6000 Oral Abstract Session

Adjuvant radiotherapy versus observation following curative surgery for early-stage oral squamous cell carcinoma (AREST; CTRI/2017/07/009114).

Sudhir Vasudevan Nair, Tejpal Gupta, Swapnil Ulhas Rane, Sadhana Kannan, Sarbani Ghosh-Laskar, Gouri Pantvaidya, Pankaj Chaturvedi, C. S. Pramesh, Asawari Patil, Rajendra Toprani, Kaustubh Patel, Kinjal Jani, Aseem Mishra, Sambit Swarup Nanda, Ashok Kumar Das, Mouchumee Bhattacharyya, Krishnakumar Thankappan, Subramania Iyer Sr., Geetha Muttath, Samarth Kamlesh Chhatbar, AREST Study - Head and Neck Cooperative Oncology Group; Tata Memorial Center, Mumbai, India; Tata Memorial Centre, Mumbai, India; Tata Memorial Centre, Navi Mumbai, India; Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India; Tata Memorial Centre, Mumbai, Maharashtra, India; Tata Memorial Hospital, Mumbai, India; HCG Cancer Centre, Ahmedabad, India; HCG Aastha Cancer Center, Ahmedabad, India; Mahamana Pandit Madan Mohan Malviya Cancer Centre & Homi Bhabha Cancer Hospital, Tata Memorial Centre, Varanasi, India; Dr. Bhubaneswar Borooah Cancer Institute (BBCI), Guwahati, India; Dr Bhubaneswar Borooah Cancer Institute, Guwahati, India; Amrita Institute of Medical Sciences, Kochi, India; Malabar Cancer Centre, Thalassery, India; Kailash Cancer Hospital & Research Centre, Vadodara, India

Background: The role of adjuvant radiotherapy (RT) in early-stage, node-negative oral squamous cell carcinoma (OSCC) with one or more intermediate risk factors - such as depth of invasion (DOI) ≥5 to ≤10mm, perineural invasion (PNI), lymphovascular emboli (LVE), or poor differentiation - remains debatable and is largely based on retrospective data. This multicenter, open-label, phase III randomized controlled trial was designed to assess the impact of post-operative adjuvant RT in this setting. **Methods:** Patients with early-stage (pT1-T2), node-negative (pN0) OSCC undergoing adequate surgery (defined as clear margins ≥5mm and at least ipsilateral level I-III neck dissection with ≥16 nodes) with presence of one or more intermediate risk factors were screened. Eligible patients underwent stratified randomization (oral cavity subsite, PNI/LVE, and differentiation) in 1:1 ratio to either observation or adjuvant RT (60Gy in 30 fractions over 6-weeks) to the resected tumor-bed and at-risk neck nodal region after written informed consent. Primary endpoint was loco-regional recurrence-free survival (LRFS) measured from randomization to first documented event of local and/or regional recurrence from index cancer. All time-to-event outcomes were computed using Kaplan-Meier (KM) method with log-rank test for comparison and expressed as 3-year point estimates with 95% confidence intervals (CI). The planned sample size (N=392) provided 80% power at an α of 0.05 to detect a Hazard Ratio (HR) of 0.6256, assuming 3-year LRFS of 70% in the observation arm. **Results:** Following curative surgery, a total of 392 patients were randomized (191 to adjuvant RT; 201 to observation). Baseline characteristics were balanced between the two arms. At a median follow-up of 47.2 months (inter-quartile range=30-59.4 months), 3-year KM estimate of LRFS was 89.2% in adjuvant RT arm vs 80.9% in observation arm (HR=0.52, 95%CI=0.30-0.91; p=0.02) in the intention-to-treat (ITT) population and 91.1% vs 80.9% (HR=0.43, 95% CI=0.23-0.80; p=0.01) on per-protocol (PP) analyses. Cumulative incidence of loco-regional failure with death as competing event was 10.6% (95%CI=6.1%-15.1%) with adjuvant RT and 18.9% (95%CI=13.3%-24.6%) with observation (HR=0.52, 95%CI=0.30-0.91; p=0.021) in the ITT population and 8.7% (95%CI=4.3%-13.1%) vs 18.9% (95%CI=13.3%-24.6%) (HR=0.43, 95%CI=0.23-0.79; p=0.007) on PP analyses. Disease-free and overall survival were not significantly different between the two arms. Subgroup analysis identified oral tongue deriving higher benefit of adjuvant RT compared to buccal mucosa. **Conclusions:** Adjuvant RT significantly reduces risk of loco-regional recurrence for early-stage, node-negative adequately resected OSCC, particularly oral tongue. However, such reduction in loco-regional failure does not translate into significant survival benefit. Clinical trial information: CTRI/2017/07/009114. Research Sponsor: NATIONAL CANCER GRID; NCG Project No.2019/01.

6001 Oral Abstract Session

Impact of lymph node dissection extent on disease-free survival with postoperative nivolumab plus concurrent chemoradiotherapy in head and neck squamous cell carcinoma: A post-hoc analysis of the NIVOPOSTOP trial.

Ariane Lapierre, Anne Auperin, Juliette Thariat, Christian Borel, Gautier Lefebvre, Severine Racadot, Lionnel Geoffrois, Xu Shan Sun, Esma Saada, Joanna Kazmierska, Amanda Psyrri, Ricard Mesia, Jean Bourhis, Yungan Tao; Hospices Civils de Lyon, Pierre Benite, France; Gustave Roussy, Villejuif, France; François Baclesse Centre, Caen, France; Centre Paul Strauss, Strasbourg, France; Centre Oscar Lambret, Lille, France; Centre Léon Bérard, Lyon, France; Institut de Cancérologie de Lorraine, Medical Oncology Department, Vandoeuvre-Lés-Nancy, France; Hopital Nord Franche Comté, Montbelliard, France; Centre Antoine Lacassagne, Nice, France; Greater Poland Cancer Center, Poznan, Poland; University of Athens, Chaidari, Greece; Institut catala D'Oncologia, Badalona, Spain; Department of Radio-oncology, Lausanne University hospital CHUV and University of Lausanne, Lausanne, Switzerland; Institut Gustave Roussy, Villejuif, France

