open-label, multicenter, phase 1/1b trial.

Christine H. Chung, Glenn J. Hanna, Dan Paul Zandberg, Deborah J.L. Wong, Eric Jeffrey Sherman, Assuntina G. Sacco, Tamara A. Sussman, Alberto Hernando Hernando-Calvo, Ralf Reiners, David Bohr, Rachel Salazar, Brenda O'Connell, David Raben, Jeltje Schulten, John M. Kaczmar; Moffitt Cancer Center and Research Institute, Tampa, FL; Center for Head & Neck Oncology, Dana-Farber Cancer Institute, Boston, MA; UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; UCLA Medical Center, Los Angeles, CA; Memorial Sloan Kettering Cancer Center, New York, NY; UC San Diego Moores Cancer Center, La Jolla, CA; Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain; Bicara Therapeutics, Cambridge, MA; Bicara Therapeutics, Boston, MA; BICARA Therapeutics, Boston, MA; Hollings Cancer Center, Medical University of South Carolina, Charleston, SC

Background: HPV-negative head and neck squamous cell carcinoma (HNSCC) is an aggressive disease characterized by high recurrence, metastasis (R/M), and resistance to standard treatments. While anti–PD-1 therapies have improved outcomes, the prognosis for R/M HNSCC remains poor, necessitating novel approaches to achieve deeper, more durable responses and improved overall survival (OS). Ficerafusp alfa is a first-in-class bifunctional antibody targeting EGFR and TGF-β. **Methods:** This single-arm, multicenter, dose expansion of an ongoing phase 1/1b study (NCT04429542) enrolled patients (pts) aged ≥18 years with treatment-naive, unresectable R/M HNSCC, with a CPS ≥1. Pts received ficerafusp alfa (1500 mg IV on days 1, 8, and 15) combined with pembrolizumab (200 mg IV on day 1) every 21 days. Study objectives included objective response rate (ORR) per RECIST v1.1, duration of response (DOR), progression-free survival (PFS), OS, safety (CTCAE v5), and pharmacodynamic analyses. This report presents updated findings after two years of follow-up. **Results:** As of December 16, 2024, 42 pts were treated (71% male, median age: 63 years [range: 31–84]); 39 were efficacy evaluable (EE). Among the EE pts, the ORR was 54% (21/39; 95% CI: 37–70) in the overall cohort and 64% (18/28; 95% CI: 44–81) in HPV-negative pts. Notably, 21.4% of HPV-negative pts achieved a complete response (CR). A confirmed durable response of ≥6 and ≥12 months was observed in 72% (13/18) and 56% (10/18) of overall and 73% (11/15) and 60% (9/15) of HPV-negative responders, respectively. Median PFS was 7.4 months (95% CI: 2.9–14.5 overall, and 9.8 months (95% CI: 4.4–23.2) in the HPV-negative subgroup. The 12-month OS rate was 61.5% (95% CI: 44.5–75.7) across the cohort and 60.7% (95% CI: 40.4–76.0) for HPV-negative pts. At data cutoff, all evaluable pts had been followed for at least 20 months. Median OS and DOR had not been reached yet in HPV-negative pts, with mOS surpassing 20 months. Safety findings were consistent with the known safety profile of ficerafusp alfa plus pembrolizumab, while pharmacodynamic analyses demonstrated encouraging post-treatment downregulation of pSMAD2 supporting targeted TGF-β inhibition. **Conclusions:** Ficerafusp alfa combined with pembrolizumab continues to show promising efficacy relative to historical data on the current standard of care, particularly in HPV-negative HNSCC. Median PFS and 12-month OS, ORR, and CR rates are encouraging relative to historical benchmarks in pts with HPV-negative HNSCC. 24-month OS and mature OS/DOR outcomes are anticipated. These findings provide compelling rationale for FORTIFI-HN01, the ongoing multicenter, randomized, double-blind phase 2/3 clinical trial evaluating this combination in first-line PD-L1–positive, HPV-negative R/M HNSCC. Clinical trial information: NCT04429542. Research Sponsor: Study funded by Bicara Therapeutics Inc. with access to pembrolizumab in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (NCT04429542).

6018 Rapid Oral Abstract Session

Neoadjuvant PD-1 inhibitor combined with Nab-paclitaxel and cisplatin in resectable locally advanced head and neck squamous cell carcinoma (NCT05522985): A randomized, controlled, open label, phase II clinical trial.

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Background: More than 60% of head and neck squamous cell carcinoma (HNSCC) patients (pts) were locally advanced at diagnosis. Many previous clinical trials have confirmed that induction chemotherapy can improve the functional retention rate of HNSCC and improve the quality of life. However, pts have no long-term survival benefits from it. In recent years, immunotherapy has brought hope for long-term survival to pts with recurrent and metastatic HNSCC. The exploration of neoadjuvant immunotherapy in HNSCC is also gradually carried out. **Methods:** This was a randomized, controlled, open label, phase II study. 122 pts were panned to enrolled. Key inclusion criteria: pts aged ≥18 years; histologically or cytologically confirmed stage III or IV resectable HNSCC; without prior system anticancer therapy; ECOG≤1. Eligible pts were randomized 1:1 to receive toripalimab (240mg, D1, q3w) in combination with nab-paclitaxel (260 mg/m2,d1,q3w) and cisplatin (75mg/m^2,q3w) for 3 cycles (experimental arm) or nab-paclitaxel (260 mg/m^2,d1,q3w) and cisplatin (75mg/m^2, q3w) for 3 cycles (control arm). Then surgery and pathological remission evaluation was performed. The primary endpoint was pathologic complete response (pCR) rate. Secondary endpoints were major pathological response (MPR), objective response rate (ORR), 2-year progression-free survival (PFS) rate, 2-year overall survival (OS) rate, and safety. **Results:** A total of 122 pts were enrolled (experimental 61, control 61). Median age was 59.5 years (range: 34–83) and 80.33% were male. After neoadjuvant treatment, 88 pts underwent surgery (experimental 45, control 43). pCR rate was significantly different between the two arms (experimental 57.78%, control 34.88%, p = 0.03). More pts achieved MPR (experimental 82.22%, control 53.46%, p = 0.004) in experimental arm. In experimental arm, 2-year DFS (experimental 86.67%, control 71.95%) and 2-year OS (experimental 90.61%, control 77.74%) were higher, the statistical significance was undetermined. The proportion of Grade ≥3 treatment-related adverse events (TRAEs) in the experimental and control arms were 16.39% and 9.84%, respectively. The most common TRAEs are Agranulocytosis, Nausea, Alopecia and Vomiting. No new safety signals were observed and no TRAEs leading to death. There was no significant difference in TRAEs of two arms. **Conclusions:** Comparing to chemotherapy, neoadjuvant immunochemotherapy can significantly improve the pCR and MPR rate of HNSCC. Moreover, adverse events are controllable. And immune neoadjuvant therapy demonstrates a trend towards improving survival. Clinical trial information: NCT05522985. Research Sponsor: None.

6019 Rapid Oral Abstract Session

An open-label, phase Ib trial of the SIRPα inhibitor BI 765063 in combination with the PD-1 inhibitor ezabenlimab and cetuximab in patients (pts) with head and neck squamous cell carcinoma.

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Background: BI 765063 is a first-in-class, humanized IgG4 monoclonal antibody that binds the V1 allele of signal regulatory protein α (SIRPα) and blocks the 'don't eat me' signal of the SIRPα/CD47 axis. This leads to reactivation of innate antitumor responses, restoring phagocytosis and antigen presentation. In a Phase Ia/Ib trial in pts with advanced solid tumors (NCT03990233), BI 765063 ± ezabenlimab was well tolerated with no dose-limiting toxicities and preliminary efficacy was observed (Kotecki et al, ESMO 2021). This Phase Ib study (NCT05249426) is investigating the efficacy and safety of BI 765063 in combination with ezabenlimab + cetuximab (Cohort A) or ezabenlimab + chemotherapy (Cohort B) in pts with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), or in combination with ezabenlimab ± BI 836880 (anti-VEGF/Ang2) in pts with hepatocellular carcinoma. Here, we focus on pts with HNSCC who received BI 765063 combined with ezabenlimab + cetuximab (Cohort A). **Methods:** In Cohort A, adult pts with R/M HNSCC who had received 1 previous systemic therapy (excluding immune checkpoint inhibitors) were eligible. Other inclusion criteria included SIRPα V1/V1 homozygosity (detected in plasma), ≥1 measurable lesion (RECIST v1.1) and ECOG performance status of 0/1. Pts received BI 765063 (24 mg/kg every 3 weeks [q3w]), ezabenlimab (240 mg q3w) and cetuximab (per local guidelines). Primary endpoint was confirmed objective response (OR; RECIST v1.1). Secondary endpoints included disease control (DC) and treatment-emergent adverse events (TEAEs). **Results:** At data cut-off (Dec 2, 2024), 18 pts had been enrolled to Cohort A and received BI 765063 plus ezabenlimab + cetuximab (1 pt was subsequently found to be ineligible). Of the 17 eligible pts, median age was 51 years (range, 33–81), 88% were male and all had received 1 prior therapy. Eight pts (47%) achieved a confirmed OR (3 complete and 5 partial responses) and a further 7 (41%) achieved stable disease to give a DC rate of 88%. Median duration of DC was 7.6 months. TEAEs were reported in all 17 pts. Most common TEAEs were acneiform dermatitis (any grade/grade ≥3, 53%/0%), anemia (35%/24%), hypokalemia (29%/6%), hypothyroidism (29%/0%) and rash (29%/0%). Most common BI 765063 treatment-related AEs (TRAEs) were hypothyroidism (24%) and acneiform dermatitis (18%), all grade 1/2. Grade 3 TRAEs (asthenia, cardiac failure, epistaxis, hypoalbuminemia, lymphopenia, mouth hemorrhage, post-procedural hemorrhage and suspected drug-induced liver injury) were each reported in 1 pt. There were no grade 4/5 TRAEs. **Conclusions:** These preliminary data indicate that BI 765063 in combination with ezabenlimab and cetuximab has a manageable safety profile and promising efficacy as second-line treatment in pts with R/M HNSCC. Biomarker data will be presented at the meeting. Clinical trial information: NCT05249426. Research Sponsor: Boehringer Ingelheim.

6020 Rapid Oral Abstract Session

Dose expansion data from iintune-1, a phase 1/2 study of the STING agonist dazostinag plus pembrolizumab as first-line (1L), in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (RM-SCCHN).

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Background: Checkpoint inhibitors (CPIs) such as pembrolizumab (pembro) can lead to improved outcomes and durable responses in patients (pts) with RM-SCCHN. However, only a subset of pts with RM-SCCHN experience this benefit, and an unmet need for better treatments remains. STimulator of INterferon Genes (STING) agonism enhanced the response to CPIs preclinically. Dazostinag (dazo) is a small molecule STING agonist that has shown antitumor activity and activation of innate and adaptive immune responses in pts with solid tumors in the dose escalation part of iintune-1, with a recommended dose for expansion of 5 mg in combination with pembro. We report data from the ongoing dose expansion cohort 2A of iintune-1 in the first 30 pts with incurable 1L RM-SCCHN with a PD-L1 combined positive score (CPS) ≥1, treated with dazo in combination with pembro (NCT04420884). **Methods:** Pts receive dazo 5 mg IV on Days 1, 8, 15 plus pembro 200 mg IV on Day 1, in 21-day cycles. Primary endpoints are safety and tolerability. Secondary endpoints include investigator-assessed overall response rate (ORR) per RECIST 1.1 and duration of response (DOR). Dose optimization is planned as part of expansion. **Results:** As of Dec 16, 2024, 30 pts had been enrolled and received treatment. Median age was 64 years and 73% of pts were male. The most common primary tumor locations were oral cavity (n=10, 33%), oropharynx (n=8, 27%), and larynx (n=6, 20%). Median CPS score was 13.5 (range, 1–101). A median of 4.5 treatment cycles (range 1–15) were received. Treatment-emergent adverse events (TEAEs) occurred in all pts (grade ≥3 in 37%); the most common were fatigue (40%), nausea (27%), cough (23%), and headache (20%). Dazo-related TEAEs occurred in 80% of pts (grade ≥3 in 13%); the most common was fatigue (30%). Cytokine release syndrome was reported in 4 pts (13%; all dazo-related and grade 1–2). TEAEs led to dazo discontinuation in 1 pt. No treatment-related deaths were reported. Among 29 response-evaluable pts, 1 had a confirmed complete response and 7 had confirmed partial responses (+2 unconfirmed), for an ORR of 34%. Median DOR was not reached. Pharmacodynamic analyses revealed biomarker changes consistent with the expected mechanism of action and dose escalation data, including induction of a STING gene signature, cytokine induction, peripheral immune cell activation and CD8+ T cell recruitment to the tumor. Analyses of changes in peripheral ctDNA pre- and post-treatment are ongoing. **Conclusions:** This early study of dazo 5 mg IV in combination with pembro showed a manageable safety profile with an encouraging ORR in pts with RM-SCCHN. Pharmacodynamic findings demonstrate peripheral and intratumor changes consistent with STING agonism. Clinical trial information: NCT04420884. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA), Lexington, MA.

6021 Poster Session

Real world utilization of comprehensive genomic profiling (CGP) in head and neck squamous cell carcinoma (SCCHN).

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Background: In Head and Neck Cancer, practice trends of utilizing comprehensive genomic profiling (CGP) vary depending on physician preference and test availability. Here, we examined the impact of CGP on treatment decision-making and patient outcomes in SCCHN at a single institution. **Methods:** Patients with suspected SCCHN underwent tumor-based CGP using the UCSF500 or TEMPUS xT NGS panel. In addition to demographic and clinicopathologic data, we obtained the reason for CGP when noted, disease stage and line of therapy at the time of CGP, CGP results, and post-CGP treatments. OncoKB was used to annotate actionable mutations in Head and Neck Cancer, in addition to other biomarkers when available (microsatellite instability (MSI), tumor mutation burden (TMB), and EGFR amplification). **Results:** Between January 2016 and December 2023, 301 unique patient tumor specimens underwent CGP in the setting of suspected or known SCCHN. Sequencing was performed to refine a diagnosis in 57 samples (18.9%). CGP influenced the determination between cutaneous and mucosal primary in 35 samples, clarified the histology in 9, and clarified the origin of a metastatic lesion in 13. For patients with confirmed SCCHN (N = 246), CGP was performed for therapy selection in 193 (78.5%) of patients. Of these, 19 (9.8%) patients were TMB-high (TMB>10), 2 (1.0%) patients were MSI-high, 77 (39.9%) patients were found to have actionable genomic alterations, and clinicians had access to OncoKB-specified agents for 50 (25.9%) of the patients. Anti-PD-1 antibody therapy was administered to 15/20 (75%) of TMB-high and/or MSI-high patients compared to 38 (53.5%) with low TMB or MSI-stable disease. The most common actionable individual gene alterations were in *CDKN2A* (37.3%), *PIK3CA* (14.5%), *PTEN* (7.2%), *FBXW7* (6.0%), and *HRAS* (6.0%) genes. Six of 77 (7.8%) patients with actionable genomic alterations received targeted therapy based on drug availability and the clinical discretion of the treating physician.In these, the overall response rate was 50% (3/6), and the median PFS was 2.6 months. Thus, at this site, the number needed to treat to gain one response in SCCHN patients undergoing sequencing for oncogene-targeted options was 64.5 patients. **Conclusions:** CGP in HNSCC was used most commonly to increase diagnostic accuracy, often providing diagnostic information that guided therapeutic decision-making. It was used infrequently for therapy selection, but in the few patients selected for targeted therapy based on NGS, objective responses were observed. Research Sponsor: None.

6022 Poster Session

Pembrolizumab plus nab-paclitaxel and platinum as first-line treatment in patients with recurrent or metastatic nasal cavity and paranasal sinus squamous-cell carcinoma: A prospective phase II study.

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Background: Patients with recurrent or metastatic sinonasal squamous-cell carcinoma (R/M SNSCC) lack standardized systemic treatment protocols and prospective studies. While pembrolizumab with platinum and fluorouracil is established as first-line treatment for R/M head and neck squamous-cell carcinoma, and its combination with carboplatin and paclitaxel shows promise, we evaluated the efficacy and safety of pembrolizumab with nab-paclitaxel and platinum in R/M SNSCC. **Methods:** This is a single-arm phase 2 study, patients with R/M SNSCC received pembrolizumab 200mg, nab-paclitaxel 260mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin AUC5 on day 1 every 21 days for up to six cycles followed by pembrolizumab maintenance therapy until progression or unacceptable toxicity or 35 cycles, whichever occurred first. The primary endpoint was objective response rate (ORR). Secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and safety. Immunohistochemistry and high-resolution sequencing of the tumor samples were performed. **Results:** From 10 March 2022 to 31 October 2024, 20 patients were enrolled. The ORR was 60% (95%CI: 0.36-0.81) and two patients (2/20, 10%) achieved CR. The DCR was 100%. Median follow-up was 18.05 months(range:5.2-31.7), with a median PFS of 12.2 months (95% CI: 9 months-not estimated) and an unreached median OS. Patients with PD-L1 CPS $\geq$20 exhibited better ORR (80% vs 28.6%, p=0.144), median PFS (not reached vs 7 months, p=0.0137), and median OS (not reached vs 17.8 months, p=0.0401) compared to those with PD-L1 CPS $<$ 20. ORR was 50% (2/4) in HPV-positive patients and 53.8% (7/13) in HPV-negative patients. The most common genetic alterations were TP53, EGFR, CDKN2A mutations and amplifications in the 11q13 region (including CCND1, FGF19, FGF4, and FGF3 genes). Median TMB was 4 mut/Mb (range 2-13), with no significant difference observed between responders and non-responders. Grade 3/4 Treatment-Related Adverse Events (TRAEs) only accounted for 30% (6/20), and all come from hematologic toxicity. Hypothyroidism was the most common irAEs (12/20, 60%). **Conclusions:** Pembrolizumab plus nab-paclitaxel and platinum shows promising antitumor activity and manageable safety in first-line R/M SNSCC patients. Clinical trial information: ChiCTR2200057343. Research Sponsor: Beijing Hope Run Special Fund of Cancer Foundation of China; LC2022A30; CAMS Innovation Fund for Medical Sciences (CIFMS); 2023-I2M-C&T-B-072; Capital's Funds for Health Improvement and Research; 2024-2-40212.

6023 Poster Session

Phase 2 trial of dual EGFR inhibition with cetuximab and afatinib in patients with recurrent/metastatic head and neck squamous cell cancers (HNSCC).

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Background: Cetuximab is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) but its clinical activity is limited by resistance mechanisms. Our previous HNSCC trial of chemotherapy, cetuximab and erlotinib demonstrated a 62.5% objective response rate (ORR) including 2 durable complete responses (CR), with greater inhibition of phosphorylated EGFR in post-treatment biopsies. Because human epidermal growth factor receptor (HER)-2 and HER3 are overexpressed in cetuximab-resistant HNSCC, we postulated that the combination of cetuximab and afatinib, an irreversible, pan-HER inhibitor, would overcome resistance by inhibiting EGFR/HER dimers and inhibiting nuclear translocation and resulting non-canonical EGFR activities in R/M HNSCC. **Methods:** The primary objective of this single-arm phase II trial was ORR to the combination of cetuximab and afatinib in patients with R/M HNSCC refractory to platinum-based chemotherapy and/or immune checkpoint therapy. Cetuximab was administered at standard doses weekly/bi-weekly. Afatinib was initially dosed at 40 mg orally daily, amended to 30 mg orally daily after 25 patients, to improve tolerability. Key secondary endpoints were median progression-free survival (mPFS), median overall survival (mOS) and toxicity. Radiographic tumor assessment was performed, using RECIST version 1.1 every 8 weeks. Biopsy was obtained at baseline, 4 weeks after treatment initiation and at end of treatment, where medically feasible. **Results:** The study protocol was approved by the institutional review board and written informed consent was obtained from all participants. Fifty patients were enrolled between 7/3/2017 and 10/16/2024 at Yale Cancer Center, 47 were evaluable for response. Median age was 63 years (range 43-81 years), 39 (83%) were male, 21 (44.7%) had p16 positive tumors, 26 (55.3%) were p16 negative. Most common primary tumor location was oropharynx (n, %: 21, 44.7). ORR was 23.4% (2 complete responses, 9 partial responses, 95% CI: 12.3%-38%) for the entire population, 10 responses were in p16- patients (ORR 38.5%) and 1 response (4.8%) in a patient with p16+ disease. Median PFS was 3.8 months (95% CI: 2.1-not reached) for p16- patients and 1.8 months (95% CI: 1.7-8.9) for p16+ patients. Median OS was 7.5 months (95% CI: 4.8-12). Commonest adverse events (n, %) were diarrhea (19, 40), anemia (17, 36) rash (14, 30) and fatigue (13, 28). Correlative analyses are underway. **Conclusions:** This trial of dual EGFR targeting demonstrated high clinical efficacy, especially in the p16- population. Adverse events were consistent with those associated with EGFR inhibitor treatment. Clinical trial information: NCT02979977. Research Sponsor: NCCN; Boehringer Ingelheim.

6024 Poster Session

Petosemtamab (MCLA-158) with pembrolizumab as first-line (1L) treatment of PD-L1+ recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC): Phase 2 trial.

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Background: EGFR is a known oncogenic driver in HNSCC, and the leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) is associated with cancer stem cells in solid tumors and expressed in HNSCC. Petosemtamab is a human, common light chain, IgG1 bispecific antibody with ADCC-enhanced activity, targeting EGFR and LGR5. Promising interim data from this phase 2, single-arm trial of petosemtamab 1500 mg every 2 weeks (Q2W; 28-day cycles) with pembrolizumab (400 mg Q6W) as 1L treatment in PD-L1+ HNSCC (NCT03526835) demonstrated a 67% overall response rate (ORR) in 24 efficacy evaluable patients (pts) [Fayette, ASCO 2024]. **Methods:** Primary endpoints are investigator-assessed ORR (RECIST v1.1) and safety. Secondary endpoints include duration of response (DOR), progression-free survival (per investigator), and overall survival (OS). Key eligibility criteria were r/m HNSCC with no prior systemic therapy in the r/m setting, PD-L1 combined positive score ≥1, ECOG PS 0–1, measurable disease, and primary tumor location in oropharynx (regardless of p16 status), oral cavity, hypopharynx, or larynx. **Results:** A total of 45 pts were treated; as of a September 16, 2024 data cutoff, 18 pts continuing on therapy. Median age was 64 years (range 23–80), ECOG PS 0/1 in 16/29 pts, and 78% were male. The most frequent primary tumor locations were oropharynx (31%), oral cavity (31%), larynx (16%), and hypopharynx (11%). A median of 8 cycles (range 1–17) were administered. Among 43 pts evaluable for efficacy (pts with ≥1 dose and ≥1 post-baseline scan, or who discontinued early due to progressive disease or death), the ORR was 60% (26/43) with 5 complete responses; median DOR was 11 months with 17 responders still on treatment at data cutoff. Of the 8 pts with p16+ oropharyngeal disease, 4 had confirmed responses (ORR 50%). The median follow-up for OS was 9.6 months; median OS was not reached. Kaplan–Meier estimate of OS at 6 months was 93%. The combination was well tolerated, and no significant overlapping toxicities were observed. Treatment-emergent adverse events (AEs) were reported in 45 pts, most were Grade (G) 1 or 2 in severity; one previously reported unrelated G5 AE occurred. The most frequent AEs (all G/G≥3) were acneiform dermatitis (49%/7%), asthenia (49%/7%), and rash (44%/0%). Infusion-related reactions (composite term) were reported in 38% (all G) and 7% (G3) of pts, mainly occurred at first infusion, and all resolved. Updated data to be presented. **Conclusions:** Petosemtamab, a first-in-class EGFR x LGR5 bispecific antibody, in combination with pembrolizumab continues to demonstrate promising clinical efficacy and a well-tolerated safety profile as 1L treatment for pts with r/m PD-L1+ HNSCC. A global phase 3 trial, LiGeR-HN1 (NCT06525220), is ongoing to evaluate petosemtamab in combination with pembrolizumab in 1L PD-L1+ r/m HNSCC. Clinical trial information: NCT03526835. Research Sponsor: Merus N.V.

Using longitudinal spatial-omics to demonstrate in-situ Epstein-Barr virus reduction in responders to immunotherapy treated nasopharyngeal cancer.

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Background: Epstein-Barr virus (EBV) related nasopharyngeal cancer (NPC) is endemic in Southern China and Southeast Asia. Limited studies of tumor-immune microenvironment (TIME) modulated by dual checkpoint inhibitors (CPI) exist in relation to intratumoral EBV viral load. **Methods:** Spatial-omic analysis on longitudinally collected fresh frozen tissue from a phase 2 study of nivolumab/ipilimumab in NPC (NCT03097939) was done. Serial sections (10 μm) were cut for both H&E staining, and Stereo-seq assay (BGI, USA) that uses DNA nanoballs to capture mRNA which is amplified & reverse transcribed into cDNA, and then sequenced to a depth of 1 billion reads. Sequencing data was mapped to the human genome GRCh38.p14 and EBV-1 genome to identify Unique Molecular Identifiers (UMI), summarized into BIN100 niches (50μm by 50μm), processed into counts per million (CPM) and normalized for analysis. Cell type composition was estimated for each BIN100 using EBV+ NPC scRNA-seq datasets and *cell2location*. EBV viral load and the proportions of different cell types were associated with pre/post CPI in responders (R) and non-responders (NR) using Generalized Estimation Equation to account for repeated measures in the same slide. Colocalizations of different cell types within each BIN100 were also evaluated, adjusting for cell type proportions across all samples. P-value < 0.05 on two sided testing was considered statistically significant. **Results:** Samples were collected at baseline pre-treatment, and 2 weeks into treatment, and associated with clinical response. Although 21/40 patients were biopsied, only 7 pairs of pre- and on-treatment samples (3R vs 4NR) had sufficient tissue quality for analysis. The most abundant EBV genes were RPMS1, EBNA1.1, LMP2B, LMP2A, and LMP1 (using mean expression). In pre/post treatment comparisons, the EBV viral load significantly reduced in R, as reflected by EBNA1.1 (p=4.9E-11) and LMP2A (p=7.4E-23), controlling for the proportion of epithelial cells (EC), but it did not change in NR. In R, a significant reduction of B cells (p=8.2E-71) and increase of myeloid (p=1.3E-3) and natural killer cells (p=3.1E-3) was observed, while no changes in cell composition were seen in NR. Colocalization analysis of EC with two immune cell (IC) types, CD4+ T cell and CD8+ T cell, identified significantly increased colocalization only in NR (CD4+ T cell: p=4.1E-7; CD8+ T cell: p=4.6E-4), suggesting IC infiltration is induced by CPI in NR but insufficient for cell kill. **Conclusions:** This is the first study to suggest intratumoral viral transcriptional activity reflected by reduction in EBNA1.1 and LMP2A on CPI treated NPC correlates with response and changes in immune cell composition and colocalization. Validation of these findings at protein level using multiplex IHC/IF and spatial analysis of the virus and epithelial/immune cell neighborhood is being completed. Clinical trial information: NCT03097939. Research Sponsor: A*STAR Biomedical Engineering Programme; C211318003; National Medical Research Council (NMRC), Singapore; MOH-001448-00; National Medical Research Council (NMRC), Singapore; MOH-000323; National Medical Research Council (NMRC), Singapore; OFLCG18May-0028; National Medical Research Council (NMRC), Singapore; NMRC OF-LCG-18May-0028; Ministry of Health, Singapore.

Cetuximab plus dalpiciclib in patients with HPV-negative, anti-PD-1-resistant recurrent or metastatic head and neck squamous cell carcinoma.

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Background: Human papillomavirus (HPV)-negative head and neck squamous cell carcinoma (HNSCC) is characterized by hyperactivation of the cyclin-dependent kinase 4/6 (CDK4/6) pathway. As immunotherapy has become the first-line treatment for HNSCC, resistance to anti-programmed death-1 (PD-1) agents has emerged as a pivotal challenge. This phase II study evaluated the efficacy and safety of dalpiciclib, a CDK4/6 inhibitor, combined with cetuximab in patients with anti-PD-1-resistant, HPV-negative recurrent or metastatic (R/M) HNSCC. **Methods:** Patients diagnosed with p16-negative R/M HNSCC resistant to first-line anti-PD-1 therapy and cetuximab-naïve were enrolled. Patients received oral dalpiciclib 150 mg daily for 21 consecutive days and intravenous cetuximab (400 mg/m^2 on day 1 of cycle 1, followed by 250 mg/m^2 weekly) in 28-day cycles. The primary endpoint was the objective response rate (ORR). Secondary endpoints included safety, progression-free survival (PFS), and overall survival (OS). Simon's two-stage design was used, with study termination planned if ≤1 response was observed among the first 14 patients. If met, an additional 12 patients were enrolled. **Results:** A total of 28 patients were enrolled, with a median age of 58 years (range 30-75 years). Among 28 evaluable patients, 3 had disease progression, 6 had stable disease, and 19 achieved partial response. The ORR was 67.9% (95% confidence interval [CI], 49.0%-82.0%), and the disease control rate was 89.3% (95% CI, 72.0%-97.0%). As of December 31, 2024, 9 patients remained on treatment. With a median follow-up of 7.34 months, the median PFS was 5.3 months (95% CI, 1.33-9.27), and the median OS was 17.0 months. Treatment-related adverse events (TRAEs) occurred in all patients, predominantly grade 1-2. The most common TRAEs were neutrophil count decreased (25/28, 89.3%), white blood cell count decreased (25/28, 89.3%), and acneiform rash (16/28, 57.1%). Grade 3 TRAEs included neutrophil count decreased (9/28, 32.1%) and white blood cell count decreased (9/28, 32.1%). No grade 4/5 TRAEs were observed. **Conclusions:** Dalpiciclib combined with cetuximab was well-tolerated and demonstrated potentially favorable efficacy in patients with anti-PD-1-resistant, HPV-negative R/M HNSCC. Clinical trial information: NCT05721443. Research Sponsor: Clinical Research Special Project of Shanghai Municipal Health Commission.

6027 Poster Session

Analysis of gene mutations, TMB, and PD-L1 in relation to ICI response in HNSCC.

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Background: Immune checkpoint inhibitors (ICI) have changed the treatment of incurable advanced, recurrent, or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Yet only a subset of patients respond, and predicting response remains challenging. We analyzed tumor genomic profiles and PD-L1 expression in a retrospective cohort of R/M HNSCC patients treated with ICI to evaluate the association with treatment response. **Methods:** We evaluated a single-institution cohort of 119 patients with R/M HNSCC treated with PD-1 inhibitors as monotherapy or in combination with palliative radiotherapy or chemotherapy, and who had genomics tested in tumor (tDNA) and/or in blood (ctDNA) samples. We analyzed clinical characteristics, treatment outcomes, PD-L1 expression, tumor mutation burden (TMB), and genomic profiles. Treatment response was assessed using iRECIST criteria. Responders were defined as complete response (CR), partial response (PR) $\geq$ 6 months, or stable disease (SD) $\geq$1 year. TMB and tDNA were tested by FoundationOne and ctDNA by Guardant. PD-L1 IHC used DAKO 22C3 antibodies. **Results:** Of 119 patients, 43 (36.1%) were considered responders (24 CR, 11 PR, and 8 SD $\geq$ 1 year). 97 patients had tDNA and TMB and 93 patients had ctDNA tested. 91 patients had PD-L1 results. In binary analysis, TMB $\geq$ 10 was significantly associated with response (P = 2.15e-5), while PD-L1 $\geq$ 20 was not (P = 0.83). A combined analysis of tDNA and/or ctDNA evaluated 273 genes. Univariate analysis showed that mutations in DNMT3A (P = 0.005), RET (P = 0.021), FAM123B (P = 0.021), and KDM6A (P = 0.043) were significantly associated with response. In a Lasso Logistic Regression model of the 27 most frequently mutated genes, 7 genes were significantly mutated in responders: DNMT3A (P = 0.0001), MAP2K4 (P = 0.025), FANCA (P = 0.036), ASXL1 (P = 0.019), EGFR (P = 0.0008), STK11 (P = 0.022), and BARD1 (P = 0.042), while TP53 was significantly mutated in non-responders (P = 0.010). Adding TMB to the multivariate model retained the significant association of DNMT3A (P = 0.021) and MAP2K4 (P = 0.015) mutations with response, and included ERBB4 (P = 0.037) mutations and TMB (P = 0.001) as additional significant indicators of response. DNMT3A was mutated only in responders (4 CR and 1 PR), with a positive predictive value of 1.00 and a negative predictive value of 0.74. In the multivariate analyses for tDNA and ctDNA, DNMT3A remained the only gene mutation significantly associated with response (P = 0.004 and P = 0.012). **Conclusions:** In this cohort of 119 patients with R/M HNSCC treated with PD-1 inhibitors, TMB, but not PD-L1, was associated with treatment response in univariate and multivariate analysis. Multivariate models identified eight genes significantly associated with treatment response. DNMT3A was the most remarkable gene, consistently associated with response in univariate and multivariate models. Further, larger studies are needed to validate these findings. Research Sponsor: None.

6028 Poster Session

Personalized biomarker-based treatment strategy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: Results of the biomarker-driven cohorts of the EORTC-HNCG-1559 trial (UPSTREAM).

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Background: Platinum-refractory recurrent/metastatic squamous cell carcinoma (R/M SCCHN) has a poor prognosis. Several molecular pathways are dysregulated in SCCHN, providing potential targets for treatment. The UPSTREAM trial aimed to develop a personalized treatment strategy for R/M SCCHN. **Methods:** UPSTREAM was a biomarker-driven umbrella trial for post-platinum R/M SCCHN, investigating the activity of targeted agents in patients (pts) with tumors harboring pre-defined biomarker(s) identified on a fresh biopsy. Five biomarker-driven (B) cohorts were conducted as distinct phase 2 trials. The first 4 cohorts focused on p16-negative disease: cohort B1 investigated afatinib in pts with *EGFR* amp/mut and/or *HER2* amp/mut and/or PTEN high; cohort B2 investigated afatinib in cetuximab-naïve pts; cohort B3 investigated palbociclib in pts with *CCND1* amp and cohort B4 investigated niraparib in platinum-sensitive disease. Cohort B5 investigated niraparib in p16 positive oropharyngeal carcinoma. Cohorts B1, B2 and B3 were randomized (versus physician's choice of treatment) with progression-free survival rate at 16 weeks (PFSR 16W) as primary endpoint. Cohorts B4 and B5 were single-arm trials with objective response rate (ORR) over the first 16 weeks as primary endpoint. **Results:** A total of 250 pts were enrolled in UPSTREAM across 5 European countries, of whom 152 were allocated to a biomarker-driven cohort. Only B1 met its primary endpoint. In B1 (n=38 under afatinib), the PFSR 16W was 34.2%. B2 cohort experienced slow recruitment, with only 8 patients treated with afatinib, the PFSR 16W was 12.5%. In B3 (n=12 under palbociclib), PFSW 16W was 16.7%. In B4 (n=28) and B5 (n= 33), the ORR with niraparib was 3.6% (1/28) and 6.1% (2/33), respectively. More detailed results are shown in the table. **Conclusions:** UPSTREAM demonstrated the feasibility of conducting a biomarker-driven clinical trial in R/M SCCHN. The clinical activity observed across the biomarker-driven cohorts is limited. Potential explanations for these results include the absence of clearly identified high-level drivers in SCCHN, the limited evidence supporting some biomarkers (mainly derived from genomic data), and the use of single-agent treatment approaches. These findings highlight the need for further research to identify and refine biomarkers to explore new treatment strategies. Clinical trial information: NCT03088059. Research Sponsor: Boehringer Ingelheim; Pfizer; GSK.

Cohort	Biomarker	Drug	N evaluable patients	ORR	Median PFS (months)	Median OS (months)
B1	p16- and *EGFR* amp/mut or *HER2* amp/mut or PTEN high	afatinib	38	10.5%	2.2	7.2
		physician's choice	17	5.9%	2.4	5.0
B2	p16- and cetuximab-naïve	afatinib	8	0%	2.6	10.7
		physician's choice	4	0%	4.0	4.0
B3	p16- and *CCND1* amp	palbociclib	12	8.3%	1.9	4.3
		Physician's choice	6	0%	1.9	5.1
B4	p16- and platinum-sensitive	niraparib	28	3.6%	2.0	6.8
B5	P16 pos OPC	niraparib	33	6.1%	1.8	6.9

6029 Poster Session

Retlirafusp alfa-a bifunctional anti-PD-L1/TGF-βRII agent plus nab-paclitaxel and carboplatin in pre-treated recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): A prospective, single-arm, phase II clinical trial.

Dongmei Ji, Xin Liu, Yanjin Guo, Yanan Yang, Youzhou Sang, Guangliang Chen, Shu Dong, Yulong Wang, Xiayun He, Hongmei Ying, Xueguan Lu, Yu Wang, Chaosu Hu, Changhong Zhao, Jiahuan Zhou, Qinghai Ji; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Fudan University Shanghai Cancer Center; Shanghai Medical College, Fudan University, Shanghai, China; Department of Oncology, Shanghai Medical College, Fudan University, China, Shanghai, China; Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: Treatment for pre-treated patients (pts) with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) is an important unmet clinical need. Dual blockade of PD-L1 and TGF-β could reshape the tumor microenvironment. The aim of this study is to evaluate the efficacy and safety of retlirafusp alfa (SHR-1701, a bifunctional anti-PD-L1/TGF-βRII agent) plus nab-paclitaxel and carboplatin in platinum-refractory R/M HNSCC pts. **Methods:** Patients with R/M HNSCC who received ≥1 line of prior systemic anti-tumor therapy were included. Pts received retlirafusp alfa 30mg/kg, once every 3 weeks, combined with nab-paclitaxel (125mg/m^2) and carboplatin (AUC=1.5), on day 1 and day 8 of a 21-day cycle for up to six cycles, followed by retlirafusp alfa maintenance therapy. The primary endpoint was objective response rate (ORR). Secondary endpoints comprised progression free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. **Results:** From September 5, 2023 to September 25, 2024, 12 eligible pts were enrolled. The median age was 60 (range: 35-72). Among these 12 patients, 11 (91.7%) had received prior immune checkpoint inhibitors (ICIs) and 8 (66.7%) had undergone at least two previous lines of treatment. The median follow-up was 5.45 (95%CI 3.93-6.97) months, and data cutoff was December 31, 2024. All the 12 pts had at least one post-baseline assessment, and 4 pts achieved partial response with a confirmed ORR of 33.33% (95%CI 13.81%-60.93%). Disease control was observed in 8 patients resulting in a DCR of 66.67% (95%CI 39.07%-86.19%). The median PFS was 4.21 (95%CI 0.59-7.83) months. The median OS was immature. Treatment-related adverse events (TRAEs) occurred in 11 (91.67%) pts, mainly grade 1-2. The most common TRAEs (≥30%) were anaemia (8/12, 66.67%), white blood cell count decreased (5/12, 41.67%), hypoalbuminaemia (5/12, 41.67%), haemoptysis (5/12, 41.67%) and epistaxis (4/12, 33.33%). Grade 3-4 TRAEs were observed in 4 (33.33%) pts, with more than 1 patient experiencing white blood cell count decreased (3/12, 25%), neutrophil count decreased (2/12, 16.67%) and anaemia (2/12, 16.67%). **Conclusions:** Even as most pts have progressed on ICIs before enrollment, retlirafusp alfa plus nab-paclitaxel and carboplatin demonstrated promising anti-tumor efficacy and manageable toxicities in pre-treated R/M HNSCC. Long-term efficacy needs to be confirmed by further follow-up. Clinical trial information: ChiCTR2300070675. Research Sponsor: None.

6030 Poster Session

Camrelizumab combined with cetuximab and chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): 1-year outcomes from the phase II trial.

Dongmei Ji, Youzhou Sang, Yanan Yang, Guangliang Chen, Xin Liu, Yanjin Guo, Shu Dong, Yulong Wang, Xiayun He, Hongmei Ying, Xueguan Lu, Yu Wang, Chaosu Hu, Qinghai Ji; Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; BGI Research, Chongqing, China; Minimally Invasive Therapy Center, Shanghai Cancer Center, Fudan University, Shanghai, China; Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Pembrolizumab or cetuximab combined with platinum-based-chemo are standard first-line regimen for R/M HNSCC, but the efficacy is far from optimal. We conducted an open-label, single-arm, Simon' s two-stage, phase II study of camrelizumab (PD-1 monoclonal antibody) with cetuximab and cisplatin-based chemotherapy as first-line treatment in R/M HNSCC (NCT05673577). The outcomes from the 1st stage showed promising efficacy. **Methods:** Eligible patients with R/M HNSCC not amenable to curative treatment were enrolled. Patients were treated with camrelizumab 200mg Q3W, cetuximab 400mg/m^2 loading dose followed by 250mg/m^2 weekly, cisplatin 75mg/m^2 Q3W, and nab-paclitaxel 125mg/m^2 on d1, d8 (21-day cycle), for up to 6 cycles. Maintenance therapy with camrelizumab 200mg Q2W, cetuximab 500mg/m^2 Q2W were given until intolerable toxicity or disease progression. Primary endpoint of this study is objective response rate (ORR). Secondary endpoints include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), adverse events (AEs) (CTCAE v5.0) andmolecular biomarkers will be tested as exploratory endpoints. **Results:** Between April 2023 and September 2024, 41 patients were enrolled. The confirmed ORR per RECIST 1.1 was 90.0% (95% CI: 75.0-97.0), which met the prespecified criteria for the primary endpoint of ORR. The confirmed DCR was 100.0%. With the median follow-up duration of 14.5 months, the median PFS was 13.2 months (95% CI: 9.3-NR). The 1-year PFS rate was 54.6% (95% CI: 39.1-76.1). The median OS was not reached. The 1-year and 2-year OS rates were 88.4% (95% CI: 78.2-100.0) and 84.6% (95% CI: 72.8-98.3), respectively. The most common grade 3-4 AEs related to chemotherapy included neutropenia (16.7%), anemia (7.1%). Possible grade 3-4 targeted therapy-related AE was rash (7.1%). Additionally, 14.3% of the patients were administered anti-angiogenic medications to treat reactive cutaneous capillary endothelial proliferation mucositis that was specifically induced by camrelizumab. These AEs were manageable with dose modification. **Conclusions:** Camrelizumab combined with cetuximab and cisplatin-based chemotherapy showed encouraging efficacy and tolerability in the scenario of first-line R/M HNSCC. Further evaluation including a phase III study is warranted. Clinical trial information: NCT05673577. Research Sponsor: Clinical Research Project of Shanghai Municipal Health Commission in Health Industry, 202340122, (2023-2026); National Health Commission: Special Research Project for Clinical Studies of Innovative Drugs After Market Launch, WKZX2024CX01206, (2004-2007)).

Demographics and baseline characteristics.

		N=41 (100%)
Age	Median (range)	59 (34-72)
Sex-n (%)	Male/Female	36/5 (87.8% vs. 12.2%)
HNSCC Primary site of disease	Larynx	15 (36.5%)
	Oral Cavity	14 (34.1%)
	Oropharynx	4 (9.8%)
	HPV-pos	1 (25.0% of Oropharynx)
	HPV-neg	2 (50.0% of Oropharynx)
	unclear	1 (25.0% of Oropharynx)
	Hypopharynx	4 (9.8%)
	Others	4 (9.8%)
Distant metastasis-n (%)		19 (46.3%)
ECOG Performance Status-1 vs. 2 (%)		39 vs. 2 (95.1% vs. 4.9%)

6031 Poster Session

Combination of Tim-3 blockade TQB2618 with penpulimab and chemotherapy in the first-line treatment of recurrent/metastatic nasopharyngeal carcinoma (R/M NPC): A multicenter, single-arm, two-cohort, phase 2 study.

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Background: T cell immunoglobulin and mucin domain molecule 3 (Tim-3) is an inhibitory immune checkpoint receptor that negatively regulates the immune response. This multicenter, single-arm, two-cohort, phase 2 study (NCT05563480) aimed to explore the efficacy and safety of TQB2618, a novel monoclonal antibody blockading Tim-3, plus PD-1 blockade penpulimab as subsequent-line treatment in immunotherapy-resistant R/M NPC (cohort 1) or as first-line treatment by incorporating into chemotherapy in treatment-naïve R/M NPC (cohort 2). Here, we report the results of cohort 2. **Methods:** Eligible pts were ECOG PS 0–1, aged 18–70, diagnosed with histologically confirmed R/M NPC with ≥ 1 measurable lesion. Previous systemic treatment was not allowed, except as a part of curatively intended treatment for locoregionally advanced NPC and develop disease progression at least 6 months after last dose. TQB2618 and penpulimab were administered intravenously at doses of 1200 mg and 200 mg, respectively, on the first day of a 21-day cycle until disease progression or unacceptable toxicity while gemcitabine (1000 mg/m^2, d1&8) and cisplatin (75mg/m^2, d1) were given intravenously for the first 4–6 cycles. The primary endpoint is progression-free survival (PFS). **Results:** Between February 2023 and October 2023, 30 pts were enrolled (median [range] age, 52 [33–70] years; 16.7% women). Seventeen were diagnosed with metastatic disease at the first visit and others developed disease recurrence after definitive treatment. Liver metastasis was found in 10 pts. Median follow-up was 12.5 months (mo) (95% CI: 12.4–NE) at the data cut-off date on December 20, 2024. The median PFS reached 10.8 mo (95% CI, 9.6–16.4) and the 12 mo- and 15 mo-PFS were 40.9% and 34.1%, respectively. For the 17 pts with PD-L1 positive expression, the median PFS was 13.6 mo (95% CI: 8.4–16.6). The tumor response was complete response in 4 pts (13.3%), partial response in 21 pts (70.0%), stable disease in 4 pts (13.3%), and 1 could not be estimated, giving an objective response rate of 83.3%. A total of two pts died, both due to disease progression after 7.9 mo of enrollment. All pts experienced at least one adverse event (AE) and 25 pts (83.3%) were observed ≥ grade 3 (G3) AEs. The most common AEs of all grades (G1–4) or ≥ G3 were chemotherapy-related, including leukopenia (G1–4: 96.7%; ≥ G3: 40.0%), neutropenia (G1–4: 90.0%; ≥ G3: 36.7%), and anemia (G1–4: 93.3%; ≥ G3: 33.3%). **Conclusions:** To our knowledge, this is the first study to evaluate the addition of Tim-3 blockade to the standard first-line treatment of R/M NPC. The results demonstrated that this combination therapy provided clinical benefits comparable to those observed in the historical cohort treated with PD-1 blockade plus chemotherapy, while maintaining a manageable safety profile. Clinical trial information: NCT05563480. Research Sponsor: Chia Tai TianQing Pharmaceutical Group Co., Ltd; Basic and Applied Research Project of Science and Technology of Guangzhou city.

The molecular landscape of immunotherapy treatment and advanced disease in head and neck squamous carcinoma (HNSCC).

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Background: Advanced head and neck squamous cell carcinoma (HNSCC) exhibits variable responses to immunotherapy, highlighting the need to understand its complex molecular landscape. While immune checkpoint inhibitors show promise, optimizing treatment and predicting outcomes requires deeper molecular insights. Here, we leverage the cBioPortal for Cancer Genomics, analyzing ~800 HNSCC genomic and transcriptomic profiles, to investigate the molecular landscape influencing immunotherapy response in advanced disease. **Methods:** In this retrospective study, we analyzed publicly available data from 825 HNSCC patients treated with immunotherapy, enrolled in participating institutions between 2017 and 2022, sourced from the cBioPortal for Cancer Genomics. We investigated the frequency of most common mutations, copy number alterations, and mRNA expression levels, along with clinicopathological factors and overall survival (OS). **Results:** Genomic analysis of 809 HNSCC samples revealed TP53 as the most frequently mutated gene (63.5%, 514/809), followed by TTN (37.4%), FRG1BP (20.7%), FAT1 (19.3%), and CDKN2A (19.0%). Other genes were mutated at frequencies between 18.7% and 15.2%. Copy number alterations analysis (n=673) showed frequent homozygous deletions in 9p21.3, affecting CDKN2A-AS1 (30.3%, 158/673) and CDKN2A (26.0%, 175/673), and amplifications in 11q13.3, including PPFIA1 (25.7%), FADD (25.3%), CTTN (25.1%), and ANO1 (25.1%). Notably, TP53 mutations and CDKN2A-AS1 deletions were associated with inferior OS (log-rank $P < 0.001$; mOS mutated vs wild-type 45.93 vs 156.37 months and $P = 0.006$; mOS altered vs non-altered 35.45 vs 65.77 months, respectively). Transcriptomic and GSEA profiling linked these alterations to dysregulation of oncogenic pathways, including DNA replication stress, p21 activation, apoptosis, and immune evasion. **Conclusions:** This study of immunotherapy-treated advanced HNSCC provides a valuable resource for understanding the complex genomic landscape of this disease. We identified frequent mutations and copy number alterations which were associated with inferior OS and linked to dysregulation of key oncogenic pathways. These findings underscore the potential of this to facilitate biomarker discovery and the development of personalized medicine approaches to improve outcomes in advanced HNSCC. Research Sponsor: None.

Initial safety and efficacy of PDL1V (PF-08046054), a vedotin-based ADC targeting PD-L1, in combination with pembrolizumab in patients with recurrent or metastatic (R/M) HNSCC.

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Background: PDL1V is a novel investigational antibody-drug conjugate that delivers monomethyl auristatin E (MMAE) to cells that express programmed cell death ligand 1 (PD-L1) without anticipated checkpoint blockade. Immunogenic cell death via the MMAE payload can be further amplified by traditional immune checkpoint inhibitors, providing strong scientific rationale for combination with pembrolizumab. The objective of Part D of the phase 1 trial is to assess the safety/tolerability and preliminary antitumor activity of PDL1V and pembrolizumab combination in patients with R/M HNSCC. **Methods:** C5851001 (NCT05208762) includes a phase 1 safety run-in cohort (Part D) enrolling patients with untreated R/M HNSCC with PD-L1 CPS ≥1 and no prior therapy with anti-PD-1/PD-L1 antibodies in any setting. Measurable disease per RECIST v1.1 and ECOG PS ≤1 were required. The first patient group received PDL1V 1.25 mg/kg on days 1 and 8 every 21 days (2Q3W) using adjusted ideal body weight (AIBW). Once safety was demonstrated, a second cohort was initiated at 1.5 mg/kg 2Q3W AIBW. All patients received pembrolizumab 200 mg every 3 weeks. The primary objectives of this study are safety/tolerability and pharmacokinetics. A secondary objective is antitumor activity. **Results:** As of December 20, 2024, 14 patients were dosed; median age was 61 years (range 36–76). Eight patients received 1.25 mg/kg and 6 received 1.5 mg/kg; 92.9% were male, 71.4% had ECOG PS 0, 64.3% were P16 positive oropharyngeal, and 57.1% had CPS 1–<20. Eight patients remain on active therapy at the data cut time. No dose-limiting toxicities (DLTs) were observed. The most frequent PDL1V treatment-related adverse events (TRAEs) were fatigue and nausea (50.0% each), peripheral sensory neuropathy (35.7%), diarrhea (28.6%), and anemia, constipation, decreased appetite, muscle spasms, pneumonitis, and pyrexia (14.3% each); pembrolizumab TRAEs were fatigue (42.9%), diarrhea, and nausea (28.6% each); and abdominal pain, decreased appetite, peripheral sensory neuropathy, pneumonitis, and pyrexia (14.3% each). The most frequent grade ≥3 TRAEs for either agent were diarrhea (14.3%) and anemia, decreased appetite, fatigue, and neutropenia (7.1% each). Treatment-related immune-mediated AEs by investigator assessment were observed in 7.1% of patients; 7.1% grade 3. Investigator-assessed, objective response rate at this time for 14 response-evaluable patients was 50.0%; complete response (CR) rate was 21.4%. The median duration of response has not been reached. **Conclusions:** The combination of PDL1V and pembrolizumab was generally well tolerated with no DLTs. Early encouraging objective responses were observed in half of the patients treated, including 21.4% with a CR. Enrollment in multiple combination expansion cohorts in PD-L1 expressing tumors is ongoing. Clinical trial information: NCT05208762. Research Sponsor: Pfizer Inc.

6034 Poster Session

A prospective, single-arm, phase II study of adebrelimab plus carboplatin and albumin-bound taxanol as neoadjuvant therapy in patients with resectable locally advanced head and neck squamous cell carcinoma.

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Background: Currently, clinical studies have shown that patients with tumor remission after preoperative induction chemotherapy have a higher survival rate and a lower risk of distant metastasis, but the pathological complete remission rate of tumor after surgery is low. With the rise of tumor immunology, more and more immunotherapy methods have been applied to the treatment of clinical tumors. In terms of head and neck squamous cell carcinoma, we hereby investigate the efficacy of a PD-L1 inhibitor (Adebrelimab) combined with chemotherapy in patients with resectable advanced head and neck squamous cell carcinoma. **Methods:** This study hypothesized that preoperative induction of PD-L1 inhibitors combined with chemotherapy in patients with resectable advanced head and neck squamous cell carcinoma was superior to conventional chemotherapy regiments recommended by NCCN guidelines. As a course of treatment every three weeks, albumin-bound paclitaxel 260 mg/m2, carboplatin AUC=5 and Adebrelimab 1200 mg were given intravenously on the first day of every three weeks. After three doses, surgery was performed and radiotherapy was performed according to the stage of the tumor. The main index observed in this study was postoperative pathological complete response rate (PCR), and the secondary index was major pathological response rate (MPR) and 2-year survival rate (OS). **Results:** As of December 31, 2024, a total of 30 patients were enrolled in the study. Among them, the median age was 52 years, and 23 patients were male. During immunochemotherapy, the most common adverse reactions were alopecia (100%, 30/30), pruritus (16%, 5/30), and limb weakness (60%, 18/30). At present, 26 patients have completed all preoperative neoadjuvant therapy and successfully received surgical treatment. By comparing the MRI imaging images of these patients before and after medication, the efficacy evaluation of 14 patients was PR (53.9%, 14/26), 1 patient was CR (3.8%, 1/26), 1 patient was PD (3.8%, 1/26), and 10 patients was SD (38.5%, 10/26). In postoperative pathological specimens, 12 patients achieved pathological complete response (PCR: 46%, 12/26) and 3 patients achieved major pathological response (MPR: 11.5%, 3/26). We will follow up these patients and calculate their 2-year survival rate (OS). This study is still ongoing. **Conclusions:** In terms of head and neck squamous cell carcinoma, Phase I clinical studies have confirmed the therapeutic safety and tumor activity of PD-L1 inhibitors. In this Phase II study, the PD-L1 inhibitor (Adebrelimab) demonstrated a favorable therapeutic response to locally advanced head and neck squamous cell carcinoma, and we look forward to final therapeutic data. Clinical trial information: NCT06016413. Research Sponsor: Jiangsu Hengrui Pharmaceutical Co., Ltd.

6035 Poster Session

Survival for head and neck squamous cell carcinoma treated with versus without neoadjuvant systemic therapy: A national propensity score–matched analysis.

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Background: Neoadjuvant systemic therapies, including immunotherapy and chemotherapy, offer a promising approach for treating head and neck squamous cell carcinoma (HNSCC). These therapies aim to reduce tumor burden and enable personalized treatment. While pivotal studies like KEYNOTE 689 may redefine therapeutic paradigms, the survival outcomes associated with neoadjuvant systemic therapies in HNSCC remain underexplored. **Methods:** A retrospective cohort analysis using the National Cancer Database evaluated patients with HNSCC surgically treated with versus without neoadjuvant systemic therapies from 2015 to 2022. Overall survival (OS) was compared by using a Cox proportional hazards regression model. Propensity score matching was performed to adjust for stage, age, sex, race, insurance status, urban/rural, Charlson–Deyo score. **Results:** Among 3,569 patients (74% male, 26% female), 1,311 received neoadjuvant chemotherapy, 632 received neoadjuvant immunotherapy, 114 received a combination of neoadjuvant chemotherapy and immunotherapy, and 1,512 were matched HNSCC patients who did not receive any neoadjuvant therapy prior to surgery. Most patients had overall stage IVa/b (59%) tumors of the oral cavity (62%). On univariate analysis, neoadjuvant immunotherapy alone was associated with a 43% reduced the risk of mortality, compared to neoadjuvant chemotherapy alone (HR: 0.57; 95% CI: 0.48–0.68, $P < .001$). Combination therapy was not significantly associated with lower mortality than chemotherapy alone (HR: 0.87; 95% CI: 0.63–1.21, $P = .41$). After adjustment using a propensity matched cohort of patients with HNSCC treated without neoadjuvant therapy, neoadjuvant immunotherapy was associated with significantly improved OS (HR: 0.55; 95% CI: 0.35-0.75, $P < .001$). However, neoadjuvant chemotherapy (HR: 1.07; 95% CI: 0.96–1.18, $P = .23$) and combination therapy (HR: 0.84; 95% CI: 0.49-1.19, $P = .33$) were not significantly associated with improved OS. **Conclusions:** Neoadjuvant immunotherapy may potentially provide improved survival in HNSCC. Further research is needed to assess these findings through prospective trials. Research Sponsor: None.

Overall survival for patients with head and neck squamous cell carcinoma treated with versus without neoadjuvant systemic therapy.

Overall Survival	HR (95% CI)	P
No neoadjuvant therapy	Ref.	
Neoadjuvant chemotherapy	1.07 (0.96–1.18)	0.23
Neoadjuvant combination therapy	0.84 (0.49-1.19)	0.33
Neoadjuvant immunotherapy	0.55 (0.35-0.75)	<0.001

HR, hazard ratio; CI, confidence interval.

6036 Poster Session

ctDNA-based clinicogenomic analysis of advanced head and neck cancer patients treated with immune checkpoint inhibitors.

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Background: Head and Neck cancer (HNC) is among the diverse group of malignancies affecting the head and neck region including the oral cavity. Being the most prevalent malignancy in Southeast Asia, it has a high mortality rate. Despite the advancement in treatment, 5 years survival rate for HNC remains below 50%, and the majority of Pts receiving frontline therapy experience locoregional or incurable metastatic relapse. Immune checkpoint inhibitors (ICI) are recommended for relapsed patients, but only 20% of patients show measurable response. Currently, no predictive biomarkers are available to predict ICI response and there is an urgent need for genomic markers to predict ICI outcomes. Here we report comprehensive genomic profiling (CGP) of advanced HNC patients receiving ICI. **Methods:** ctDNA from 69 advanced HNC patients receiving combinational immune-chemotherapy were serially profiled at the baseline (BL) and post-treatment (Tx) by targeted, hybridization-based CGP using OncoIndx comprehensive gene panel (CGP) comprising 1080 genes. The ctDNA differential features at BL and post-Tx as well as among responders (R) and non-responders (NR) were correlated with Progression-free survival (PFS) and Overall survival (OS) using Kaplan-Meier statistics and multivariate analysis. **Results:** Among total patients, 58% (40/69) were responders (R) while the remaining were non-responders (NR). At the population level, HRR pathway tumor suppressors and epigenetic modifiers were the most frequent pathogenic variants. At BL, the NR population was enriched with oncogenic gene mutations compared to the R population. TP53 and BRCA pathway mutations (mTP53 + BRCA) showed a strong association with progression-free survival (PFS) and overall survival (OS). Pts with cooccurring mTP53 + BRCA had significantly lower PFS (median PFS: 2.77 months for mTP53 + BRCA pathway vs 9.1 months for wt TP53 + BRCA pathway. P=<0.0001, HR=3.2-11.6) and OS (median OS: 4.67 months for mTP53 + BRCA pathway vs 12.63 months for wtTP53 + BRCA pathway. P=<0.0001, HR = 11.18-55.27). NOTCH 1 or 2 variants were enriched in R population, with a beneficial effect on survival outcomes. Elevated ctDNA alterations and Tumor fraction (TF) concentrated in the NR population disproportionately contained subclonal potential drivers of immunotherapy resistance including NF1, STAT5 B, and STK11 mutations, and were associated with short survival. Univariate and multivariate analysis suggested that ctDNA mutations, TF, and high mutational heterogeneity emerged as risk factors for shorter PFS and OS. In contrast, total Indel burden and NOTCH mutations had beneficial effects on PFS and OS. **Conclusions:** Minimally invasive plasma ctDNA CGP showed heterogenous actionable mutations at BL and post Tx and identified immunotherapy resistance conferring genomic markers for stratifying potential responders for immunotherapy guidance. Research Sponsor: None.

6037 Poster Session

Versatile-002: Overall survival of HPV16-positive recurrent/metastatic head and neck squamous cell carcinoma patients treated with T cell stimulating immunotherapy PDS0101 and pembrolizumab.

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Background: The incidence of HPV-associated head and neck squamous cell carcinoma (HNSCC) continues to rise with over 90% of cases being driven by HPV16. Median overall survival (OS) with pembrolizumab in first-line recurrent/metastatic (R/M) HNSCC is 12.3 months in subjects with CPS ≥1, 10.8 months for CPS ≥1-19, and 14.9 months for CPS ≥20. There is an urgent need to improve survival rates in the growing population of HPV16-positive R/M HNSCC. PDS0101 (Versamune HPV) is an investigational T cell stimulating immunotherapy that unleashes a potent, durable attack against HPV16-positive cancers and is being studied in combination with pembrolizumab. Preliminary results were presented at ASCO 2023. (Price KAR, et al. ASCO 2023. Abstract 6012). **Methods:** VERSATILE-002 is a single-arm phase 2 study evaluating PDS0101 and pembrolizumab for first-line HPV16-positive R/M HNSCC with CPS ≥1. Subjects received pembrolizumab 200 mg IV Q3W with PDS0101 1 mL SC administered concurrently during Cycles 1, 2, 3, 4, and 12 and pembrolizumab alone for all other Cycles up to Cycle 35 (approx. 2 years). The primary study endpoint is confirmed objective response rate (ORR) per RECIST 1.1. Secondary endpoints include progression-free survival (PFS), OS, and safety. **Results:** The median follow-up is 18.4 months (range 0.2-42.7 months). The efficacy population consists of 53 subjects: 32 (60%) with CPS ≥1-19 and 21 (40%) with CPS ≥20. The median OS for subjects with CPS ≥1 is 30 months (95% CI 23.9, NE). For the CPS ≥1-19 subgroup, the median OS is 29.5 months (95% CI 15.3, NE). For the CPS ≥20 subgroup, the median OS is 39.3 months (95% CI 18.4, NE). Confirmed response rates by investigator assessment are shown in the Table. Twenty-three subjects are still on study: 3 on treatment and 20 in long-term follow-up. No new safety signals have emerged. The most common TRAEs are injection site reactions, fatigue, headache, and pruritus. Only 19% of subjects experienced Grade ≥3 TRAEs. No subject had a Grade 5 TRAE. **Conclusions:** These data represent one of the most extended follow-up periods to date of subjects receiving an HPV16-targeted therapy for HPV16-positive R/M HNSCC. The PDS0101 and pembrolizumab combination is well tolerated and has demonstrated deep and durable clinical responses. Median OS is promising in light of historic expectations, both overall and relative to PD-L1 subgroup, and remains durable with continued follow up. The results support further evaluation in a randomized phase 3 study with OS as the primary endpoint. Clinical trial information: NCT04260126. Research Sponsor: PDS Biotechnology Corporation.

Summary of results.

	CPS ≥1-19 (N=32)	CPS ≥20 (N=21)	CPS ≥1 (N=53)
ORR, %	28.1	47.6	35.8
DCR, %	75.0	81.0	77.4
Median DOR, months (95 % CI)	21.8 (4.2, NE)	NE (5.6, NE)	21.8 (11.5, NE)
Median PFS, months (95% CI)	5.1 (2.4, 8.1)	14.1 (2.1, NE)	6.3 (3.5, 9.0)
Median OS, months (95% CI)	29.5 (15.3, NE)	39.3 (18.4, NE)	30.0 (23.9, NE)

Assessing the safety and efficacy of GT201: A first-in-class autologous tumor-infiltrating lymphocyte monotherapy in advanced solid tumors.

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Background: For patients with unresectable recurrent or metastatic solid tumors that progress after chemotherapy, immune checkpoint inhibitors (ICIs), or targeted therapy, treatment options are limited. GT201, featuring membrane-bound IL-15 (mbIL-15) expressed on TILs, aims to enhance immune activation in the tumor microenvironment and may demonstrate efficacy and durable responses in these advanced cases. We present data from nine patients enrolled in open-label, single-arm studies to investigate the safety and efficacy trends of GT201 therapy. **Methods:** The GT201 study's primary endpoint was to assess TEAEs, including SAEs and AEs, using the CTCAE version 5.0 grading scale. The secondary endpoint focused on preliminary efficacy parameters, including ORR, DCR, PFS, DOR, OS following RECIST v1.1 guidelines. **Results:** As of January 15, 2025, nine patients have been enrolled in the study, with a median age of 52 years and a median of two prior therapy lines. Among them, one patient had bone metastases, two had liver metastases, and one had brain metastases. After standard FC lymphodepletion, patients received GT201 infusions at doses of $\geq 5\times10^9$ viable cells. Seven patients subsequently received IL-2 post-infusion. Most adverse events (AEs) were Grade 1 or 2. Grade $\geq$3 AEs, related to lymphodepleting chemotherapy and IL-2, included decreased lymphocyte, neutrophil, and white blood cell counts, pyrexia, and tachycardia. All Grade $\geq$3 AEs resolved or downgraded to Grade $\leq$2 within 14 days. Among the nine response-evaluable patients with various cancers, including head and neck squamous cell carcinoma (HNSCC), non-small-cell lung cancer (NSCLC), melanoma, cervical cancer, and ovarian cancer, the objective ORR was 55.6% (5/9), and the disease control rate (DCR) was 77.8% (7/9). One patient (11.1%) achieved complete response (CR), four (44.4%) had partial responses (PR), and two (22.2%) had stable disease (SD) as their best response. Notably, in the HNSCC subgroup, both patients achieved objective responses (CR and PR) (2/2, 100%). In the NSCLC subgroup, all three patients achieved disease control (SD $\geq$24 weeks or PR) (3/3, 100%). GT201 cells were detected in all patients, indicated by IL15RA protein staining on peripheral T cells and transgene copy number in peripheral white blood cells. GT201 cells expanded robustly and persisted in peripheral blood for at least six months post-infusion. **Conclusions:** In patients with heavily pretreated advanced or metastatic solid tumors, GT201, infused after FC lymphodepleting chemotherapy and high-dose IL-2, exhibited a manageable safety profile. GT201 demonstrated a favorable clinical profile in HNSCC, with an encouraging objective response rate and durable responses. No Grade $\geq$3 adverse events related to GT201 treatment were observed, supporting its potential as a treatment option worth further exploration. Clinical trial information: NCT05729399, NCT06190275. Research Sponsor: None.

6039 Poster Session

Two cycles of neoadjuvant therapy with low-dose radiotherapy, PD-1 inhibitor tislelizumab, albumin-bound paclitaxel, and cisplatin for resectable locally advanced head and neck squamous cell carcinoma (NeoRTPC02): A phase II, open-label, single-arm trial.

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Background: Despite standard treatments, mortality rates remain high in locally advanced head and neck squamous cell carcinoma (LA HNSCC). Neoadjuvant immunotherapy combined with chemotherapy has improved response rates, but further enhancement is needed. Recent studies suggest that low-dose radiotherapy (LDR) can reprogram the tumor microenvironment, reversing immune suppression and improving the efficacy of PD-1 inhibitors. This study aims to evaluate the safety and efficacy of neoadjuvant LDR combined with tislelizumab and chemotherapy in LA HNSCC. **Methods:** This was an open-label, single-arm, phase II clinical trial for patients with untreated, histologically confirmed stage III-IVB HNSCC. Patients received neoadjuvant low-dose radiotherapy (1 Gy/1F, days 1, 2, 8, and 15, Q3W) combined with tislelizumab (200 mg, day 1, Q3W), albumin-bound paclitaxel (100 mg/m^2, days 1, 8, and 15, Q3W), and cisplatin (25 mg/m^2, days 1, 8, and 15, Q3W) for two cycles. Afterward, patients underwent radical surgery approximately 4 weeks later. The primary endpoint was the pathological complete response (pCR) rate, while secondary endpoints included major pathological response (MPR) rate, ORR, R0 resection rate, safety, and treatment-related surgical delay rate. The exploratory endpoints were the 3-year progression-free survival and 3-year overall survival. To further investigate the underlying mechanisms of treatment effects, we used single-cell RNA sequencing (scRNA-seq) to explore how this combination modulates the tumor microenvironment(TME) in HNSCC. **Results:** A total of 37 patients were assessed for eligibility, of which 28 patients were enrolled and received the assigned neoadjuvant treatment. A total of 23 patients proceeded to surgery, and pathological response evaluation was conducted in these patients. Among the 23 patients, 14 (60.9%) achieved pCR, and the MPR and pCR/MPR rates were 21.7% and 82.6%, respectively. The ORR was 64.3% (18/28), including 2 (7.1%) complete response and 16 (57.1%) partial response. The R0 resection rate was 100%. Treatment-related adverse events (TRAEs) were manageable, with grade 3 or 4 TRAEs occurring in 12 (42.9%) patients. The main side effects included neutropenia and decreased white blood cell count. No surgical delays were observed. ScRNA-seq results suggested that this neoadjuvant regimen may reshape the HNSCC TME by enhancing adaptive immunity and potentially increasing FOLR2$^+$ macrophage infiltration. **Conclusions:** Neoadjuvant LDR combined with tislelizumab, albumin-bound paclitaxel, and cisplatin resulted in an impressive pCR rate and demonstrated promising efficacy with manageable toxicity in patients with resectable LA HNSCC. Long-term survival data are still follow-up. Clinical trial information: NCT05343325. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation.

Effect of induction chemo-immunotherapy on the chance for re-irradiation in high-risk recurrent nasopharyngeal carcinoma: A prospective, single-arm, phase II trial.

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Background: The PRANCIS model has been shown to be robust for identifying patients with recurrent nasopharyngeal carcinoma (rNPC) who are at high risk of treatment-related adverse events from re-irradiation (reRT). Here, we investigate the efficacy of combination doublet gemcitabine-cisplatin (GP) and PD-1 inhibitor (Toripalimab) to down-classify PRANCIS high risk (>252) to low-risk post-3 cycles of treatment, and the survival outcomes of these patients. For patients who converted to low-risk, reRT may be considered (NCT03930498). **Methods:** Eligibility criteria included diagnosed as local ± regional recurrence after ≥1 year of radical treatment, not suitable for surgery, histologic or clinically diagnosis of NPC, stage rII-IVa (AJCC/UICC 8th), PRANCIS model > 252 points. All patients received 3 cycles of GP + PD-1 inhibitor, then received reRT (GTV, 60-66Gy, 1.8-2.0Gy/f) plus PD-1 inhibitor if got CR/PR (reRT group), or received another 3 cycles of GP+PD-1 inhibitor if got SD (no reRT group), finally all got 4 cycles of PD-1 inhibitor maintenance. Primary end point was 2-year overall survival (OS). **Results:** Between Mar 2020 to Nov 2023, 68 high-risk patients were recruited (Table 1). After 3 cycles of GP + PD-1 inhibitor, 44 (64.7%) patients got PR (34 down-classify to low-risk and 10 still high-risk) and received full-course reRT, 22 (32.4%) got SD (all high-risk) and kept receiving GP + PD-1 inhibitor, and 2 (2.9%) could not be evaluated due to 1 died of COVID-19 and 1 withdrew after 2 cycles of treatment. 56 (82.4%) patients finished the scheduled treatment, and 12 discontinued chemo-immunotherapy. With a median follow-up time of 32.7 months, the 2-year OS of whole cohort was 67.2%, and 73.8% vs 51.2% (P = 0.019) in reRT group vs no reRT group. The 2-year progression-free survival (PFS) of whole cohort was 47.9%, and 61.0% vs 24.3% (P < 0.0001) in reRT group vs no reRT group. The most common ≥grade 3 toxicities included neutropenia (30.9%), lymphopenia (22.1%), and xerostomia (16.2%). The incidences of grade 3 nasopharyngeal necrosis was 5.9%. Two (2.9%) patients died of massive nasal bleeding. **Conclusions:** Induction chemo-immunotherapy offered the chance of reRT for high-risk rNPC patients and improved their overall survival with acceptable toxicities. Clinical trial information: NCT03930498. Research Sponsor: National Natural Science Foundation of China for Young Scholars; Sun Yat-sen University Young Teachers Cultivation Program; Sun Yat-sen University Cancer Center 308 Program.

Basic information.

Variables	Whole cohort	reRT group	no reRT group
Age†, year	52.0 (43.0 - 58.0)	54.5 (42.8 - 58.8)	47.0 (43.0 - 54.8)
Sex			
Male	51 (75.0)	30 (68.2)	21 (87.5)
Female	17 (25.0)	14 (31.8)	3 (12.5)
rT stage			
T3	36 (52.9)	28 (63.6)	8 (33.3)
T4	32 (47.1)	16 (36.4)	16 (66.7)
rN stage			
N0	36 (52.9)	25 (56.8)	11 (45.8)
N1-3	32 (47.1)	19 (43.2)	13 (54.2)
rTNM stage			
III	35 (51.5)	27 (61.4)	8 (33.3)
IVa	33 (48.5)	17 (38.6)	16 (66.7)
pre-treatment EBV DNA, copy/ml			
0	23 (33.8)	14 (31.8)	9 (37.5)
>0	41 (60.2)	27 (61.4)	14 (58.3)
Missing	4 (5.9)	3 (6.8)	1 (4.2)
PRANCIS model†, points	295.3 (264.1 - 321.8)	270.8 (258.1 - 340.5)	309.2 (297.5 - 319.4)

†median (IQR).

6041 Poster Session

Optimal maintenance therapy strategy for metastatic nasopharyngeal carcinoma: Insights from a cohort study in an endemic region.

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Background: Managing metastatic nasopharyngeal carcinoma (mNPC) remains challenging due to its high incidence and mortality rates. While maintenance therapy shows promising potential, the optimal strategy remains unclear. A prior ranking question is if combined therapy of anti-PD-1 antibodies and capecitabine an effective maintenance strategy for mNPC patients who achieved disease control after first-line therapy. **Methods:** Eligible patients with mNPC who achieved disease control following first-line therapy and subsequently received maintenance therapy were included at Sun Yat-sen University Cancer Center between 2018 to 2023. Progression-free survival and overall survival were analyzed using the Kaplan–Meier method and log-rank test. Cox proportional hazards model and inverse probability of treatment weighting analysis were applied to adjust for confounders. Based on interaction effects, stratification analysis was performed. A sensitivity analysis was based on the E-value from the weighted Cox proportional hazards model. **Results:** This cohort study included 300 mNPC patients receiving maintenance therapy with monotherapy (n=211), anti-PD-1 immunotherapy (n=94) or capecitabine (n=117), and their combination (n=89). 234 patients (78.0%) were male, and the median age was 45 years (interquartile range [IQR]: 36–54). At median follow-up of 37.8 months (IQR: 35.6–40.1), combination maintenance significantly improved progression-free survival (PFS) compared to single-drug maintenance [median PFS: not reached *vs* 27.0 months; weighted hazard ratio (HR): 0.569, 95% Confidence Interval (CI): 0.368-0.878, P = 0.011; E-value, 2.32], though no improvement in overall survival was observed. Stratification analysis revealed enhanced efficacy of combination maintenance in patients without prior local treatment (HR: 0.411, 95% CI: 0.266–0.748, P = 0.004) or with elevated pre-maintenance Epstein-Barr virus (EBV) DNA levels (HR: 0.312, 95% CI: 0.106–0.917, P = 0.034). No significant difference in prognosis was observed between capecitabine and anti-PD-1 monotherapy groups. Combination regimen obtained significantly superior progression-free survival compared to either monotherapy alone. The safety profile was similar between combination maintenance and single-drug groups. **Conclusions:** Combined anti-PD-1 and capecitabine maintenance therapy significantly improved prognosis in mNPC with disease control after first-line therapy, particularly in patients with elevated premaintenance EBV DNA levels or those without local treatment. Research Sponsor: National Natural Science Foundation of China; 822029005; National Natural Science Foundation of China; 82172863; National Natural Science Foundation of China; 82002855; Natural Science Foundation of Guangdong Province; 2023B1515020044; Guangzhou Basic and Applied Basic Research Project; 2023A04J2136; Guangzhou Basic and Applied Basic Research Project; 2023A04J2142.

6042 Poster Session

Major pathological response to neoadjuvant immune-related therapy and influence on long-term survival in patients with locally advanced oral squamous cell carcinoma.

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Background: In neoadjuvant immune-related therapy (NAIT) for patients with locally advanced oral squamous cell carcinoma (LAOSCC), it has been highly anticipated whether major pathological response (MPR) can translate into long-term survival benefits. The aim of this study was to demonstrate the relationship between MPR to NAIT and long-term survival in LAOSCC. **Methods:** Two single-arm trials were included in this study on NAIT of neoadjuvant immunochemotherapy (NAICT) with Toripalimab plus albumin paclitaxel/cisplatin (NCT04473716) or neoadjuvant immunotarget therapy (NAITT) with Camrelizumab plus Apatinib (NCT04393506) in LAOSCC patients at clinical stage III and IVA (AJCC 2018). The patients received two cycles (21 days each) of NAICT with intravenous albumin paclitaxel (260mg/m^2), cisplatin (75mg/m^2) and Toripalimab (240mg) on day 1 and day 22; or three cycles of NAITT with intravenous Camrelizumab (250mg) on d1, d15, d29, and oral Apatinib daily, initiating on d1, ending on the 5th day before surgery. Then, radical surgery and post-operative radiotherapy/chemoradiotherapy was performed. Primary tumors were assessed for the percentage of residual viable tumor that was identified on HE staining, and tumor with no more than 10% viable tumor cell was considered as MPR. **Results:** From April 2020 to April 2021, 40 patients received NAIT and radical surgery. The rate of CPS>10 in the biopsy and the MPR rate was 20% and 60% in the NAICT group, 24% and 40% in the NAITT group, respectively. The follow-up period ranged from 45 to 53 months. The 4-year OS and DFS rate was 90% and 85% in the NAICT group, 90% and 80% in the NAITT group. In the patients archived MPR, the 4-year OS and DFS rate was 100% and 95%, in the non-MPR patients, the 4-year OS and DFS rate was 80% and 70%. In the nine patients with CPS>10, they were all alive without local tumor recurrence or metastasis. **Conclusions:** NAICT and NAITT are safe and effective, the LAOSCC patients with CPS>10 or archiving MPR could have long-term survival benefit from NAIT. Clinical trial information: NCT04473716, NCT04393506. Research Sponsor: None.