Background: Postoperative nivolumab added to concurrent Chemo-Radiotherapy (CRT) after surgery has been shown to improve disease-free survival (DFS) in patients with resected head and neck squamous cell carcinoma (HNSCC) at high risk of relapse. However, extensive nodal dissection has long be suspected to hinder response to immunotherapy but prospective data remains scarce. **Methods:** We analyzed the surgical procedures of the patients included in the primary analysis of the NIVOPOSTOP study regarding neck lymph node dissection (LND). Patients were classified with either uni- or bilateral LND. The number of nodes in the pathological report was also studied. The extent of the LND on DFS was analyzed in univariate and multivariate analysis. **Results:** Surgical information was available for all 666 patients. Four patients did not undergo any LND. Of the 662 patients who underwent nodal surgery, 239 (36%) underwent unilateral LND and 423 (64%) bilateral LND. The proportion of patients with bilateral / unilateral LND was similar in both treatment. Patients who underwent bilateral LND had statistically higher stage tumors versus unilateral LND (76% vs 61% stage IV) and a significantly higher proportion of laryngeal and hypopharyngeal tumors (17% vs 3% and 16% vs 7% respectively). The median numbers of nodes removed were 39 overall, 25 on the right side of the neck, and 24 on the left. As compared to unilateral LND, bilateral LND was associated with worse DFS in univariate analysis (HR 1.56 (95%CI 1.18; 2.05)). After adjusting for performance status, tumor site and p16 status, clinical stage, pathological risk factors of relapse (nodal extracapsular extension, margin status, perineural invasion, $\geq$ 4 involved nodes), the association was no longer statistically significant: HR 1.26 (95%CI 0.92; 1.71), Wald test p-value 0.15. There was no interaction between the type of LND (unilateral or bilateral) and the type of treatment (without or with nivolumab) on DFS. The benefit of adding Nivolumab to CRT was similar for unilateral LND (HR 0.79 (95%CI 0.50; 1.26)) and bilateral LND (HR 0.77 (95%CI 0.57; 1.03)) in Cox model stratified for p16 status. Regarding the extent of LND, the benefit of adding Nivolumab to CRT in the 330 patients who underwent removal of more than 39 neck lymph nodes, on one or both sides, was similar to that of the whole population (HR 0.75 (95%CI 0.54; 1.05)). **Conclusions:** The DFS benefit of adding nivolumab to standard postoperative therapy (cisplatin-RT) was not changed by whether the LND was bilateral or unilateral and persisted in patients in whom more than 39 cervical lymph nodes were removed, on one or both sides. As such, no evidence supports reducing the extent of neck LND when immunotherapy is incorporated into the management of high risk resected HNSCC. Clinical trial information: NCT03576417. Research Sponsor: None.

6002 Oral Abstract Session

Metronomic adjuvant chemotherapy (MACE) in locally advanced oral cavity squamous cell carcinoma post-surgery and adjuvant treatment (MACE postop): A phase III randomized controlled trial.

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Background: The role of maintenance systemic therapy following definitive surgery and adjuvant treatment in locally advanced oral cavity squamous cell carcinoma (OCSCC) remains undefined. This phase III trial evaluated whether oral metronomic adjuvant chemotherapy (MACE) improves survival compared with observation. **Methods:** This multicenter, open-label, phase III superiority trial conducted in India enrolled patients with stage II–IV OCSCC (AJCC 7th edition) who were clinico-radiologically disease-free 1–2 months after completion of definitive surgery with adjuvant treatment. Patients were randomly assigned (1:1) to observation (OBS) or oral MACE for up to 18 cycles. MACE comprised methotrexate 15 mg/m^2 once weekly (four doses per 28-day cycle) plus celecoxib 200 mg twice daily. Adherence to MACE was monitored at 3-monthly follow-up visits using patient-reported medication logs, supplemented by objective verification through review of returned empty drug containers. The primary endpoint was 2-year overall survival (OS). The planned sample size was 712; accrual was stopped early following emerging external evidence, with ethics committee approval. **Results:** Between February 2017 and April 2025, 410 patients were enrolled (OBS, n=208; MACE, n=202); approximately three-quarters had stage IV disease in both arms. The median number of MACE cycles delivered was 15; 92 patients discontinued treatment, most commonly because of noncompliance (n=55) or disease progression (n=27). At a median follow-up of 42.5 months, 129 deaths were observed (70 in OBS and 59 in MACE). Two-year OS was 70.2% (95% CI, 63.0–76.2) in the OBS arm and 79.2% (95% CI, 72.5–84.4) in the MACE arm (hazard ratio [HR], 0.76; p=0.13). Two-year progression-free survival was 68.0% (95% CI, 61.0–74.1) with OBS and 77.0% (95% CI, 70.2–82.4) with MACE (HR, 0.72; p=0.044). Distant recurrences occurred in 30 patients (14.4%) in the OBS arm and 17 patients (8.4%) in the MACE arm, while second primary malignancies were observed in 8 (3.8%) and 3 (1.5%) patients, respectively. Grade 3–4 toxicity with MACE was observed in 6.9%. Exploratory subgroup analyses suggested greater benefit in patients with extranodal extension and stage IV disease. The average cost of MACE per cycle, including toxicity management, was approximately USD 10. **Conclusions:** MACE following definitive local therapy did not significantly improve overall survival in locally advanced OCSCC. However, a statistically significant improvement in progression-free survival was observed, driven by a reduction in distant metastases and second primary malignancies. These findings suggest that selected high-risk subgroups—particularly patients with extranodal extension and advanced-stage disease—may derive benefit from this low-cost and well-tolerated strategy. Clinical trial information: CTRI/2017/02/007777. Research Sponsor: None.

6003 Oral Abstract Session

Two-cycle versus three-cycle induction chemotherapy followed by concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: A phase III randomized noninferiority trial.