6043 Poster Session

Neoadjuvant immunotherapy in combination with chemotherapy in resectable locally advanced head and neck squamous cell carcinoma: A randomized, open label, phase II clinical trial.

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Background: The efficacy and safety of neoadjuvant immunotherapy (NAI) for resectable locally advanced head and neck squamous cell carcinoma (LAHNSCC) remain unclear, requiring further exploration. While PD-1 inhibitors combined with chemotherapy have shown promise, most regimens focus on single-target inhibitors. Dual-target inhibitors, such as PD-1/CTLA4 or PD-1/VEGF combinations, demonstrated superior efficacy in recurrent/metastatic HNSCC. This study aims to compare the efficacy and safety of single- and dual-target NAI combined with chemotherapy for resectable LAHNSCC to identify the optimal strategy. **Methods:** This phase II randomized trial will enroll resectable LAHNSCC patients eligible for surgery. Patients will be randomized into three cohorts: Cohort 1 will receive ivonescimab (PD-1/VEGF antibody, 10 mg/kg), Cohort 2 will receive cadonilimab (PD-1/CTLA-4antibody, 6 mg/kg), and Cohort 3 will receive penpulimab (PD-1 antibody, 200 mg), all in combination with cisplatin and nab-paclitaxel. Dose adjustments are allowed based on toxicity, and surgery will be performed within 2-4 weeks after 3 cycles of neoadjuvant treatment. Patients achieving pCR will receive 16 cycles of adjuvant immunotherapy. Those without pCR will undergo adjuvant radiotherapy or chemoradiotherapy, followed by 16 cycles of adjuvant immunotherapy. The primary endpoints were pCR and safety. Secondary endpoints include MPR, ORR, EFS and OS. **Results:** A total of 24 patients were enrolled, with 13 evaluable for analysis. The median age was 58 (range 34-70). The primary site included oral cavity (n=7), oropharynx (n=2, including 1 HPV-positive), and larynx (n=4). The clinical stages were as follows: T2 (n = 3), T3 (n = 6), T4a (n = 5), and cN0/1 (n = 3), cN2 (n = 9), cN3 (n = 1). The pCR rates were 80% (4/5), 0% (0/2), and 66.7% (4/6) in Cohort 1, 2, and 3, respectively. The major pathologic responses (MPR) rates were 80% (4/5), 100% (2/2), and 66.7% (4/6) in Cohort 1, 2, and 3, respectively. Pathological non-response (pNR) occurred more frequently in Cohort 3 (2/6) and absent in Cohorts 1 (0/5) and 2 (0/2). The ORR was 100% in Cohort 1 (CR: 3/5, PR: 2/5) and Cohort 2 (100%, PR: 2/2), while Cohort 3 showed a lower ORR of 83.3% (CR: 3/6, PR: 2/6, SD: 1/6). There were no Grade ≥3 TRAEs or unexpected surgical delays/complications. **Conclusions:** Neoadjuvant single- or dual-target immunotherapy combined with chemotherapy showed promising pathological responses in resectable LAHNSCC. While dual-target therapy showed potential benefits, the small sample size limits definitive conclusions. The treatment was well-tolerated, with no serious TRAEs. Further analyses will be conducted as patient enrollment continues in larger cohorts. Clinical trial information: NCT06444009. Research Sponsor: None.

RECIST and pathologic response.

	RECIST				Pathologic Response		
	CR	PR	SD	PD	MPR	pPR	pNR
					pCR		
Cohort 1	3	2			4	1	
Cohort 2		2			2		
Cohort 3	3	2	1		4		2

6045 Poster Session

Spatial transcriptomics analysis to predict response to immune checkpoint blockade (ICB) in recurrent or metastatic head and neck squamous cell cancer (RM-HNSCC).

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Background: Spatial transcriptomics (ST) revealed conserved malignant leading edge (LE) and tumor core (TC) architectures in primary oral squamous cell carcinoma (OSCC) with potential for biomarker discovery. Spatial organization of tumor cells, as well as composition and prognostic significance of neighboring stromal cells in RM-HNSCC remain unknown. **Methods:** 21 tumor biopsy samples (14 baseline, 7 paired on-treatment) from 14 ICB-naive RM-HNSCC patients (pts) treated with pembrolizumab in INSPIRE (NCT02644369) were profiled using 10x Visium. Spatial organization was refined by scoring LE and TC gene sets identified in OSCC (Arora and Bose et al. Nat Comm 2023). Malignant (2,671 spots) and nonmalignant (8,177 spots) subclusters were annotated, with the latter classified into five cell subtypes using canonical markers: tumor-associated macrophages (TAMs) (*CD68*, *CD14*, *SCF1R*), regulatory stromal cells (reg) (*KRT17*, *COL10A1*, *SRBP1*), plasma cells (*CD38*, *IRF4*, *PRDM1*), T cells (*CD3D*, *CD3E*, *PTPRC*), and cancer-associated fibroblasts (CAFs) (*FAP*, *COL1A1*, *PDGFRB*). Neighborhood analyses compared normalized counts of stromal cells adjacent to LE and TC, accounting for variations in cell density and sampling differences. A signature was built through *k*-means clustering of the five cell subtypes. Pts were stratified into high/low signature-score groups using the median cutoff and tested for association with progression-free survival (PFS). **Results:** Spatial organization revealed conserved malignant subclusters (C0 and C1) in 19/21 samples from 13 pts (11 non-responders). Top C0 genes were *COL21A1*, *S1PR3*, *LIFR*, and *ZEB1*. Top C1 genes were *KRT6B*, *KRT6C*, *KRTDAP*, and *LCN2*. Pathway analysis predicted activation of cell cycle and glycoprotein 6 in C0, and keratinization and neutrophil degranulation in C1. Comparative expression of OSCC-related gene sets revealed LE correlation with C0, and TC correlation with C1 (both $p < 0.0001$); stronger overlap was seen with the latter highlighting TC as a more conserved feature in HNSCC. Among non-responders, dominant communication patterns in LE and TC included claudins, cadherins, WNT, and IL-6, linked to cell adhesion, migration/invasion, and immune evasion. Signature generated by neighborhood analysis was enriched in TAMs and T cells, depleted in CAFs and reg near LE and TC, while plasma cells were depleted near LE but enriched near TC. Pts with high signature scores (6/13) exhibited improved PFS compared to low scores (7/13), median PFS 6.0 months [95% CI, 2.3-NA] versus 1.9 months [95% CI, 1.8-NA] (p = 0.059). **Conclusions:** To our knowledge, this is the first report using ST analysis to characterize LE and TC architectures in RM-HNSCC, along with heterogeneous neighboring stromal cells with prognostic potential for ICB. Ongoing cohort expansion will elucidate the clinical significance of these findings. Research Sponsor: G. M. is supported by CRIS-Princess Margaret Cancer Centre Drug Development Fellowship Program.

Effect of fusion of radiomic, pathomic, and clinical biomarkers on multi-scale tumor biology and OS stratification in HNSCC receiving standard of care (SOC).

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Background: SOC immunotherapy (IO) for head and neck squamous cell carcinoma (HNSCC) has limited efficacy with inadequate biomarkers (BMs), necessitating improved strategies. Routine radiology and pathology scans provide underutilized tumor data that can address this need. BMs built from these scans can be integrated - along with existing BMs and clinical data - into multimodal predictors for improved stratification by clinical benefit. We evaluated (1) separate BMs using radiomics, pathomics, or clinical data, (2) their cross-modality correlations, and (3) a fused multimodal predictor of overall survival (OS). **Methods:** 100 HNSCC patients (96% male; mean age: 55 yrs; mean BMI: 22.6) treated primarily with pembrolizumab or nivolumab ± chemotherapy in 1L setting were analyzed. Radiomic and pathomic features were extracted via the Picture Health Px Platform. Tumors and adjacent vessels were segmented on pre- and on-treatment CT. Radiomic features (shape, texture, quantitative vessel tortuosity) were extracted, and longitudinal changes were distilled into feature clusters. Pathomics features of tumor and immune cell nuclei morphology and spatial interactions were extracted from baseline H&E whole-slide images. Clinical variables included: PD-L1 CPS, local/regional/distant recurrence, M stage, oral/non-oral cavity site, P16 status, and BMI. Uni- and multimodal models were trained and evaluated by cross-validation to predict OS. **Results:** Radiomics and pathomics models outperformed the clinical model, P16 (HR=0.9, p=0.82) and PD-L1 status (HR=0.7, p=0.08) alone. A fused multimodal model of 6 radiomic clusters, 10 pathomic features, and 6 clinical variables achieved strongest OS stratification (Table 1). High pathomic tumor-immune cell interaction - indicating immune activation - was associated with PD-L1 (p=0.020) and P16 status (p<1e-5), and tied to on-treatment decreases in radiomic wavelet-entropy features of heterogeneity (r=-0.30, p=0.044) and increases in radiomic structural homogeneity (r=0.27, p=0.024). Despite these correlations, each modality contributed independently to the multimodal prediction (R2<0.03), emphasizing complementarity. **Conclusions:** A multimodal BM integrating radiology and pathology to capture tumor properties (heterogeneity, angiogenesis, immune infiltration, nuclei morphology) refined understanding of tumor behavior and IO outcome. Findings suggest an interpretable multimodal BM may better identify high-risk patients who would benefit from alternative therapies, enabling more personalized and effective HNSCC management. Research Sponsor: Genmab.

Model summaries by modality.

Modality	N	Low risk N	High risk N	High Risk HR (p-value)	Median Shortened OS (yrs)
Clinical	100	47	53	1.8 (0.049)	1.09
Pathology	85	62	23	2.4 (0.012)	3.04
Radiology	68	54	14	3.2 (0.0004)	3.06
Multimodal	57	33	24	6.3 (0.0001)	4.20

6047 Poster Session

ctDNA tumor fraction (TF) to predict response to nivolumab in recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): An analysis of the multicentric phase 2 TOPNIVO trial.

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Background: Anti-PD1 provides clinical benefits in HNSCC, yet biomarkers of response remain poorly defined. In other cancer types, measures of ctDNA shedding, such as TF, have been shown to correlate with treatment outcomes. Little is known about ctDNA shedding in HNSCC and its prognostic role. TOPNIVO was a single-arm phase 2 trial designed to assess the tolerability of nivolumab in pretreated R/M HNSCC. The aim of this study is to explore plasma estimation of TF with plasmatic ctDNA and its prognostic role in HNSCC patients receiving nivolumab at 2nd line or later. **Methods:** Plasma samples were obtained at baseline in the phase 2 TOPNIVO study (NCT03226756), just before treatment initiation. Genomic copy number alteration and TF were investigated using low-pass Whole Genome Sequencing performed with ctDNA extracted from plasma. Bioinformatic analysis was based on the ichorCNA (V0.2.0). TF $>$ 3% was considered positive. For Tumor Volume (TV) assessment, primary and secondary lesions were analyzed. When available, all lesions were included if fewer than five were present; otherwise, at least five per organ were manually delineated by two experienced physicians. Volume of each lesion were extracted using LIFEx software V.3.44 (Local Image Feature Extraction, www.lifexsoft.org). Patient's TV was then defined by the sum of the volume of all measured lesions. Primary endpoint was overall survival (OS). **Results:** Plasma samples were available for 86 out of 343 patients, with no major differences compared to the overall cohort in terms of baseline characteristics. In particular, 65 (76%) were male, 12 (14%) had an ECOG PS of 2, 42 (49%) had locally recurrent disease only, and 9 (10%) had HPV-positive oropharyngeal disease. ctDNA TF was positive in all patients (median TF 7.4%, range 4.8% to 35.9%). Median OS of the selected population was 7.4 months (95% CI 5.4 - 11.2). TF was correlated with TV (Spearman 0.31, p = 0.008). Moreover, it was higher in patients with liver metastasis (n = 8, median TF 14% vs 7 %,) and, for oropharynx, higher in patients with HPV positive disease (n= 9 vs 30, median TF 17% vs 6.7%,). TF was correlated with OS both in univariate (Hazard Ratio - HR 1.9, p = 0.015) and multivariate Cox models (HR 3.12, p = 0.003). **Conclusions:** In HNSCC patients of the TOPNIVO study, ctDNA TF was always detectable and depends on tumor volume and on the biology of the disease. TF retains independent prognostic validity. More translational data will be presented on biological correlates of ctDNA shed. Research Sponsor: None.

Multivariable Cox model for overall survival.

Variable	p	HR	95% CI
Sex (male vs female)	0.34	1.40	0.70 - 2.83
Age (> 70)	0.87	1.06	0.53 - 2.11
ECOG PS (2 vs 0-1)	0.97	1.02	0.40 - 2.59
Metastatic only disease vs local recurrence	0.028	0.43	0.20 - 0.91
HPV+ oropharynx vs other	0.99	1	0.39 - 2.52
Log TV	0.78	1.03	0.82 - 1.31
Log TF	0.0032	3.12	1.46 - 6.65

6048 Poster Session

Phase 2 trial of ozuriftamab vedotin (BA3021), a conditionally binding ROR2-ADC, in patients with heavily pretreated squamous cell carcinoma of the head and neck.

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Background: Recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) represents a marked unmet need. ROR2 is a cell-surface transmembrane receptor protein tyrosine kinase highly expressed in several tumor types including HNSCC. Ozuriftamab vedotin is a conditionally binding ROR2 antibody-drug conjugate designed to reduce off-tumor toxicity and improve pharmacokinetics by conditionally binding to ROR2 under low-pH conditions (pH<6.7) of the tumor microenvironment, thus sparing normal tissue. This novel mechanism avoids tissue-mediated drug disposition and improves pharmacokinetics. The recommended Phase 2 dose of 1.8 mg/kg was determined from the Phase 1 trial (NCT03504488). **Methods:** This multi-center, open-label, single-arm Phase 2 trial evaluated ozuriftamab vedotin in patients (pts) with R/M SCCHN previously treated with anti-PD-1 agents. Patients with SCCHN were enrolled and received 1.8 mg/kg of ozuriftamab vedotin given in 2 schedules: once every two weeks (Q2W) or days 1 and 8 of a 21-day cycle (2Q3W). Tumor assessments were conducted by CT or MRI every 6 weeks from Cycle 1 Day 1 until week 12, then every 8 weeks up to 1 year. Evaluable pts included those with at least one post-treatment scan. ROR2 expression was characterized by immunohistochemistry. Additional assessments included pharmacokinetic, pharmacodynamic, immunogenicity, and biomarker evaluations to characterize efficacy and safety. **Results:** As of May 31, 2024, 31 pts received ozuriftamab vedotin either Q2W (n=12) or 2Q3W (n=19) for a median of 84 days. Pts had a median of 3 prior lines of therapy, and all had experienced failure of anti–PD-1 therapy. Among 28 evaluable pts (evaluable as defined as having complete 1 post dose tumor assessment) for best overall response, there were 10 responders (36%; 1 confirmed complete response, and 5 confirmed/4 unconfirmed partial responses, and 14 stable disease. A disease control rate of 86% was observed. Median duration of response for all confirmed responders has not been reached (>3.6 months; 95% CI, 0.4–NE). Most adverse events (AEs) were grade 1-2, with fatigue (59%), anemia (34%), and nausea (34%) being the most frequent. Six pts (19%) experienced grade 3 treatment-related AEs (TRAEs). Two pts experienced a grade 4 TRAE (1 pt with hyponatremia in 2Q3W cohort, and 1 pt with neuropathy in Q2W cohort). No grade 5 TRAEs were observed. **Conclusions:** Pts treated with ozuriftamab vedotin achieved a high rate of disease control with acceptable tolerability. Shows promising efficacy, including in pts refractory to anti-PD1 and warrants further evaluation in SCCHN. Clinical trial information: NCT03504488. Research Sponsor: None.

6049 Poster Session

Establishment and validation of a dynamic prognostic model using serial circulating tumor DNA (ctDNA) for endemic EBV-related nasopharyngeal carcinoma (NPC): A secondary analysis of EP-SEASON.

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Background: Published risk prediction tools have focused on pretreatment factors, whereas the accuracy remains challenging in cancer care. Emerging evidences emphasize the dynamic rather than static recurrence risks during treatment course, and non-invasive diagnostics tools have advanced opportunities for serial tumor assessments. Here, we present an effective dynamic risk individualized prediction model (NPC-DRIM) incorporating serial ctDNA data, using the endemic EBV-related NPC as a model. **Methods:** This study included 1000 patients (pts) enrolled from a prospective biomarker study EP-SEASON, with complete longitudinal ctDNA data at 11 timepoints across treatment: after each neoadjuvant chemotherapy (NAC) circle (T1-3), every week during radiotherapy (T4-T9), within 1 week after radiotherapy (T10), and 1-3 months after radiotherapy (T11). Pts were divided into subcohort$_{NAC}$ (n=752) and subcohort$_{no-NAC}$ (n=248) according to receiving NAC or not, and randomly 70/30% split into training and validation cohort. Time-series and statistical features characterizing the dynamic change of ctDNA at each timepoint were extracted. The NPC-DRIM at T3-T11 were developed using the features selected via Cox univariate analysis in training cohort and then validated. The performance of NPC-DRIM was determined by C-index, time-dependent AUC, calibration curves, and decision curves, and compared with existing models. **Results:** The NPC-DRIM incorporated 4 clinical variables, 8 time-series features and 10 statistical features of ctDNA data. The C-index for predicting recurrence increased with time: 0.64 at T2, 0.69 at T3-T4, 0.70 at T5, 0.71 at T6, 0.73 at T7-T9, 0.77 at T10, and 0.76 at T11 in subcohort$_{NAC}$; 0.70 at T5, 0.68 at T6, 0.82 at T7, 0.78 at T8, 0.73 at T9, 0.74 at T10, and 0.83 at T11 in subcohort$_{no-NAC}$. The NPC-DRIM at T11 had statistically improved outcome prediction compared to other dynamic models (Landmark Cox and Joint Model), and static models (AHR_Chen, RPA_Guo, RPA_Lee, and AJCC_8th staging system) (Table). For individualized dynamic risk prediction, we developed a web-based calculator to visualized the estimated changing recurrence risks. In addition, we showed that the high-risk pts identified by NPC-DRIM benefit from immune checkpoint inhibitors (ICI), while the low-risk pts did not. **Conclusions:** We introduce for the first time that the dynamic risk prediction model NPC-DRIM outperformed the conventional models, facilitating personalized therapeutic paradigms. Clinical trial information: NCT03855020. Research Sponsor: National Natural Science Foundation of China; 92259202; National Natural Science Foundation of China; 82441026; Science and Technology Projects in Guangzhou; 2024B01J1301; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2024ZD0520700; Guangzhou Municipal Health Commission; 2023P-GX02; Cancer Innovative Research Program of Sun Yat-sen University Cancer Center; CIRP-SYSUCC-0010.

	Subcohort$_{NAC}$		Subcohort$_{no-NAC}$	
	C-index	*p* value	C-index	*p* value
NPC-DRIM	**0.76**		**0.83**	
Landmark Cox	0.65	0.01	0.63	<0.01
Joint Model	0.63	<0.01	0.61	0.01
AHR Model (Chen et al. 2021)	0.61	<0.01	0.57	<0.01
RPA Model (Guo et al. 2019)	0.59	<0.01	0.59	<0.01
RPA Model (Lee et al. 2019)	0.59	<0.01	0.66	0.02
AJCC_8th	0.56	<0.01	0.57	<0.01

6050 Poster Session

Mechanisms of resistance to anti-PD1 treatment in recurrent and/or metastatic squamous cell carcinoma of the head and neck: A multi-omics IMMUCAN/EORTC analysis.

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Background: Anti-PD1 therapies improve overall survival (OS) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN), but only a minority of patients (pts) achieve durable responses. The mechanisms driving resistance to anti-PD1 in SCCHN remain poorly understood. **Methods:** Using the IMMUcan multi-omics workflow combining WES, RNAseq, multiplex immunofluorescence and Imaging mass cytometry, we characterized the molecular and immune profiles of R/M SCCHN progressing on anti-PD1 treatment and compared them to an anti-PD1-naïve cohort. **Results:** 74 R/M SCCHN patients who progressed on PD1 inhibitors at the time of tumor biopsy were analysed and compared to a different cohort of 79 R/M SCCHN patients naïve of any anti-PD1 treatment. Among the 74 anti-PD1 resistant patients, 60 patients had primary resistance, and 14 had secondary resistance. Compared to anti-PD1 naïve SCCHN, tumor biopsies from anti-PD1 resistant SCCHN patients exhibited significantly more *EGFR*, *MYCL* and *RRAGC* amplifications, and more genomic alterations of the MYC pathway. Tumor samples harboring MYC pathway alterations were characterized by lower T cell infiltration compared to MYC pathway wild type (WT) tumors, and those harboring an amplification of *EGFR* had less B cells and dendritic cells in the tumor microenvironment compared to *EGFR*-WT. Moreover, transcriptomic and proteomic analyses revealed that secondary resistant SCCHN had increased CD8+ T cell infiltration and higher levels of immune exhaustion markers compared to anti-PD1 primary resistant and to anti-PD1-naïve SCCHN. 48 pts from the anti-PD1-naïve cohort were subsequently treated with PD(L)1 inhibitors. In this subgroup, pts with high B2M expression on tumor cells had better OS. SCCHN with high B2M expression on tumor cells also showed greater T cell infiltration compared to SCCHN with low B2M expression. **Conclusions:** Our data provide a rational to guide the development of therapeutic strategies aimed at reversing acquired resistance to PD-1 blockade in SCCHN. Our data suggest the potential use of B2M expression on tumor cells as predictive biomarker of response to anti-PD1 therapy. Research Sponsor: None.

Clinical characteristics.

	Anti-PD1 naïve cohort (N=79)	Anti-PD1 resistant cohort (N=74)
Substance abuse		
Smoker and/or drinker	68 (86.1%)	62 (83.8%)
HPV-status		
Positive	11 (13.9%)	10 (13.5%)
Primary disease location		
Oral cavity	19 (24.1%)	17 (23.0%)
Oropharynx	34 (43.0%)	33 (44.6%)
Hypopharynx	14 (17.7%)	14 (18.9%)
Larynx	12 (15.2%)	10 (13.5%)
Disease extent at the time of tumor biopsy		
Locoregional only disease	32 (40.5%)	26 (35.1%)
Distant metastatic disease	47 (59.5%)	48 (64.9%)
Number R/M treatment lines prior to biopsy		
0	57 (72.2%)	5 (6.8%)
1	17 (21.5%)	23 (31.1%)
2+	5 (6.4%)	46 (62.2%)

6051 Poster Session

Comprehensive profiling of circulating tumor DNA and microbial landscapes in nasopharyngeal cancer across Asia: NCCH1905/A-TRAIN study.

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Background: Nasopharyngeal cancer (NPC), a malignancy of the nasopharynx, is strongly associated with Epstein-Barr virus (EBV) infection. Although rare in Western countries, NPC is significantly more prevalent in Southeast Asia, likely due to a combination of environmental and dietary factors, though these remain incompletely understood. Current treatments, primarily radiation and chemotherapy, may not fully address the unique challenges posed by NPC. This study aims to conduct a comprehensive genomic analysis, including circulating tumor DNA (ctDNA), and microbial analysis to clarify NPC pathogenesis by examining patient backgrounds in Asian populations. **Methods:** This is an Asian multicenter prospective observational study conducted by nine institutions in Japan, Philippines, Malaysia, Thailand, Singapore, Taiwan and Vietnam. Eligible patients had histological diagnosis of NPC with metastatic and/or recurrent disease. ctDNA will be analyzed in blood samples collected at newly initial diagnosis of metastatic disease and/or at disease progression. Genomic profiling will be analyzed using TruSight Oncology 500 ctDNA for plasma (Illumina) and TruSight Oncology 500 (Illumina) for tumor tissue, respectively. Furthermore, we analyzed more than 3,000 viral genes using tumor tissue. **Results:** Seventy-two samples from 72 NPC patients were analyzed. The median age of the patients was 52 years old (range, 25-78), with 53 (73.6%) males. All the patients were Asian, and the details are as follows: 23 Vietnamese, 15 Chinese, 7 Thai, 6 Taiwanese, 5 Iban, 4 Filipino, 3 Japanese and 3 Malay. The number of patients with a history of surgery and radiotherapy was 10 (13.9%) and 45 (62.5%), respectively. Forty-nine patients (68.1%) had a history of chemotherapy, and all had a history of platinum-based drug administration, while eight (11.1%) had a history of immuno-checkpoint inhibitors administration. Pathogenic variants in ctDNA were detected in 40 out of 72 patients (55.6%). The most frequently deleterious mutations were *TP53*, *NRAS* and *TGFBR2*. Copy number alteration was observed in 33 patients (45.8%). Comprehensive viral and bacterial analysis was available in 20/72 patients (27.8%), with EBV found in 17 patients and none of the viruses in 3 patients. Actinomyces was dominant in all cases, although the bacterial flora was somewhat different. **Conclusions:** In this study, we conducted comprehensive genomic and microbial analyses of samples collected from NPC patients in Asia, and detected various genomic features as well as elucidating the characteristics of the microbial flora present in the background. As a result, it was shown that anaerobic bacteria may be involved in the pathogenesis of NPC. These bacterial groups form a tumor microenvironment through inflammation and immune modulation, and it is suggested that they promote tumor formation. Clinical trial information: NCT05099978. Research Sponsor: AMED (Japan Agency for Medical Research and Development).

6052 Poster Session

Characterizing the prevalence and prognostic significance of MTAP loss in endemic nasopharyngeal cancer using immunohistochemistry (IHC) versus fluorescent in situ hybridization (FISH).

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Background: Methylthioadenosine phosphorylase (MTAP) loss has been associated with poor outcomes in various cancers, including nasopharyngeal carcinoma (NPC). Homozygous deletion of the MTAP locus is one of the most frequent somatic changes in NPC, creating opportunities for therapeutic targeting. However, the concordance between MTAP IHC and FISH for detecting MTAP loss, and the prognostic impact of partial MTAP loss, has not been fully explored. This study evaluated the prevalence of MTAP loss, correlation between IHC and FISH, and association of MTAP expression with time to progression (TTP), progression-free survival (PFS) and overall survival (OS). **Methods:** MTAP expression was analyzed by IHC, and locus loss was confirmed using FISH in tumors M0 (non-metastatic) NPC patients. Correlations between MTAP IHC and FISH results were analyzed to assess concordance, sensitivity, and specificity. Kaplan-Meier survival curves and log-rank tests compared survival distributions, while Cox proportional hazards models were applied for univariate and multivariate analyses. Subgroup analyses were performed by tumor, nodal and overall stage (AJCC 8th edition). **Results:** Among 175 patients, 65 (36.0%) exhibited IHC 0 and FISH-negative MTAP loss. Concordance rate between IHC 0 and FISH-negative was 94.9%. MTAP loss was significantly correlated with higher N2–3 and stage III–IVA disease (Pearson correlation coefficients: 0.81 and 0.73, respectively; $p < 0.0001$). Based on receiver operating curve (ROC) analysis, the optimal MTAP cutoff for progression was 110. Partial MTAP loss (MTAP 0–109) was significantly associated with shorter TTP compared to MTAP 110–300 (median TTP: 4.6 years vs. 15.8 years; $p = 0.04$). In multivariate analysis, MTAP <110 remained significant for TTP (HR = 0.65; CI 0.48-0.98 $p = 0.04$) after adjusting for grouped N stage. Subgroup analyses demonstrated that MTAP <110 was significantly associated with shorter PFS in N2–3 patients (HR 0.5 CI 0.28-0.9 $p = 0.02$) and shorter TTP in stage III–IVA patients (HR 0.61 CI 0.37-1.0 $p = 0.05$). **Conclusions:** Partial MTAP loss (IHC <110) is associated with worse outcomes in NPC, particularly shorter TTP and PFS, with significant prognostic value in advanced nodal and overall stage disease. High concordance between IHC and FISH supports IHC as a reliable diagnostic tool. These findings highlight MTAP expression as a potential prognostic biomarker for NPC, warranting further validation and exploration of targeted therapies. Research Sponsor: Viracta Therapeutics and ScinnoHub Pharmaceutical Co., Ltd.

Tracking circulating tumor DNA through liquid biopsy after radiotherapy for dynamic risk monitoring in cancer patients.

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Background: Circulating tumor DNA (ctDNA) analysis provides a useful tool for non-invasive tumor burden assessment. However, the management of detectable ctDNA without clinical or radiographic evidence of disease during follow-up remains poorly studied and clinically challenge. Here, we explored whether monitoring ctDNA dynamics can differentiate phenotypes in these patients. Nasopharyngeal carcinoma (NPC) is an ideal model for the sensitive detection of cell-free Epstein-Barr virus DNA (cfEBV DNA). **Methods:** The study analyzed medical records of 14,611 non-metastatic NPC cases treated with definitive radiotherapy with or without chemotherapy from two cohorts: a discovery cohort (n = 4,485) and an independent validation cohort (n = 10,126). Cox regression and recursive partitioning analysis (RPA) were used for survival analyses and patient stratification. **Results:** In the discovery cohort, 23.1% of cases presented detectable cfEBV DNA during follow-up and experienced significantly worse survival compared to those with longitudinally undetectable cfEBV DNA (5-year DFS: 39.1% vs. 91.5%, $p< 0.001$). Pre-treatment cfEBV DNA level ($\geq$2000 vs. $<$ 2000 copies/ml) and the maximum level during follow-up ($\geq$500 vs. $<$ 500 copies/ml) were significantly associated with disease failure. Based on the longitudinal dynamic changes, patients with bounce of cfEBV DNA after its clearance had worse survival than those without bounce (HR_{DFS}= 4.3 [3.1-6.0], $p<$ 0.001), and patients with persistent cfEBV DNA had the worst survival (HR_{DFS} = 11.5 [8.3–15.9], $p<$ 0.001). RPA was then conducted incorporating other clinical prognostic factors and four distinct prognostic phenotypes were identified (Table). The model showed a significantly higher positive predictive value (96.6% vs. 60.5%) and similar negative predictive value (67.4% vs. 65.8%) compared to single-point cfEBV DNA assessments. Patients who had clearance of low cfEBV DNA burden had a favorable prognosis (5-year DFS, 83.4%). In contrast, most patients with persistent cfEBV DNA had disease failure (5-year DFS, 8.0%); this subgroup can be defined as molecular relapse. The results were consistent in the validation cohort. Notably, patients in the molecular relapse group benefited from early salvage therapy with improved DFS, whereas patients in other phenotypes responded poorly. **Conclusions:** Tracking longitudinal ctDNA dynamics after definitive treatment can enable more precise risk assessment and facilitate risk-adapted, individualized patient management. Research Sponsor: None.

Prognostic phenotypes based on RPA and cfEBV DNA dynamics.

	HR_{DFS}	
Group	**Discovery cohort**	**Validation cohort**
Clearance of low cfEBV DNA burden (<500 copies/ml)	Reference	
Clearance of high cfEBV DNA burden (≥500 copies/ml)	3.0 [1.9-4.7]	1.6 [1.1-2.2]
Bounce after clearance	5.9 [4.1-8.7]	3.5 [2.5-4.7]
Persistent cfEBV DNA	15.7 [10.8-22.7]	13.0 [9.6-17.7]
	$p<0.001$	$p<0.001$

Induction chemotherapy followed by chemoradiotherapy with cisplatin or cetuximab for unresectable locally advanced head and neck cancer (TTCC-2007-01 trial): Analysis of genomic biomarkers by next-generation sequencing after long-term outcomes.

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Background: Induction chemotherapy (ICT) may provide survival benefit in some patients (pts) with unresectable locally advanced squamous head and neck carcinoma (LA-SCCHN). Objective: Study the benefit of ICT followed by radiotherapy plus cetuximab versus (vs) cisplatin (RT/CET vs RT/CDDP) by profiling predictor biomarkers of response from pts of TTCC-2007-01 trial (NCT00716391). **Methods:** Design TTCC-2007-01: studied the non-inferiority of RT/CET (70Gy + 400mg/250mg/m2 weekly) vs RT/CDDP (70Gy + 100mg/m2 d1-22-43) after ICT (docetaxel 75mg/m2 + platinum 75mg/m2 + 5-FU 750mg/m2 d1-5) in unresectable LA-SCCHN (Oral Oncology, 2022 Nov:134:106087). A cohort of samples were analyzed after DNA extraction and processed using OncoScan platform and TruSight Panel (next-generation sequencing). Survival analysis was performed using Kaplan-Meier (log-rank or Breslow test, survival in months 'm') and Cox regression (HR 95% CI). Statistical significance was $p<0.05$ (SPSSv28). **Results:** In total, 70 pts (male 90% / female 10%) were analyzed in RT/CDDP arm (mean age 55 [45-68]) versus 72 pts (male 88,9% / female 11.1%) in RT/CET arm (mean age 60 [32-70]). The most frequent localizations in RT/CDDP arm were oropharynx (44.3%) and hypopharynx (21.4%). In RT/CET were oropharynx (37,5%) and hypopharynx (23,6%). In RT/CDDP arm HPV was positive in 17.1% of tumors versus 13,1% in RT/CET. In RT/CDDP arm the median overall survival (OS) was 65m [25.6-105.4] vs 36.8m [14.3-59.2] in the RT/CET arm. The progression-free survival (PFS) was 33.2m [16.2-50-1] in the RT/CDDP arm vs 18.3m [9.1-28.6] in the RT/CET arm. *TP53* was the most frequent mutation without differences in OS in either arm. However, mutations were associated with unfavorable PFS in the RT/CDDP arm (22.6 vs 66.2; p=0.025 Breslow), with no difference in RT/CET arm (20.1 vs 15.2; p=0.885 Breslow). HPV+ tumors were associated with better OS (83.9 vs 33.2; p=0.027 Breslow) in RT/CDDP arm. There was no difference in the RT/CET arm (28.1 vs 23.9; $p>0.05$). In the RT/CDDP arm the chromosomal biomarker that was associated with worse OS was 18q12.2- (22.7 vs 85.6; HR 3.3 [1.6-6.6]). Focal alterations 3p14.2- had superior OS (83.9 vs 22.9m; HR 0.1 [0.04-0.30]). In the RT/CET arm the 6p25.3+ biomarker was associated with superior OS (not reached vs 26.6m; HR 0.42 [0.2-0.8]). In terms of PFS in RT/CDDP arm, gains in 2p were associated with worse PFS (12.0 vs 41.7m; HR 2.9 [1.4-6.2]). 6p25.3+ alterations had better PFS in the RT/CET arm (38.8 vs 11.5; HR 0.40 [0.2-0.8]). **Conclusions:** ICT plus RT/CDDP was shown most beneficial in pts with *TP53* wild type, HPV+ and 3p14.2-. In contrast, ICT plus RT/CET is not influenced by *TP53* or HPV. 6p25.3+ is a robust biomarker of response in RT/CET arm in terms of OS and PFS. Correct pts selection may allow for further standardization of ICT in LA-SCCHN. Research Sponsor: Carlos III Health Institute; PI18/01476.

6055 Poster Session

Characterization of dynamic changes in tumor-infiltrating lymphocytes (TIL) after neoadjuvant administration of CUE-101, an HPV16 E7-HLA-IL2 fusion protein, to patients with HPV+ locally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC).

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Background: CUE-101 is a novel fusion protein designed to selectively engage and expand HPV16-specific T-cells to promote an anti-tumor immune response in HPV+ malignancies. CUE-101 is comprised of the HPV16 $E7_{11-20}$ epitope, HLA-A*0201, and a reduced affinity human IL2. In this single-arm Phase 2 trial (NCT04852328), CUE-101 is administered to HLA-A*0201+ patients with HPV16+ LA-OPSCC in three schedules (A, B, and C) before curative-intent surgery and adjuvant therapy or definitive chemoradiation therapy. Primary endpoints were safety of CUE-101 and changes in the frequency of HPV16 $E7_{11-20}$-specific CD8+ T cells in blood and tumor. Correlates in TIL for Schedules A and B are presented here. **Methods:** CUE-101 (4 mg/kg IV) was administered 14 days (Schedule A), 14 and 7 days (Schedule B), or 7 days (Schedule C) before curative-intent treatment. Biopsies of the primary tumor were collected before CUE-101 administration and within 2 days prior to curative-intent therapy. Single-cell RNA and T-cell receptor (TCR) sequencing (scRNAseq, 10X Genomics) was performed on fresh sorted CD8 T-cells. HPV16 $E7_{11-20}$ dextramer staining and flow cytometry assessed reactivity to HPV E7. Multiplex immunofluorescent (mIF) tissue staining with a 30-marker Phenocycler panel (Akoya Biosciences) assessed tumor, myeloid, and T-cell states. Changes in T-cell clonal frequency were significant if fold change >2 and fisher exact test adjusted $p < 0.05$. Changes in cell populations after treatment were evaluated by two-tailed paired student's t-test. **Results:** Of 20 total patients enrolled, paired biopsies from 13 of sufficient quality were analyzed by scRNAseq, flow cytometry, and mIF. In a joint analysis of Schedules A (n=7) and B (n=6), we identified multiple T-cell clones that significantly expanded following CUE-101 treatment, representing 4-51% (mean 18.3%) of tumor-infiltrating CD8 cells by scRNAseq. Among these, we found significant enrichment for phenotypes of chronic T cell activation (PD1+CD39+, often associated with tumor reactivity, $p = 0.041$). In agreement with this finding, flow cytometry of TIL showed increased CD8+CD39+ cells (mean 10.9%, $p = 0.026$) among CD45 cells, and a small increase in NK cells (1.7%, $p = 0.005$). Absolute cell counts by mIF confirmed these trends. Direct dextramer staining of TIL samples has not specifically identified HPV $E7_{11-20}$ reactive T cells pre- or post-treatment, therefore cloning of TCRs from expanded T-cells is being performed to enable functional testing of HPV reactivity. **Conclusions:** Significant clonal expansion of intra-tumoral CD8 T-cells with signatures associated with tumor reactivity were observed within 2 weeks of CUE-101 administration in HPV16+ LA OPSCC. Studies in blood and of T-cell specificities are ongoing. Clinical trial information: NCT04852328. Research Sponsor: CUE Biopharma.

6056 Poster Session

Survival association of PIK3CA in HPV-driven head and neck squamous cell carcinoma (HNSCC).

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Background: Across many solid tumor malignancies, including head and neck squamous cell carcinoma (HNSCC), clinical trial data has supported the integration of PD1 Immune Checkpoint Inhibitors (ICIs) into treatment algorithms; however, durable response to single agent therapy occurs in only a fraction of patients. Thus, there is a great need to understand the molecular underpinnings of response and resistance mechanisms. PIK3CA mutation is a common driver of HPV+ mediated malignancy. We sought to understand the prevalence and clinical impact of PIK3CA mutation in HPV+ and HPV- cancer by applying a multi-omics approach to a large, clinically appended dataset. **Methods:** HNSCC (N = 1901) patient who underwent DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing at Caris Life Sciences (Phoenix, AZ) was queried to identify HPV+ and HPV- HNSCC cohort. Tumor mutational burden (TMB) was measured by totaling all somatic mutations (mt) per tumor (TMB-H: $>$ 10 mt/MB). Real-world overall survival (rwOS) was obtained from insurance claims data, calculated from either time of biopsy (OS) or start of immunotherapy ($_{IO}$OS) to last contact, or time on ICI ($_{IO}$TOT). Mann-Whitney U and X^2/Fisher-Exact tests were applied, with *p*-values adjusted ($p < .05$). **Results:** Compared to HPV- samples, PIK3CA mutation was highly associated with HPV+ primary (28.5% vs 11.4%, p $<$0.01) and metastatic (23.8% vs 11.2%, p$<$0.01) lesions. The prevalence of TMB-H was significantly higher in both HPV+ (30.7% vs 7.9%, p$<$0.01) and HPV- (30.7% vs 18.2%, p$<$0.01) with PIK3CA mutation compared to WT. HPV- disease showed significantly worse survival as expected (HR = 0.63, p$<$0.001), while PIK3CA mut /wt status was not associated with differences in OS among HPV+ (HR = 1.05, p = 0.78) or HPV- cohorts (HR = 1.11, p = 0.44). However, irrespective of tumor site and metastatic status, mutPIK3CA HPV+ patients' trend towards an increased $_{IO}$OS (HR = 0.64, p =0.176) and increased $_{IO}$TOT compared to wtPIK3CA patients (HR = 0.72, p = 0.073). In contrast, mutPIK3CA HPV- HNSCC showed worse $_{IO}$OS (HR = 1.65, p$<$0.001) and a trend toward decreased $_{IO}$TOT (HR = 1.20, p=0.248) compared to wtPIK3C patients. **Conclusions:** Data from this cohort indicate potential survival association for PIK3CA mutation, with differing impact in HPV+ and HPV- HNSCC. Further research is needed to explore the mechanism underlying these findings and identify other molecular factors that might contribute to the observed outcomes. Research Sponsor: None.

6057 Poster Session

Evaluation of plasma methylated DNA markers for detection HPV-positive oropharyngeal squamous cell carcinoma: A case control study.

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Background: The incidence rate of human papillomavirus associated oropharyngeal squamous cell carcinoma (HPV(+)OPSCC) has persistently increased over the past decade and is anticipated to rise further over the next decade. Cost effective, accurate, and less invasive screening options for HPV(+)OPSCC have remained stagnant leading to the interrogation of circulating tumor DNA in liquid biopsies such as plasma. We hypothesized that candidate methylated DNA markers (MDMs), previously described by our group, would be present in the plasma of patients with HPV(+)OPSCC and absent in controls. **Methods:** HPV(+)OPSCC cases were enrolled from a high-volume referral practice. Cancer-free control patients were identified from the surrounding 7-county catchment area and frequency matched to cases by age and alcohol use. cfDNA was extracted from 4 mL of plasma and bisulfite converted prior to Target Enrichment Long-probe Quantitative Amplified Signal assays for 15 MDMs. Strand counts for individual MDMs were normalized to a methylated genomic reference marker. An MDM score was derived via random forest modeling of the 15 MDMs. Area under the receiver operator characteristic curve (AUC) for discriminating cases from controls was evaluated for individual markers and for the MDM score. The sensitivity of the MDM score at 95% specificity was also evaluated. **Results:** The study consisted of 96 HPV(+)OPSCC and 100 cancer-free controls. The study population was predominately white (95%) with a median age of 61 yrs (IQR: 52-69 yrs). Eighty-nine percent of the cases were male with cancers affecting either the tonsil in 50 (52%) or base of the tongue in 46 (48%) patients; by design 50% of controls were male. Stage I:II:III:IV disease was present in 66%:22%:9%:3% of the cases. The median (IQR) AUC across the 15 MDMs was 0.83 (0.82-0.85) overall: 0.78 (0.77-0.83) for stage I disease and 0.92 (0.91-0.93) for stage II-IV disease. The MDM score for the combined panel of 15 MDMs achieved a cross-validated AUC of 0.93 (CI: 0.89-0.97) overall: 0.90 (CI: 0.84-0.96) for stage I disease and 0.98 (CI: 0.97-1.00) for stage II-IV disease. At 95% specificity, the cross-validated sensitivity of the MDM score for HPV(+) OPSCC was 80% (CI: 71-87%) overall: 73% (CI: 60-83%) for stage I disease and 94% (CI: 78-99%) for stage II-IV disease. **Conclusions:** We validated a set of previously discovered MDM markers in HPV(+)OPSCC in a robust case control cohort using plasma. The MDMs were detected in both early and late-stage disease. Additional prospective studies in larger intended use cohorts are needed to validate our results for clinical use. Research Sponsor: None.

6058 Poster Session

Evidence of a role for oropharyngeal cancer cells with low HPV gene expression in treatment failure.

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Background: A subset of tumor cells with reduced HPV gene expression, here termed HPV-lo cells, are proposed contribute to therapy resistance in HPV+ oropharyngeal cancers (OPCs). However, the biologic and clinical significance of this cell state is unclear because it has been analyzed in relatively few HPV+ OPCs and total tumor cells and remains to be directly linked to therapy resistance and recurrence. We aimed to evaluate HPV-lo cells for their biologic traits, cytotoxic drug responses, and association with recurrence. **Methods:** Single cell mRNA sequencing (scRNAseq) was performed on 64,822 tumor cells from five HPV+ OPC PDXs, and HPV-lo cells were defined by presence of <1.0 normalized HPV mRNA reads. Expression profiles distinguishing HPV-lo cells were assessed by gene set enrichment analysis. Changes in HPV-lo cell frequency and gene expression were examined by scRNAseq after two weeks of *in vivo* cisplatin treatment in NSG mice. To test for association of HPV-lo cells with recurrence, a single institution cohort of 851 therapy-naïve p16+ OPC patients receiving primary surgery was used to curate 50 pT1/2 tumors that later recurred (cases) and match 50 tumors that were cured (controls) for pathologic stage, smoking history, and adjuvant therapy. A clinical *in situ* hybridization (ISH) assay was used to probe for HPV E6/E7 in the case-control cohort. Digital image analysis segmented the ISH(+) vs. ISH(-) cells in tumor regions plus the subset of ISH(-) cells comprised of CD45-IHC(+) tumor infiltrating leukocytes (TILs). The ISH(-) tumor cell fraction was estimated by calculating total %ISH(-) cells - %TILs. **Results:** Content of HPV-lo cells in PDXs ranged from 32% to 65%. These cells showed significant downregulation of E2F target genes and upregulation of p53 target genes, supporting presence of reduced HPV E6/E7 activity. Their relative quiescence was further supported by transcriptional inference of fewer cells in the $S/G_2/M$ cell cycle fractions. HPV-lo cell content in the PDXs negatively correlated with cisplatin response measured by T/C ratio ($r=-0.96$, $p=0.007$), and the size and gene expression profile of this fraction were largely unaltered by cisplatin. In the case-control cohort, the HPV ISH(-) tumor cell fraction was larger in cases ($p<0.001$), which often contained large tumor regions devoid of ISH(+) cells. The %ISH(-) tumor cells provided favorable discrimination of cases vs. controls based on an area under the ROC curve of 0.77 ($p<0.001$, OR=66, 95% CI=11-547). **Conclusions:** HPV+ OPCs contain a subset of tumor cells with reduced HPV gene expression and a relatively quiescent phenotype, and increased size of this cell fraction appears predictive of recurrence. Cell state dynamics maintaining this fraction during cytotoxic therapy may contribute treatment failure. Thus, HPV-lo cells merit evaluation for generalizability as a biomarker and mechanistic interrogation as an etiology for tumor recurrence. Research Sponsor: None.

6059 Poster Session

Risk factors for aspiration pneumonia related to postoperative chemoradiotherapy for high-risk head and neck cancer: A supplementary analysis of a phase II/III JCOG1008 trial.

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Background: A randomized phase II/III trial (JCOG1008) suggested that postoperative chemoradiotherapy (POCRT) with weekly cisplatin is a treatment option for patients with postoperative high-risk locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). Aspiration pneumonia (AP) is one of the most important toxicities associated with CRT. This study investigated the clinical risk factors for AP during and after POCRT. **Methods:** Patients enrolled in JCOG1008 were analyzed to evaluate the incidence of AP, to identify the clinical risk factors for AP during and after POCRT, and to assess the influence of AP on treatment outcomes. AP was defined as a clinical condition meeting all of the following criteria: (i) patients had both subjective and objective symptoms suggesting pneumonia, (ii) the presence of aspiration was suspected clinically or by endoscopic or video-fluorographic examinations, (iii) no evidence of micro-organisms that cause atypical pneumonia. Analyses were performed by logistic regression model. **Results:** Of 251 patients who underwent POCRT, 100 patients who underwent laryngectomy was excluded. Among the 151 patients who received POCRT, 93 (61.6%), 85 (56.3%), and 113 (74.8%) developed AP during, after, and overall period of POCRT, respectively. The multivariable analyses identified two independent risk factors for AP occurring during or after POCRT: PS 1 [vs. PS 0; odds ratio (OR) 3.416, 95% CI (1.192-9.789), p = 0.0222] and dysphagia ≥grade 3 (vs. grade 1-2; OR 46.333, 95% CI (2.901-740.080), p = 0.0067). The multivariable analyses also identified two independent risk factors for AP occurring after POCRT: dysphagia ≥grade 3 (OR 3.995, 95% CI (1.538-10.375), p = 0.0045) and reconstruction surgery (OR 3.452, 95% CI (1.616-7.374), p = 0.0014). Charlson comorbidity score ≥4 and the use of sleeping pills at the end of POCRT were marginally associated with the onset of AP after POCRT (OR 2.699, 95% CI (0.919-7.926), p = 0.0708, OR 2.107, 95% CI (0.918-4.837), p = 0.0788, respectively). The occurrence of AP was not significantly associated with overall survival, relapse-free survival, and local relapse-free survival. **Conclusions:** PS 1, dysphagia ≥grade 3, and prior reconstruction surgery were associated with the onset of POCRT-related AP. Careful attention should be paid to these risk factors for AP in patients with LA-SCCHN undergoing POCRT. Clinical trial information: jRCTs031180135. Research Sponsor: National Cancer Center Research and Development Funds; Grant-in-Aid for Clinical Cancer Research; The Japan Agency for Medical Research and Development.

Anti-programmed death-1 inhibitors and nimotuzumab in combination with induction chemotherapy for locoregionally advanced nasopharyngeal carcinoma: A propensity score-matched analysis.

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Background: The poor prognosis of locoregionally advanced nasopharyngeal carcinoma (LANPC) due to the high incidence of metastasis necessitates effective treatment strategies. Synergistic effects have been observed when anti-programmed death-1 (anti-PD-1) inhibitors are combined with chemotherapy or targeted therapy. **Methods:** In total, 319 patients with LANPC were retrospectively enrolled between December 2017 and November 2022. The primary endpoint was progression-free survival. Propensity score matching was performed to adjust for potential confounders. **Results:** Overall, 150 patients were included after propensity score matching. The immunotherapy + nimotuzumab + chemotherapy (INC) group (n=50) had a higher 3-year progression-free survival rate (96.6% [95% confidence interval (CI): 93.2–100.0]) than the nimotuzumab + chemotherapy (NC) group (n=100) (79.8% [95% CI: 75.6–84.0]). The INC group had a hazard ratio of 0.16 (95% CI: 0.02–1.22; P=0.04). The objective response rates were 100% and 99% for the INC and NC groups, respectively. Grade ≥3 treatment-related adverse events were reported in eight (5.3%) patients, and hyponatremia (2.0%) was the most common. Grade ≥3 immune-related adverse events (rash and reactive capillary proliferation) were reported in two (4.0%) patients. **Conclusions:** Neoadjuvant therapy with anti-PD-1 inhibitors and nimotuzumab combined with chemotherapy demonstrates promising anti-tumor activity with acceptable safety for LANPC. More well-designed randomized trials with larger patient cohorts are needed to confirm long-term efficacy. Research Sponsor: None.

Short-term efficacy of three months after the end of treatment.

Response evaluation	INC group [n = 50 (%)]	NC group [n = 100 (%)]
CR	38 (76.0)	19 (19.0)
PR	12 (24.0)	80 (80.0)
SD	0	1 (1.0)
PD	0	0
ORR (95% CI)	100% (92.9%, 100%)	99% (94.6%, 100%)
DCR (95% CI)	100% (92.9%, 100%)	100% (96.4%, 100%)

CI, confidence interval; CR, complete response; DCR, disease control rate; IC, induction chemotherapy; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

6061 Poster Session

Initial results of MC200710 investigating therapeutic vaccine (PDS0101) alone or with pembrolizumab prior to surgery or radiation therapy for locally advanced HPV associated oropharyngeal carcinoma, a phase 2 window of opportunity trial.

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Background: PDS0101 is a T cell stimulating immunotherapy (therapeutic vaccine) targeting HPV16. The combination of PDS0101 + pembrolizumab (5 cycles) has shown durable clinical responses in HPV-positive recurrent/metastatic HNSCC. MC200710 is a window of opportunity study in patients with HPV-associated oropharyngeal squamous cell carcinoma (HPV+ OPSCC). This prospective phase II trial utilized 2 cycles of neoadjuvant PDS0101 aloneor in combination with pembrolizumab prior to surgical resection or chemoradiotherapy (CRT). Herein, we report the initial results, including primary endpoint of ctDNA response. **Methods:** Between June 2022 and September 2024, 20 patients (10 per Arm) with locally advanced HPV+ OPSCC were enrolled in a sequential alternating design. Arm A received 2 cycles of PDS0101 and Arm B received 2 cycles of PDS0101 and pembrolizumab with all patients undergoing subsequent surgery or CRT. Assessments were done at baseline, post cycle 1, and post cycle 2 (prior to surgery or CRT). The coprimary endpoint of ctDNA response was defined as a $\geq$50% decline in ctDNA post cycle 2 compared to baseline as quantified using NavDx (TTMV fragments/mL). Radiologic objective response rate (ORR) was assessed as per RECIST 1.1. Toxicity through the neoadjuvant period was assessed using CTCAE criteria and recurrence rates following surgery or CRT are reported. **Results:** Patients were similar between arms: male 90%, median age 61 years, cT1/T2 70%, cN1 65%, and no smoking history 65%. All patients completed both cycles of therapy with 13 (65%) undergoing primary operative management and 7 CRT (35%). The most common toxicity was injection site reaction 85% grade 1, 15% grade 2, 0% grade 3, consistent with prior studies. One patient experienced grade 2 pneumonitis during the neoadjuvant window (Arm B). There was one grade 3 toxicity (5%) possibly attributable to study intervention with one patient experiencing transient hepatitis requiring hospitalization (Arm A). Zero of 10 patients in Arm A had a $\geq$50% decline in ctDNA from baseline while 5 of 10 patients (50%) met this primary endpoint in ARM B (p=0.03). After Cycle 2, based on RECIST 1.1, no Arm A patients had a partial response (PR), with 7 having stable disease (SD); Arm B had 2 patients with PR and 8 with SD. With median follow up of 6 months, 2 patients in Arm A recurred and 0 patients in Arm B. **Conclusions:** The combination of PDS0101 and pembrolizumab met the trial's primary endpoint of ctDNA response and shows promise for further evaluation. ctDNA can be used to assess early response and future studies could use ctDNA to adapt neoadjuvant therapy. Based on these findings, a neoadjuvant dose optimization study in HPV16+ oropharyngeal carcinoma is warranted and evaluation of PDS0101 and pembrolizumab in comparison to pembrolizumab alone. Clinical trial information: NCT05232851. Research Sponsor: PDS Biosciences.

6062 Poster Session

Efficacy of definitive radiotherapy with concurrent and adjuvant immune checkpoint inhibitors in patients with locally advanced head and neck squamous cell carcinoma (LA HNSCC).

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Background: Head and neck squamous cell carcinoma (HNSCC) is the most common type of head and neck cancers, associated with a high incidence and mortality. In 2019, the FDA approved pembrolizumab for the treatment of recurrent/metastatic (RM) HNSCC. While many promising results were noted in the RM setting, unfortunately this was not the case for locally advanced HNSCC (LA HNSCC). Multiple studies have yielded negative results. This meta-analysis aims to further explore the efficacy of immune checkpoint inhibitors (ICIs) in the treatment of LA HNSCC. **Methods:** MEDLINE and EMBASE databases were systematically searched up to December 31, 2024. Randomized controlled trials (RCTs) evaluating ICIs in patients with LA HNSCC were included. The primary outcome was 2-year progression-free survival (PFS). A generic inverse variance method was used to calculate the estimated pooled hazard ratio (HR) for PFS with 95% confidence interval (CI). Heterogeneity was assessed with Cochran's Q test. Fixed effects model was applied. **Results:** A total of 1,687 patients from 2 phase III RCTs (KEYNOTE-412, JAVELIN Head and Neck 100) and 1 phase II/III RCT (NRG-HN004) were analyzed. NRG-HN004 compared durvalumab + radiotherapy (RT) vs cetuximab + RT, while KEYNOTE-412 and JAVELIN Head and Neck 100 compared pembrolizumab or avelumab + chemoradiotherapy (CRT) vs CRT alone, respectively. In PD-L1 positive cohort, longer PFS was noted in the ICIs arm (HR 0.81; 95% CI: 0.67-0.99; P=0.04), while in PD-L1 negative cohort, we noted the opposite with a shorter PFS in the ICIs arm (HR 1.34; 95% CI: 1.02-1.76; P=0.03). PFS was not different between the two treatment arms in the overall population and all the other subgroups, including HPV negative, HPV positive, males, and females. We conducted a subset analysis of cisplatin-eligible (CE) LA HNSCC including KEYNOTE-412 and JAVELIN Head and Neck 100 trials to assess the addition of ICIs to definitive CRT. We also noted increased PFS in PD-L1 positive cohort in the ICIs arm (HR 0.78; 95% CI: 0.63-0.97; P=0.02). However, in PD-L1 negative cohort, PFS was near significant to be decreased in the ICIs arm (HR 1.31; 95% CI: 0.99-1.75; P=0.06). **Conclusions:** This study showed that definitive radiotherapy with concurrent and adjuvant ICIs in LA HNSCC was associated with increased PFS in the PD-L1 positive group but decreased PFS in the PD-L1 negative arm. NRG-HN004 trial demonstrated that immunoradiotherapy was inferior to radiation plus cetuximab in cisplatin-ineligible LA HNSCC. In the subset analysis of CE LA HNSCC, addition of ICIs to standard CRT has more pronounced significant PFS in the PD-L1 positive cohort, while there is a trend towards decreasing PFS in the PD-L1 negative cohort. Further studies are needed in the future to evaluate the efficacy of ICIs addition to standard definitive CRT in PD-L1 positive or high LA HNSCC. Research Sponsor: None.

6063 Poster Session

Prognostic impact of preoperative imaging-detected extranodal extension in head and neck squamous cell carcinoma treated with postoperative chemoradiotherapy.

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Background: In 2024, the Head and Neck Cancer International Group (HNCIG) newly defined imaging-detected and pathological extranodal extension (iENE/pENE). We previously reported the utility of iENE in induction chemotherapy followed by definitive chemoradiotherapy (Onaga R, et al. ASCO Annual Meeting, 2024). However, the significance of iENE in surgically treated head and neck squamous cell carcinoma (HNSCC) remains unclear, particularly in high-risk populations with positive pENE. We aimed to investigate the prognostic value of iENE in patients treated with completed surgery and postoperative chemoradiotherapy (poCRT) due to pENE-positivity. **Methods:** We retrospectively analyzed patients with HNSCC (oral cavity, oropharynx, hypopharynx, or larynx) who underwent surgical resection between 2013 and 2023 at our hospital. pENE-positive patients who received poCRT (cisplatin $\geq$ 200 mg/m^2 and radiation therapy $\geq$ 60 Gy) were included, excluding those with positive surgical margins of the primary site. iENE grading on preoperative CT or MRI and pENE assessment in surgical specimens were re-evaluated according to HNCIG consensus recommendations. Relapse-free survival (RFS) and Overall survival (OS) were analyzed using the log-rank test. **Results:** We identified 95 patients with a median age of 62 years (range: 16-76). The primary tumor sites included oral cavity (58 patients), hypopharynx (29), larynx (5), and oropharynx (3). iENE grades were 0/1/2/3 in 24/29/13/29 patients, and pENE was categorized as minor ENE/major ENE/soft tissue metastasis (STM) in 40/20/35 patients. With a median follow-up of 42.1 months, 43 patients developed recurrence (local/regional/distant/regional and distant: 1/7/30/5). In the iENE classification, the 5-year RFS for iENE Grades 0/1/2/3 was 77.8%, 60.3%, 35.9%, and 33.4% (p=0.003), and the 5-year OS was 88.8%, 70.5%, 37.8%, and 63.0% (p=0.021), respectively. When iENE grades were grouped into Grade 0/1 and Grade 2/3, the latter group had significantly shorter RFS (5-year RFS: 68.0% vs. 34.2%, $p < 0.001$) and OS (5-year OS: 78.3% vs. 55.9%, p = 0.008). In the pENE classification, no significant differences in RFS and OS were observed among minor ENE, major ENE, and STM (p=0.380 for RFS, p=0.617 for OS). **Conclusions:** Our study revealed for the first time that preoperative iENE was a significant prognostic factor for pENE-positive patients treated with poCRT. Specifically, patients with iENE grade 2/3 exhibited a poor prognosis, emphasizing the need for additional treatment strategies tailored to this very high-risk group. Research Sponsor: None.

Prognosis based on iENE grades and pENE category.

		N=95	5-year RFS	p-value	5-year OS	p-value
iENE	Grade 0	24	77.8%	0.003	88.8%	0.021
	Grade 1	29	60.3%		70.5%	
	Grade 2	13	35.9%		37.8%	
	Grade 3	29	33.4%		63.0%	
pENE	Minor ENE	40	60.9%	0.380	70.6%	0.617
	Major ENE	20	56.4%		70.1%	
	Soft tissue metastasis	35	45.1%		66.6%	

Concurrent chemoradiotherapy with or without nimotuzumab in induction chemotherapy resistant locoregionally advanced nasopharyngeal carcinoma: An open-label randomised, controlled, phase 2 trial.

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Background: Induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) is the current standard of care for locoregionally advanced nasopharyngeal carcinoma (LA-NPC). Patients resistant to IC have a high risk of treatment failure. Nimotuzumab, a humanized anti-epidermal growth factor receptor (EGFR) antibody, has shown potential efficacy in combination with CCRT. This randomized phase 2 trial aimed to evaluate the efficacy and safety of nimotuzumab plus CCRT compared to CCRT alone in IC-resistant LA-NPC. **Methods:** We conducted an open-label, randomized phase 2 trial at Sun Yat-sen University Cancer Center, Guangzhou, China. Eligible patients (aged 18–70) had untreated, nonkeratinizing, IC-resistant stage II–IVa (the 8th edition of the American Joint Committee on Cancer classification system) LA-NPC, defined as detectable plasma Epstein-Barr virus (EBV) DNA and/or stable/progressive disease after two cycles of IC. Other inclusion criteria were ECOG performance status of 0–1, positive EGFR expression and adequate organ function. Patients were randomized (1:1) to receive CCRT plus nimotuzumab or CCRT alone. Cisplatin (100 mg/m^2) was given on days 1, 22, and 43 of intensity-modulated radiotherapy in both groups. In the experimental group, nimotuzumab (200 mg) was administered weekly during CCRT. Randomization was done using a computer-generated code random number code with a block size of six, stratified by disease stage. The primary endpoint was 2-year progression-free survival (PFS) in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of the assigned treatment. The study was registered at ClinicalTrials.gov (NCT04223024), and patients are under follow-up. **Results:** Two hundred forty-six patients were enrolled and randomized (121 to CCRT plus nimotuzumab, 125 to CCRT alone). At a median follow-up of 47 months (IQR 44–50), the 2-year PFS was 81.0% (95% CI 72.8–86.9) in the CCRT plus nimotuzumab group and 80.8% (95% CI 72.7–86.7) in the CCRT group (stratified HR 0.93 [95% CI 0.59–1.47], p=0.70). The most frequent grade 3–4 adverse events were mucositis (24 [20.2%] vs 22 [17.6%]), leukopenia (23 [19.3%] vs 21 [17.2%]), and nausea (14 [11.8%] vs 16 [13.8%]) in the CCRT plus nimotuzumab group compared with CCRT group. A higher frequency of grades 1–2 rash was observed in the CCRT plus nimotuzumab group (15 [12.6%] vs 6 [4.9%]). Late adverse events were predominantly mild, with no grade 4 events reported in either group. No treatment-related deaths occurred in either group. **Conclusions:** In IC-resistant LA-NPC, the addition of nimotuzumab to CCRT did not provide a significant survival benefit. Further research into predictive biomarkers and novel combinations is needed to optimize treatment for high-risk populations. Clinical trial information: NCT04223024. Research Sponsor: None.

6065 Poster Session

Patient-reported outcomes (PROs) in the C-POST trial of adjuvant cemiplimab (cemi) vs placebo (pbo) for high-risk cutaneous squamous cell carcinoma (CSCC).

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Background: C-POST is a phase 3, double-blind, pbo-controlled trial (NCT03969004) of adjuvant cemi for treatment of patients (pts) with CSCC at high risk of recurrence after surgery and radiation therapy. Positive results for the primary endpoint of disease-free survival (DFS) at interim analysis 1 are reported in a separate ASCO abstract. Here we evaluate adjuvant cemi vs pbo on PROs as exploratory endpoints. **Methods:** Pts (N=415) were randomized 1:1 to adjuvant cemi or pbo for up to 48 weeks (4 cycles). The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) was administered at Day 1 of every cycle, end of treatment, and during follow-up. The pre-specified PRO analysis focused on 6 QLQ-C30 scales of global health status (GHS)/QoL; 3 functional scales (physical [PF], role [RF], emotional [EF]); and 2 symptom scales (fatigue [FA], pain [PA]). Overall changes from baseline across treatment cycles were analyzed using mixed effects models for repeated measures; if 95% CIs did not cross zero, differences were considered of nominal statistical significance (α=0.05) as no adjustment was made for multiplicity. PRO responder analysis used a published threshold of 10 points for clinically meaningful change across scales; median time to first deterioration was determined using Kaplan–Meier analyses. **Results:** QLQ-C30 completion rates from baseline through all cycles were >88% in both arms. Baseline scores showed moderate-to-high GHS/QoL and functioning and low symptom burden (Table). Overall changes from baseline on QLQ-C30 GHS/QoL, functioning, and symptom scores were small and similar between arms (Table). In the PRO responder analysis, most pts in both arms reported maintenance or clinically meaningful improvement in QoL in all scales across all cycles (cemi: 55.9–86.8%; pbo: 55.5–88.2%). Median time to first deterioration was also similar between arms in all scales (cemi: 5.3–25.6 months; pbo: 8.3–22.2 months). **Conclusions:** QoL was maintained during treatment with adjuvant cemi, with no clinically meaningful worsening vs pbo. These PRO results complement the observed improvement in DFS and support the favorable risk profile of adjuvant cemi for pts with high-risk CSCC. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals, Inc.

	Baseline mean (SD)		Overall LS mean change from baseline (95% CI)		
QLQ-C30 scale	Cemi (n=209)	Pbo (n=206)	Cemi (n=209)	Pbo (n=206)	Difference (95% CI)
GHS/QoL	75.4 (17.5)	75.8 (17.4)	−2.0 (−4.3, 0.4)	−1.0 (−3.4, 1.4)	−0.9 (−3.7, 1.8)
PF	87.1 (16.0)	90.6 (13.9)	−1.4 (−3.2, 0.5)	−1.9 (−3.9, 0.0)	0.5 (−1.7, 2.7)
RF	83.8 (24.8)	84.2 (20.8)	−4.2 (−7.3, −1.2)	−1.6 (−4.8, 1.5)	−2.6 (−6.2, 0.9)
EF	84.6 (18.7)	85.1 (16.7)	0.2 (−2.2, 2.7)	−0.4 (−2.9, 2.1)	0.7 (−2.2, 3.5)
FA	20.9 (19.9)	20.5 (20.1)	5.0 (2.2, 7.7)	4.2 (1.4, 7.0)	0.8 (−2.4, 4.0)
PA	14.7 (21.2)	13.1 (20.4)	3.2 (−0.1, 6.5)	2.1 (−1.3, 5.6)	1.1 (−2.8, 5.0)

6066 Poster Session

Osteoradionecrosis as a complication following intensity-modulated radiation therapy or proton therapy in the treatment of oropharyngeal carcinoma.

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Background: Osteoradionecrosis (ORN) is a late complication of head and neck radiotherapy (RT) that negatively impacts survivorship. Although there is an abundance of literature reporting on ORN for photon-based RT, few studies have investigated the correlation between proton therapy and ORN; also, the current literature on ORN incorporates a broad mix of head and neck subsites. Therefore, we report our 10-year institutional experience to assess rates of ORN in a homogenous and consecutive cohort of patients with oropharyngeal squamous cell carcinoma (OPSCC) treated with curative-intent radiotherapy, representing the largest available institutional series. **Methods:** A consecutive cohort of 1564 OPSCC patients (1344 definitive, 220 post-operative) who received at least 50Gy were treated at our institution between 2013 and 2023 were included in this study. Patients were treated with either IMRT or proton therapy. CTCAE version 5 was used for ORN grading. **Results:** Overall ORN rate was 4.35%. Of 1389 patients who underwent IMRT, 56 (4.03%) developed ORN, vs 12/175 (6.86%) treated with proton therapy (hazard ratio [HR] 2.62, 95%CI 1.39–4.93, P=0.003). Median time to ORN in the IMRT arm was 25mo (range, 2mo–91mo). Median time to ORN in the proton arm was 23.5mo (2mo–45mo). Post-operative vs definitive treatment setting was not associated with the rate of ORN (univariate Cox HR 1.00, 95% CI 0.51–1.95, P=0.99). On subset analysis of the 1344 patients treated in the definitive setting, 47/1210 (3.88%) patients treated definitively with IMRT developed ORN as compared to 11/134 (8.21%) patients treated definitively with protons (univariable Cox HR 3.62, 95% CI 1.85–7.09, P<0.001). On multivariable analysis including treatment modality and use of chemotherapy, proton therapy was associated with increased hazard of ORN (HR 2.75, 95%CI 1.46–5.19, P=0.002). Concurrent chemotherapy was also independently associated with increased hazard of ORN (HR 3.34, 95%CI 1.05–10.65, P=0.041). A total of 10 out of 1564 (0.64%) patients developed CTCAE grade 3 ORN. The rates of grade 3 ORN were 2/175 (1.14%) in the proton cohort and 8/1389 (0.58%) in the IMRT cohort. This difference was not statistically significant on univariable Cox analysis (HR 2.44, 95%CI 0.51–11.60, P=0.26). **Conclusions:** The overall prevalence of ORN was 4.35%; the prevalence of >/= grade 3 ORNs was 0.64% in this consecutive cohort of patients with OPSCC treated with either IMRT or proton therapy. The overall prevalence of ORN of any grade was statistically higher for protons versus IMRT, a difference that was more pronounced in the definitive setting. Given the uncertainties with relative biological effectiveness calculations in proton therapy, avoidance of hot-spots, frequent replanning, and use of empirical proton-specific normal tissue constraints may help to reduce rates of ORN. Future work should explore the role of combination proton and photon treatment, especially in the definitive setting. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30 CA008748.

6067 Poster Session

Efficacy analysis of neoadjuvant PD-1 inhibitor combined with chemotherapy in various subanatomical sites of locally advanced and recurrent resectable head and neck squamous cell carcinoma: A retrospective real-world study.

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Background: Clinical research on Head and Neck Squamous Cell Carcinoma (HNSCC) often considers the disease as a whole. However, the therapeutic outcomes may vary significantly across different subanatomical sites, as well as between locally advanced (LA) and recurrent resectable (RR) HNSCC. Therefore, we stratified HNSCC according to specific anatomical sites and initial diagnosed versus recurrent tumors, and analyzed the efficacy of neoadjuvant PD-1 inhibitor + chemotherapy. **Methods:** Retrospectively analyzed patients with LA and RR HNSCC admitted to Hunan Cancer Hospital from October 2021 to December 2024, who received neoadjuvant PD-1 inhibitor and chemotherapy. Post-treatment efficacy was evaluated using imaging, endoscopy, or pathology. Differences in efficacy outcomes between different subanatomical sites and between LA and RR tumors were classified and statistically analyzed. **Results:** 1) A total of 482 patients were included: 434 with LA HNSCC(90.04%) and 48 with RR HNSCC (9.96%), 453 males (93.98%) and 29 females (6.02%). Patient ages ranged from 17 to 77 years, with a mean age of 52.43 ± 9.83 years. 2). The top three types of LAHNSCC that underwent neoadjuvant therapy were: tongue (N=157, 36.180%), buccal oris (N=105, 24.19%),and hypopharynx (N=92, 21.20%). 3)The objective response rates (ORR) following neoadjuvant therapy were as follows: 90.32% for oropharyngx, 83.33% for gingiva, 80.25% for tongue, 79.35% for hypopharynx, 68.57% for buccal oris, and 56.25% for RR HNSCC. The highest pathological deep response rates (pCR+MPR) was observed in tongue (34.40%), followed by oropharynx (29.04%), gingiva (26.67%), and only 33% for RR HNSCC. **Conclusions:** There are significant variations in the sensitivity of HNSCC to neoadjuvant immunotherapy + chemotherapy across different subanatomical sites. Oropharynx exhibits the highest response to this regimen, whereas RR cases demonstrate relatively poor responsiveness. In terms of pathological deep response, tongue, oropharynx, and gingiva show favorable response rates, while RR cases exhibit significantly lower response rates. Research Sponsor: Hunan Provincial Major Science and Technology Project, Research and Application of Key Technologies for Oral Cancer Prevention and Treatment; 2023ZJ1120; Hunan Provincial Natural Science Foundation Project; 2024JJ9264.

Disease status	Tongue	Buccal oris	Hypopharynx	Oropharynx	Gingiva	Others	Recurrent Resectable HNSCC
Number	157	105	92	31	30	19	48
CR	31(19.75%)	12(11.43%)	13(14.13%)	8(25.81%)	3(10.00%)	7(36.84%)	4(8.33%)
MPR	23(14.65%)	13(12.38%)	7(7.61%)	1(3.23%)	5(16.67%)	0(0.00%)	0(0.00%)
PR	72(45.86%)	47(44.76%)	53(57.61%)	19(61.29%)	17(56.67%)	10(52.63%)	23(47.92%)
SD	20(12.74%)	18(17.14%)	11(11.96%)	2(6.45%)	1(3.33%)	0(0.00%)	16(33.33%)
PD	8(5.10%)	11(10.48%)	7(7.61%)	0(0.00%)	3(10.00%)	0(0.00%)	10(10.42%)
NA	3(1.91%)	4(3.81%)	1(1.09%)	1(3.23%)	1(3.331%)	2(10.53%)	0(0.00%)
ORR	126(80.25%)	72(68.57%)	73(79.35%)	28(90.32%)	25(83.33%)	17(89.47%)	27(56.25%)

Functional and survival outcomes in HPV positive oropharyngeal squamous cell cancer treated with response-adaptive de-escalation: A pooled analysis.

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Background: Human papillomavirus (HPV) positive OPSCC is known to have a favorable prognosis compared to its HPV negative counterparts. It is thus important to limit treatment-related toxicity while preserving functional and survival outcomes. In this pooled study, we report functional and survival outcomes across prospective cohorts treated with chemotherapy-response-adaptive dose and volume de-escalation of radiation. **Methods:** Patients with non-metastatic HPV positive OPSCC were sequentially treated at an academic center on either an interventional de-escalation trial: OPTIMA 1 (NCT02258659); OPTIMA II (NCT03107182); (NCT04572100) or off-protocol in a prospective registry. Eligible patients had N1-3 or T3-4 (AJCC 8th edition) disease. Very low-risk patients T0-2N0-1 (single lymph node <3cm) were excluded. Patients were stratified as low risk (LR) or high risk (HR) according to T/N stage and smoking history. Following chemotherapy (carboplatin and paclitaxel or *nab*-paclitaxel) with or without nivolumab, patients received de-escalated treatment with low dose arm (LDA; radiation [RT] alone to 50Gy or transoral robotic surgery), intermediate dose arm (IDA; chemoRT [CRT] to 45-50Gy) or regular dose arm (CRT to 70-75Gy). To analyze functional outcomes, we compared swallowing performance scores (SPS), trismus, percutaneous endoscopic gastrostomy (PEG) tube placement obtained from pre- and post-(C)RT. Comparisons across risk categories and treatment arms using Chi-square, Fisher, and Student t-tests. Survival outcomes were compared using log-rank statistic. **Results:** Eligible patients (n=242) started treatment between 2014 and 2024: 116 LR and 126 HR patients; 83% received de-escalated treatment (LDA/IDA) and 17% received standard dose (RDA). Post-treatment SPS (p=0.0002) and trismus scores (p=0.0013) was better among de-escalated versus non-de-escalated patients. Lower PEG placement rates were observed among de-escalated patients 33/196 (16.8%) vs 27/39 (69.2%) (p<.0001). With median follow-up of 48 months, no statistically significant differences in overall survival or progression free survival were observed between treatment arms. OS (95.1% (95% CI 90.8%-97.4%) vs 93.7%(95% CI 77.72%- 98.4%), P=0.185) and PFS (92.2% (95% CI 87.1%-95.2%) vs 90.7% (95% CI 73.9% - 96.9%, p=0.202) were similar in deescalated and non-deescalated patients at 3 years. Low risk individuals also had better OS (97.1% vs 92.1%, p=0.01) and PFS (96.1% vs 88.3%, p=0.004) at three years. **Conclusions:** Improved functional outcomes including posttreatment swallowing function, trismus, and lower PEG placement rates were observed with chemotherapy-response-adaptive radiation de-escalation with excellent survival in the largest prospective cohort reported to date. Response-adaptive de-escalation warrants further comparative study.
Research Sponsor: Chicago Institute of Translational Medicine.

6069 Poster Session

Neoadjuvant chemoimmunotherapy with afatinib for locally advanced head and neck squamous cell carcinoma (neoCHANCE-2): An open-label, single-arm, phase 2 study.