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Background: Although two- and three-cycle induction chemotherapy are both widely utilized and confer significant survival benefits in locoregionally advanced nasopharyngeal carcinoma, direct comparative evidence remains lacking. Furthermore, given the cumulative treatment-related toxicity, economic burden, and potential delays in the initiation of radiotherapy, the optimal number of induction chemotherapy cycles remains undefined. **Methods:** We conducted a phase 3, open-label, multicenter, randomized controlled noninferiority trial in an endemic area. Patients with previously untreated, stage III-IVB (except T3-4N0, AJCC 8th edition) nasopharyngeal carcinoma, aged 18-70 years without severe comorbidities were enrolled. Eligible patients were randomly assigned to receive two cycles or three cycles induction chemotherapy followed by concurrent chemoradiotherapy in a 1:1 ratio. The primary endpoint was failure-free survival (FFS) and the noninferiority margin was defined as an 8% absolute between-group difference, with an 80% statistical power and a one-sided α of 0.025. The secondary endpoints included overall survival, distant metastasis-free survival, locoregional relapse-free survival, and toxicity, , among others. **Results:** Among 654 eligible patients, 327 were allocated to each group (two-cycle vs three-cycle). Two groups were well-balanced in all prognostic factors. After a median follow-up of 34.3 months, intention-to-treat analysis showed that estimated 3-year FFS was 85.4% (95% CI 80.9-89.9) in the two-cycle group and 86.7% (95% CI 82.4-91.0) in the three-cycle group, with a difference of -1.3% (95% CI, -7.54% to 4.94%; hazard ratio 1.11, 95% CI 0.72-1.71; P = 0.0031 for noninferiority). Similar result was found in the per-protocol analysis: estimated 3-year FFS for two-cycle group and three-cycle group was 86.5% (95% CI 82.0-91.0) and 87.0% (95% CI 82.7-91.3), respectively, with a difference of -0.5% (95% CI, -6.74% to 5.74%; hazard ratio 1.10, 95% CI 0.69-1.75; P = 0.0014 for noninferiority). No differences were observed between groups in terms of overall survival and the cumulative incidences of locoregional relapse and distant metastasis. Patients in the three-cycle group developed significantly more grade 3-4 adverse events such as neutropenia (three-cycle group 34.3% vs two-cycle group 24.8%), leukopenia (32.7% vs 24.5%) and vomiting (15.9% vs 10.4%). No patients died from treatment-related causes. **Conclusions:** Two-cycle induction chemotherapy followed by concurrent chemoradiotherapy provides comparable disease control and survival, with less toxicity, compared to three-cycle counterpart in locoregionally advanced nasopharyngeal carcinoma. Clinical trial information: ChiCTR1800018417.
Research Sponsor: None.

Carboplatin-based versus cisplatin-based induction-concurrent chemoradiotherapy with locoregionally advanced nasopharyngeal carcinoma: A multicenter, parallel-group, non-inferiority, randomized, phase 3 trial.

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Background: Cisplatin-based chemoradiotherapy has been the standard of care in locoregionally advanced nasopharyngeal carcinoma (LA-NPC). However, the cisplatin-based chemotherapy is known to the severe side-effects and poor compliance. Carboplatin is the second-generation platinum drug with similar anti-cancer efficacy but less side-effects. The purpose of this study is to investigate whether the carboplatin-based induction-concurrent chemoradiotherapy was non-inferior to the cisplatin-based induction-concurrent chemoradiotherapy in LA-NPC. **Methods:** We performed a multicentre, parallel-group, non-inferiority, randomized, phase 3 trial at six institutions in China. Patients initially diagonosed with non-keratinizing NPC and stage III-IVa were randomly assigned to carboplatin group or cisplatin group. Patients in the carboplatin or cisplatin group received two cycles carboplatin-based or cisplatin-based induction chemotherapy, followed by concurrent chemoradiotherapy with carboplatin or cisplatin for two or three cycles. Allocation was done by a central randomization system using sequentially numbered, opaque, sealed envelopes. The primary endpoint was 3-year failure-free survival (FFS). Secondary endpoints are overall survival (OS), distant metastasis-free survival (DMFS), loco-regional failure-free survival (LRFFS), and toxic effects. If the upper limit of the 95% CI for the difference in 3-year failure-free survival between the carboplatin-based and cisplatin-based groups did not exceed 10%, non-inferiority was met. This trial is registered with ClinicalTrials.gov, NCT03919552. **Results:** From Apr 16, 2018 to Aug 7, 2024, a total of 482 patients were enrolled and randomly assigned to carboplatin group (n=241) or cisplatin group (n=241). With a median follow-up of 40.0 months (IQR 21.0-57.0), the 3-year FFS was 85.7% (95%CI 80.4-91.0) in carboplatin group and 87.6% (83.1-92.1) in the cisplatin group (stratified hazard ratio [HR]1.234, 95% CI: 0.744-2.045, p=0.414), with a difference of 1.9% (95% CI −8.9 to 5.1; p non-inferiority=0.0112). Patients in the cisplatin group had a higher frequency of grade 3 or 4 neutropenia (31.6% vs 22.5%, $p < 0.001$), and anorexia (16.9% vs 3.6%, $p < 0.001$). A significantly higher frequency of any grade nausea (4.8% vs 3.6%, $p < 0.001$), vomiting (2.6% vs 0.5%, $p < 0.001$), and nephrotoxicity (1.3% vs 0%, $p < 0.001$). No patients died from treatment-related causes. **Conclusions:** The primary results indicated that carboplatin-based induction-concurrent chemoradiotherapy represents an alternative doublet treatment strategy to cisplatin-based induction-concurrent chemoradiotherapy for patients with LA-NPC. A longer follow-up is needed to confirm the promising regimen. Clinical trial information: NCT03919552. Research Sponsor: National Natural Science Foundation of China; NO.82303684; Medical Scientific Research Foundation of Guangdong Province; B2021449; China Postdoctoral Science Foundation; NO. 2023M741560; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503000; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503005; National Natural Science Foundation of China; China Postdoctoral Science Foundation; NO. 2025M782041; Guangdong Basic and Applied Basic Research Foundation; NO. 2022A1515010509.

LBA6005 **Oral Abstract Session**

Adjuvant sintilimab-capecitabine versus capecitabine alone in locoregionally advanced nasopharyngeal carcinoma with suboptimal response to induction chemotherapy: An open-label, randomized, controlled, phase 2 trial.

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

6006 Oral Abstract Session

A phase 2 study of ipatasertib in combination with pembrolizumab for first-line treatment of recurrent or metastatic squamous cell cancer of the head and neck.