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Background: Neoadjuvant chemoimmunotherapy has been an emerging hotspot for the treatment of locally advanced head and neck squamous cell carcinoma (LA-HNSCC), but the treatment response still requires improvement. Given the potential synergistic antitumor effects of dual inhibition of the PD-1/L1 and EGFR pathways, we proposed a novel neoadjuvant treatment regimen combining chemoimmunotherapy with EGFR-TKI, followed by adjuvant immunotherapy treatment, and evaluated the efficacy and safety of this approach. **Methods:** This open-label, single-arm, phase 2 trial was done at a tertiary hospital in China. Patients were eligible if they were aged at least 18 years old; had pathologically confirmed HNSCC with locally advanced disease according to the AJCC 8th Edition; had an ECOG performance status of 0–1; had at least one measurable target lesion according to RECIST 1.1 criteria; and had sufficient organ function. Patients with LA-HNSCC received two cycles of tislelizumab (200mg) and TP (nab-paclitaxel and cisplatin) chemotherapy, administrated on day one of each three-week cycle, along with afatinib (30mg) during the intermittent period between chemoimmunotherapy cycles, followed by 15 cycles of adjuvant tislelizumab treatment. The primary endpoint was the complete pathologic response (pCR) rate, defined as the percentage of patients with no detectable RVT cells in the resected primary tumor. **Results:** A total of 40 patients were enrolled and received neoadjuvant treatment, 32 of whom proceeded to surgical resection and achieved a pCR rate of 40.6% (95% CI: 23.7–59.4%). The overall response rate (ORR) was 82.5% (95% CI: 67.2–92.7%). The median follow-up time was 14.4 months (range: 2.4–27.6 months) . The estimated 1-year overall survival (OS) was 96.7% (95%CI: 90.5%–100%). No deaths occurred among patients who achieved pCR/MPR. The most common treatment-related adverse events (TRAEs) of any grade were alopecia (100%), followed by nausea (62.5%), lymphopenia (57.5%), diarrhea (55%), and rash (55%). The most common TRAE of grade 3–4 was lymphopenia (5/40, 12.5%). No treatment-related surgical delays were observed. Neoadjuvant treatment induced a significant increase in the proportion of peripheral CD8+ T cells, along with a reduction in B cells. TP53 wild-type patients were more likely to achieve a more favorable pathologic response compared to those with a TP53 mutation. A significant difference in oral microbial composition was found between patients with different pathologic responses. **Conclusions:** This study firstly reported the promising efficacy and acceptable safety profile of neoadjuvant chemoimmunotherapy combined with apatinib in the treatment of patients with LA-HNSCC. Further evaluation in large-scale clinical trials with longer follow-up periods is needed. Clinical trial information: NCT05516589. Research Sponsor: None.

6070 Poster Session

Induction pembrolizumab plus cisplatin and 5-FU chemotherapy followed by chemoradiotherapy in locally advanced squamous cell cancer of oropharynx, hypopharynx or larynx: Results of multicenter prospective phase II study.

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Background: Chemoradiation with cisplatin or induction chemotherapy with docetaxel, platinum agent and 5-FU are associated with high toxicity. We hypothesized that immunochemotherapy with pembrolizumab and platinum-based chemotherapy followed by chemoradiotherapy (CRT) might be associated with higher clinical efficacy along with a lower likelihood of adverse effects (AE). **Methods:** We conducted the multicenter single-arm phase II study (NCT05551767), including patients (pts) with stage III-IV, PD-L1 positive (CPS≥1), squamous cell carcinoma of larynx, oropharynx or hypopharynx. Pts with ECOG > 2 were excluded. All enrolled pts received 3 cycles of induction therapy with pembrolizumab 200 mg on day (d) 1, cisplatin 100 mg/m^2 on d1 and 96-hour infusion of 5-FU 1000 mg/m^2/d followed by CRT. We aimed to evaluate response rate, survival, safety and incomplete CRT rate after induction therapy. **Results:** Since 2022 to August 2024 120 pts were enrolled, including 82 (72.5%) with oropharyngeal, 21 (17.5%) hypopharyngeal and 12 (10%) laryngeal cancer. The median age was 60 (range 35 - 75), most patients were male (87.5%) and 108 (90%) had ECOG 0-1. Objective response rate (ORR) by RECIST 1.1 was assessed after induction therapy in 116 of 120 pts: 73 (62.9%) pts had response including 19 pts (16.4%) with complete responses (CR). The median change of target lesions was -55% (from -100% to 65%). ORR after CRT was assessed in 102 pts: 84 (82.4%) responders were identified with a 71.6% CR rate. Only 8 (6.7%) pts did not start CRT after induction therapy. Among other 112 pts 92.9% received radiation dose ≥66Gy. With a median follow-up 16.6 months 1-year progression-free survival was 73.5% and 1-year overall survival was 80%. There were no treatment-related deaths on induction therapy although 6 (5%) pts required hospital readmission due to adverse events (AE). The incidence of grade 3-4 AE by CTC AE v.5.0 was 30.8% with asymptomatic neutropenia grade 3-4 being the most frequent AE (23.3%). **Conclusions:** The study demonstrated promising ORR, progression-free survival rate and acceptable safety profile of induction therapy with pembrolizumab, cisplatin and 5-FU in head and neck cancer. High response rate to induction therapy was associated with a high number of CRT completion. Clinical trial information: NCT05551767. Research Sponsor: Moscow Center For Healthcare Innovations.; #2112-10/22.

6071 Poster Session

Primary results from IChoice-02, a phase 2 trial of induction chemoimmunotherapy followed by response-adapted de-escalation of chemoradiation in HPV-associated oropharyngeal cancer.

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Background: Despite multiple attempts to de-intensify treatments in HPV-associated oropharyngeal cancer (OPC), data with incorporation of immunotherapy remain scarce. Neoadjuvant platinum-based chemotherapy and anti-PD-1 therapy has shown promising pathological response after radical surgery. In IChoice-02 trial, we evaluated the efficacy of induction chemoimmunotherapy followed by response-adapted de-escalation of radiotherapy and omission of concurrent chemotherapy in HPV-associated OPC. **Methods:** IChoice-02 trial enrolled T1-2/N1-3M0 (excluding T1N1M0 patients with single and≤3cm lymph node) or T3-4N0-3M0 (UICC/AJCC 8th staging system) HPV+ OPC. Following two cycles of induction toripalimab (240mg), docetaxel (75mg/m2) and cisplatin (75mg/m2) every 3 weeks, patients with deep response (CR or ≥50% PR per RECIST in both oropharynx and nodes) were subjected to de-intensified radiotherapy (60Gy) alone with no concurrent chemotherapy, while those otherwise received standard-dose radiation to 70Gy with two cycles of concurrent cisplatin (80mg/m2 every three weeks). The primary endpoint was 2-year progression-free survival (PFS). **Results:** 97 patients were enrolled from March 2021 until July 2024, including 44 (45.3%) stage I, 28 (28.9%) stage II and 25 (25.8%) stage III. Following induction chemoimmunotherapy, 60.8% (59/97) achieved radiological deep response. 53/73 (72.6%) of stage I-II and only 6/25 (24%) of stage III patients underwent subsequent de-escalation. With 16.5 months median follow-up, 2/59 patients had loco-regional relapse (both in-field) in the de-escalation arm, and 6/38 in the standard arm experienced treatment failure (3 locoregional, 2 distant and 1 with both). 1-year PFS was 92.9%, 96.1% and 87.8% in the full cohort, de-escalation arm and standard arm, respectively. 1-year overall survival (OS) was all 100%. There were no treatment-related deaths. Unexpectedly, two cases of second primary malignancy (one with intracranial lymphoma and the other with melanoma) were observed within 4 months after treatment completion. **Conclusions:** Induction toripalimab in combination with platinum-based doublet chemotherapy followed by de-escalation of chemoradiation to lower radiation dose with omitted concurrent chemotherapy yielded outstanding 1-year survival. Long-term survival is awaited with further follow-up. Clinical trial information: NCT04867330. Research Sponsor: Shanghai Junshi Biosciences.

6072 Poster Session

Preoperative steroid for enhancing patients' recovery after head and neck cancer surgery with free tissue transfer reconstruction: Phase III, placebo-controlled, randomized, double-blind study (J-SUPPORT 2022, PreSte-HN Study).

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Background: The enhanced recovery after surgery (ERAS) pathway integrates evidence-based protocols to optimize recovery during the perioperative period. It has recently been applied to head and neck cancer surgery with free tissue transfer reconstruction (HNS-FTR). While preoperative corticosteroid administration has shown benefits in reducing postoperative pain and nausea/vomiting in certain surgeries, its role in the ERAS pathway for HNS-FTR remains unclear. This study aimed to assess the impact of adding preoperative corticosteroid administration on the quality of postoperative recovery within the ERAS pathway for HNS-FTR. **Methods:** This phase III, placebo-controlled, randomized, double-blind trial included 180 patients undergoing HNS-FTR. Patients were randomly assigned (1:1) to receive either 8.0 mg of dexamethasone phosphate in 100 mL of saline or placebo (100 mL of saline) as a single intravenous dose preoperatively. All patients received standardized perioperative care under the multicenter ERAS pathway for HNS-FTR. The primary endpoint was the quality of postoperative recovery, assessed by the area under the curve (AUC) for the total scores of the Japanese version of the Quality of Recovery Score (QOR-40J) on postoperative days 2 and 4. Key secondary endpoints included the AUC of visual analog scale (VAS) scores for pain and nausea on postoperative days 1 to 3. Complications were analyzed using the Clavien-Dindo classification. **Results:** Data from 87 and 91 patients in the dexamethasone and placebo groups, respectively, were evaluated. ERAS pathway completion rates were 97.7% and 97.8% for the dexamethasone and placebo groups, respectively. The estimated AUC for QOR-40J total scores on postoperative days 2 and 4 was 295.7 in the dexamethasone group and 299.8 in the placebo group, with no significant difference ($p = 0.665$). Similarly, no significant differences were observed in VAS scores for pain ($p = 0.829$) and nausea ($p = 0.649$). While there were no significant differences in complications of Grade 2 or higher ($p = 0.584$) or wound-related complications ($p = 0.938$), a significant difference was found in postoperative bleeding, with no cases observed in the placebo group ($p = 0.039$). **Conclusions:** Preoperative corticosteroid administration in the ERAS pathway for HNS-FTR did not yield clinically significant benefits. Ensuring the successful implementation of the ERAS pathway is crucial. Clinical trial information: jRCTs031210593. Research Sponsor: AMED.

6073 Poster Session

Association of AI-informed biomarkers of spatial organization of tumor-infiltrating lymphocytes with loco-regional recurrence in laryngeal squamous cell cancer.

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Background: Laryngeal Squamous Cell Carcinoma (LaSCC) has varying outcomes based on the stage of cancer patients present with. Currently, a high proportion of patients are diagnosed with advanced-stage LaSCC complicating the treatment landscape and over-treating low risk patients. Risk stratification of LaSCC can help tailor treatment plans. Numerous studies have identified spatial architecture of tumor-infiltrating lymphocytes (TILs) as a prognostic biomarker in oral cavity and oropharyngeal SCC. In this work, we evaluate the prognostic value of an artificial intelligence (AI)-leveraged approach that characterizes the spatial architecture of TILs on digitized hematoxylin and eosin (H&E)-stained slides from patients with LaSCC. **Methods:** H&E slides from 192 patients with LaSCC were collected from Baylor Medical Center. This dataset was randomly divided into two equal cohorts, A and B. The slides were digitized as whole slide images at 40x magnification. The nuclei of all cells were automatically segmented using a deep-learning model (Hover-Net). Each nucleus was then classified as TIL or non-TIL based on morphological features. TILs and non-TILs were clustered based on proximity, and features related to the density and spatial distribution were extracted. The top features, determined by the least absolute shrinkage and selection operator, were used to train a Cox Proportional Hazards regression model that assigned a risk score for recurrence of cancer to each patient in cohort A. For validation, the model was applied to patients in cohort B. The 25^{th} percentile training risk score was used as a cutoff for classifying patients as high or low risk. The performance of the model in prognosticating loco-regional recurrence (LRR) was evaluated using survival analysis. **Results:** Patients in Cohort B identified as "high risk" by the model based on spatial organization of TILs had a significantly shorter survival time. Univariate survival analysis showed this model was prognostic for DFS with a hazard ratio of 2.57 (95% Confidence Interval: 1.12-5.89, p-value=0.048), meaning that patients classified as "high risk" are approximately 2.5 times more likely to develop LLR. **Conclusions:** We used computational pathology to characterize the architecture of TILs and develop a model to predict risk of LLR in LaSCC. With additional validation, this approach can be used to assist clinicians with making clinical decisions. Research Sponsor: None.

Multivariate analysis.

Variable	Reference vs Comparison	Pr(>|z|)	HR (95% CI)
Race	Black vs Caucasian	0.93	0.92 (0.40 - 2.31)
N	N0 vs N+	0.67	1.80 (0.12 - 26.06)
T	1-2 vs 3-4	0.83	1.28 (0.13 - 12.38)
Chemo	Yes vs No	0.38	3.49 (0.21 - 56.90)
Tobacco	Yes vs No	0.26	2.08 (0.58 - 7.47)
Alcohol	Yes vs No	0.43	1.53 (0.54 - 4.35)
TIL Architecture Risk	High vs Low	0.03 *	0.26 (0.08 - 0.89)

Decision analysis of PD-1 inhibitor combined with chemotherapy in neoadjuvant therapy of resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC).

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Background: Neoadjuvant therapy (NAT) with PD-1 inhibitors plus chemotherapy has been shown to have a high pathological response rate in LA HNSCC, but there is controversy over factors such as the number of treatment cycles and biomarkers. This trial explored multiple factors that may affect NAT and provided patients with an individualized treatment strategy. **Methods:** Untreated pts with AJCC 8th edition stage III-IVB (HPV-positive oropharyngeal : stage II-III) LA HNSCC were selected between 2021 and 2024. After enrollment, pts received 2 cycles of PD-1 inhibitors combined with chemotherapy, and RT was used when CR was achieved on imaging. If PR, SD or PD was achieved, direct surgery or RT could be chosen, or 1-2 cycles of PD-1 inhibitors plus chemotherapy could be received again before curative treatment. The primary endpoint was 1y-DFS. The sample size was N=80, which provided 0.8 power based on Exact Test at One-Sided alpha level of 0.05. **Results:** A total of 82 pts were included. Median age was 59 yrs (23-76), and 81 (98.8%) were male. Location: oropharyngeal was 22 (26.8%) (HPV-positive was 61.9%), laryngeal was 10 (12.2%), hypopharynx was 48 (58.5%), nasal cavity and sinuses was 2 (2.4%). T3 +T4 was 55.3%, N2+N3 was 44.7%. CPS of pts who underwent testing was 89.0% (73/82), and 48.0% pts were CPS≥20. Pts received 2 cycle (45.1%), 3cycle (50%), 4 cycle (4.8%) NAT. Median follow-up time was 15.9 months, 1y-PFS was 95.9% and 1y-OS was 98.4%. The PFS of pts with pCR or (CR+PR) were both significantly higher than that of pts with non-pCR or (SD+PD)(p=0.049 and p=0.024). The ORR was 84.1%, and ORR of 2-cycle was lower than muti-cycle (81.1% vs 86.7%,p=0.544) . 49.1% pts achieved pCR of primary lesion. pCR of 2-cycle was little higher than muti-cycle (53.3% vs 44.4%, p=0.867). However, the T3-4 in the 2-cycle group was significantly lower than that in the multi-cycle group (43.2% vs 68.9%, p=0.037). In T3-4 pts, pCR in multiple cycles was higher than that in 2 cycles (56.3% vs 38.5%, p=0.339). In addition, pCR of CPS ≥ 20 was significantly higher than that of CPS < 20 (66.7% vs 34.6%, p=0.028). In T1-2 population, pCR of CPS≥20 vs <20 was 81.8% vs 28.6% (p=0.006), while no significant different in T3-4 population. Poorly differentiated patients with CPS ≥ 20 vs. moderately/highly differentiated pts was 85% and 30.6% (p<0.001). 1y - laryngeal function preservation rate was 98.3% (1/58). The overall TRAEs incidence rate was 72%, the most common Grade 3-4 TRAEs were myelosuppression (8.9%). **Conclusions:** Increasing the number of cycles may be beneficial for T3-4 pts. In addition, CPS≥20 pts can achieve higher pCR, especially in T1-2 pts. CPS is also associated with worse pathological differentiation type. Clinical studies (NCT06100497) are currently underway to further explore the efficacy and safety of PD-1 inhibitors combined with chemotherapy in poorly differentiated LA HNSCC. Research Sponsor: None.

6075 Poster Session

Efficacy and safety of Sapylin versus dexamethasone atomized inhalation for CCRT-induced oral mucositis in patients with nasopharyngeal carcinoma: A randomized, parallel design, and non-inferiority clinical trial.

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Background: Radiation-induced oral mucositis (RIOM) is a common adverse reaction to radiotherapy and chemotherapy in patients with nasopharyngeal carcinoma (NPC). Sapylin is an immune adjuvant with anti-tumor effects in multiple malignancies. This study investigated the efficacy and safety of Sapylin versus dexamethasone for treating RIOM in patients with NPC. **Methods:** This prospective, parallel-design, non-inferiority randomized study aims to investigate the effects of inhaling atomized Sapylin versus dexamethasone on the incidence and severity of RIOM in patients with NPC undergoing concurrent chemoradiotherapy (CCRT). A total of 100 patients were enrolled and randomized in a 1:1 ratio into the intervention (Sapylin) and control (dexamethasone) groups. Both groups received cisplatin-based CCRT. The Sapylin and dexamethasone groups received Sapylin (1 KE) and dexamethasone (10 mg), respectively, both via atomized inhalation once daily. Both treatments commenced on the first day of CCRT and continue until the conclusion of radiotherapy. **Results:** Comparisons among groups showed no statistically significant differences in patient characteristics after randomization of patients. Compared to the dexamethasone group, the Sapylin group demonstrated a lower incidence of RIOM (78.9% vs. 83.6%, $P < 0.05$) and a significantly reduced incidence of severe RIOM (grades III-IV) (37.1% vs. 42.5%, $P < 0.05$). The onset times for grades I, II, III, and IV RIOM in the Sapylin group were later than those observed in the dexamethasone group ($P < 0.05$). From baseline to the conclusion of radiotherapy (RT), the changes in Body Mass Index (BMI) in both groups were statistically significant ($P < 0.001$). During RT, the decrease in BMI was less pronounced in the Sapylin group, with a mean change of 0.97 ± 0.76 (mean $\pm$ SD), compared to a larger decrease in the dexamethasone group, which had a mean reduction of 2.02 ± 0.81 (mean $\pm$ SD). A significant positive correlation was found between changes in BMI and the severity of RIOM ($r = 0.671$, $p < 0.003$). No significant difference in the incidence of adverse reactions was observed between the two groups ($P > 0.05$). **Conclusions:** Compared to dexamethasone group, Sapylin group resulted in a decrease in the incidence and severity of RIOM in patients with NPC without obvious side effects. The use of Sapylin atomized inhalation regimen is both safe and effective, and it positively influences the improvement of nutritional status. Clinical trial information: ChiCTR2200064576. Research Sponsor: None.

Use of early EBV DNA clearance to select optimal induction chemotherapy cycles for locoregional advanced nasopharyngeal carcinoma.

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Background: Based on 3 cycles of induction chemotherapy (IC) followed by concurrent chemo-radiotherapy (CCRT) is the standard treatment for locoregional advanced nasopharyngeal carcinoma (LA-NPC). However, it remains unclear whether all patients benefit from 3 cycles of IC. Epstein-Barr virus (EBV) DNA is a key biomarker for NPC, and changes of cell-free EBV DNA (cfEBV DNA) may reflect tumor dynamics. This study aims to use early cfEBV DNA clearance to guide optimal IC cycle selection for LA-NPC patients. **Methods:** We included 1541 LA-NPC patients treated with IC+CCRT between 2010 and 2023, all with early cfEBV DNA data (pre-treatment, and after 1st IC cycle). Independent prognostic factors were identified by COX regression, and predictive accuracy was assessed using receiver operating characteristic (ROC) curves. Propensity score matching (PSM) balanced covariates between groups receiving different IC cycles. The primary outcome, progression-free survival (PFS) was analyzed using Kaplan-Meier and log-rank tests. **Results:** After the 1st IC cycle, 693 (44.97%) patients had undetectable cfEBV DNA. cfEBV DNA after the 1st IC ($p=0.014$) and N stage ($p=0.048$) were significant predictors of PFS. The combination of N stage and cfEBV DNA after the 1st IC cycle had a higher AUC for 5-year PFS (0.610) compared to N stage, cfEBV DNA after 1st IC, or TNM stage alone (0.543, 0.588, 0.557). Based on these two factors, patients were divided into high-risk (N2-3 and detectable cfEBV DNA after 1st IC) and low-risk (N0-1 or undetectable cfEBV DNA after 1st IC) groups. The 5-year PFS for low-risk and high-risk groups was 81.2% vs. 65.1% ($p<0.001$). After PSM, low-risk patients receiving 3 cycles of IC showed significantly better PFS compared to those receiving 2 cycles (5-year PFS: 86.0% vs. 72.5%, $p<0.001$). However, high-risk patients showed similar PFS regardless of IC cycles (5-year PFS: 66.1% vs. 63.7%, $p=0.306$). **Conclusions:** EBV DNA clearance after the first cycle of IC is a sensitive predictor of outcomes in LA-NPC. Low-risk patients may benefit from an additional cycle of IC, while high-risk patients require alternative strategies such as immunotherapy or earlier initiation of CCRT. Research Sponsor: National Natural Science Foundation of China; National Natural Science Foundation of China; Science and Technology Program of Guangzhou.

6077 Poster Session

Induction chemotherapy with or without toripalimab followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: A multicenter, open-label, randomized, controlled, phase 2 trial.

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Background: Although nasopharyngeal carcinoma (NPC) treatment has entered the era of immunotherapy, the optimal treatment model for locoregionally advanced nasopharyngeal carcinoma (LANPC) remains unclear. This trial aimed to evaluate the efficacy and safety of adding toripalimab to induction chemotherapy (IC) in patients with LANPC. **Methods:** Patients with LANPC (T4NanyM0 or TanyN2/N3M0, AJCC 8th edition) were enrolled at 8 centers across China and randomized (1:1) into two arms: the standard arm (gemcitabine and cisplatin IC followed by cisplatin concurrent chemoradiotherapy [CCRT]) and the toripalimab arm (toripalimab plus IC followed by CCRT). Both arms received intravenous gemcitabine (1g/m^2) on days 1 and 8, and cisplatin (80 mg/m^2) on day 1, every 3 weeks for 3 cycles, followed by standard CCRT (cisplatin 100 mg/m^2 every 3 weeks for 3 cycles). In the toripalimab arm, patients also received intravenous toripalimab (240 mg) on day 1 every 3 weeks for 3 induction cycles. The primary endpoint was failure-free survival (FFS). Secondary endpoints included complete response (CR) rate after neoadjuvant treatment, locoregional failure-free survival (LRRFS), distant metastasis-free survival (DMFS), overall survival (OS), and toxicity. Response evaluation was conducted according to RECIST 1.1, and adverse events (AEs) were assessed by CTCAE v5.0. This study is registered with ClinicalTrials.gov (NCT05340270), and follow-up is ongoing. **Results:** Between July 2022 and March 2024, 150 patients (mean age 47 years, 72% male) were randomized to the toripalimab arm (n = 75) and the standard arm (n = 75). As of November 30, 2024, the median follow-up duration was 23.4 months, and 15 patients had reached the primary endpoint. Long-term efficacy data are still awaited. The CR rate after neoadjuvant treatment was 36.0% (27 of 75) in the toripalimab arm and 13.3% (10 of 75) in the standard arm (P= 0.001). The overall response rate (ORR) after neoadjuvant treatment was 94.7% (71 of 75) in the toripalimab arm and 85.3% (64 of 75) in the standard arm (P= 0.042). Grade 3-4 acute treatment-related adverse events (trAEs) occurred in 50 (66.7%) patients in the toripalimab arm and46 (61.3%) patients in the standard arm (P= 0.496), with immune-related AEs (irAEs) reported in 5 (6.7%) patients in the toripalimab arm and none (0.0%) in the standard arm (P= 0.058). All grade 3-4 irAEs were manifested as rashes and pruritus. **Conclusions:** Adding toripalimab to standard IC followed by CCRT resulted in a superior CR rate and ORR compared to IC-CCRT alone, with manageable toxicity profiles in patients with LANPC. Further follow-up is needed to confirm long-term efficacy, and this combination may offer an optimal, cost-effective therapeutic model for LANPC. Clinical trial information: NCT05340270. Research Sponsor: None.

Radiotherapy plus nimotuzumab versus cisplatin in low-risk locoregionally advanced nasopharyngeal carcinoma who had favorable response to induction chemotherapy: A randomised, phase III, non-inferiority trial.

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Background: Patients with low-risk locoregionally advanced nasopharyngeal carcinoma (LA-NPC) have high survival when treated with radiotherapy (RT) plus cisplatin after induction chemotherapy (IC). Whether replacement of cisplatin with nimotuzumab—a humanized antibody against the epidermal growth factor receptor (EGFR)—can preserve high survival and reduce treatment toxicity is unknown for patients with good response to IC. Therefore, we assessed whether nimotuzumab plus RT was non-inferior to cisplatin plus RT in low-risk LA-NPC with favorable response to IC. **Methods:** The study was a randomised, non-inferiority, phase 3 trial at Sun Yat-sen University Cancer Centre, China. Adult patients (aged 18–70 years) with non-keratinizing stage II-IVA (except N3 category; the eighth edition of the American Joint Committee on Cancer classification system) NPC, with pre-treatment plasma EBV DNA<1500 copies/mL, positive EGFR expression and an Eastern Cooperative Oncology Group performance status of 0–1, were treated with 2 cycles of paclitaxel-cisplatin-fluorouracil IC, those achieved CR/PR with undetectable EBV DNA were randomly assigned (1:1) to receive either intravenous nimotuzumab at a dose of 200 mg weekly or cisplatin 100 mg/m^2 on days 1, 22 and 43 of intensity-modulated radiotherapy. Randomization was done using a computer-generated code random number code with a block size of six, stratified by overall stage. The primary endpoint was 2-year progression-free survival (PFS) in the intention-to-treat population. Safety was assessed in all participants who received at least one dose of the assigned treatment. This study is registered with ClinicalTrials.gov, number NCT 04456322. **Results:** Of the 381 patients who underwent randomization, 191 were assigned to RT plus nimotuzumab and 190 to RT plus cisplatin. After median follow-up duration of 39.5 months, in the evaluation of 2-year PFS, RT plus nimotuzumab was noninferior to RT plus cisplatin (94.2% and 95.8%, respectively; absolute difference, 1.6 percentage points; 95% CI, −2.8 to 6.0, [noninferiority margin, -10 percentage points], $P_{noninferiority}$=0.0001). The most common grade 3-4 acute toxicities were leucopenia (37 [19.5%] of 190 patients in the cisplatin group vs. 2 [1.1%] of 189 patients in the nimotuzumab group), mucositis (36 [18.9%] vs. 28 [14.8%]), and vomiting (21 [11.1%] vs. 0). No patients died during treatment. Patients in the cisplatin group also showed more grade 1-2 auditory or hearing loss and peripheral neuropathy in late adverse events, and impaired long-term quality of life. **Conclusions:** Our findings show that nimotuzumab plus RT represents an alternative concurrent treatment strategy for patients with low-risk LA-NPC with a favorable response to IC. Clinical trial information: NCT04456322. Research Sponsor: None.

6079 Poster Session

5-year survival outcomes after perioperative pembrolizumab (pembro) in patients with human papillomavirus (HPV)-unrelated, locally advanced head and neck squamous cell carcinoma (LA-HNSCC): A multi-center, two-cohort, phase 2 trial.

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Background: A phase 2 trial (NCT02296684) demonstrated that perioperative pembro added to standard of care (SOC) surgery/adjuvant radiation-based therapy resulted in frequent pathologic tumor responses (pTR) and favorable 2-year survival relative to historical rates in patients with HPV-unrelated, LA-HNSCC (Uppaluri et al., CCR 2020; Oliveira et al., Sci Immunol 2023). The early results of this institutional phase 2 trial provided necessary rationale for the Merck-sponsored, KEYNOTE-689 phase 3 trial that compared perioperative pembro with SOC versus SOC in patients with resectable LA-HNSCC. Here, we report 5-year survival outcomes from the phase 2 trial. We also evaluated the effect of two pembro dosing schedules and the presence or absence of pTR at the primary tumor site on long-term survival outcomes. **Methods:** Cohort 1 received one dose of neoadjuvant pembro (200 mg IV) and, in patients with high-risk pathology, six doses of adjuvant pembro. Cohort 2 received two doses of neoadjuvant but no adjuvant pembro. $pTR_{primary}$ was defined as the proportion of the resected primary site tumor bed that exhibited pathologic response: 0 (<10%), 1 (10%-49%), and 2 (≥50%). Event-free survival (EFS), defined as the time from surgery to disease progression, recurrence, or death, and overall survival (OS) was analyzed by the Kaplan-Meier method with log-rank testing for significance. **Results:** Sixty-five patients enrolled (36 in cohort 1 and 29 in cohort 2). The median follow-up was 48.4 months (IQR: 30.1-60.9). The 5-year OS for all patients was 73% (95% CI: 62-85%) and the EFS was 71% (95% CI: 61-83%). A comparison of patients in cohort 2 versus 1 showed no significant differences in OS (HR = 0.39; 95% CI: 0.12-1.20; p = 0.09) or EFS (HR = 0.72; 95% CI: 0.28-1.84; p = 0.48). For all patients, those with $pTR_{primary}$ 1 or 2 versus 0 had significantly better EFS (HR = 0.34; 95% CI: 0.11-1.02; p = 0.04), but not OS (HR = 0.42; 95% CI: 0.14-1.3; p = 0.10). **Conclusions:** Among patients with HPV-unrelated, LA-HNSCC treated with perioperative pembro and SOC, the 5-year OS and EFS were favorable relative to historical results (~40-50% 5-year OS and EFS) with SOC alone. While OS was numerically better in cohort 2 compared to cohort 1, and among patients with $pTR_{primary}$1 or 2 compared $pTR_{primary}$ 0, the differences did not reach statistical significance, possibly due to the small sample size. $pTR_{primary}$ after neoadjuvant pembro was significantly associated with better EFS, suggesting its potential utility as an early surrogate marker for EFS. Clinical trial information: NCT02296684. Research Sponsor: "Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA provided pembrolizumab and financial support for the study".

6080 Poster Session

AI-based classification of laryngeal dysplasia and lymphocytic activity quantification from routine histology.

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Background: Laryngeal Dysplasia (LD) is a premalignant condition arising in the lining of the larynx. It is graded based on cytological and architectural features present in the epithelium of H&E-stained histology images. However, LD grading suffers from high inter- and intra-rater variability and is not always predictive of malignant transformation. Additionally, distinguishing LD from other laryngeal lesions, such as squamous cell carcinoma (SCC) or benign polyps, remains challenging. Artificial intelligence (AI) offers a solution by enabling objective classification of lesion types, whilst identifying key features associated with LD progression, including lymphocytic infiltration. We propose an AI model using weakly-supervised deep learning to classify LD and highlight potential diagnostic features. **Methods:** We used 109 H&E-stained whole slide images (WSIs) from 82 cases (UHCW and Dundee) scanned at 40× magnification (0.12 microns-per-pixel, mpp) using a Pannoramic 250 whole-slide scanner. The dataset comprised 50 LD cases (65 WSIs), 20 laryngeal SCC cases (28 WSIs), and 12 benign polyp cases (16 WSIs). Using a pre-trained H-optimus-0 model, we extracted patch-level (224×224 pixels) features from the slides (20× magnification, 0.5 mpp), with a TransMIL aggregator predicting slide-level classifications for dysplasia, SCC, and polyps. Additionally, we derived slide-level intra-epithelial lymphocyte (IEL) and peri-epithelial lymphocyte (PEL) scores using HoVer-NeXt based lymphocyte segmentation, in and around the epithelium (segmented by HoVer-Net+) in LD cases, and compared these scores across WHO LD grades using Mann-Whitney U tests. **Results:** In Monte Carlo cross-validation experiments (10 repeats), the model achieved an average one-versus-all AUROC of 0.85 and AUPRC of 0.73 for lesion classification (dysplasia vs SCC vs polyp). In LD cases, both IEL and PEL scores were significantly higher in severe dysplasia cases compared to moderate (IEL: r_{rb} = 0.09, p = 0.02; PEL: r_{rb} = 0.36, p = 0.02) and mild dysplasia (IEL: r_{rb} = 0.09, p = 0.01; PEL: r_{rb} = 0.36, p = 0.003). This suggests a potential link between increased lymphocyte presence (activity) and higher grades of dysplasia. **Conclusions:** We present a novel AI model for classifying laryngeal lesions and quantifying lymphocytic activity in LD. Our findings suggest the diagnostic potential of AI in identifying LD, whilst highlighting peri- and intra-epithelial lymphocyte density as a potential biomarker, which has not been previously linked to dysplasia grade. Further validation in large, multi-centric datasets is required. Research Sponsor: None.

6081 Poster Session

Examining age-specific trends in the incidence of human papillomavirus-associated oropharyngeal cancer in the United States.

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Background: The incidence of human papillomavirus (HPV) infection-associated oropharyngeal cancer (OPC) has been steadily rising in the United States, with HPV surpassing behavioral risk factors like tobacco and alcohol use as the leading cause of OPC, particularly in men. We examined the impact of the HPV vaccine on the incidence of OPC, accounting for age, gender, and lifestyle behavior. **Methods:** Cancer incidence was extracted from the United States Cancer Statistics Public Use Database (USCS). Data on alcohol and tobacco consumption were obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA). The Behavioral Risk Factor Surveillance System (BRFSS) was employed to collect HPV vaccination and screening information. Information on HPV infection and number of sexual partners was provided by the National Health and Nutrition Examination Survey (NHANES). The Joinpoint Regression Program (National Cancer Institute) and Pearson correlation coefficients were used for statistical analyses. **Results:** Between 2001 and 2021, oropharyngeal cancer (OPC) incidence rates increased in males by 2.3% ($p<0.001$) compared to a 0.74% annual increase in females ($p=0.002$). Compared to the rising incidence of OPC in older men, the younger cohort showed a significant decrease in the incidence of OPC. Specifically, younger males 35-39 years old and 40-44 years old had a 1.86% decrease ($p=0.004$) and 1.37% decrease ($p=0.005$) in OPC incidence per year, compared to a rising incidence of 1.66% ($p<0.001$) and 2.56% ($p<0.001$) annually among males 60-64 years old and 65-69 years old, respectively. With the 2009 approval of the HPV vaccine for young men, we investigated whether this was associated with decreased OPC incidence. Indeed, HPV vaccination showed a significant negative correlation with OPC incidence in men younger than 45 ($r=-0.818$; $p=0.001$). We then evaluated whether substance use and sexual practices, both risk factors for OPC, have changed during this time. Among 18-25 year olds surveyed in SAMHSA from 2003 to 2021, we found that overall consumption of alcohol decreased by 11.0% ($p<0.05$) and tobacco use decreased by 22.8% ($p<0.05$), even though alcohol and tobacco use were initiated at higher rates in this younger age cohort. Using the NHANES database from 2009-2016, we found that the rate of oral HPV infection, assessed via oral cavity rinses, has not significantly changed (7.6% to 7.2%; $p=0.896$). Similarly, there was no change in the proportion of people with more than four lifetime oral sex partners (36.0% to 39.0%; $p=0.684$). **Conclusions:** This study reveals a strong inverse relationship between HPV vaccination rates and OPC incidence in men under 45 years, suggesting that vaccination efforts may be effectively reducing cancer risk in this group. The decreasing rate of alcohol and tobacco consumption in this age group may also contribute to our findings. Research Sponsor: None.

6082 Poster Session

AI-driven reflectance confocal microscopy for noninvasive diagnosis and accurate surgical margin assessment intra-operatively in oral cavity squamous cell carcinoma.

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Background: Oral cavity squamous cell carcinoma (SCC) remains a common malignancy in the head and neck region, with challenges in tumor resection and recurrence prevention. Traditional methods like frozen-section analysis are limited by time delays, sampling errors, and tissue distortion. Reflectance Confocal Microscopy (RCM) provides a noninvasive alternative for real-time, high-resolution imaging, but interpreting RCM images accurately requires expert knowledge. Integrating artificial intelligence (AI) could improve the accuracy and reliability of RCM image interpretation for diagnosing SCC and assessing surgical margins. The integration of machine learning and artificial intelligence (AI) has the potential to enhance the accuracy and reliability of RCM image interpretation, providing a more efficient tool for diagnosing oral cavity SCC and assessing surgical margins in real-time during surgery. **Methods:** We developed an AI model using Google Cloud's AutoML platform to classify RCM images for diagnosing oral cavity SCC and evaluating tumor margins. The dataset comprised 4,090 RCM images from 83 patients, including 1,998 images of benign tissue and 2,092 images of malignant tissue. The dataset was divided into training (80%), validation (10%), and test (10%) sets. A single-label classification approach was employed to differentiate benign and malignant tissue. Model performance was evaluated using sensitivity, specificity, accuracy, F1 score, and negative predictive value. **Results:** The AI model achieved an area under the curve (AUC) of 0.99, sensitivity of 98.09%, specificity of 95.00%, accuracy of 96.58%, and an F1 score of 96.70%. In comparison, expert human readers in our prior study achieved accuracies of 90.91% for normal tissue and 81.7% for tumor detection, highlighting the accuracy of the AI model's diagnostic performance. **Conclusions:** The combination of RCM imaging with AI-powered analysis provides an accurate, noninvasive method for real-time diagnosis and surgical margin assessment in oral cavity SCC. The AI-driven model has excellent sensitivity, specificity, and overall accuracy, offering a potentially efficient and reliable modality for the real-time evaluation of digital RCM images. This approach can reduce the time required for intraoperative margin assessment, minimize patient anesthesia time, and overcome challenges related to conventional histopathology, ultimately improving surgical outcomes in patients with oral cavity SCC. Research Sponsor: None.

6083 Poster Session

Artificial intelligence-powered real-time model for predicting recurrence and survival in head and neck squamous cell carcinoma after curative intent surgery.

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Background: Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5.3% of cancer-related mortality worldwide, with an estimated 660,000 new diagnoses and 325,000 deaths annually. Curative-intent surgery or definitive chemoradiotherapy remain the only two curative treatment modalities for patients with HNSCC but recurrence rates vary from 10–50% and survival is still limited for some patients emphasizing the need for accurate predictive and prognostic models. This study developed and validated an AI model that integrates clinical, pathological, laboratory, and radiologic data to predict recurrence and survival in HNSCC, aiming to optimize patient outcomes and personalize treatment strategies. **Methods:** The model was developed using XGBoost and Cox regression, internally validated, and tested using data from Samsung Medical Center (SMC). Data in the model included baseline data collected at the time of surgery and longitudinal laboratory data gathered during surveillance. An 80/20 ratio was applied to randomly allocate patients to the developing set and internal validation sets from the SMC dataset. The dataset included patients with HNSCC who underwent curative intent surgery between January 2008 and August 2024. Two models were developed: one to predict progression-free survival (PFS) and overall survival (OS) within 12 months after the surgery, and another to predict PFS and OS within 12 months of the surveillance monitoring point, thus creating a real-time prediction model. External validation was conducted using data from Massachusetts General Hospital (MGH). **Results:** A total of 1,062 patients with HNSCC (oral cavity cancer, oropharyngeal cancer, and laryngeal cancer) were included in the study. The AUC for predicting 12-month PFS after surgery was 0.804 (sensitivity: 82.4%, specificity: 77.3%), with a C-index of 0.802 for RFS. For predicting OS at 12 months after surgery, the AUC was 0.875 (sensitivity: 100%, specificity: 73.1%), with a C-index of 0.862 for RFS. For external validation using MGH data, the AUC for predicting 12-month PFS was 0.875, with a C-index of 0.793 for RFS. The C-index for OS in the MGH dataset was 0.75. In the longitudinal surveillance model, the AUC for predicting 12-month PFS at each monitoring point was 0.883, while the AUC for 12-month OS was 0.902. **Conclusions:** This study successfully developed and validated an AI-powered model for predicting RFS and OS in HNSCC patients, achieving strong performance in both internal and external validations. These findings highlight the potential of AI-based approaches to support personalized treatment strategies and improve prognostic accuracy in HNSCC. Research Sponsor: None.