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Background: Single agent pembrolizumab in relapsed/metastatic head and neck squamous cell carcinoma (R/M HNSCC) has limited activity. The immunosuppressive tumor microenvironment (TME) includes regulatory T cells (Treg)s and myeloid-derived suppressor cells (MDSC)s, which may contribute to the low responses to anti-PD-1 therapy. Preclinical studies demonstrate that anti-PD-1 antibodies induce Treg activation through the AKT pathway. AKT blockade selectively inhibits the proliferation of human Tregs compared to conventional T cells. Furthermore, inhibiting the AKT pathway limits MDSC infiltration and differentiation while boosting effector T cell function within tumors. Ipatasertib is an oral highly selective small-molecule inhibitor of all three isoforms of AKT. This phase II trial compares the efficacy of combination ipatasertib plus pembrolizumab (I+P) versus pembrolizumab (P) monotherapy in R/M HNSCC. **Methods:** This is a prospective, two-arm, phase II, multicenter trial for 1st line treatment of R/M HNSCC. Patients were randomized 1:1 to either Arm 1 - P 200mg on day 1 with I 400mg daily on days 1-14 of 21-day cycles, or Arm 2 – P monotherapy. PD-L1 CPS score ≥1 was required. The primary objective is to compare the PFS between the two arms. Secondary objectives included safety and ORR per RECIST 1.1. **Results:** As of 1/21/2026, 52 patients were randomized, with 27 enrolled in the I+P arm. The median age was 67 and 77% were male. The primary tumor sites were 46% oral cavity, 38% oropharynx, and 15% larynx. Among pts with oropharynx primary, 75% were p16 positive. PD-L1 CPS score was ≥20 in 60%. In the I+P arm the most common G1-3 treatment-related adverse events (TRAEs) occurring in ≥10% were diarrhea (70.4%), fatigue (44.4%), Nausea (40.7%), AST increase (18.5%), ALT increase (14.8%), and maculopapular rash (14.8%). Only 1 pt had grade 3 diarrhea. In P arm the most common G3 TRAEs were maculopapular rash (29.2%), AST increase (16.7%), and diarrhea (12.5%). There were no G4 or G5 TRAEs. Four patients required dose reduction of ipatasertib, primarily for diarrhea. Ten pts in the I+P arm and 6 pts in P arm required dose interruptions. One patient in each arm discontinued due to adverse events. At the data cutoff 4 pts remain on treatment in I+P arm and 2 remain on P arm. The ORR in I+P arm and P arm was 41% and 17% respectively. The CR rate was 15% in I+P arm and 4.2% in P arm. The DCR (CR+PR+SD) was 70% in I+P arm and 42% in P arm. With a median follow up of 7.0 months, the PFS in I+P arm is 8.1 months (95% CI: 4 – NA) and in P arm is 6.2 months (95% CI 1.9 – 13.5). **Conclusions:** I+P demonstrated an acceptable safety profile and shows promising clinical activity in R/M HNSCC. Clinical trial information: NCT05172258. Research Sponsor: National Cancer Institute.

LBA6007 **Oral Abstract Session**

Ultra-low-dose immunotherapy plus oral metronomic chemotherapy versus paclitaxel-carboplatin in platinum-sensitive recurrent or metastatic head and neck squamous cell carcinoma: A randomized phase III trial.

Minit Jalan Shah, Vanita Noronha, Nandini Sharrel Menon, Gaurav Kumar, Laxman Sahu, Yashashree Parida, Prajakta Dhanvijay, Kamesh Maske, Srushti Shah, Kavita Prakash Nawale, Manish Pachpande, Amit Janu, Nivedita Chakrabarty, Neha Mittal, Munita Bal, Swapnil Ulhas Rane, Asawari Patil, Kumar Prabash; Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India; Homi Bhabha Cancer Hospital & Research Center - Muzaffarpur, Tata Memorial Centre, Muzaffarpur, India; Tata Memorial Hospital, Mumbai, India; Tata Memorial Centre, Mumbai, Maharashtra, India; Tata Memorial Centre, Mumbai, India; ACTREC, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India

6008 Oral Abstract Session

Amivantamab in HPV-unrelated recurrent/metastatic head and neck squamous cell cancer after disease progression on immune checkpoint inhibitor and chemotherapy: Pivotal results from the phase 1b/2 OrigAMI-4 study.

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Background: Prognosis is poor for patients with HPV-unrelated recurrent/metastatic (R/M) head and neck squamous cell cancer (HNSCC) after disease progression on immune checkpoint inhibitor (ICI) and chemotherapy, with participants (pts) who received cetuximab showing an objective response rate (ORR) of 24% and median progression-free survival (PFS) of 3.8 months (Fayette *Clin Cancer Res* 2025). In addition to EGFR, MET expression is also elevated in R/M HNSCC. Therefore, we evaluated amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity, as monotherapy in HPV-unrelated R/M HNSCC after progression on platinum-based chemotherapy and a PD-(L)1 inhibitor. **Methods:** Cohort 1 of OrigAMI-4 (NCT06385080) evaluated subcutaneous (SC) amivantamab at a dose of 1600 mg (≥80 kg, 2240 mg) on Cycle 1 Day 1, then 2400 mg (≥80 kg, 3360 mg) on Cycle 1 Day 8 and Day 15, and then every 3 weeks. Pts with R/M HNSCC who had disease progression on a PD-(L)1 inhibitor and platinum-based chemotherapy were enrolled. Prior anti-EGFR therapy was exclusionary. The primary endpoint was ORR per RECIST v1.1. The sample size provided >99% power to reject the null hypothesis (ORR ≤10%) assuming an ORR of 30% with a 2-sided alpha of 5%. Secondary endpoints included duration of response (DoR), PFS, and safety. **Results:** As of 6 Jan 2026 (median follow-up: 9.0 months), the cohort was fully enrolled with 102 pts having received ≥1 dose of SC amivantamab. The median age was 63 years (range, 30–81), 77% were male, and 67% had an ECOG performance status of 1. All pts had received prior PD-(L)1 inhibitor and platinum-based chemotherapy. The confirmed ORR was 47% (48/102; 95% CI, 37–57), with 4 complete responses, 44 partial responses, and 39 pts with stable disease. A majority (79%) experienced shrinkage of target lesions. Among confirmed responders, the median DoR was 7.2 months (95% CI, 5.8–not estimable [NE]). Responses were rapid, with a median time to initial response of 6.6 weeks (range, 5.6–43.4). Median PFS was 6.8 months (95% CI, 5.2–8.2). Treatment-emergent adverse events (AEs) were mainly EGFR/MET-related, with the most common (>25%) being hypoalbuminemia, rash, dermatitis acneiform, paronychia, stomatitis, and fatigue. Administration-related reactions were seen in 13% of pts (all grade 1–2). In total, 6 (6%) pts discontinued due to treatment-related AEs. Longer follow-up, subgroup, and biomarker analyses will be presented at the meeting. **Conclusions:** SC amivantamab monotherapy demonstrated an ORR of 47%, with rapid and durable responses in pts with HPV-unrelated, R/M HNSCC after disease progression on an ICI and chemotherapy. The safety profile and tolerability are consistent with prior reports. Clinical trial information: NCT06385080. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

6009 Clinical Science Symposium

Clinical activity of REM-422, a MYB mRNA degrader, in recurrent/metastatic adenoid cystic carcinoma: Final results from the phase 1/2 dose-escalation cohort.