6084 Poster Session

Pathologic response to neoadjuvant sequenced, lymphatic-sparing SBRT plus pembrolizumab in HPV-negative head and neck squamous cell carcinoma.

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Background: The Neoadjuvant Immuno-Radiotherapy Trial (NIRT-2) is a phase II study, conducted at 2 institutions, that evaluated in patients (pts) with locoregionally advanced HPV-negative head and neck squamous cell carcinoma (HNSCC) whether the combination of neoadjuvant sequenced, lymphatic sparing stereotactic body radiation therapy (SBRT) delivered to gross tumor volume (GTV) plus pembrolizumab is effective in enhancing major pathologic response (MPR) compared to historical controls of anti-PD-1 alone. **Methods:** 27 pts with resectable clinical stage III-IVA HPV-negative HNSCC who would warrant adjuvant RT per the investigators were enrolled. Neoadjuvant therapy consisted of SBRT 8Gy X 3 delivered over 1 week (GTV +/-3mm) followed by 3 cycles of pembrolizumab (200mg) prior to definitive surgical resection + neck dissection at week 7. Standard of care adjuvant RT +/- chemotherapy was administered based on pathologic staging, followed by adjuvant pembrolizumab for 6 months (14 doses). The primary endpoint was MPR (defined as $<$/=10% viable tumor cells), assessed using a single-arm Simon Two-stage design to test the hypothesis that SBRT would improve MPR to pembrolizumab from 22%, rejecting the null hypothesis if 10 or more responses (37%) are observed in 27 pts (Type 1 error 5%, 90% power, alternative rate 50%). Secondary endpoints included pathologic down-staging allowing for surgical de-escalation and omission of adjuvant RT. **Results:** The study completed enrollment (N=27) on January 17, 2025, at which time 22 pts had completed surgery. 22/27 (81%) pts enrolled were clinically staged as T3/T4 and 8/27 (30%) were N2b/c (AJCC 8th Ed). Pathologic down-staging was observed in 16/22 (73%) pts, which permitted surgical de-escalation (no tracheostomy or free flap, $>$50% organ preservation) in 11 pts (50%). 16/22 (73%, one-sided 95% CI =53%-100%, p$<$.0001) had a MPR, of which 6 had a pathologic complete response (pCR), thus meeting the study's primary endpoint of 10 MPR. Adjuvant RT was omitted in 17/22 (77%) pts. All pts remain disease-free at a median follow-up of 8.5 months (IQR=3.9, 21.2; range=0-32). **Conclusions:** Neoadjuvant sequenced, lymphatic sparing SBRT followed by pembrolizumab led to notable pathologic down-staging allowing for surgical de-escalation and omission of adjuvant RT. Clinical trial information: NCT04938609. Research Sponsor: Providence Portland Medical Center Foundation.

6085 Poster Session

Omission of concurrent chemotherapy in and out of a phase III randomized controlled trial for stage II nasopharyngeal carcinoma.

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Background: In the era of intensity-modulated radiotherapy (IMRT), the precision of radiotherapy has been greatly enhanced, allowing for more precise targeting of tumor tissue while minimizing damage to surrounding normal tissues. Therefore, whether radiotherapy alone can replace the traditional chemoradiotherapy regimen, which may cause substantial side effects, particularly hematologic toxicity, gastrointestinal adverse reactions, and immune suppression, has become a key focus of current clinical research. This investigation explores the potential benefits of IMRT as a standalone treatment, particularly its ability to offer similar efficacy in terms of overall survival and disease control while sparing patients from the added toxicities associated with chemotherapy. **Methods:** In a parallel-group, multicenter, randomized, controlled phase III trial, we compared cisplatin-based concurrent chemoradiotherapy with radiotherapy alone. Stage II NPC patients (2010 UICC staging) were randomly assigned in a 1:1 ratio to receive concurrent chemoradiotherapy (IMRT combined with cisplatin, 100 mg/m^2 every 3 weeks for 3 cycles) or IMRT alone. The primary endpoint was overall survival in the intention-to-treat population. Secondary endpoints included progression-free survival, locoregional relapse-free survival, distant metastasis-free survival, and safety. **Results:** A total of 211 patients were enrolled (106 in the IMRT alone group, 105 in the concurrent chemoradiotherapy group). The median follow-up time was 37 months. The 3-year overall survival rate was 96.3% for the IMRT alone group and 98.2% for the concurrent chemoradiotherapy group (HR = 0.650, 95% CI: 0.109-3.889; p-value = 0.637). No significant differences were observed between the groups in progression-free survival, locoregional recurrence, or distant metastasis (all p-values $>$ 0.05). The incidence of grade 3-4 adverse events was significantly lower in the IMRT alone group (p-value $<$ 0.05), including hematologic toxicity (leukopenia) and non-hematologic toxicity (hypokalemia). **Conclusions:** In stage II NPC patients, IMRT alone can achieve comparable 3-year overall survival to concurrent chemoradiotherapy, while significantly reducing side effects, which may provide a feasible treatment option for these patients, particularly for those with early-stage II nasopharyngeal carcinoma, where radiotherapy alone offers high therapeutic potential and lower treatment risks. Clinical trial information: NCT02610010. Research Sponsor: Sun Yat-sen University Clinical Medical Research 5010 Program.

6086 Poster Session

The use of docetaxel as a radiosensitizer in patients with head and neck cancer unsuitable for cisplatin based chemoradiation: Landmark 3-year survival analysis of a randomized phase III trial (DHANUSH).

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Background: Patients with cisplatin-ineligible locally advanced head and neck squamous cell carcinoma (LA-HNSCC) have limited guideline-recommended treatment options. DHANUSH (CTRI/2017/05/008700), an open-label, phase II/III randomized controlled trial, was among the first studies to demonstrate superior disease-free survival (DFS) and overall survival (OS) in this patient population. Here, we present the 3-year landmark survival analysis update of our study cohort. **Methods:** This was a single-centre, open-label, randomized controlled phase II/III study conducted at our institute between July 2017 and May 2021. Cisplatin-ineligible patients with LA-HNSCC who were planned for definitive or adjuvant chemoradiation in the multidisciplinary joint clinic were enrolled. Patients were randomly assigned in a 1:1 ratio to receive either radiation therapy alone or concurrent weekly docetaxel (15 mg/m^2) for up to seven cycles. The primary endpoint of the study was 2-year disease-free survival (DFS). Here, we present the 3-year landmark survival update, including disease-free (DFS) and overall survival (OS), as of January 25, 2025. **Results:** The study recruited 356 patients, with 179 receiving concurrent docetaxel and 177 receiving radiation therapy alone. The median follow-up for the entire cohort was 67.9 months (95% CI, 65.7–70.3). At the time of the median follow-up, 123 deaths occurred in the concurrent docetaxel arm compared to 136 deaths in the radiation therapy alone arm. The median DFS in the concurrent docetaxel arm was 11.9 months (95% CI, 8.3–21.7) compared to 5.9 months (95% CI, 4.9–8.2) in the radiation therapy alone arm (p = 0.003). Similarly, the median OS was 23.1 months (95% CI, 17.4–30.6) in the concurrent docetaxel arm versus 15.3 months (95% CI, 13.9–22.3) in the radiation therapy alone arm (p = 0.048). The 3-year DFS was 36.3% (95% CI, 29.9–44.1) in the concurrent docetaxel arm versus 23.2% (95% CI, 17.7–30.3) in the radiation therapy alone arm. Similarly, the 3-year OS was 40.2% (95% CI, 33.7–48.1) in the concurrent docetaxel arm compared to 28.8% (95% CI, 22.9–36.3) in the radiation therapy alone arm. **Conclusions:** The addition of concurrent docetaxel to radiation therapy significantly improved survival outcomes (DFS and OS) in cisplatin-ineligible LA-HNSCC patients at the 3-year survival landmark. Clinical trial information: CTRI/2017/05/008700. Research Sponsor: None.

6087 Poster Session

Neoadjuvant APG-157 monotherapy in patients with locally advanced squamous cell carcinoma of head and neck: A phase IIA, single arm trial.

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Background: Newly diagnosed, locally advanced squamous cell carcinoma of the head and neck (SCCHN) poses significant treatment challenges due to its infiltrative nature, and high recurrence risk. From diagnosis to definitive curative-intent therapy, patients may experience rapid disease progression leading to a poor prognosis. A safe and effective therapy to halt tumor growth during this period is critical to improve patient outcomes. **Methods:** APG-157, a first-in-class immuno-oncology drug was evaluated in Phase 2A trial (NCT05312710) of 24 patients with stage I–IVA SCCHN in oral cavity (54.2%) and oropharynx (45.8%). Fifty percent had stage III & IVA disease. 91% of oropharyngeal cases were HPV+. APG-157 was administered orally as a soft lozenge - 200 mg, 3X a day before meals - for 4-6 weeks between initial diagnosis and definitive therapy. The primary and secondary endpoints included overall response rate (ORR) using RECIST v1.1 and safety, respectively. The exploratory endpoints included changes in tissue biomarkers, circulating tumor DNA (ctDNA), salivary cytokines, and post-hoc analysis of Event-Free Survival (EFS). **Results:** APG-157 was well tolerated with no treatment-related Grade 3 or 4 adverse events. There was no delay in subsequent definitive therapy. Of 13 oral cavity patients, 10 completed surgery, 3 had post-operative radiotherapy, and all achieved R0 resection. 11 patients with oropharyngeal cancer had chemoradiation (n=10) or radiation alone (n=1). APG-157 showed antitumor activity as 77% of the subjects achieved pathological responses (23% near-complete, 23% major, 31% partial), while 15% had stable disease and 8% showed progression. Among the patients undergoing surgery as definitive therapy, 46% demonstrated clinical-to-pathological downstaging, while 8% experienced upstaging. The (ORR) was 16.7% (n=24), with tumor reduction observed in 45% of the patients. No primary tumor progression occurred, achieving a 100% disease control rate (DCR) with 2 complete responses (CRs), 2 partial responses (PRs), and 20 cases of stable disease (SD). Median EFS was not reached at 2 years. All patients remain alive with no recurrence except one subject who died from a non-cancer-related cause. Pre- and post-treatment multiplex IHC analysis showed APG-157 reduced Ki-67+ tumor cells, increased CD8+ infiltration, and reprogrammed macrophages to the M1 phenotype. Post-treatment ctDNA clearance correlated with complete (30%) and partial (70%) disease control, resulting in ORR of 100% (Gouda MA, et al. Liquid Biopsy Response Evaluation Criteria in Solid Tumors (LB-RECIST). Ann Oncol. 2024 Mar;35(3): 267-275). **Conclusions:** APG-157 is a safe and effective oral therapy addressing a critical unmet need in SSCHN. It is a convenient neoadjuvant treatment option with a strong safety profile and durable long-term outcomes after curative-intent therapy. Clinical trial information: NCT05312710. Research Sponsor: Aveta Biomics, Inc.

6088 Poster Session

Induction chemotherapy (IC) followed by concomitant radiotherapy and weekly cisplatin (CCRT) versus CCRT alone in patients with locally advanced (LA) nasopharyngeal carcinoma (NPC): Twenty-year follow-up of a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation.

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Background: Non-endemic NPC is associated with inferior outcomes compared to the endemic form. HeCOG conducted a randomized phase II study to compare IC followed by CCRT with CCRT alone in patients with LA NPC. Here, we report the 20-year follow-up data with biomarker analysis. **Methods:** Patients were randomly allocated 1:1 to CCRT alone or 3 cycles of IC with Epirubicin, Paclitaxel, and Cisplatin followed by CCRT. Random assignment was stratified by histology (type I versus type II+III) and stage (IIB+III versus IV). The primary objective of this analysis was to identify clinical and molecular features associated with PFS and OS. Clinical (141 cases /72 Group A, 69 Group B) and biomarker data (IHC / CISH: 109 Cases, NGS: 61 Cases / 29 Group A; 32 Group B) were analyzed using descriptive statistics, traditional survival Analysis techniques (Kaplan-Meier, Cox) and machine learning approaches (random survival forest). **Results:** Regarding the clinicopathological characteristics, only age at the beginning of the study (HR=1.05, 95%CI=(1.03, 1.06), p<0.001) and the CCRT response was associated with OS (PD: HR=20.03, 95%CI=(9.02, 44.48), p<0.001; SD: HR=5.17, 95%CI=(2.01, 13.32), p=0.001, respectively). For NGS mutational status, irrespective of effect, only *MSH2* (HR=3.37, 95% CI=(1.27, 8.92), p=0.015) and *PIK3CA* (HR=2.71, 95%CI=(1.03, 7.12), p=0.043) displayed significant association with OS, while random survival forest additionally yielded significant associations for *BRCA1*, *CD274*, *TSC1*, *KRAS* and *KIT*. Considering pathogenic mutations only, *CD8B*, *KDM4A, MLH1*, *MSH6*, and *RANBP2* displayed significant association with OS. Concerning IHC, ECADH (HR=1.16, 95%CI=(1.03, 1.32), p=0.018), GSK3B (HR=1.21, 95%CI=(1.01, 1.44), p=0.036) and AE1AE3 (HR=0.13, 95%CI=(0.02, 0.96), p=0.018), displayed significant association with OS, with higher values of ECADH and GSK3B indicating worse outcome, whereas AE1AE3 expression indicates better outcome. **Conclusions:** Age at diagnosis and response to CCRT emerge as the most important clinical factors forlong-term survival in LA non-endemic NPC.We identified potential molecular correlates for long-term outcomes to be validated in prospective studies. Clinical trial information: ACTRN 12609000730202. Research Sponsor: None.

6089 Poster Session

Transoral robotic surgery (TORS) and de-escalated adjuvant therapy for human papillomavirus-related oropharyngeal carcinoma (HPVOPC): Long-term follow up of the Sinai Robotic Surgery (SIRS) trial (NCT02072148).

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Background: De-escalation therapy for HPVOPC remains undefined and controversial. Definitive and postoperative chemoradiation are associated with significant toxicity. Efforts to de-intensify treatment with CRT only, such as HN002 and HN005, were unsuccessful. A previous investigation by this group (SIRS 1.0) and E3311 have highlighted the potential value of TORS with pathological risk stratification of patients for de-escalated adjuvant therapy. Our early work demonstrated that TORS, in combination with reduced-dosed adjuvant therapy for early and intermediate HPVOPC, resulted in equivalent progression-free survival (PFS) and overall survival (OS) while reducing toxicity in the first two years of treatment. Here we report the 5-year results for SIRS. **Methods:** This is a nonrandomized phase II trial for early-stage molecularly confirmed HPVOPC patients (n=63) treated with TORS followed by reduced-dose adjuvant therapy based on pathological risk-stratification into one of three groups: Group 1 (n=31) with no adjuvant therapy, Group 2 (n=15) with 50-Gy radiotherapy, and Group 3 (n=17) with 56-Gy chemoradiotherapy concurrent with weekly cisplatin. Patient demographics, baseline tumor characteristics, clinical outcomes, and adverse events during treatment and surveillance were recorded across the full 5-year study period. **Results:** Among the 63 total patients, median follow-up is 58 months (IQR 43—76 months). In the first two years following TORS, 5 patients experienced locoregional recurrence (7.9%); of these, one later had distant metastasis and one had a second HPV+ recurrence in the ipsilateral neck. All were salvaged by TORS, neck dissection, and/or chemoradiation. No patients had an HPVOPC recurrence between years 2 to 5 of follow-up. Two patients, one each from Group 1 and Group 2, developed a molecularly proven HPV+ contralateral second primary tumor at the tonsils approximately 5 years following TORS. Both patients were successfully salvaged and remain disease-free. Two patients (one each in Group 2 and 3) died from causes unrelated to cancer. The five-year OS is 96.8% (61/63) and the disease-specific survival (DSS) is 100% (63/63). Five-year PFS is 87.1% (27/31) for Group 1, 86.7% (13/15) for Group 2, 94.1% (16/17) for Group 3, and 88.9% (56/63) for the full cohort. **Conclusions:** Long-term follow-up of SIRS demonstrates de-escalation TORS and pathologic risk stratification is safe and effective in molecularly proven HPVOPC and reduces the lethal and morbid long-term side effects of full dose radiation and CRT. All recurrences occurred in the first two years postoperatively and were salvaged. Multidisciplinary decision-making utilizes the benefits of each specialty to optimize outcomes in de-escalation. Clinical trial information: NCT02072148. Research Sponsor: None.

Which systemic regimen to choose in cisplatin-ineligible patients with concurrent radiation therapy for head and neck cancers: carboplatin/5-flurouracil or carboplatin/paclitaxel?

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Background: For locally advanced head and neck cancer, concurrent chemotherapy-radiation therapy (ChemoRT) is mainstay of treatment. Carboplatin and 5-Flurouracil (CF) is category 1 recommendation per NCCN guidelines and used mainly in Cisplatin ineligible patients. In this study we aim to compare the outcomes of concurrent radiation therapy with either CF or Carboplatin/Paclitaxel (CP). **Methods:** TrinetX, a global federated research network that provides a dataset of electronic medical records from different healthcare organizations (HCOs), was utilized. Initial query was made to isolate patients who had head and neck cancer (ICD 10 codes C02, C03, C04, C05, C06, C09, C10, C12, C13, C14, C32) and received radiation therapy, concurrently either with CP or CF. Further, propensity score matching (PSM) was carried out to match age, sex, and race. Outcomes of all-cause mortality (ACM), sepsis, septic shock, neutropenia, nausea/vomiting (NV), diarrhea were evaluated. **Results:** 8,310 cases were identified who received ChemoRT, of whom 26% (2,160) received CF. Caucasians were the predominant race in both groups, but Asians received more CF (14% vs 4%, $p<0.0001$). Patients receiving CF were younger (61.4 ± 9.87 vs 63.5 ± 10.4, $p<0.0001$). It was seen that patients who received CF had higher ACM rate (51.54% vs 48.52%, p=0.0163; median overall survival (OS) 571 days vs 781 days, p=0.0007). Risk of sepsis (21.24% vs 17.05%, $p<0.0001$), septic shock (7.11% vs 5.24%, p=0.0014), neutropenia (21.98% vs 17.05%, $p<0.0001$), NV (32.79% vs 28.58%, p=0.0003) was more with CF compared to CP, while no difference in neuropathy and diarrhea. After PSM, though elevated but no statistical difference was seen in ACM (50.95% vs 48.75%, p=0.1593), septic shock (7.09% vs 5.77%, p=0.0852), and neutropenia (22.10% vs 19.66%, p=0.0544), while there was still difference in sepsis (21.17% vs 17.8%, p=0.0065), and NV (33.74% vs 29.73%, p=0.0059). **Conclusions:** Concurrent chemoRT with CP offers similar efficacy compared to CF, with less toxicity and can be established as to go chemotherapy regimen with radiation therapy in patients who are ineligible for Cisplatin. Research Sponsor: None.

Circulating tumor HPV-DNA dynamics and neoadjuvant chemotherapy with or without nivolumab in viral-mediated oropharyngeal cancer.

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Background: Human papillomavirus-associated (HPV+) oropharyngeal carcinoma (OPC) is linked to favorable survival outcomes, prompting efforts to de-intensify treatment strategies. Circulating tumor HPV-DNA (ctHPV-DNA) is a promising biomarker for assessing treatment response and guiding de-escalation strategies. This study evaluates how patient characteristics influence ctHPV-DNA dynamics during neoadjuvant therapy across two de-escalation clinical trials. **Methods:** Patients with non-metastatic HPV+ OPC enrolled across two trials of neoadjuvant carboplatin/paclitaxel (NCT04572100) or carboplatin/*nab*-paclitaxel/nivolumab (OPTIMA II, NCT03107182), with ctHPV-DNA available at baseline and post-neoadjuvant, were eligible. All participants received three cycles of neoadjuvant therapy followed by response-adapted de-escalated locoregional treatment. ctHPV-DNA values (copies per ml plasma) were measured at baseline and after 2-3 cycles of neoadjuvant therapy, and percentage reductions were calculated. We defined "ctHPV-DNA clearance" as $\geq$ 95% reduction from baseline and compared data distribution between patients who achieved clearance and those who did not using Kruskal-Wallis, Pearson's $\chi 2$, or Fisher's exact tests. Overall survival (OS) and progression free survival (PFS) probabilities were compared using log-rank test. **Results:** The study included 84 patients. The mean age was 60.9 years. 93% of patients with neoadjuvant nivolumab/chemotherapy achieved ctHPV-DNA clearance compared to 82% with chemotherapy alone, p=0.298. Patients with T1-T2 tumors (AJCC 8th edition) were significantly more likely to achieve ctHPV-DNA clearance compared to those with T3-T4 tumors (p=0.0254). Age, race/ethnicity, smoking history, tumor site (e.g., tonsil), and risk group were not significantly associated with ctHPV-DNA clearance rates. ctHPV-DNA clearance by cycle 2-3 of neoadjuvant therapy predicted radiographic response per RECIST v1.1 (p=0.001), and significantly improved OS (p=0.025) and PFS ($p<0.001$). Survival outcomes were similar across OPTIMA II and NCT04572100 as previously reported. **Conclusions:** Earlier T-stage tumors were associated with rapid ctHPV-DNA clearance by cycle 2 with a trend towards higher clearance rate with neoadjuvant nivolumab/chemotherapy. Rapid clearance predicts radiographic response, OS, and PFS, supporting ctHPV-DNA as a useful biomarker for treatment monitoring with neoadjuvant treatment in HPV+ OPC. Clinical trial information: NCT03107182. Research Sponsor: American Cancer Society; University of Chicago Cancer Center.

ctHPV-DNA % reduction between baseline and follow up at cycle 2-3.

	≥ 95% reduction N (%)	< 95% reduction N (%)	*p*
Age, (mean ± sd)	60.4 ± 10	61.3 ± 8.5	0.656
Gender (Male)	59 (86.8)	9 (13.2)	1
Race (Caucasian)	54 (86)	9 (14)	0.583
Risk (High)	34 (92)	3 (8)	0.309
T1 stage	**12 (75)**	**4 (25)**	**0.0254**
T2 stage	**30 (97)**	**1 (3)**	
T3 stage	**8 (89)**	**1 (11)**	
T4 stage	**3 (60)**	**2 (40)**	
Tumor shrinkage (median %, range)	**-64.2 (-23, -100)**	**-42 (-14, -71)**	**0.001**

6092 Poster Session

Evolving beyond the "unknown primary": Investigating histopathology after diagnostic transoral robotic surgery for microscopic HPV-associated oropharyngeal carcinoma.

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Background: Squamous cell carcinoma metastatic to the head and neck arising from an unknown primary tumor (hnSCCUP) is a common presentation for HPV-associated oropharyngeal carcinoma. Previously, with traditional approaches, rates of primary site identification for hnSCCUP were low. Using diagnostic transoral robotic surgery (TORS), primary tumors are now routinely found. In this report, we evaluate the histopathology and oncologic outcomes of these tumors. **Methods:** A retrospective review was conducted on 100 patients referred to Stanford University for hnSCCUP evaluation between October 2013 and April 2022. A final cohort of 80 patients who remained classified as hnSCCUP after comprehensive multidisciplinary review was analyzed. Surgical excision followed a standardized protocol targeting oropharyngeal subsites, and specimens were meticulously analyzed by three H&N pathologists. **Results:** The primary site was identified in 66 of 80 patients (83%), with a mean tumor size of 6 mm (range: 2–20 mm). Among the identified tumors, 97% were staged as T1, and 71% measured ≤1 cm, confirming their predominantly microscopic nature. The most common tumor locations were the palatine tonsil (26%), lateral tongue base (24%), glossopharyngeal sulcus (21%), and midline tongue base (18%). Histologically, most tumors exhibited a pushing pattern embedded within lymphoid stroma, while 29% demonstrated a pagetoid growth pattern, spreading in a ribbon-like distribution along the superficial lymphoepithelium. Following diagnostic TORS, 23 patients (29%) underwent further surgery, including 10 with surgery alone and 13 with adjuvant therapy. Radiation alone was administered to 15 patients (19%), while 42 patients (53%) underwent chemoradiation. At a median follow-up of 38 months (range: 12–101 months), 77 patients (97%) were alive with no locoregional tumor recurrence. Two patients (2.5%) developed distant metastases, with one death, and one patient (1.2%) experienced persistent regional disease after chemoradiation. Functional swallowing outcomes declined temporarily across all treatment groups. At six months, patients who underwent surgery alone had the least decline in Functional Oral Intake Scale (FOIS) scores, while those receiving chemoradiation experienced the greatest impact. By one year, all patients showed significant recovery, with no long-term feeding tube dependence. **Conclusions:** With a systematic surgical technique for p16+ oropharyngeal carcinoma, diagnostic TORS has revealed a unique pattern of small-volume, often microscopic primary tumors often initially mistaken as hnSCCUP. In many cases, it seems the unknown primary represents a T1-microscopic tumor measuring < 1 cm in maximum diameter with a prominent pattern of submucosal spread. Research Sponsor: The Isackson Family Fund for Research; The Stanford Head and Neck Surgery Research Fund.

6093 Poster Session

Dabrafenib and trametinib in the treatment of BRAF-mutated anaplastic thyroid cancers (ATC).

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Background: ATCs are rare, aggressive tumors with poor median overall survival (OS). Approximately 45% harbor BRAF V600 mutations driving tumor progression. We evaluated the outcomes of BRAF-V600E-mutated ATC treated with dabrafenib and trametinib (D/T), with or without local therapy. **Methods:** Consecutive ATC patients with BRAF-V600E mutations treated at our institution from 2016-2024 that received D (150 mg twice daily) and T (2 mg once daily) as a component of their multiple lines of therapies were included. Locoregional therapies included surgery alone, surgery and radiation, or radiation alone. We reported the OS of these patients. **Results:** Out of 82 BRAFV600E mutated ATC patients, 61 pts. (74%) were metastatic at the time of D/T initiation. Median age was 71 years (range 47-86 yrs). Locoregional therapies given: surgery only (n=8); surgery and RT (n=24); RT only (n=23). Median follow-up for all patients is 10 months, and 19 months for alive patients. Median OS for all patients is 14 months. Among those who had surgery only (n=8), the median OS was not reached. Patients who had surgery and radiation had a median OS of 22 months. Lastly, the patients who had RT only as local therapy had a median OS of 14 months. Patients without residual ATC after surgery had a median OS of 39 months versus 21 months for those with residual neck disease. 14 patients who received D/T prior to surgery had a median OS of 39 mo. Table 1 provides details of outcomes by metastatic status. **Conclusions:** This is the largest study to date reporting on outcomes of patients with BRAF V600 mutated ATC receiving D/T. This regimen demonstrates highly favorable results. Our data suggests that patients should undergo surgery when feasible and that D/T should be given prior to surgical intervention. However, the optimal timing, integration as well as the types of local therapy should be prospectively evaluated. Research Sponsor: None.

Patient outcome by metastatic status.

	Overall Survival	
	M0 (N=21)	**M1 (N=61)**
All Patients		
Median Follow-up (all)	15 months (range 2-49)	9 mo (range 0-71)
Median Follow-up (alive)	34 mo. (range 7-49)	16 mo. (range 0-71mo)
Median OS	22 mo. (95% CI 4-40mo.)	10 mo. (95% CI 5-15mo.)
12-month	66%	48%
18-month	55%	37%
Surgery (vs. No surgery)	N=13 versus N=8	N=19 versus N=42
Median OS	22 mo. versus 10 mo.	28 mo. versus 9 mo.
12-month	77% versus 47%	68% versus 38%
18-month	68% versus 47%	61% versus 25%
Surgery* (No residual neck disease versus residual)	N=5 versus N=8	N=15 versus N=4
Median OS	Not reached versus 22 mo.	39 mo. versus 9 mo.
12-month	80% versus 75%	73% versus 50%
18-month	53% versus 47%	65% versus 50%
Radiation (vs. No RT)	N=6 versus N=2	N=17 versus N=25
Median OS	7 mo. versus 10 mo.	9 mo. versus 6 mo.
12-month	50% versus 0%	41% versus 36%
18-month	50% versus 0%	29% versus 22%
Surgery + RT	N=6	N=12
Median OS	22 mo.	21 mo.
12-month	75%	58%
18-month	55%	58%
Order of D/T		
Before Surgery	N=3	N=11
Median OS	Not reached	28 mo.
12-month	100%	82%
18-month	67%	72%

*Surgery with or without RT.

Efficacy and safety of larotrectinib in patients with TRK fusion thyroid carcinoma: An updated analysis.

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Background: *NTRK* gene fusions are oncogenic drivers in various tumor types, including thyroid carcinoma (TC). Larotrectinib (laro) is the first-in-class, highly selective, central nervous system-active TRK inhibitor, approved for tumor-agnostic use in patients (pts) with TRK fusion cancer. Here, we report updated long-term efficacy and safety data in pts with TRK fusion TC treated with laro. **Methods:** Pts with TRK fusion TC enrolled in 3 laro clinical trials (NCT02576431, NCT02122913, NCT02637687) were included. Laro was administered at 100 mg twice daily (BID) to adults; 2 pediatric pts received 100 mg/m^2 BID (maximum dose 100 mg BID). Responses were independent review committee-assessed per RECIST v1.1. Data cutoff: July 20, 2024. **Results:** At data cutoff, 31 pts were enrolled; 24 (77%) had differentiated TC (DTC) and 7 (23%) had anaplastic TC (ATC). Median age was 60 years (range 6–80). Median time since initial cancer diagnosis was 5 years (range 0–46). Seventeen pts (55%) were systemic treatment-naïve in the metastatic/unresectable setting, 6 (19%) received 2 or more prior therapies, and 24 (77%) received prior radioiodine. All *NTRK* gene fusions were identified by next-generation sequencing. Overall response rate (ORR) was 65% (95% confidence interval [CI] 45–81): 3 (10%) complete responses, 17 (55%) partial responses (PR), 5 (16%) stable disease (SD), 4 (13%) progressive disease (PD), and 2 (6%) not evaluable. For pts classified as DTC, ORR was 79% (95% CI 58–93). For pts classified as ATC, ORR was 14% (95% CI 0–58). Three (10%) pts had poorly differentiated TC, 1 classified as DTC (PR) and 2 as ATC (1 SD for >36 months and 1 PD). Median time to response for all pts was 1.9 months (range 1.6–16.2). Median duration of response, progression-free survival, and overall survival (OS) were 35 months (95% CI 19–not estimable [NE]), 39 months (95% CI 17–NE), and not reached (NR; 95% CI 28–NE), respectively, at median follow-ups of 48, 42, and 68 months. Median OS was NR (95% CI 56–NE) in DTC and 9 months (95% CI 3–NE) in ATC. The 6-year OS rate for all pts was 60% (95% CI 41–79). The 6-year OS rate was 71% (95% CI 50–91) for pts with DTC and 17% (95% CI 0–46) for pts with ATC. Median duration of treatment was 31 months (range 1–88). At data cutoff, 7 (23%) pts remained on treatment, 5 of whom had disease control. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 5 (16%) pts. There were no discontinuations due to TRAEs. **Conclusions:** Laro demonstrates rapid and durable responses, extended survival, and a favorable safety profile in pts with TRK fusion DTC. Limited single-agent activity is observed in pts with ATC. This supports the use of a TRK inhibitor to treat TRK fusion DTC and the importance of testing for *NTRK* gene fusions in patients with advanced TC needing systemic therapy. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc.

6095 Poster Session

Comparative transcriptomic analysis to identify similarities and therapeutic vulnerabilities in olfactory neuroblastoma (ONB), sinonasal neuroendocrine carcinoma (SNEC) and sinonasal undifferentiated carcinoma (SNUC).

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Background: ONB, SNEC and SNUC are rare sinonasal epithelial/neuroepithelial tumors, underserved by clinical trials, with few treatments available despite novel therapeutic agents against surface targets approved or in clinical development. Transcriptomic similarities of ONB with small cell lung cancer (SCLC), pheochromocytoma (PH), paraganglioma (PG), glioblastoma (GB) and low-grade glioma (LGG) are reported, but not for SNUC or SNEC. We examined the transcriptome of ONB, SNUC, SNEC, neuroendocrine (NE) and central nervous system tumors from a real-world (RW) patient cohort to identify similarities and uncover therapeutic vulnerabilities. **Methods:** Tumor specimens (pathology per referring clinician) tested (Caris Life Sciences, Phoenix, AZ) included ONB (n = 26), SNUC (n = 9), SNEC (n = 6), SCLC (n=1751), pancreatic NE tumors (PNET, n=16), PH (n=23), PG (n=50), LGG (n=657), GB (n=4524) and neuroblastoma (NB, n=47). RNA sequencing data were processed to obtain transcripts per million (TPM) values. Clustering was performed with a random subset of 50 samples for tumor types with n>100. ONBs were subtyped to neural and basal (Classe *et al.* 2018). RW overall survival (rwOS) was calculated from insurance claims (tissue collection to last contact), compared with log-rank test; Cox proportional hazard model was used for hazard ratio (HR). Selected genes encoding surface targets included *DLL3*, *PMEL*, *PVRL4*, *TACSTD2*, *ERBB2*, *F3*, *CLDN18*, *EGFR*, *ERBB3*, *MET*, *GPC3*, *CD276*, *VTCN1* and *FOSL1*. Median TPM values for genes of interest in ONB, SNUC and SNEC were examined. **Results:** There were 5 transcriptomic clusters (C1-5) (Table). Across clusters, median rwOS was worse for C1 (11.6 mo) and C3 (16.6 mo) vs. C2, C4, and C5 (all not reached), (p = 0.0) and was numerically better in neural (C4) vs. basal ONB (C0) (HR = 0.388, p=0.199). Highest expression for *F3* (34.5), *CD276* (15.6), *GPC3* (7.2) and *CLDN18* (1.1) was in ONB; *ERBB2* (16.4), *TACSTD2* (13.9), *EGFR* (9.2), *PVRL4* (6.2), *PMEL* (2.0) and *FOLR1* (1.5) in *SNUC*; *ERBB3* (83.3), *MET* (32.4), *DLL3* (3.5) and *VTCN1* (1.7) in SNEC. **Conclusions:** We show that neural ONBs cluster independently and basal ONBs co-cluster with SCLC and PNET, joined also by SNUC and SNEC. In our dataset, this cluster is associated with worse rwOS. We also show expression of surface target genes in ONB, SNUC and SNEC, indicating the presence of actionable subsets with existing drugs approved in other tumor types. Our findings provide targets for protein expression validation and expansion of therapeutic options for patients with these rare tumors. Research Sponsor: None.

Cluster	Tumor type, samples over N
C1	**ONB basal, 6/7**
	SNUC, 9/9
	SNEC, 5/6
	SCLC, 48/50
	PNET, 15/16
	NB, 2/47
C2	**ONB neural, 2/18**
	SNEC, 1/6
	PH, 22/23
	PG, 47/50
	NB, 4/47
C3	LGG, 50/50
	GBM, 50/50
	PG, 1/50
C4	NB, 41/47
	PG, 1/50
	PH, 1/23
C5	**ONB neural, 16/18**
	ONB basal, 1/7
	PG, 1/16

Efficacy and safety of anlotinib in neoadjuvant treatment of locally advanced differentiated thyroid cancer (DTC): A multicenter, single-arm, phase II study.

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Background: Neoadjuvant therapy is often necessary for patients with locally advanced inoperable or locally recurrent thyroid cancer without chance of surgery. Anlotinib is a small molecule multi-targeted tyrosine kinase inhibitor that can inhibit tumor angiogenesis while simultaneously inhibiting tumor growth, and has demonstrated significant benefit in radioiodine (RAI)-refractory differentiated thyroid cancer (DTC). Our study aims to evaluate the efficacy and safety of anlotinib in the preoperative neoadjuvant therapy with unresectable DTC. **Methods:** The study (ChiCTR2100048077) was a single-arm, open-label, multicenter phase II study. Eligible patients were between 18-75 years old with histopathological confirmed locally advanced differentiated thyroid cancer at high surgical risk and susceptible to postoperative recurrence. Patients with locally advanced DTC with distant metastasis and potential for local resection were also included. Patients received 12mg of anlotinib once daily on a schedule of 2 weeks on and 1 week off until surgery or disease progression and treatment discontinuation. The primary endpoint was objective response rate (ORR). The secondary endpoints included time to response (TTR), disease control rate (DCR), actual surgery rate, rate of R0 resection and safety. The objective response was evaluated according to RECIST 1.1. Here we report the results of this study. **Results:** 50 patients (20 males vs. 30 females) were enrolled from 3/2022 to 12/2023, with a median age was 56.5 (range: 26.0-74.0), 52% of patients had undergone previous surgery and 14% of patients had received radioiodine (iodine-131) treatment. At the cutoff date (November 30th, 2024), out of 43 patients with assessable efficacy, no CR occurred, 18 patients achieved PR, 24 patients achieved SD and 1 patients had PD.ORR and DCR was 41.86% (95%CI: 27.01-57.87) and 97.67% (95%CI: 87.71-99.94) respectively. 21 patients underwent surgery, 57.1% (12/21) achieved R0 resection. Median time to response was 2.84 months (range: 1.31-5.16 months). In patients who did not undergo surgical treatment, the median progression-free survival (mPFS) had not yet reached. The 6-month progression-free survival rate (PFS rate) was 95.83% (95%CI:73.92-99.40). 76%(38/50) of patients had experienced anlotinib treatment-related adverse events (TRAEs), Grade 3+ TRAEs were observed in 9 patients (18%, most common hypertension). 16% (8/50) of patients were discontinued due to TRAEs. No deaths attributable to adverse events (AEs) were observed. **Conclusions:** The study indicated that anlotinib was safe and effective as a neoadjuvant therapy for patients with locally advanced DTC. Clinical trial information: ChiCTR2100048077. Research Sponsor: None.

Updated efficacy, safety and biomarker analysis of a phase 2 study of LBL-007 (alcestobart, an anti-LAG-3 mAb) combined with tislelizumab (an anti–PD-1 mAb) and chemotherapy in previously untreated recurrent or metastatic nasopharyngeal carcinoma (R/M NPC).

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Background: For the first time weevaluated LBL-007 in combination with tislelizumab and chemotherapy in previously untreated R/M NPC in a prospective, multi-center phase 2 study. Preliminary findings indicated this combination had encouraging ORR in this patient population (2024 ASCO, abstr 6033). Here we present the updated efficacy, safety and biomarker analysis of this study focusing on previously untreated R/M NPC (NCT05516914). **Methods:** Untreated R/M NPC patients received gemcitabine at 1 g/m^2 on days 1 and 8, cisplatin at 80 mg/m^2 on day 1 (GP) in combination with LBL-007 600 mg and tislelizumab 200 mg on day 1 of every 3 weeks, the chemotherapy was up to 6 cycles, followed by LBL-007 and tislelizumab on day 1 of every 3 weeks as maintenance therapy. The primary endpoint was efficacy, and the secondary endpoints included safety and biomarker analysis. **Results:** As of January 13, 2025, 42 patients with NPC were enrolled and received LBL-007 in combination with tislelizumab plus chemotherapy as first-line treatment. The median follow-up was 17.1 months. Out of 41 efficacy evaluable patients, the ORR and DCR were 85.4% and 100%, the mPFS was 15.0 months and the mDoR was 14.7 months. mOS is not mature. A favorable trend of improved efficacy with LBL-007 combined with tislelizumab plus chemotherapy was observed compared to tislelizumab plus chemotherapy (mPFS 9.6 months, mDoR 8.5 months; NCT03924986). All-grade TRAEs occurred in 39 patients (92.9%), with grade ≥3 TRAEs in 29/42 patients (69.0%). Treatment permanent discontinuance due to LBL-007 TRAEs occurred in 2 (4.8%) patients. 16 patients (38.1%) experienced LBL-007 treatment related SAEs. TRAEs leading to death occurred in 1 patient and infusion-related reaction happened in 4 patients. No new safety signal was observed. Patients with LAG-3 expression ≥5% potentially had improved efficacy compared to those with <5% (Table 1). **Conclusions:** LBL-007/tislelizumab combined with GP chemotherapy has shown encouraging ORR, PFS and DoR in R/M NPC as first-line treatment with favorable safety profiles. These findings support a pivotal phase III study comparing LBL-007/tislelizumab plus GP with tislelizumab plus GP in R/M NPC in 1L setting. The correlation between higher LAG-3 expression and improved efficacy was observed, which warranted further validation in larger population. Clinical trial information: NCT05516914. Research Sponsor: Nanjing Leads Biolabs Co., Ltd.

Clinical outcomes of efficacy evaluable patients.

	LAG-3 < 5% N=10[a]	LAG-3≥5% N=27[a]	Total N=41
ORR, N(%)	7 (70%)	25 (92.6%)	35 (85.4%)
DCR, N(%)	10 (100%)	27 (100%)	41 (100%)
mPFS (95%CI), months	12.1 (3.3, NE)	15.8 (9.7, NE)	15.0 (9.7, NE)
mDoR (95%CI), months	8.8 (3.2, NE)	14.7 (8.3, NE)	14.7 (8.6, NE)
15-month PFS rate, % (95%CI)	40.0% (12.3%, 67.0%)	53.9% (33.4%, 70.7%)	49.8% (33.6%, 64.1%)

[a]LAG-3 was evaluated in 37 patients.

Results from a phase I study of KL590586 in patients with advanced RET-mutant medullary thyroid cancer.

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Background: *RET* mutations occur in 70% of medullary thyroid cancers (MTC). KL590586 (A400/EP0031) is a potent next-generation brain-penetrant selective RET inhibitor (SRI) with activity against acquired resistance mutations to first-generation SRIs (Zhou et al. 2023, Garralda et al. 2024). Here we present the preliminary safety and efficacy data of KL590586 in patients (pts) with advanced RET-mutant MTC from the phase I part of a phase I/II study completed in China (KL400-I/II-01, NCT05265091). **Methods:** The phase I part, comprising a dose-escalation phase and a dose-expansion phase, was conducted to evaluate the safety, pharmacokinetics, and efficacy of KL590586 in pts with RET-altered solid tumors. Eligible pts with advanced RET-mutant MTC were enrolled to receive KL590586 once a day (QD) until disease progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks as per RECIST v1.1. **Results:** As of September 20, 2024, 27 advanced RET-mutant MTC pts without prior SRIs were enrolled and treated in the phase I part across 4 dose levels (20 to 90 mg QD). The median age was 49 years, and 66.7% of pts were male. Among these 27 pts, 8 were treatment-naïve, and 19 had received previous systemic treatment, with 84.2% of them treated with multikinase inhibitors (MKIs). The median follow-up was 19.0 months. Adverse events were reported for all pts. The most common adverse events considered treatment related (TRAEs, ≥ 35%) were increased ALT (77.8%), increased AST (70.4%), headache (48.1%), increased blood creatine phosphokinase (40.7%), increased blood lactate dehydrogenase (37.0%), and hyperuricaemia (37.0%), with grade ≥3 TRAEs occurring in 22.2% of pts. The most frequent grade ≥ 3 TRAEs (≥ 5%) were increased ALT (7.4%) and increased GGT (7.4%). No TRAEs led to treatment discontinuation or death. At data cut-off, the confirmed objective response rate (cORR) was 63.0% (17/27) and the disease control rate was 100% for overall population. The cORR was 56.3% (9/16) and 62.5% (5/8) in pts with prior MKI or treatment naïve, respectively. Median duration of response was not reached (95% CI, 7.4 to NE), with the longest duration still ongoing at 25.8 months. Similarly, median progression-free survival (PFS) was not reached, with the 24-month PFS rate of 77.8%. **Conclusions:** KL590586 was well tolerated in pts with advanced RET-mutant MTC, exhibiting a safety profile consistent with that previously reported in NSCLC (Zhou et al. 2023). In MTC pts with or without previous MKIs, KL590586 demonstrated robust clinical activity with durable responses. The findings support further investigation of KL590586 as a potential therapeutic alternative for this patient population. Phase II trials are evaluating KL590586/EP0031 in China and US/Europe/UAE. Clinical trial information: NCT05265091. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

6099 Poster Session

BRAF-V600E papillary thyroid cancer: Updated analysis of real-world patient data.

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Background: Papillary thyroid cancer (PTC) is the most common type of thyroid cancer, usually characterized by a good prognosis after surgery with or without radioactive iodine therapy (RAI). However, ~5-15% of patients become RAI refractory, and some require systemic therapy, often with multi tyrosine kinase inhibitors (mTKIs).*BRAF*-V600E, the most common mutation in PTC (~60% of patients), is associated with poor outcomes. The effectiveness of mTKIs compared to BRAF-targeted therapy (BRAF/MEKi) and immunotherapy (IO) remains unclear in the *BRAF*-V600E mutant (*BRAF*-m) population. Therefore, we conducted an updated analysis comparing real-world (rw) survival and molecular/transcriptional signatures in patients with *BRAF*-m and *BRAF*-wildtype (WT) PTC. **Methods:** Differentiated thyroid cancer (DTC) tumor samples underwent DNA/RNA next-gen sequencing at Caris Life Sciences. Tumor microenvironment (TME) cell fractions were estimated by RNA deconvolution using QuanTIseq. A transcriptional IFNγ signature score associated with response to IO was calculated. PD-L1$^+$ (SP142) was defined as $\geq 2^+$ in stain intensity and $\geq$5% of tumor cells stained. Insurance claims data was used to infer rw overall survival (rwOS) from the time of initial diagnosis to death/last contact, and time on treatment (TOT) was assessed from the first to last date of treatment, with hazard ratios (HR) and p-values calculated using the Cox proportional hazards model and log-rank test, respectively. **Results:** A total of 1,348 patients with DTC were identified, of which 82% (n=1,102) were PTC and 18% (n=246) were follicular thyroid cancer (FTC). The majority (95%) of PTC patients were naïve to mTKIs or BRAF/MEKi. *BRAF*-V600E mutations were present in 68% (n=754) PTC patients and only 0.8% (n=2) FTC patients. *TERT* promoter mutations were the most common mutation overall in PTC (72%), more prevalent in *BRAF*-m *vs* *BRAF*-WT PTC (79% *vs* 54%, p<0.001). Mutations in *NRAS*, *HRAS* and *KRAS* were largely exclusive to *BRAF*-WT PTC (22%, 9% and 6% *vs* 0.1%, 0% and 0% in *BRAF*-m PTC, p<0.001), as were *RET*, *BRAF*, and *ETV6* gene fusions (24%, 5% and 5% *vs* 0%, 0.4% and 0% in *BRAF*-m PTC, p<0.01). *BRAF*-m PTC were more often PD-L1$^+$ (33% *vs* 18%, p<0.001), consistent with higher IFNγ scores. This was accompanied by higher Treg and M1 macrophage TME fractions, and lower M2 macrophage, T cell (CD4$^+$ and CD8$^+$), NK cell, monocyte and myeloid dendritic TME fractions compared to *BRAF*-WT PTC (p<0.05). There was no difference in rwOS between *BRAF*-m and *BRAF*-WT PTC (HR=0.845, 95% CI 0.654-1.092, p=0.197), nor per treatment received in *BRAF*-m PTC (BRAF/MEKi *vs* mTKIs, BRAF/MEKi *vs* IO, IO *vs* mTKIs). Similarly, TOT for BRAF/MEKi, mTKIs and IO were similar between *BRAF*-m and *BRAF*-WT PTC. **Conclusions:** *BRAF*-m PTC is associated with a more pro-inflammatory TME milieu compared to *BRAF*-WT PTC. However, in this limited data set, treatment choice was not associated with differences in overall survival in *BRAF*-m PTC. Research Sponsor: CARIS Life Sciences.

6100 Poster Session

Anti-TROP2 ADC ESG401 in a master protocol clinical trial for salivary gland cancer based on molecular typing.

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Background: Salivary gland carcinomas (SGC) are rare, with limited prospective clinical outcome data. There is no standard of care or FDA-approved systemic therapy for recurrent and/or metastatic (R/M) disease. Precision therapy targeting specific gene alterations is emerging as a promising approach for SGC. We designed a single-center, open-label, master protocol clinical trial evaluating the efficacy and safety of molecular subtype-guided precision neoadjuvant/transformative or rescue therapy for SGC. This report focuses on the preliminary results of the TROP2-targeted group. **Methods:** Pts with locally advanced/recurrent SGC received neoadjuvant/transformative therapy, while pts with locally advanced/recurrent who could not tolerate or refused surgery/radiotherapy and pts with symptomatic, rapidly progressive metastatic SGC received rescue therapy. Pts were divided into molecular subtypes (HER2, NTRK, AR, TROP2) or assigned to chemotherapy if no molecular alterations were detected. Trop2-positive pts were assigned to the TROP2 group and treated with ESG401 (16 mg/kg i.v. on days 1, 8, and 15 of each 28-day cycle). The primary endpoint was ORR per RECIST1.1; secondary endpoints included AEs, DCR, PFS, and OS. **Results:** As of Jan 22, 2025, 14 Trop2-positive pts were enrolled, including 4 receiving neoadjuvant/transformative therapy and 10 receiving rescue therapy. Among the 12 efficacy-evaluable pts, pathological types included salivary duct carcinoma (n=3), adenoid cystic carcinoma (n=5), and others (n=4). Safety findings were consistent with the ESG401-101 study, with no new safety signals observed. Among 4 pts receiving neoadjuvant/transformative therapy, 2 achieved decreased SD, though not meeting PR criteria. Among 8 pts receiving rescue therapy, 4 achieved PR with ORR was 50% (4/8). For 12 efficacy-evaluable pts, DCR was 100% (12/12). Three pts with brain metastases achieved IC-PR/CR, yielding an IC-ORR of 100%. **Conclusions:** ESG401 demonstrated promising efficacy in Trop2-positive SGC, providing a rationale for molecular subtype-based targeted therapy in this population and warranting further investigation in larger studies. Clinical trial information: NCT06145308. Research Sponsor: None.

6101 Poster Session

Amivantamab for recurrent/metastatic adenoid cystic carcinoma: A multicenter, single-arm, phase 2 clinical trial.

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Background: Adenoid cystic carcinoma (ACC) is a rare salivary gland cancer with heterogenous clinical behavior. ACC typically presents with locoregional disease and is treated with curative intent surgery and adjuvant radiation, but many patients develop locally recurrent/metastatic (R/M) disease even years later. Two recognized molecular subtypes exist: ACC 1 (37%), characterized by *MYC* amplification and *NOTCH*-activating mutations and a poor prognosis, and ACC 2 (63%), which demonstrates P63 expression and upregulated EGFR and MET and a better prognosis. There is no standard treatment for R/M ACC, but multi-targeted tyrosine kinase inhibitors are a mainstay of treatment despite their limited efficacy. Amivantamab is a bispecific antibody that binds to the extracellular domains of EGFR and MET, causing immune-directed destruction of cancer cells. Since MET expression renders EGFR inhibitors ineffective, we hypothesized that amivantamab would overcome resistance especially in the ACC 2 subtype. This multicenter, single arm, Phase 2 clinical trial (NCT05074940) evaluated the efficacy of amivantamab in patients with R/M ACC supported by Janssen Pharmaceuticals. **Methods:** Eligible patients were ≥18 years of age with R/M ACC and had progressive disease (PD) within 6 months of enrollment, ECOG ≤1, with adequate organ and marrow function. Patients received amivantamab 1050 mg or 1400 mg (≥80kg) IV weekly for 4 weeks then Q2 weeks until PD or unacceptable toxicity. The primary end point was overall response rate (ORR) assessed by RECIST 1.1. Among 18 treated patients the lower limit of a one-sided 90% exact binomial CI would be >14% if ≥5 patients respond. Adverse events (AEs) were assessed by CTCAE v5. Secondary end points included progression- free survival (PFS) and overall survival (OS). Key exploratory end points were P63 and MYC expression. **Results:** We enrolled 21 patients with 17 evaluable for response at time of submission. Most were male (14, 67%) non-Hispanic (20, 95%), and White (19, 90%) with a median age of 61 (range, 36-76) years. The majority received prior treatment. The best ORR was 6% (1 partial response), while 9 (53%) had stable disease (SD) and 7 (41%) PD. Median duration of SD was 5.4 months. The most common treatment-related AEs (TRAEs) were acneiform rash (17, 81%), infusion related reaction (16, 76%), and fatigue (15,71%). Grade 3 TRAEs occurred in 3 patients (14%) including acneiform rash, oral mucositis, and elevated alkaline phosphatase with no Grade ≥4 TRAEs. Median PFS and OS were 4.8 (95% CI, 1.84-7.64) and 10.4 months (95% CI, 5.48-NR), respectively. There was no correlation between tumor P63 or MYC levels and clinical benefit (PR+SD). **Conclusions:** While amivantamab did not achieve the target ORR, the safety profile was manageable and clinical benefit was observed in 59% of patients. Clinical trial information: NCT05074940. Research Sponsor: Janssen Pharmaceuticals.

6102 Poster Session

A phase 2 study of novel MDM2 inhibitor alrizomadlin (APG-115) with or without toripalimab in patients (pts) with advanced adenoid cystic carcinoma (ACC) or other solid tumors.

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Background: Alrizomadlin, an investigational MDM2 inhibitor, has shown a manageable safety profile with preliminary efficacy in liposarcoma (LPS) and ACC and in combination with a PD-1/PD-L1 inhibitor in advanced solid tumors. **Methods:** This multicenter trial (APG115XC102) assessed alrizomadlin (± toripalimab) in pts with advanced ACC, malignant peripheral nerve sheath tumor (MPNST), LPS, biliary-tract cancer (BTC), or other solid tumors in China. Enrolled pts had an ECOG PS 0-1 and were without central nervous system metastases. Alrizomadlin was administered orally at 50, 100, or 150 mg every other day for 2 weeks, with 1 week off, in repeated 21-day cycles, and combined with toripalimab 240 mg IV for 30 minutes on Day 1 of repeated 21-day cycles until disease progression or unacceptable toxicity. The primary endpoint was RP2D for the combination. ORR was assessed per RECIST v1.1. **Results:** As of January 5, 2025, 54 pts were enrolled. In the monotherapy arm, 22 pts were treated with alrizomadlin 150 mg; common treatment-related adverse events (TRAEs) included nausea (68.2%), decreased appetite (45.5%), thrombocytopenia (40.9%), white blood cell count decreased (40.9%), neutropenia (36.4%), and hypoalbuminemia (22.7%). Grade ≥ 3 TRAEs included neutropenia (13.6%) and thrombocytopenia (9.1%). No treatment-related serious adverse events (SAEs) were reported. In the combination arm, 32 pts were treated with alrizomadlin at 50 (n = 3), 100 (n = 3), or 150 mg (n = 26). No DLT was observed; the expansion dose was 150 mg plus toripalimab. Common TRAEs at 150 mg included nausea (73.1%), thrombocytopenia (65.4%), neutropenia (50.0%), decreased appetite (42.3%), and anemia (38.5%). Grade ≥ 3 TRAEs included thrombocytopenia (38.5%) and neutropenia (34.6%). Treatment-related SAEs were reported in 8 pts, including 6 thrombocytopenia, 1 neutropenia, 1 intestinal fistula, and 1 peptic ulcer. One pt (3.8%) discontinued treatment because of grade 4 thrombocytopenia; no treatment-related death was reported. Regarding efficacy, in the monotherapy arm, 14 pts were evaluable, with 2 unconfirmed partial responses (PRs) in 9 pts with ACC (ORR 22.2%, DCR 100%). All 5 pts with MPNST achieved SD (DCR 100%). In the combination arm, 28 pts were evaluable: 1 of 5 pts with BTC had a confirmed PR, and the ORR (CR + PR) was 20% and DCR 80%; 1 unconfirmed PR was reported in 6 pts with LPS, for an ORR of 16.7% and DCR of 66.7%. Pts with MPNST had an ORR of 14.3% and a DCR of 53.6%, and 2 pts with MPNST had confirmed PRs with prolonged PFS (1 pt > 60 weeks, 1 > 96 weeks). **Conclusions:** Alrizomadlin monotherapy showed promising antitumor activity in pts with advanced ACC or MPNST. Alrizomadlin combined with toripalimab was also well tolerated, showing antitumor activity in MPNST, BTC, and LPS and an acceptable safety profile (NCT04785196). Clinical trial information: NCT04785196. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

6103 Poster Session

A phase II study of lenvatinib plus pembrolizumab in patients with recurrent/metastatic salivary gland cancers.

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Background: Recurrent/metastatic (R/M) salivary gland cancers (SGCs) are rare diseases without standard therapies. Based on the hypothesis that VEGFR inhibition can enhance immune checkpoint-induced responses against SGCs, we conducted a phase II trial of the multikinase inhibitor lenvatinib (len) plus the programmed death-1 (PD-1) inhibitor pembrolizumab (pem) in two R/M SGC cohorts: adenoid cystic carcinoma (ACC) and non-ACC histologies. Here we report results from the completed non-ACC cohort. **Methods:** Patients (Pts) with R/M SGC (except ACC) were enrolled. RECIST v1.1 measurable disease was required; prior therapies were allowed. Pts with acinic cell carcinoma (AcCC) were required to have progression of disease (PD) or worsening disease-related symptoms. Len 20 mg oral daily and pem 200 mg intravenously every 3 weeks was given. The primary endpoint was best overall response (BOR) rate using a minimax Simon two-stage design. In the first stage, >1 confirmed complete and/or partial responses (CRs, PRs) was required among 18 pts to enroll 14 more pts. >4 responses among 32 pts would be considered positive (BOR 5% vs 20%, 1-sided alpha 0.1, power 0.9). Secondary objectives were progression-free survival (PFS) and safety/tolerability per CTCAE v5.0. **Results:** 27 pts with R/M SGC pts were enrolled; 26 evaluable for the study endpoints. Among evaluable pts, the median age was 62 and 15 were men. SGC histologies included 9 AcCC, 8 salivary duct carcinoma (SDC), 4 myoepithelial carcinoma, 2 mucoepidermoid carcinoma, and 1 each of polymorphous adenocarcinoma, epithelial-myoepithelial carcinoma, and mucinous adenocarcinoma. 5/26 (19.2%) had confirmed PR. 18 pts had stable disease (SD), 1 PD as best response; 2 evaluable pts did not reach first scan assessment. As of 1/20/25, median PFS was 47 weeks. Among the 9 AcCC pts, 4 (44.4%) had PR and 5 SD; 8/9 pts had tumor regression in target lesions. For the 8 SDC pts, 1/8 (12.5%) had PR. Per protocol, 2 pts (AcCC and SDC) stopped treatment after 2 years; both resumed treatment when PD occurred, achieving SD and PR, respectively. Six deaths were observed, 4 possibly related to treatment: 3 SDC (respiratory failure due to pneumonitis vs. cancer progression [1]; cardiac arrest after polymyositis/myocarditis/aspiration pneumonia [1]; stroke [1]) and 1 myoepithelial carcinoma (respiratory failure due to pneumonitis vs. infection [1]). **Conclusions:** Trial enrollment was completed after 26 evaluable pts given the study was positive for the primary BOR endpoint and the grade 5 events observed. Len+pembro may be active and safe among pts with AcCC, though further study is needed. This combination may be less promising for SDC given the grade 5 events and low response rate observed. (Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA provided lenvatinib and pembrolizumab for the study.) Clinical trial information: NCT04209660. Research Sponsor: Merck; U.S. National Institutes of Health.

Trop2-targeted PET/CT with ^{68}Ga-MY6349 for detecting metastatic lesions in metastatic thyroid cancer: Prospective comparison of diagnostic accuracy with ^{18}F-FDG PET/CT.

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Background: Trophoblast cell surface antigen 2 (Trop2) targeted molecular imaging with ^{68}Ga-MY6349 has been proposed as a potential modality for visualizing cancerous lesions, but its utility for identifying metastatic thyroid cancer (TC) is not well-established in the literature. This study aims to evaluate the clinical utility of ^{68}Ga-MY6349 PET/CT for detecting metastatic TC and to compare the results with those of ^{18}F-fluorodeoxyglucose (FDG) PET/CT. **Methods:** This was a prospective, single-center, open-labeled, single-arm comparative imaging trial. Patients with clinically suspected or confirmed metastatic TC were prospectively enrolled and underwent paired ^{68}Ga-MY6349 and ^{18}F-FDG PET/CT from November 2023 to January 2024. Histopathology and clinical follow-up (mean 12 months ± 0.7 [standard deviation] (range: 11-13 months) were used as reference standards for the final diagnosis. ^{18}F-FDG and ^{68}Ga-MY6349 uptake were compared by using the Wilcoxon signed-rank test. The McNemar test was used to compare the diagnostic efficacy of the two techniques, and the influence of various clinicopathological characteristics on ^{18}F-FDG and ^{68}Ga-MY6349 uptake was evaluated by Mann-Whitney and Kruskal-Wallis tests. **Results:** In total, 55 participants (median age, 51 years [interquartile range, 35-61 years]; 17 men) were evaluated. In all 55 participants, the ^{68}Ga-MY6349-derived SUV_{max} was higher than the ^{18}F-FDG-derived SUV_{max} in the local recurrence (24.9 vs. 10.7, $P = .026$), metastatic central compartment (12.7 vs. 4.9, $P < .001$), metastatic lateral compartment (11.0 vs. 5.4, $P < .001$), and mediastinal lymph nodes (LNs) (9.5 vs. 4.6, $P = .012$). ^{68}Ga-MY6349 PET/CT had a higher sensitivity than ^{18}F-FDG PET/CT for detecting neck lesions (88% vs. 56%; $P < .001$). **Conclusions:** ^{68}Ga-MY6349 PET/CT was superior to ^{18}F-FDG PET/CT for detecting metastatic TC, especially in local recurrence and LNs metastases. Clinical trial information: NCT06465017. Research Sponsor: None.

Comparison of ^{18}F-FDG and ^{68}Ga-MY6349 uptake in metastatic thyroid cancer.

Site of Disease	^{18}F-FDG Uptake (SUV max)	^{68}Ga-MY6349 Uptake (SUV max)	*P* value
Local recurrence	10.7±7.6	24.9±23.7	0.026
Central compartment LNs	4.9±4.6	12.7±10.9	<0.001
Lateral compartment LNs	5.4±6.4	11.0±10.23	<0.001
Mediastinal LNs	4.6±2.8	9.5±7.5	0.012
Pulmonary metastases	2.4±0.7	3.4±1.5	0.175
Other sites*	8.5±3.8	14.2±17.1	0.691

LNs, lymph nodes; Other sites include bone and subcutaneous metastasis.

6105 Poster Session

Dual immune checkpoint inhibition in advanced incurable radioidine-refractory differentiated thyroid carcinoma (RAIR DTC), anaplastic (ATC), and medullary thyroid carcinoma (MTC): Long-term survival results from phase II clinical trial.

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Background: Immunoprofiling and preclinical studies with patient derived organotypic tumor spheroids supported therapeutic targeting of programmed death (PD)-1 and cytotoxic T lymphocyte antigen (CTLA)-4 pathways in thyroid tumors. We previously presented initial results of a phase 2 clinical trial evaluating dual immune checkpoint inhibition with nivolumab (N) and ipilimumab (I) in advanced incurable thyroid carcinoma (TC) (ASCO 2020, PMID: 39446365) with data cutoff at 24 months (mo) follow up. **Methods:** This nonrandomized phase 2 clinical trial evaluated N (3 mg/kg every 2 weeks) + I (1 mg/kg every 6 weeks) in the primary patient population of RAIR DTC, with exploratory cohorts in ATC and MTC. Primary endpoints were objective response rate (ORR), with secondary endpoints of safety, progression-free survival (PFS), and overall survival (OS). Here, we present long term results (data cutoff 12/27/24), with median follow up of 75.3 mo for the overall population. **Results:** 49 patients (32 RAIR DTC, 10 ATC, and 7 MTC) were evaluable, 51% female, with median age of 65 years (range 30-88). Median duration of follow up (by cohorts) for this analysis was 74.9 mo (range 12.7 - 82.1) for RAIR DTC, 67.6 mo (29.9 - 84.4) for ATC and 81.1 mo (75 - 82.1) for MTC. ORR was 9.4% (in RAIR DTC), 30% (ATC), and 0% (MTC), all partial responses. Previously unreported, median duration of response (DoR) was 30 mo (range: 18.1 – 69.7) for RAIR DTC, and 23.2 mo (9.1 - 73.1) for ATC. Updated median PFS was 4.9 mo (95% CI 2.1, 17.0) for RAIR DTC, 4.3 mo (0.5, NA) for ATC, and 2.1 mo (0.9, 4.0) for MTC. 5-year PFS rates were 14.6% (95% CI 4.3%, 30.9%) for RAIR DTC, and 26.7% (4.8%, 56.3%) for ATC. Updated median OS was 44.6 mo (95% CI 24.6, NA) for RAIR DTC, 13.8 mo (1.2, NA) for ATC, and 46.1 mo (12.2, NA) for MTC. 5-year OS rates were 39.0% (95% CI 22.2%, 55.4%) for RAIR DTC, 30.0% (7.1%, 57.8%) for ATC, and 42.9% (9.8%, 73.4%) for MTC. **Conclusions:** Exceptionally durable responses were observed in the exploratory cohort of ATC (median DoR: 23.2 mo). To the best of our knowledge, this is the longest follow up reported for patients with aggressive thyroid carcinoma treated with immunotherapy. 5-year OS rate of 30% in incurable ATC is congruent with one prior report of 25.7% at another large volume cancer center (PMID: 3597734), but compares favorably with the historical rates reported for ATC in the SEER database (8% for all stages and 4% for distant metastatic disease). Biomarker studies are currently underway to identify exceptional responders and long-term survivors. Clinical trial information: NCT03246958. Research Sponsor: Bristol Myers Squibb.

	RAIR DTC (N=32)	ATC (N=10)
Median PFS (95% CI), mo	4.9 (2.1, 17.0)	4.3 (0.5, NA)
5 year PFS (95% CI)	14.6% (4.3%, 30.9%)	26.7% (4.8%, 56.3%)
Median OS (95% CI), mo	44.6 (24.6, NA)	13.8 (1.2, NA)
5 year OS (95% CI)	39.0% (22.2%, 55.4%)	30.0% (7.1%, 57.8%)

A phase II study of pemetrexed and pembrolizumab in patients (pts) with recurrent and/or metastatic (R/M) salivary gland cancer (SGC): Results from non-adenoid cystic cohort.

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Background: Treatment options for pts with R/M SGC are limited. Responses to chemotherapy (CT) are low with high toxicity and responses to immune checkpoint inhibition (ICI) are <10%. Pemetrexed (PTX) is safe and tolerable with responses reported in pts with R/M SGC.[1] Given enhanced responses with PTX and pembrolizumab (PMB) for lung cancer, we hypothesized that PTX and PMB will have activity for SGC. Herein we present the efficacy results in pts with non-adenoid cystic carcinoma (ACC). **Methods:** MC200708 is a single arm phase II study of PTX and PMB in pts with R/M SGC (NCT04895735). Pts were treated in 2 cohorts: ACC (cohort A) and non-ACC (cohort B). Key eligibility criteria: ≥18 years, ECOG 0-1, measurable disease. Prior ICI and/or PTX was allowed. Key exclusion criteria: serious comorbidities, autoimmune disease, and brain metastases. Simon's 2-stage design was used for each cohort. Primary endpoint was overall response rate (ORR). Secondary endpoints: progression free survival (PFS), overall survival (OS), and toxicity. All pts received PTX 500 mg/m2 IV + PMB 200 mg IV q3 weeks until progression or treatment intolerance. Imaging was q3 cycles. **Results:** 25 pts were enrolled Aug 2021-Feb 2024; 1 cancelled prior to treatment. Of 24 eligible and treated pts, median age was 59.5 years (46-77), 66.7% male, performance status 0 (62.5%) or 1 (37.5%). Histologies were salivary duct carcinoma (SDC, 11), acinic cell carcinoma (8), mucoepidermoid carcinoma (MEC, 3), myoepithelial carcinoma (1), and carcinoma NOS (1). 7 pts had no prior therapies (29.2%). The remaining pts had 1 (33.3%), 2 (29.2%), or ≥ 3 lines of therapy (8.3%). 83.3% of pts had no prior ICI. Median cycles of treatment was 8 (2-34), and duration of response was 12.5 months (4.1-20.6). 9 of 24 pts had a confirmed partial response (PR) for ORR of 37.5% (CI: 18.8-59.4). PRs were seen in 7 pts with SDC (7 of 11, 63.6% PR), 1 with MEC, and 1 with acinic cell. Stable disease (SD) was seen in 5 (20.8%), progressive disease in 8 (33.3%), and 2 didn't have post-baseline imaging, but were considered non-responders per protocol. Clinical benefit rate was 58.3% (CI: 36.6-77.9). With median follow-up of 12.0 months (2-34.7), median OS is 20.7 months (CI: 17.3-not reached) and median PFS is 6.2 months (CI: 2.1-17.3). 1-year OS and PFS rate is 76.3% (95% CI: 59.9-97.2) and 36.1% (CI: 21.01-62.2), respectively. Common toxicities were grade 1 fatigue and nausea. 6 pts (25.0%) had ≥1 grade 3-4 toxicity possibly related to treatment, mostly hematologic. The 4 pts with grade 3-4 non-heme toxicity had grade 3 fatigue, rash, and heart failure, and 1 grade 4 hypokalemia. Correlative studies investigating biomarkers of response are underway. **Conclusions:** PTX and PMB has activity in pts with R/M SGC, with promising responses in pts with SDC and median response duration of 1 year. [1] Viscuse et al. *Head Neck* 2019;41(6):E99-103. Clinical trial information: NCT04895735. Research Sponsor: Merck.

6107 Poster Session

A multisite randomized trial of an advanced pneumatic compression device vs usual care for head and neck cancer related lymphedema: Short-term results.

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Background: Lymphedema is common in head and neck cancer survivors (HNCS). Published data indicate that an Advanced Pneumatic Compression Device (APCD) is an effective intervention for lymphedema refractory to Therapist Guided Lymphedema Treatment (TGLT). It may also address barriers to TGLT. We therefore conducted a study in which HNCS with previously untreated lymphedema were randomized to APCD or Usual Care. We report short-term, two-month outcomes. **Methods:** This was a six-month, multi-site (community/academic), stratified, randomized effectiveness trial. Eligible patients were lymphedema therapy naïve HNCS with internal or external lymphedema on exam or imaging and at least 1 moderate ($\geq$ 4/10) lymphedema associated symptom. Participants were randomized (1:1) to APCD or Usual Care. Those randomized to APCD were to use the device for 32 minutes per day. Participants randomized to Usual Care were referred for lymphedema therapy per institutional standards. The primary outcome was improvement in lymphedema associated symptom severity. Additional outcomes included anatomical measures, patient reported biopsychosocial outcomes, barriers to care, and patient satisfaction. **Results:** 236 participants were enrolled (119 APCD group, 117 Usual Care group). At two-months there was a similar decrease in lymphedema associated symptom burden and internal soft tissue swelling in both groups. We demonstrated a statistically significant external soft tissue swelling benefit favoring the APCD group as measured by the Head and Neck Cancer Related Lymphedema and Fibrosis Grading score (p=0.016). Digital photography identified a reduction in number of grids with swelling (p=$<$0.001) in the APCD group only. No reduction of internal swelling was noted in either group by imaging measures. 95% of APCD participants and 71% of Usual Care participants received assigned therapy. Time to therapy initiation was 29.8 days (SD 23.5) for Usual Care and 17.86 days (SD 10.53) for APCD. **Conclusions:** We demonstrated that APCD therapy is an effective treatment modality in lymphedema therapy naïve HNCS. Furthermore, participants experienced significant barriers to TGLT which may be effectively addressed with use of the APCD. A hybrid multi-modal approach to treatment associated lymphedema may further optimize patient outcomes. Clinical trial information: NCT04797390. Research Sponsor: Tactile.

Outcomes with 177 lutetium-dotatate (177Lu-dotatate) in olfactory neuroblastoma (ONB): A case series.

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Background: Olfactory neuroblastoma (ONB) is a rare malignant tumor of the nasal cavity with a high recurrence rate after local therapy. Effective treatments for recurrent/metastatic (R/M) ONB are lacking. ONB frequently expresses somatostatin receptor (SSTR). Radionuclide bound to somatostatin analogues is an established treatment for SSTR-expressing gastrointestinal and pancreatic neuroendocrine tumors. This study reports the efficacy and survival outcomes of ONB patients treated with 177Lu-dotatate at a comprehensive cancer center. **Methods:** We conducted a retrospective analysis of ONB patients treated with 177Lu-dotatate at MD Anderson Cancer Center through NOV 1 2024, with a follow-up cutoff date of DEC 1 2024. Time-to-event outcomes were estimated with the Kaplan-Meier method, and comparisons of survival were done with the log-rank test. Objective response rate (ORR) to 177Lu-dotatate was assessed by RECIST v1.1 and PERCIST criteria adapted to Ga-60 Dotatate PET-CT. The magnitude of effect was estimated with Cox proportional hazards model, with statistical significance set at $p < 0.05$. **Results:** Thirteen R/M ONB patients were identified, 8 were female, and the median age at first dose of 177Lu-dotatate was 54 years. Overall, 6 (46%) ONB tumors were Hyams grade 2, 5 (38%) were grade 2-3, 1 (8%) grade 3, and 1 (8%) grade 4. All patients had distant metastasis prior to 177Lu-dotatate treatment, with the most common sites being bone (76%), and dura (38%), while 6 (46%) also had locoregional disease. Six (46%) patients received 177Lu-dotatate as first line therapy, 4 (31%) as second line, and the remaining 3 (23%) in later lines. Prior therapies included somatostatin analogues (n=4), chemotherapy plus PD-L1 inhibitor (n=1), Lenvatinib (n=1), and clinical trials with experimental drugs (n=3). Among 10 patients with post-treatment restaging scans, PERCIST showed partial response in 7 (70%) and stable disease in 3 (30%). Of these pts, 7 were evaluable per RECIST, demonstrating partial responses in 4 (57%) and stable disease in 3 (43%). At a median follow-up of 19.8 months from starting 177Lu-dotatate, the median progression-free survival (PFS) was 17.43 mo. (95% CI 8.29-NE). For patients treated with 177Lu-dotate in second-line or beyond, the median PFS significantly shorter at 4.18 mo. (95%CI 1.35-NE); hazard ratio (HR) 0.22 (95%CI 0.08-0.60; p = 0.001). Median time-to-progression for 177Lu-dotatate was not achieved. There was no statistical difference in PFS between first or later lines 177Lu-dotatate use (HR 1.74; 95%CI 0.38-7.86; p = 0.47). **Conclusions:** 177Lu-dotate demonstrates activity in R/M ONB, with a favorable PFS compared to previously administered lines of systemic therapy. This case series, the largest reported to date to our knowledge, supports the growing evidence supporting for the use of 177Lu-dotate in this orphan disease. Research Sponsor: None.

TPS6109 Poster Session

HexAgon-HN: Phase 2/3, randomized study of the hexavalent OX40 agonist INBRX-106 in combination with pembrolizumab vs pembrolizumab alone as first-line treatment for recurrent/metastatic head and neck cancer with a PD-L1 combined positive score of ≥20.

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Background: Pembrolizumab (pembro) ± chemotherapy is a standard-of-care first-line treatment option for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Pembro monotherapy is commonly used in patients with a PD-L1 combined positive score (CPS) of ≥20, with an objective response rate (ORR) of <25% and median overall survival (OS) of <15 months.[1] Therefore, a high unmet need exists for more effective, non–chemotherapy-based treatment options. INBRX-106 is a novel, hexavalent OX40 agonist designed to promote higher-order clustering of the costimulatory receptor OX40, leading to more potent agonism than the bivalent first generation of OX40 agonists. Combining INBRX-106 with pembro may amplify and prolong the antitumor immune response. In an ongoing phase 1/2 study (NCT04198766), INBRX-106 + pembro has demonstrated robust pharmacodynamics, a favorable safety profile, and promising clinical activity in multiple tumor types, including R/M HNSCC. These findings supported the initiation of HexAgon-HN (NCT06295731), a phase 2/3, randomized study evaluating INBRX-106 + pembro vs pembro alone as first-line treatment for R/M HNSCC with a PD-L1 CPS of ≥20. **Methods:** Eligible patients must have biopsy-confirmed R/M HNSCC that is considered incurable; a primary tumor in the oral cavity, oropharynx, hypopharynx, or larynx; no previous receipt of therapy for R/M disease; a centrally confirmed PD-L1 CPS of ≥20; measurable disease per RECIST 1.1; and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Prior curative-intent treatment for locoregionally advanced HNSCC is allowed if progressive disease occurred ≥6 months (≥12 months if immunotherapy) after completion of treatment. Up to 410 patients will be randomized 1:1 (stratified by locoregional advanced vs distant metastatic disease, HPV status, and ECOG PS) to INBRX-106 + pembro 200 mg every 3 weeks or pembro (alone in the open-label, phase 2 part or in combination with placebo in the double-blind, phase 3 part). If the phase 2 part (N≈60) shows favorable results for the primary efficacy endpoint (ORR) and secondary safety and efficacy endpoints (eg, duration of response [DOR], progression-free survival [PFS] rate at 6 months, and clinical benefit rate [CBR]), the study can seamlessly proceed to the phase 3 part. The phase 3 part (N≈350) has dual primary efficacy endpoints of PFS and OS; secondary endpoints include ORR, DOR, CBR, time to chemotherapy, safety, and patient-reported quality of life. This study is currently enrolling in the US (30 sites), Europe (40 sites), and Asia-Pacific region (15 sites). 1. Burtness B, et al. *Lancet*. 2019;394:1915-1928. Clinical trial information: NCT06295731. Research Sponsor: Inhibrx Biosciences, Inc.

TPS6110 **Poster Session**

A phase II study of ACR-368 and low dose gemcitabine combination therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma.