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Background: Adenoid cystic carcinoma (ACC) is a malignant neoplasm characterized by dysregulation of MYB, with the majority of tumors containing a hallmark t(6:9) rearrangement resulting in a MYB:NFIB fusion oncogene, or aberrant MYB overexpression. There are no FDA approved systemic therapies for the treatment of ACC. REM-422 is a first-in-class, potent, selective, oral small molecule mRNA degrader of MYB. **Methods:** This Phase 1/2 study aims to determine the safety, PK/PD and efficacy of REM-422 in patients (pts) with recurrent or metastatic (R/M) ACC. During Phase 1 Dose Escalation and Optimization, patients received oral REM-422 once daily (3-48mg) in 28-day cycles. Enrollment was biomarker-agnostic; MYB mRNA transcripts targetable by REM-422 (biomarker positive) were retrospectively assessed in tumor specimens. **Results:** In the Phase 1 study, 69 pts were enrolled (median age 57 [range 20-82]); 75% received ≥1 prior line of systemic therapy. Fifty-nine pts were efficacy evaluable: 32 biomarker positive, 24 biomarker negative, and 3 unknown. Fifteen patients received REM-422 at the recommended phase 2 dose (RP2D) of 24 mg. REM-422 was generally well-tolerated. No dose-limiting toxicities were observed. The most common treatment-related adverse events at the RP2D included epistaxis (60%), fatigue (60%) and anemia (40%), all of which were grade 1 or 2. Pharmacodynamic analysis in peripheral blood and on-treatment tumor biopsy confirmed robust target engagement including reduction in MYB mRNA and protein at efficacious exposures. In the biomarker positive population, tumor regression was observed at doses ≥12mg, with 21/30 pts (70%) experiencing reduction in target lesions and 14/30 (47%) achieving at least ≥20% shrinkage. Clinical activity was seen across both molecular subtypes (ACC-I and II) and in pts previously treated with antibody-drug conjugates. At the RP2D of 24 mg, 3 PRs were observed among 7 biomarker positive pts (ORR 42%). Time to response ranged from 4-8 months with durations up to 12 months and ongoing at the data cutoff (07 January 2026). **Conclusions:** REM-422 is the first small molecule MYB mRNA degrader to demonstrate clinical activity in R/M ACC and is generally well-tolerated. These findings support further evaluation of REM-422 in a biomarker-selected population. Accrual to the Phase 2 Confirmatory Cohort is ongoing. Clinical trial information: NCT06118086. Research Sponsor: Remix Therapeutics.

6010 Clinical Science Symposium

Emiltatug ledadotin (Emi-Le), a B7-H4–directed antibody-drug conjugate (ADC), in patients with aggressive adenoid cystic carcinoma (ACC): Phase 1 interim analysis.

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Background: ACC is a rare cancer that typically arises in the salivary glands but can affect various organs. About 40% of patients (pts) have an aggressive form of ACC (referred to as ACC-I; Ferrarotto et al., *Clin Cancer Res* 2021) characterized by solid/basaloid or high-grade transformation histology and poor prognosis with median progression-free survival (PFS) of 2–3 months and median overall survival (OS) of approximately 3 years. There are no approved systemic therapies for recurrent or metastatic ACC. B7-H4 is an immune checkpoint protein with elevated expression in ACC and other cancers. Emi-Le (XMT-1660) is a B7-H4-directed ADC with an auristatin F-HPA microtubule inhibitor payload. Here we report antitumor activity results from the Phase 1 ACC-specific dose escalation/backfill cohort, along with safety data for all enrolled pts (NCT05377996). **Methods:** Adult pts with select advanced or metastatic solid tumors, including aggressive ACC, were enrolled. Eligibility criteria for ACC pts required features consistent with aggressive disease that included 1 of the following: 1) clinically aggressive phenotype, defined as < 3 years to recurrence/progression or de novo metastatic disease with atypical metastatic sites and solid tumor morphology, and/or 2) molecular features consistent with poor prognosis (activating *NOTCH1–4* mutations or c-Myc positive or p63 negative/low per IHC). Across dose escalation and backfill, eligible pts received Emi-Le at doses of 7.2–115 mg/m^2 IV per Q3W or Q4W cycle. Pts with ACC received Emi-Le at doses of 57.4–89 mg/m^2 IV per Q3W or Q4W cycle. Primary objectives included safety and preliminary antitumor activity. **Results:** As of October 1, 2025, 221 pts were dosed. Of these, 35 pts had ACC, with a median of 1 prior line of therapy (range 0–3), median age 58 years, and 57% were female. For the safety set of 221 pts, Emi-Le was well tolerated with no new safety signals identified. The most common treatment-related adverse events (TRAEs) were proteinuria (49.8%), transient AST increase (49.3%), and fatigue (41.2%). The only Grade 3 TRAEs in ≥10% of pts were transient AST increase (17.6%) and proteinuria (17.6%). TRAEs leading to treatment discontinuation occurred in 3.6% of pts. No treatment-related deaths were reported. Among 25 evaluable (≥1 post-baseline scan) pts with ACC, objective response rate was 40% (9/25 confirmed, 1/25 unconfirmed ongoing and on treatment) and disease control rate was 76% (19/25). At data cut-off, median PFS (95% CI: 13.0 weeks, not reached [NR]) and OS (95% CI: 26.6 weeks, NR) have not been reached. **Conclusions:** Based on these data, Emi-Le appears to demonstrate favorable tolerability and promising antitumor activity in pts with aggressive ACC who have no available treatments and a poor prognosis. Further clinical development is ongoing. Clinical trial information: NCT05377996. Research Sponsor: Day One Biopharmaceuticals.

6011 Clinical Science Symposium

Trastuzumab deruxtecan in patients with HER2-low recurrent/metastatic salivary gland carcinoma: Results from the phase II MYTHOS trial.