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Background: Safe and efficacious therapeutic options for patients with recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) beyond the 1st line palliative treatment, for which the standard of care is PD-1 inhibitor with/without chemotherapy, are limited. Therefore, developing novel therapeutic strategies in this setting remains a critical unmet need. ACR-368 (prexasertib) is a potent, selective CHK1/2 inhibitor which impairs DNA damage repair (DDR) and induces cancer cell apoptosis. ACR-368 has shown single agent activity in a phase Ib trial of patients with advanced squamous cell carcinomas including heavily treated R/M HNSCC. Pre-clinical studies suggest down-regulation of DDR pathways downstream to CHK1/2 is a major resistance mechanism to ACR-368 that can be overcome with low doses of nucleoside analogs that increase replication stress. Work conducted at Acrivon Therapeutics using their AP3 platform uncovered protein signaling features linked to ACR-368 resistance that demonstrated low-dose gemcitabine (LDG) may sensitize cancer cells to ACR-368 treatment. Furthermore, combining LDG with ACR-368 induces synergistic cancer cell regression in *in vitro* and *in vivo* models of HNSCC. Therefore, combined ACR-368 and LDG warrant further evaluation. **Methods:** This is a multi-center, parallel-arm, open-label, phase II trial evaluating combined ACR-368 with LDG in patients with R/M HNSCC. Eligible patients must have been treated with 1 prior line of PD-1/L1 inhibitor with/without chemotherapy with no limitation on the number of prior therapies received in the R/M setting. Patients must agree to a biopsy after the lead-in LDG infusion and at disease progression or end of treatment. OncoSignature is a proprietary predictive biomarker designed to predict response from ACR-368 that will be evaluated as a companion diagnostic. Lead-in LDG 10 mg/m2 IV will be administered before Cycle 1 only followed by ACR-368 105 mg/m2 IV Q2W and LDG 10 mg/m2 Q2W until discontinuation due to disease progression, intolerance, or consent withdrawal. Patients with HPV-unrelated R/M HNSCC will be assigned to Cohort A and patients with HPV-related R/M HNSCC to Cohort B. Primary objective is to determine objective response rates (ORR) in Cohort A and Cohort B, respectively. Study will enroll 14 patients in Cohort A and 29 patients in Cohort B to detect an increase in ORR from 0 to 19% and 5 to 22%, in respective cohorts (type I, II errors, both 10%). Secondary objectives include safety, duration of response, progression-free survival, and overall survival. Exploratory objectives include evaluating potential predictive biomarkers and the effect of lead-in LDG on OncoSignature by comparing pre- and post-LDG tumors. Since recruitment began 09-25-2024, 5 of planned 43 patients have been enrolled as of 01-22-2025. Clinical trial information: NCT06597565. Research Sponsor: Acrivon.

TPS6111 **Poster Session**

VERSATILE-003: A phase 3, randomized, open-label trial of PDS0101 and pembrolizumab compared with pembrolizumab for first-line treatment of patients with HPV16-positive recurrent/metastatic head and neck squamous cell carcinoma.

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Background: Human papillomavirus (HPV)-related head and neck squamous cell carcinoma (HNSCC) has surpassed cervical cancer as the most common HPV-related cancer in the US, with the majority being caused by HPV16. Persistent expression of HPV16 oncoproteins E6 and E7 by host genome may promote HNSCC. HPV16-positive HNSCC may be associated with poor clinical outcomes in the recurrent/metastatic (R/M) setting. PDS0101 (Versamune HPV) is an HPV16-immunotherapy that generates a potent, targeted T cell attack against HPV16 E6 & E7. In a Phase 2 study, PDS0101 plus pembrolizumab has shown encouraging safety and survival benefit in patients with HPV16-positive R/M HNSCC. (Weiss J et al. ESMO 2024. Poster 879P. NCT04260126). **Methods:** VERSATILE-003 is a global Phase 3, randomized, controlled, open-label study evaluating PDS0101 plus pembrolizumab vs. pembrolizumab in patients with HPV16-positive R/M HNSCC with PD-L1 positive disease (CPS ≥1). Key eligibility criteria include age ≥18-years-old, histologically- or cytologically-confirmed diagnosis of R/M HNSCC with primary tumor location of oropharynx, oral cavity, hypopharynx, or larynx and no prior systemic anticancer treatment in the R/M setting, HPV16 tumor positivity (centrally tested), PD-L1 positivity defined as CPS ≥ 1 using FDA-approved PD-L1 IHC 22C3 pharmDx kit, and measurable disease based on RECIST 1.1 confirmed by blinded independent central review (BICR). Patients will be randomized 2:1 to receive pembrolizumab 200 mg IV Q3W with PDS0101 1 mL SC administered concurrently during Cycles 1, 2, 3, 4, and 12 (investigational arm), or pembrolizumab 200 mg IV Q3W alone (control arm). The primary objective is to compare overall survival (OS) between the investigational and control arms. Secondary objectives include objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) using RECIST 1.1 and assessed by BICR. Exploratory objectives include tumor response assessed by investigator and by irRECIST, PFS2, quality of life as assessed by EQ-5D, QLQ-C30, and QLQ H&N35, and assessment of ctHPVDNA. Updated enrollment data will be provided. Clinical trial information: NCT06790966. Research Sponsor: PDS Biotechnology Corporation.

TPS6112 **Poster Session**

A phase 2 study of fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus cemiplimab plus placebo in patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) with positive PD-L1 expression.

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Background: Concurrent blockade of lymphocyte activation gene 3 (LAG-3) may enhance the efficacy of anti–programmed cell death-1 (PD-1) therapies. In a multicohort study, fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) showed signs of clinical activity with durable responses and a generally manageable safety profile in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) warranting further investigation. **Methods:** This randomized, multicenter, Phase 2 study (NCT06769698) will investigate fianlimab (anti–LAG-3) plus cemiplimab (anti–PD-1) versus cemiplimab plus placebo in patients with R/M HNSCC with positive programmed cell death-ligand 1 (PD-L1) expression. The primary objective is to evaluate investigator-assessed objective response rate (ORR) with combination therapy (fianlimab + cemiplimab) versus cemiplimab monotherapy (cemiplimab + placebo). Key inclusion criteria: (1) aged ≥18 years; (2) histologically confirmed R/M HNSCC; (3) primary tumor location of oral cavity, oropharynx, larynx, or hypopharynx; (4) confirmed positive PD-L1 expression status with a Combined Positive Score of ≥1 based on a previous immunohistochemistry (IHC) test performed on a surgical/core biopsy specimen; (5) for patients with oropharynx disease, human papillomavirus (HPV) status must be established by p16 IHC or HPV DNA or RNA *in situ* hybridization (ISH) test; biopsy can be from primary tumor or nodal/distant metastasis; (6) for patients with squamous cell carcinoma of neck node with occult primary, a positive HPV DNA or RNA ISH test; (7) measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1; (8) Eastern Cooperative Oncology Group performance status of ≤1; (9) adequate bone marrow, hepatic, and renal function. Key exclusion criteria: (1) patients who have progressive disease within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC; (2) patients who have received prior systemic anticancer therapy in the R/M HNSCC setting. Approximately 120 patients will be enrolled across two cohorts. Patients will receive fianlimab + cemiplimab intravenously (IV) every 3 weeks (Q3W) or cemiplimab (350 mg) + placebo IV Q3W. Cohort 1 (n=60, HPV positive HNSCC) will be randomized 1:1 to receive: a) fianlimab + cemiplimab, b) placebo + cemiplimab. Cohort 2 (n=60, HPV negative HNSCC) will be randomized 1:1 to receive: a) fianlimab + cemiplimab, b) placebo + cemiplimab. The primary endpoint is ORR per investigator assessment. The secondary endpoints are progression-free survival, disease control rate, duration of response, safety, pharmacokinetics, and immunogenicity. Clinical trial information: NCT06769698. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS6113 Poster Session

A multicenter, randomized, double-blind, phase 2/3 study of ficerafusp alfa (BCA101) or placebo in combination with pembrolizumab for first-line treatment of PD-L1-positive, recurrent or metastatic head and neck squamous cell carcinoma: The FORTIFI-HN01 study.

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Background: HPV-negative head and neck squamous cell carcinoma (HNSCC) is an aggressive disease characterized by high rates of recurrence, metastasis, and resistance to standard treatments. Over 80% of HPV-negative HNSCC cases overexpress TGF-β, a key driver of poor survival and treatment resistance. Ficerafusp alfa, a first-in-class bifunctional antibody, targets epidermal growth factor receptor (EGFR) while neutralizing TGF-β in the tumor microenvironment. In a Phase 1/1b trial (NCT04429542), ficerafusp alfa demonstrated promising efficacy and a manageable safety profile in first-line recurrent/metastatic (R/M) HNSCC. The ongoing FORTIFI-HN01 study (NCT06788990) is a randomized, double-blind, placebo-controlled Phase 2/3 trial designed to assess the efficacy and safety of ficerafusp alfa combined with pembrolizumab versus placebo plus pembrolizumab in patients with PD-L1 positive first-line R/M HPV-negative HNSCC. **Methods:** Eligible patients must have histologically confirmed R/M HNSCC with primary lesions in the oral cavity, larynx, or hypopharynx, or OPSCC, excluding HPV-positive OPSCC confirmed by central laboratory testing. Additional criteria include no prior systemic therapy for R/M disease, PD-L1 positive tumors (CPS ≥1), measurable disease per RECIST v1.1 assessed by BICR, and ECOG performance status of 0 or 1. The Phase 2 objective is to determine the optimal biological dose (OBD) of ficerafusp alfa through an integrated analysis of safety, tolerability, PK, PD, and efficacy. Subjects will be randomized 1:1:1 to receive high-dose ficerafusp alfa, low-dose ficerafusp alfa, or placebo, each combined with pembrolizumab. Randomization is stratified by PD-L1 CPS (1-19 vs. ≥20) and disease extent (local/regional recurrence only, distant metastasis only, or both). After OBD determination, the trial will transition seamlessly into Phase 3 with a 2:1 randomization (OBD vs. control).Patients will receive pembrolizumab (200 mg i.v. every 3 weeks for up to 35 cycles) and either ficerafusp alfa (1500 mg or 750 mg) or placebo weekly until disease progression or unacceptable toxicity. Tumor imaging will occur every 6 weeks during the first year and every 9 weeks thereafter. The primary endpoints are objective response rate (ORR) per RECIST v1.1 (BICR) and overall survival (OS). Secondary endpoints include safety, additional efficacy measures, and patient-reported outcomes (PROs). The trial is actively recruiting, with a planned enrollment of (NCT06788990). Clinical trial information: NCT06788990. Research Sponsor: Study funded by Bicara Therapeutics Inc.

TPS6114 Poster Session

A phase II study of AK117 combined with cetuximab or AK104 in the treatment of recurrent or metastatic head and neck squamous cell carcinoma after the failure of PD-1 (L1) inhibitors and/or platinum-based therapy.

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Background: The administration of first-line pembrolizumab monotherapy or pembrolizumab combined chemotherapy has been shown to improve survival among patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, over 80% of the patients still experience disease progression within a year. Upon progression, treatment options are notably limited. Therefore, there is a dearth of a standardized treatment for R/M HNSCC after the failure of PD-1 (L1) inhibitors and/or platinum-based therapy. This study aims to assess the safety and efficacy of AK117 (anti-CD47) combined with Cetuximab or AK104 (PD-1/CTLA-4 Bispecial Antibody) in this patient subset. **Methods:** This is a non-randomized, two-group, phase II study. The inclusion criteria include: 1) Pathological or radiological diagnosis of R/M HNSCC (including oral cavity, oropharynx, larynx, and pharynx) and cannot be cured by local treatment; 2) Failure of PD-1 (L1) inhibitors and/or platinum-based therapy; 3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 and expected survival $\geq$3 months. Key exclusion criteria are active autoimmune diseases, use of immunosuppressive drugs, or any severe or uncontrolled systemic disease. We group the patients based on the duration of first-line PD-1 (L1) inhibitors from start to failure (Group 1: the duration $\leq$ 3 months; Group 2: the duration $>$ 3 months). Group 1 patients receive AK117 (45mg/kg, day 1, every 3 weeks) in combination with Cetuximab (initial dose 400mg/m^2, subsequent doses of 250mg/m^2, day 1, every week) maintained for one year or until progression or intolerable toxicity occurred. Group 2 patients are treated with AK117 (45mg/kg, day 1, every 3 weeks) in combination with AK104 (10mg/kg, day 1, every 3 weeks) maintained for one year or until progression or intolerable toxicity occurred. The primary endpoints are incidence of adverse events and overall survival. Secondary endpoints are objective response rate, progression free survival, disease control rate, and duration of response. Clinical trial information: NCT06508606. Research Sponsor: Akeso, Inc.

TPS6115 **Poster Session**

FIERCE-HN: A multicenter, randomized, double-blind, placebo-controlled, phase 3 study of ficlatuzumab (HGF/cMET MAb) in combination with cetuximab in participants with recurrent or metastatic (R/M) HPV negative head and neck squamous cell carcinoma (HNSCC).

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Background: Patients with HPV-negative R/M HNSCC have a worse median overall survival (OS) than HPV-positive patients and current treatments options are limited.[1] Ficlatuzumab is a humanized IgG1 MAb that binds HGF, the ligand for the c-MET tyrosine kinase receptor. HGF/c-MET pathway dysregulation is frequently observed in HPV-negative HNSCC, and has been linked to EGFR inhibitor resistance, limiting the potential efficacy of EGFR-targeting drugs like cetuximab. In a phase 2 study, both pathways were targeted using ficlatuzumab plus cetuximab in patients with HPV-negative R/M HNSCC resistant to cetuximab, platinum, and anti-PD1 immune checkpoint inhibitors (ICI) who have a very poor historical prognosis. A PFS of 4.1 months, median OS of 7.4 months, and overall response rate (ORR) of 38% (6/16; 2 CR, 4 PR) was observed.[2] FIERCE-HN compares the efficacy/safety of ficlatuzumab+cetuximab vs placebo+cetuximab in patients with R/M HPV-negative HNSCC. **Methods:** This is an international, multicenter, randomized, double-blind, placebo-controlled phase 3 study. Major enrollment criteria include confirmed diagnosis of R/M HNSCC primary tumors of the oropharynx (p-16 negative only), oral cavity, hypopharynx, or larynx. Participants must have progressed on, or be intolerant to, previous anti-PD-1/PD-L1 ICI and platinum-based chemotherapy; have 2 or fewer prior lines of anticancer therapy; and have no prior treatment with cetuximab/alternative EGFR inhibitors in the R/M setting. Patients with feeding tubes are eligible. The primary endpoint is OS; key secondary endpoints include PFS and ORR. Other secondary endpoints are DCR, DoR, safety, PK, immunogenicity and QoL. Patients will receive cetuximab 500mg/m2 and are randomized 1:1:1 to Arm A: ficlatuzumab 10mg/kg, Arm B: ficlatuzumab 20mg/kg, or Arm C: placebo. Treatments will be on Days 1 and 15 of a 28-day cycle. This is an adaptive study with two interim analyses (IAs). IA 1 will be conducted after 70 OS events, when futility and optimal dose assessments will be performed. Participants enrolled after IA 1 will be randomized 1:1 to the optimal ficlatuzumab dose or placebo, plus cetuximab. IA 2 will be conducted after 163 OS events to assess whether an event count re-estimation is needed. The final analysis will occur after 232 (or up to 279) OS events, depending on the re-estimation outcome. The study has statistical power of 80%, assuming a true OS hazard ratio of 0.667. Between 410 to 500 patients will be enrolled. The study is ongoing and actively recruiting in North America, Europe, United Kingdom, and Asia-Pacific. Clinical trial information: NCT06064877 (collaborator Eli Lilly provided cetuximab). 1. Cohen E et al., JITC. 2019;7:184. 2. Bauman JE et al., JCO. 2023. 41:3851. Clinical trial information: NCT06064877. Research Sponsor: AVEO Oncology.

TPS6116 Poster Session

Reduction of postoperative radiotherapy in head and neck squamous cell carcinoma: A single-arm, phase II trial (REPORT-HNSCC study).

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Background: Postoperative radiotherapy (PORT) significantly enhances the prognosis for high-risk patients with locally advanced squamous cell carcinoma of the head and neck (LA HNSCC). However, elective nodal irradiation (ENI) in low-risk areas can lead to serious acute and long-term toxicities, which negatively impact quality of life. In a study by Contreras (NCT00593840), 72 patients with LA HNSCC experienced a remarkable 97% regional control rate at five years after eliminating PORT to the pathologically negative (pN0) neck. Additionally, patients who responded well to neoadjuvant therapy showed better local control rates, suggesting a possible reduction in the need for radiotherapy. The RAVD study (NCT01133678) demonstrated that the elimination of ENI in patients with good response to neoadjuvant chemotherapy did not appear to compromise outcomes and resulted in significantly decreased late toxicity. Preclinical studies have also suggested that the elimination of ENI may preserve beneficial T cells in normally draining lymph nodes, enhancing the efficacy of radioimmunotherapy. The study was designed to evaluate regional control rates and quality of life in LA HNSCC patients undergoing sequential elimination of ENI to the pN0 neck by neoadjuvant chemo-immunotherapy. **Methods:** REPORT-HNSCC is a phase 2, single-arm, single-center trial assessing patients with newly diagnosed LA HNSCC. Patients receive neoadjuvant chemo-immunotherapy (flexibility in regimens and cycles). This trial targets patients with an ipsilateral and/or bilateral pN0 neck, while surgical resection will be guided by the surgeon's discretion. Key treatment components include 60 to 66 Gy to the primary tumor bed (CTVtb), 60 Gy to CTV1, and 54 to 60 Gy to CTV2, with appropriate expansion margins to optimize target volume. Eliminating ENI (that is, CTV2) to the pN0 neck. A symmetric 0.3-cm expansion around the CTV defined the corresponding planning target volume (PTV). Radiation doses were prescribed to the PTV. Intensity-modulated radiotherapy (IMRT) will be administered to all patients, while select patients with positive surgical margins or extranodal extension receive concurrent chemotherapy. The primary endpoint is 2-year region-free recurrence survival rate. Secondary endpoints include 2-year PFS, 2-year OS, 2-year DMFS, 2-year LRFS, acute and late toxicities, and quality of life. We will also explore predictive biomarkers for better understanding of responses and survival. As of January 2025, we have enrolled 14 of the planned 50 patients since the study began in October 2024, with results expected by December 2029. Clinical trial information: NCT06630780. Research Sponsor: None.

TPS6117 Poster Session

Phase II trial of neoadjuvant chemotherapy (NAC) docetaxel-cisplatin alone (DC) or with anti-human papillomavirus (HPV) gene therapy PRGN-2009 (DCP) followed by surgery in patients (pts) with newly diagnosed HPV-associated oropharyngeal cancer (HPV-OPC).

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Background: HPV-OPC is caused primarily by HPV16. Prognosis following standard-of-care (SOC) treatment, (surgery followed by adjuvant radiotherapy (RT), or concurrent chemoRT (CRT)) is favorable, with >80% 5-year recurrence-free survival (RFS). However, RT toxicity including tissue fibrosis results in long-term swallowing dysfunction and impacts quality of life (QOL). NAC treatment (DC) followed by surgery has resulted in clinical-to-pathologic down-staging or pathologic complete response (pCR) and avoidance of RT in most pts, with >90% 5-year survival, and induces HPV-specific T cell immunity. PRGN-2009 is a gorilla adenoviral vector based gene therapy harboring a DNA payload designed to induce HPV specific T-cell responses. This trial will evaluate the rate of pCR with NAC (DC) alone or combined with PRGN-2009 (DCP) in pts with newly diagnosed HPV-OPC. **Methods:** This is an investigator-initiated, single-center, randomized controlled phase II trial. Newly diagnosed HPV-positive OPC pts of stage I (cT1-2, N0-1) or II (T1-3, N0-2), M0 (AJCC Cancer Staging Manual, 8th ed.) planned for SOC surgery will be randomized to 2 treatment arms of 30 patients each, DC and DCP, to evaluate if PRGN-2009 may be associated with an increased rate of pathological CR (pCR) following neoadjuvant chemotherapy. DC consists of 3 cycles of intravenous cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 every 21 days (dose reductions allowed). DCP also includes PRGN-2009 induction dose pre-cycle 1, and one dose after each DC cycle (total 4 doses). Supportive measures include pre-infusion dexamethasone, antiemetics, neutropenia primary prophylaxis. Imaging (FDG PET, CT) will be performed at baseline. Research blood samples will be collected longitudinally. Mandatory research primary tumor biopsy will be performed at baseline and post-treatment tumor/tumor bed biopsy will be at the time of surgical resection. On-treatment tumor biopsies will be offered (optional). Study treatment and procedures will be performed at the NIH Clinical Center (Bethesda, MD). After treatment completion, pts will have surgery at their primary institution; adjuvant treatment determined per established risk factors. Primary endpoint is the rate of pCR in each arm. Secondary endpoints include safety and 2-year RFS in each arm. Exploratory objectives include assessment of changes in hearing (audiograms baseline/post-treatment), swallowing function (MD Anderson Dysphagia Inventory) and QOL (Functional Assessment of Cancer Therapy – Head & Neck); associations between changes in imaging, pathologic response, and circulating cell-free HPV DNA; changes in the tumor microenvironment and in HPV-specific T cell immunity. 8 of 60 pts planned have been enrolled. Clinical trial information: NCT06223568. Research Sponsor: NCI, NIH.

TPS6118 **Poster Session**

A phase III randomized controlled trial comparing palliative stereotactic body radiotherapy vs. palliative standard radiotherapy in patients with advanced head and neck cancer (NCT06641791).

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Background: The optimal radiotherapy (RT) treatment regimen for patients with advanced head and neck cancer (AHNC) unsuitable to receive curative intent RT is undefined. Stereotactic body radiotherapy (SBRT) is a promising technique but rigorous multicentre evaluation is required prior to adoption. **Methods:** This is a Phase III randomized controlled trial comparing palliative SBRT to palliative standard RT (SRT) in participants with advanced mucosal, squamous cell head and neck cancer unable to tolerate curative intent RT. Key eligibility criteria: Unsuitable for curative intent therapy, no evidence of metastatic disease, stages TX or T0-T4/N0-N3, geriatric 8 score [1] ≤14. Treatment arms: (Experimental) SBRT 4500 cGy/ 5fr (twice a week to primary and nodal GTV (BED_{10}85) OR 4000 cGy /5 fr twice a week if organs at risk (BED_{10}-72) versus (standard) 2400 cGy/ 3fr (day 0/7/21 (BED_{10}43) or 2500 cGy/ 5fr over 1 week (BED_{10}38). Primary objective: To compare OS between arms. Secondary objectives evaluate progression-free survival (PFS), locoregional failure-free survival, distant metastases-free survival, response rates, acute and long-term toxicity (CTCAE v5.0), treatment compliance, patient-reported outcomes (PRO-CTCAE, FACT-HN), resource utilization, and health utilities. Statistical design: The trial aims to enroll 196 patients with a 2:1 randomization ratio (SBRT: SRT). The study is powered at 80% with a two-sided alpha of 0.05 to detect a difference in 1-year OS of 40.3% vs. 22% (HR = 0.6), assuming a 15% drop-out/lost to follow-up rate. Conduct to Date: This trial was activated on October 31, 2024. Supported by CCS grant #707213; CIHR #175014. [1] Takahashi M, Takahashi M, Komine K, Yamada H, Kasahara Y, Chikamatsu S, et al. (2017) The G8 screening tool enhances prognostic value to ECOG performance status in elderly cancer patients: A retrospective, single institutional study. PLoS ONE 12(6): e0179694. https://doi.org/10.1371/journal.pone.0179694. Clinical trial information: NCT06641791. Research Sponsor: Canadian Cancer Society (CCS); 707213; Canadian Institutes of Health Research (CIHR); 175014.

TPS6119 **Poster Session**

TRENT-002: A prospective, multicenter, randomized controlled phase II study to evaluate the efficacy and safety of salvage preoperative PD-1 inhibitor combined with chemotherapy neoadjuvant therapy in recurrent laryngeal/hypopharyngeal squamous cell carcinoma (L/HPSCC).

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Background: Salvage surgery is considered the standard of care for patients with resectable recurrent L/HPSCC. However, salvage surgery achieves durable disease control in only 20% to 50% of patients. The PATHWay study showed that the subgroup that received salvage therapy indicated that adjuvant pembrolizumab could significantly improve PFS compared with placebo, but there is no OS data. This muti-center, prospective, randomized controlled phase II study will evaluate efficacy and safety of PD-1 inhibitors plus chemotherapy as neoadjuvant therapy in recurrent L/HPSCC. **Methods:** Patients who meet the inclusion criteria will be divided into groups according to whether they had received radiotherapy in the past. Arm 1 and Arm 2 are the groups that had not received radiotherapy in the past (N=100), and Arm 3 and Arm 4 are the groups that had received radiotherapy (N=160). Arm 1 and Arm 2 will be randomly assigned at a 1:1 ratio. Arm 1 will receive 3 cycles of pembrolizumab + nab-paclitaxel + cisplatin, followed by surgery. After surgery, patients will be stratified according to the presence or absence of high-risk factors (extranodal extension or positive margins). The high-risk group will receive concurrent chemoradiotherapy + pembrolizumab maintenance therapy (up to 15 cycles), and the low-risk group will receive radiotherapy + pembrolizumab maintenance therapy (up to 15 cycles). Arm 2 will undergo surgery directly, followed by concurrent chemoradiotherapy/ radiotherapy. The total radiation dose is 60-66 Gy, 2.0 Gy/fraction for high-risk group and 44-50 Gy, 2.0 Gy/fraction for low-risk group. Similarly, Arm3 and Arm4 will be randomly assigned in a 1:1 ratio. Arm 3 will receive 3 cycles of pembrolizumab + nab-paclitaxel + cisplatin, followed by surgery, and pembrolizumab maintenance treatment after surgery. Arm 4 will be directly given surgery, and after surgery, the doctor will choose observation / re-radiotherapy or chemoradiotherapy. Eligibility criteria will include patients with squamous cell carcinoma of the larynx and hypopharynx confirmed by histology and/or cytology; patients with recurrence of primary tumor or second primary tumor after receiving curative treatment; At least 6 months after the last platinum-containing treatment; ECOG performance status 0-1. Primary end points is 2y-PFS. Secondary end points include ORR, pCR, 3y-OS, safety. Recruitment is ongoing and will continue until 260 patients are enrolled. Clinical trial information: NCT06793761. Research Sponsor: None.

TPS6120 **Poster Session**

A phase II randomized trial of nano-crystalline megestrol acetate for nutritional improvement in postoperative head and neck squamous cell carcinoma undergoing radiotherapy.

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Background: Head and neck squamous cell carcinoma (HNSCC) patients frequently experience malnutrition and weight loss, exacerbated by cancer cachexia and treatment-related side effects during concurrent radiotherapy. Nano-crystalline megestrol acetate (NMA) improves bioavailability and efficacy compared to conventional formulations, demonstrating enhanced appetite, weight gain, and quality of life (QoL) in cancer cachexia. **Methods:** This randomized, parallel-controlled Phase II trial evaluates the efficacy and safety of NMA in improving nutritional outcomes in HNSCC patients undergoing postoperative CCRT. The study enrolls 96 HNSCC post-surgery patients. Participants are stratified by pre-treatment weight loss ($>5\%$ vs. $\leq 5\%$) and standard treatment regimen (radiotherapy vs. concurrent chemoradiotherapy), then randomized 1:1 to receive NMA (625 mg/day) plus standard treatment or standard treatment alone. The novel aspects of this design include the use of a nano-crystalline formulation to overcome absorption challenges, allowing effective drug delivery in fasting states. Additionally, comprehensive endpoints assess appetite status (A/CS-12 score), weight changes, lean body mass, inflammatory and nutritional markers, and QoL, providing an integrated evaluation of nutritional and clinical benefits. 12 of planned 96 patients have been enrolled. Clinical trial information: NCT06772428. Research Sponsor: None.

TPS6121 Poster Session

A phase 2 clinical trial of preoperative pembrolizumab and chemotherapy followed by adjuvant pembrolizumab in resectable locoregionally recurrent head and neck squamous cell carcinoma.

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Background: Locoregional recurrence is a major cause of death in squamous cell carcinoma of head & neck (HNSCC) initially treated with curative intent approaches. While salvage surgery may still provide a chance for cure, disease-free survival (DFS) and overall survival (OS) rates remain low for this high-risk population. Neoadjuvant programmed death (PD)-1 inhibitor based approaches have shown promising clinical outcomes compared to upfront surgery in multiple cancer types, e.g. melanoma and non-small cell lung cancer. Recently, a randomized placebo-controlled phase III (KEYNOTE-689) trial evaluating peri-operative pembrolizumab in treatment-naïve locally advanced HNSCC met its primary endpoint of event-free survival. Since our trial is targeted at a higher risk patient (pt) population of locoregionally recurrent resectable HNSCC (already managed with curative intent once), we are evaluating the combination of pembrolizumab with chemotherapy in the neoadjuvant setting followed by adjuvant pembrolizumab therapy. **Methods:** This investigator-initiated non-randomized open-label phase 2 clinical trial is enrolling pts with resectable locoregionally recurrent HNSCC, with primary sites in oral cavity, oropharynx, larynx or hypopharynx. Pts must have documented duration of ≥6 months from completion of prior curative intent treatment for HNSCC (surgery and/or radiation therapy with/without platinum chemotherapy or cetuximab targeted therapy) to diagnosis of local or locoregional recurrence, and must have resectable disease. Study treatment plan consists of three phases: pre-operative phase, curative intent surgery, and adjuvant phase. In the pre-operative phase, pembrolizumab, cisplatin (or carboplatin) and docetaxel will be administered every 3 weeks for 2 treatment cycles. This will be followed by surgery within 6 weeks of cycle 2 day 1 in pre-operative phase. Adjuvant phase consists of pembrolizumab every 3 weeks until total of 15 cycles, disease recurrence, or intolerable adverse events. The primary endpoint of the trial is major pathological response (mPR) in surgical specimens after pre-operative treatment, defined as ≤ 10% residual invasive SCC within the resected primary tumor specimen and all sampled regional lymph nodes. Key secondary endpoints include safety, DFS, and OS. Correlative biomarker analyses are planned as exploratory endpoints. We hypothesize that treatment with pre-operative pembrolizumab and chemotherapy will lead to mPR rate of 15% compared to null hypothesis of 2%. If we find ≥2 pts with disease in mPR among 25 evaluable pts, the Simon two-stage design (14 pts in first stage) will have a power of 85.5% with a type I error rate of 7.4%. Safety rule is built in to monitor delays in surgery. 12 of planned 28 pts have been enrolled as of January 2025 (ClinicalTrials.gov NCT05726370). Clinical trial information: NCT05726370. Research Sponsor: Merck.

TPS6122 Poster Session

A phase 3 randomized study of ASP-1929 photoimmunotherapy in combination with pembrolizumab versus standard of care in locoregional recurrent head and neck squamous cell carcinoma (HNSCC).

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Background: Recurrent (r) HNSCC carries a poor prognosis and a low survival rate. Locoregional (LR) progression significantly contributes to both morbidity and mortality in these patients, underscoring the importance of LR disease control. The approval of anti-PD-1 inhibitors (pembrolizumab, nivolumab) has expanded treatment options for rHNSCC, but response rates with monotherapy remain low. ASP-1929 photoimmunotherapy (PIT), a novel drug-device treatment, combines cetuximab with a light-activatable dye (IR700) to selectively target EGFR-expressing cancer cells and cause cell membrane destruction and rapid tumor necrosis after activation with local light illumination. Preclinical data have demonstrated that ASP-1929 PIT-mediated tumor necrosis and immunogenic cell death induces antitumor immunity and when combined with anti-PD-1 therapy, synergistically enhances anticancer activity. In an interim evaluation of a multicenter, phase 1/2a, open-label study of 19 patients with metastatic and/or rHNSCC, the combination of ASP-1929 PIT and pembrolizumab showed promising efficacy with a manageable safety profile.[1] The objective of this pivotal phase 3 study is to further evaluate the efficacy and safety of ASP-1929 PIT in combination with pembrolizumab in rHNSCC. **Methods:** The ASP-1929-381is a global phase 3, multi-center, randomized, open-label, controlled study of ASP-1929 PIT in combination with pembrolizumab vs pembrolizumab-based standard of care (SOC) in the first line treatment of LR rHNSCC with no distant metastases. Key inclusion criteria: rHNSCC patients without distant metastases who are candidates for SOC first-line treatment with pembrolizumab + chemotherapy; anti-PD-1 and anti-PD-L1-treatment naïve; at least one lesion accessible for PIT light treatment and RECIST 1.1 measurable; age ≥18 years; ECOG score 0 or 1. Key exclusion criteria: diagnosis and/or treatment of additional malignancy within 2 years of randomization; history of ≥ grade 3 cetuximab infusion reactions; prior allogeneic tissue/solid organ transplant; life expectancy <3 months. The study will enroll ~408 patients and begin with a 2:2:1 randomization into three arms (ASP-1929 PIT 320 mg/m^2 plus pembrolizumab vs ASP-1929 PIT 640 mg/m^2 plus pembrolizumab vs physicians' choice pembrolizumab-based SOC regimen). The SOC arm will include pembrolizumab monotherapy, or pembrolizumab in combination with platinum (cisplatin or carboplatin) + 5-fluorouracil or taxane (paclitaxel or docetaxel). The primary endpoint is overall survival (OS). Key secondary endpoints include complete response rate (CRR) and overall response rate (ORR). The study is currently enrolling in the US, with plans to expand to Taiwan, Japan, and other territories (NCT06699212). 1. Cognetti et al. J Clin Oncol 42, 2024 (suppl 16; abstr 6083). Clinical trial information: NCT06699212. Research Sponsor: Rakuten Medical, Inc.

TPS6123 Poster Session

RIBBON-UM: Treatment individualisation by EBV stratification in nasopharyngeal carcinoma (NPC): A phase 2, multi-arm umbrella platform trial.

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Background: Induction chemotherapy (IC) and chemoradiotherapy (CRT) is the current standard of care (SOC) for locoregionally advanced NPC (LA-NPC). However, CRT alone or CRT and adjuvant chemotherapy (AC) are also first-line SOC options. Plasma Epstein-Barr virus (EBV) DNA is an archetypal biomarker for endemic NPC, and has been assessed for pre-and on-treatment clinical stratification. RIBBON-UM is a phase 2, multi-arm umbrella trial investigating pre- and on-treatment plasma EBV DNA assessment to individualise treatment of patients with LA-NPC. **Methods:** Patients who are newly-diagnosed, biopsy-proven NPC of TNM-stage III-IVA by AJCC/UICC 8th ed and have DETECTABLE EBV DNA pre-treatment are eligible. RIBBON-UM incorporates a 2-tier stratification by TN-status and EBV DNA levels – (1) First, patients will be stratified into low- (LR) and high-risk (HR) based on pre-treatment EBV DNA cut-off 4000 copies/mL AND/OR T4N+ or N2-3 disease; (2) Second, for the HR patients who are assigned to IC (gemcitabine-cisplatin), patients will be further stratified into HR and very-high risk (VHR) depending on their EBV DNA clearance post-3 cycles of IC. RIBBON-UM consists of 3 treatment arms (NCT05517135): Arm I will enroll LR patients (T3N0-1, T4N0 AND EBV DNA $<$4000 copies/mL) to upfront CRT (cisplatin/carboplatin) $\pm$ AC (cisplatin and 5-fluorouracil or capecitabine based on physician's discretion). HR patients (T4N+ OR N2-3 OR EBV DNA $\geq$4,000 copies/mL) will receive upfront IC, and if UNDETECTABLE EBV DNA post-IC, they will be assigned to Arm II – CRT $\pm$ AC. For patients with a DETECTABLE EBV DNA post-IC (VHR), these patients are assigned to Arm III – a single-arm, phase 2 trial investigating experimental AC (NCT06093061), embedded within the RIBBON-UM protocol. Currently, VHR patients enrolled into Arm III will receive CRT + 1-y combined tislelizumab (200 mg IV 3-weekly) and metronomic capecitabine at 650 mg/m^2 bidaily (RIBBON-LA-01, NCT06093061) or 1-y metronomic capecitabine (if they decline). Statistical plan of RIBBON-UM consists of 2 analyses: (1) we will evaluate if our risk-stratification strategy by TN-status and pre- and on-treatment EBV DNA levels improves 2-y disease-free survival (DFS) rate of patients with LA-NPC from 65% (historical) to 75% for the modular platform trial; (2) we hypothesise that AC intensification (Arm III) will improve 2-y DFS of the VHR cohort from 60% (historical) to 75%. 133 and 62 patients are required to test these hypotheses at 5% 1-sided significance level with 80% power, respectively. The risk-stratified treatment individualisation and AC intensification strategies will be deemed successful if 96 of 133 (from Arms I-III) and 44 of 62 patients (Arm III) remain disease-free at 2 y. From Nov 2022 to Jan 2025, we have enrolled 93 and 51 patients into RIBBON-UM and RIBBON-LA-01, respectively. We expect enrolment to RIBBON-UM to complete by Jun 2025. Clinical trial information: NCT05517135, NCT06093061. Research Sponsor: BeiGene; NMRC Singapore Open-Fund Large Collaborative Grant; NMRC Singapore Clinical Trials Grant.

TPS6124 **Poster Session**

A phase 2 clinical trial of adjuvant ado-trastuzumab emtansine (T-DM1) for patients with HER2-positive salivary gland cancer.

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Background: Salivary gland carcinomas (SGCs) represent a rare, but unique group of histologically and molecularly distinct head and neck cancers. Despite aggressive locoregional management with surgery and adjuvant (chemo)radiation, distant metastatic spread is not infrequent, particularly among high-risk subtypes like salivary duct carcinoma. Strong surface expression of HER2 has been observed in 60-80% of high-risk SGCs. This is the first clinical trial exploring the early addition of concurrent and adjuvant HER2-directed therapy to improve both locoregional and distant disease control rates in a HER2-overexpressing high-risk SGC population. **Methods:** This phase 2 open-label, clinical trial (NCT04620187) is enrolling patients (pts) with newly diagnosed SGC of any histology arising in the head and neck whose tumor overexpresses HER2 (2-3+ by IHC expression or *ERBB2* amplification/select mutations) treated with upfront definitive surgery. Pts must have adequate organ and cardiac function, with stage II-IVB (AJCC 2017 8^{th} ed.) disease (stage II requires positive margins). Enrollment following surgery is permitted. Once registered post-op, adjuvant T-DM1 (3.6 mg/kg IV every 21-days) starts within 3-7 weeks of surgery prior to radiation (RT). Four to 8 weeks post-op pts receive standard RT (photon or particle) with concurrent weekly cisplatin (40 mg/m^2) for 6-weeks. T-DM1 continues every 3-weeks during RT and up to 1-year following surgery. The primary endpoint is 2-year disease-free survival (DFS). Secondary endpoints include safety and tolerability, overall survival, distant metastatic-free survival, and correlation between HER2 expression and outcomes. We hypothesize that treatment with adjuvant T-DM1 will improve historical 2-year DFS from 60 to 72%. When 24 DFS events are observed among N=47 pts who are eligible and receive protocol treatment, the design has 80% power to detect a 35% reduction in the DFS hazard to 0.1660 (using a one-sided 10% type I error rate; Wald's test). The study opened to accrual in October 2020 and is now accruing at four academic medical centers throughout the U.S. Sixteen of 47 planned subjects have been enrolled as of December 2024. Clinical trial information: NCT04620187. Research Sponsor: Genentech.