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Background: Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody–drug conjugate with established efficacy across multiple HER2-expressing malignancies. Salivary gland carcinoma (SGC) is a rare disease with limited treatment options, particularly for tumors with HER2-low expression. The MYTHOS trial is a multicenter, investigator-initiated phase II study evaluating T-DXd efficacy in recurrent or metastatic (RM) SGC patients with HER2 overexpression or HER2-low expression. Here, we report the efficacy and safety results of the HER2-low cohort (Cohort 2). **Methods:** Eligible patients had histologically confirmed RM SGC with HER2-low expression (IHC 1+ or IHC 2+/ISH−), as determined by central assessment according to the ASCO/CAP 2018 breast cancer guidelines, and no indication for curative treatment. Patients received T-DXd at 5.4 mg/kg intravenously every 3 weeks. The primary endpoint was confirmed objective response rate (ORR) assessed by independent central review (ICR) according to RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. The required sample size for Cohort 2 was 33 patients, based on a threshold ORR of 25%, an expected ORR of 50%, 83% power, and a two-sided alpha of 0.05 using an exact binomial test. The primary efficacy decision was based on the prespecified Simon's two-stage minimax design in the first 33 patients; efficacy in the full analysis set (FAS) was summarized descriptively. **Results:** A total of 36 patients were included in the FAS, including 30 with salivary duct carcinoma (SDC). HER2-low status comprised IHC 2+/ISH− in 14 and IHC 1+ in 22; 25 had received prior systemic therapy for RM disease. Median follow-up was 25.1 months. The ORR by ICR was 38.9% (14/36; 95% CI, 23.1–56.5%), and the DCR was 94.4% (95% CI, 81.3–99.3%). Median PFS was 8.7 months (95% CI, 6.5–13.3), and median OS was 24.8 months (95% CI, 18.7–NE). In a prespecified subgroup analysis by histology, the ORR by ICR was 46.7% (14/30; 95% CI, 28.3–65.7%) in SDC and 0% (0/6; 95% CI, 0–45.9%) in other SGC subtypes. Common grade ≥3 adverse events (>10%) were neutrophil count decreased (36.1%), lymphocyte count decreased (19.4%), white blood cell count decreased (11.1%), and decreased appetite (11.1%). Drug-related interstitial lung disease (ILD)/pneumonitis occurred in 9 (25.0%; grade 1/2 in 7, grade 3 in 1, and grade 5 in 1). There was one drug-related death due to ILD/pneumonitis. **Conclusions:** Although the prespecified primary efficacy endpoint was not met, T-DXd demonstrated clinically meaningful antitumor activity in patients with HER2-low RM SGC, particularly in those with SDC. The safety profile was generally consistent with the known profile of T-DXd in the Japanese population, with ILD/pneumonitis remaining an important identified risk requiring careful monitoring. Clinical trial information: jRCT2011210017. Research Sponsor: Daiichi Sankyo Company, Limited.

6012 Clinical Science Symposium

A phase 2 study of darolutamide plus leuprolide acetate in hormone therapy–naïve recurrent and/or metastatic androgen receptor (AR)–positive salivary gland cancer (ETCTN 10553).

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Background: A subset of salivary gland cancers (SGCs) express the androgen receptor (AR). A prior AR+ SGC trial with the anti-androgen enzalutamide alone failed to meet its primary endpoint. This is a multicenter, phase II study evaluating the efficacy and safety of the anti-androgen darolutamide (Bayer) in combination with androgen-deprivation therapy (ADT; leuprolide acetate) in hormone-therapy naïve patients with AR+ SGCs. **Methods:** Patients with locally advanced/unresectable or recurrent/metastatic AR+ SGCs were enrolled. AR status was determined locally by immunohistochemistry (IHC). Prior AR-targeted therapy was not allowed, unless administered in the neoadjuvant and/or adjuvant setting >6 months before disease recurrence. Darolutamide 600 mg orally twice daily was given with leuprolide acetate intramuscular injections (1 cycle= 28 days). The primary endpoint was best overall response (BOR) rate according to RECIST v1.1 within 1 year of initiating treatment. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity. Exploratory endpoints were evaluating biomarkers in serially obtained research biopsies and exploring efficacy among patients who had not received prior systemic therapy. A two-stage minimax design was used to detect a 50% BOR rate (vs. 25%) (alpha = 9%; beta = 83%). ≥3 responses in the first 9 patients would trigger accrual to 20; ≥8 responses would be considered promising. **Results:** Study accrual of 20 patients (pts) with AR+ SGCs was completed on 10/30/25. 15 males, 5 females with a median age of 70.5 years were enrolled. Among the 9 pts in the first stage, 6 confirmed partial responses (PRs) were observed, allowing for full study accrual. With a data cutoff of 1/21/26, the best RECIST v1.1 responses among 20 pts were 8 (40% [19.1% 63.9%]) PRs (7 confirmed, 1 unconfirmed with pt still on treatment), 10 (50% [27.2%, 72.8%]) stable disease (SD), 1 (5% [1%, 24.9%]) progression of disease; 1 pt on treatment has not had radiographic assessments yet. 6 (30% [11.9%, 54.3%]) pts came off trial for disease progression, 1 (5% [1%, 24.9%]) withdrew consent after 6 cycles, and 13 (65%, [40.8%, 84.6%]) remain on treatment. Among 5 female pts, best responses were 1 (5% [1%, 24.9%]) PR, 3 (15% [3.2%, 37.9%]) SD, 1 (5% [1%, 24.9%]) PD. With additional follow-up, PFS, OS, and biomarker data (AR IHC %, HER2 status) will be presented. **Conclusions:** In this molecularly selected cohort of patients with SGC, darolutamide plus ADT possesses significant clinical activity, validating AR as a relevant therapeutic target in a subset of SGCs. Analysis of serial research biopsies will be performed to identify biomarker and/or drug combination strategies to enhance the efficacy of AR-targeting. Clinical trial information: NCT05669664. Research Sponsor: U.S. National Institutes of Health; Bayer.

Induction chemotherapy with nab-paclitaxel and cisplatin versus docetaxel, cisplatin, and fluorouracil followed by chemoradiotherapy in patients with stage III–IVA nasopharyngeal carcinoma: An open-label, noninferiority, randomized, controlled, phase 3 trial.

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Background: The docetaxel, cisplatin, and 5-fluorouracil (TPF) regimen is the standard induction therapy regimen for locoregionally advanced nasopharyngeal carcinoma (LANPC). However, it is associated with poor patient compliance and notable side effects. This phase 3 trial aimed to compare the efficacy and safety of induction chemotherapy with nab-paclitaxel plus cisplatin (nab-TP) with those of the TPF regimen in patients with LANPC. **Methods:** In this multicenter, noninferiority, open-label, randomized controlled trial, treatment-naive patients with LANPC were recruited from 5 hospitals in China and were randomly assigned to receive two cycles of nab-TP (nab-paclitaxel 260 mg/m^2, cisplatin 80 mg/m^2) or TPF (docetaxel 60 mg/m^2, cisplatin 60 mg/m^2, 5-FU 3 g/m^2), followed by concurrent chemoradiotherapy. The primary endpoint was the 3-year failure-free survival (FFS) rate (non-inferiority margin 10%) in the intention-to-treat population. Secondary endpoints included overall survival, treatment response, safety, and patient-reported outcomes. This trial is registered with chictr.org.cn (ChiCTR1800019922) and is now completed. Based on previous studies, we hypothesized that the 3-year FFS (approximately 80%) is the same between the TPF regimen and the nab-TP regimen for patients with LANPC. We specify a clinically acceptable noninferiority margin of 10%. The dropout rate in both arms was set at 4% per year. Accordingly, a minimum of 506 participants was needed to achieve 80% statistical power with a one-sided type I error of 2·5%. **Results:** Between January 22, 2019 and March 24, 2023, 515 patients (71·8% male; median age: 45 years (IQR 37–51)) were randomized: 259 to the nab-TP group and 256 to the TPF group. Compared with the TPF group, the nab-TP group had significantly better treatment compliance. With a median follow-up of 55·2 months, the 3-year FFS rate in the intention-to-treat population was 86·7% (95% confidence interval (CI): 82·6–90·9) in the nab-TP group and 88·2% (95% CI: 84·2–92·1) in the TPF group. The difference in the 3-year FFS between groups was -1·4% (95% CI: -7·2 to 4·3)($P_{non-inferiority}$ = 0·0018). Compared with the TPF group, the nab-TP group had significantly lower incidences of grade 1+ leucopenia (34·0% vs. 62·6%, P < 0·0001), neutropenia (20·3% vs. 48·8%, P < 0·0001), electrolyte disturbances (86·3% vs. 96·5%, P < 0·0001), and diarrhea (28·5% vs. 39·0%, P = 0·012), whereas the nab-TP group had a higher incidence of nausea (91·0% vs. 85·4%, P =0·047). No treatment-related death was documented. **Conclusions:** In LANPC, nab-TP was non-inferior to TPF in terms of 3-year FFS rate and was associated with a significantly better safety and tolerability profile, supporting its use as a viable therapeutic alternative. Clinical trial information: ChiCTR1800019922. Research Sponsor: National Natural Science Foundation of China; No. 82172863; Natural Science Foundation of Guangdong Province.

6014 Rapid Oral Abstract Session

Neoadjuvant ivonescimab (AK112, a PD-1/VEGF bispecific antibody) combined with nab-paclitaxel and cisplatin (AP) for resectable locally advanced head and neck squamous cell carcinoma (LA-HNSCC): An exploratory phase II study.

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Background: Previously, neoadjuvant PD-1 plus AP followed by surgery and radiotherapy showed promising disease control and laryngeal preservation in resectable LA-HNSCC. Ivonescimab, a PD-1/VEGF bispecific antibody, potentially exerts synergistic anti-tumor activity by normalizing tumor vasculature and enhancing immune infiltration. This study evaluates the efficacy and safety of neoadjuvant Ivonescimab plus AP in resectable LA-HNSCC. **Methods:** This single-center phase II trial enrolled patients (18-70 yrs) with resectable stage III-IVa LA-HNSCC (oral cavity, oropharynx, hypopharynx, or larynx). Neoadjuvant therapy: 3 cycles of Ivonescimab (20mg/kg Q3W) plus AP, followed by surgery. Postoperative treatment included radiotherapy ± chemotherapy and maintenance Ivonescimab (10mg/kg Q3W) for 14 cycles. Primary endpoints: pCR and 2-year EFS. MRD and PD-L1 CPS were also investigated. **Results:** By November 2025, 36 patients were enrolled (median age 58; 75% Stage IV). Primary tumor sites were hypopharynx (50.0%), larynx (25.0%) and oral cavity (19.4%). Radiological assessment performed prior to Cycle 3 demonstrated an exceptional objective response rate (ORR) of 100% among 34 evaluable patients. Notably, a remarkably deep radiological response was achieved, with a complete response (CR) rate of 50.0% (17/34) and a partial response (PR) rate of 50.0% (17/34). Deep tumor shrinkage was observed in all cases. 30 patients underwent surgery with a 100% R0 resection rate. The overall pCR rate was 50.0% (15/30). Specifically, pCR was achieved in 70.0% (21/30) of primary lesions and 64.3% (18/28) of lymph nodes. While robust pathological responses were observed in the hypopharynx (64.3%), tongue (57.1%), and oropharynx (50.0%), the pCR rate in the larynx was markedly lower at 12.5%. Crucially, the profound tumor downsizing induced by Ivonescimab enabled volume-reduced resections, achieving 100% successful laryngeal and pharyngeal preservation while maintaining negative margins. High PD-L1 predicted efficacy; median CPS was 30.0 in pCR vs. 10.0 in non-pCR ($p=0.18$). Notably, 100% of pts with CPS $>$ 30 achieved pCR. Pre-op MRD specificity for pathological conversion was 91.7% (sensitivity 37.5%). Safety: The most common Grade$\geq$3 AEs were pharyngeal fistula (surgical-related) and transient transaminase elevation. Most drug-related AEs were manageable and consistent with the known profiles of PD-1 and VEGF inhibitors. **Conclusions:** Neoadjuvant Ivonescimab plus chemotherapy demonstrated unprecedented radiological response depth and pathological remission rates in LA-HNSCC. This novel PD-1/VEGF-based dual blockade may redefine neoadjuvant standards for head and neck cancer. High CPS and MRD negativity are robust predictors of deep pathological response. Clinical trial information: NCT06537011. Research Sponsor: None.

Timing of postoperative chemoradiotherapy and survival outcomes in high-risk locally advanced head and neck squamous cell carcinoma: A supplementary analysis of JCOG1008.

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Background: For patients with post-operative high-risk locally advanced head and neck squamous cell carcinoma (LA-HNSCC), initiation of chemoradiotherapy (CRT) within 6 weeks after surgical resection is recommended based on previous reports. However, the guideline-defined 6-week threshold for initiating post-operative radiotherapy (PORT) is derived mainly from data in patients treated with PORT alone. Therefore, its relevance in patients receiving post-operative CRT remains uncertain. **Methods:** This supplementary analysis used data from the JCOG1008 trial (jRCTs031180135), which compared post-operative CRT with weekly cisplatin versus 3-weekly cisplatin. Associations between the surgical-to-PORT interval (S-PORT) and locoregional relapse-free survival (LRFS), overall survival (OS), and relapse-free survival (RFS) were evaluated using restricted cubic spline analyses, Kaplan–Meier methods, and Cox proportional hazards models. Treatment package time (TPT), defined as the sum of S-PORT and radiotherapy duration, was also assessed. **Results:** Among 261 enrolled patients, 251 were eligible for this analysis (median age, 62 years; 16.3% female; 45.8% with oral cavity primaries). The median S-PORT and TPT were 7.0 weeks (range, 2.9–10.0) and 13.9 weeks (range, 7.6–16.9), respectively. Restricted cubic spline analyses demonstrated minimal variation in risk across the observed S-PORT range, with hazard ratios (HRs) remaining close to 1 for LRFS, OS, and RFS. Kaplan–Meier analyses using the guideline-defined 6-week cutoff showed similar 5-year LRFS between patients with S-PORT ≤6 weeks and >6 weeks (64.0% vs 64.9%; HR 0.91, 95% CI 0.60–1.37; Table), with no significant differences in OS or RFS. In multivariable Cox models adjusting for clinical covariates, S-PORT was not independently associated with outcomes. Findings for TPT closely paralleled those for S-PORT, with no significant associations observed between TPT and treatment. **Conclusions:** In this supplementary analysis of JCOG1008, no prognostic disadvantage was observed when PORT was initiated within the range observed in this trial (6–10 weeks after surgery) among patients receiving post-operative CRT. These findings support individualized S-PORT timing rather than rigid cutoff-based decision-making in contemporary standardized CRT. Clinical trial information: jRCTs031180135. Research Sponsor: Japan Agency for Medical Research and Development (AMED); Grant-in- Aid for Clinical Cancer Research from the Ministry of Health, Labor and Welfare of Japan; National Cancer Center Research and Development Funds.

Kaplan–Meier analyses according to guideline-defined 6-week surgical-to-postoperative radiotherapy interval (S-PORT) cutoff.

	S-PORT ≤ 6 weeks	S-PORT > 6 weeks
5y LRFS (95% CI)	64.0% (52.1%–73.7%)	64.9% (57.3%–71.5%)
HR (95% CI), p-value	1	0.91 (0.60–1.37), 0.65
5y OS (95% CI)	65.3% (53.4%–74.9%)	66.6% (59.1%–73.1%)
HR (95% CI), p-value	1	0.88 (0.58–1.34), 0.54
5y RFS (95% CI)	60.0% (48.0%–70.1%)	60.2% (52.6%–67.0%)
HR (95% CI), p-value	1	0.98 (0.66–1.46), 0.93

Phase II randomized trial of radiotherapy with pembrolizumab vs. cisplatin for unfavorable-risk p16+ head and neck squamous cell carcinoma (KEYCHAIN).

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Background: Standard chemoradiation (CRT) for unfavorable risk p16+ head and neck squamous cell carcinoma (HNSCC) is associated with high rates of toxicity and treatment failure. We hypothesized that concurrent and adjuvant pembrolizumab (pembro) could achieve superior PFS with acceptable toxicity compared to CRT in this population. **Methods:** KEYCHAIN was an open-label randomized phase II trial conducted at 6 US academic centers. Eligible patients had newly diagnosed unresected p16+ HNSCC with unfavorable risk (AJCC 8th edition stage II-III oropharynx or stage III-IVB non-oropharynx HNSCC). Patients were randomized 1:1 to RT (70 Gy in 35 fractions) plus pembro (200 mg, 2 weeks prior to RT then every 3 weeks starting day 1 of RT up to 20 total cycles) or RT plus concurrent cisplatin (cis) (100 mg/m^2 every 3 weeks). Age, ECOG status, and oropharynx site were stratification factors. The primary endpoint was PFS, defined as time from randomization to first progression or death from any cause. Primary analysis was in the modified intent-to-treat population, including all patients having $\geq$ 1 dose of study medication and $\geq$ 1 efficacy evaluation after baseline. The study design had 80% power with 1-sided α = 0.15 (log-rank test) and planned sample size of 50 analyzable subjects per arm. The study is registered with clinicaltrials.gov (NCT03383094). **Results:** Between Feb 2019 and Aug 2025, 108 patients were randomized (53 pembro, 55 cis), with 102 analyzable (50 pembro, 52 cis). Median follow-up was 26.5 months. 79% had minimum follow-up of 2 years. At 2 years, there were 7 PFS events and 1 death in the pembro arm, and 14 PFS events and 7 deaths in the cis arm. Two-year PFS was 84% (95% CI: 74-96%) vs. 70% (95% CI: 58-85%) in the pembro vs cis arm (HR 0.57, 95% CI: 0.25-1.31; 1-sided p = 0.09) (see Table). Two-year OS was 98% (95% CI: 94-100%) vs. 85% (95% CI: 76-96%) for pembro vs. cis (HR 0.33, 95% CI: 0.09-1.28; 1-sided p = 0.048). HRs adjusted for T3-4 and N2-3 category were 0.68 (PFS) and 0.31 (OS). As of the latest follow-up, there were 24 total PFS events and 12 deaths. Grade $\geq$ 3 adverse events definitely or probably related to treatment were 36% vs. 46% in the pembro vs. cis arm. The median number of cycles received in the pembro arm was 18. In the cis arm, 94% completed $\geq$ 2 cycles. Results by CPS status will be reported when available. **Conclusions:** Pembro plus RT met the pre-specified significance criterion for improvement in PFS compared to cisplatin plus RT in this phase II trial. A phase III trial of RT with pembrolizumab for unfavorable risk p16+ HNSCC is warranted. Clinical trial information: NCT03383094. Research Sponsor: Merck.

	Pembro	Cisplatin
N	50	52
Mean age	63.5	62.5
Male	87%	89%
White	85%	89%
Age > 65	42%	35%
ECOG 0	83%	70%
Oropharynx	94%	96%
T1	8%	10%
T2	22%	12%
T3	38%	38%
T4	32%	40%
N0	6%	8%
N1	42%	29%
N2	46%	54%
N3	6%	10%
2-yr PFS	84%	70%
2-yr OS	98%	85%
Completed RT w/in 56 days	96%	92%
Grade ≥ 3 mucositis	18%	17%
Grade ≥ 2 mucositis	72%	63%
Grade ≥ 3 dysphagia	14%	6%
Grade ≥ 2 dysphagia	48%	35%

6017 Rapid Oral Abstract Session

Final analysis of the investigator-initiated randomized study of anti–PD-L1 durvalumab (durva) with radiation versus chemoradiation (CRT) for intermediate-risk HPV-positive (HPV+) locally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC): Canadian Cancer Trials Group (CCTG) HN.9 (EORTC 1740-HNCG).

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Background: Primary immunotherapy (IO) with radiotherapy remains an investigational approach in HPV+ LA-OPSCC. The CCTG-led international phase II, randomized, non-comparative, HN.9 (NCT03410615) trial evaluated the efficacy of the of durva+RT as a chemo-sparing approach in patients (pts) with intermediate-risk, HPV+, LA-OPSCC. **Methods:** Pts with newly diagnosed, PDL1-unselected, pathologically proven, treatment-naïve HPV+ LA-OPSCC (UICC/AJCC 8th Edition T1-2N1 or T3N0-1 smokers [≥10 pack years] or T1-3 N2 with any smoking history) eligible for definitive CRT were randomized (1:2) to Arm A (CRT: 70Gy/35F + cisplatin 100 mg/m2 Q3W on days 1,22,43 of RT) vs Arm B (durva IV 1500 mg, days -7, 22 of RT, followed by adjuvant durva for 6 doses). Primary objective was 3-year EFS in Arm B (efficacy if one-sided 90% CI lower bound [LB] >83%). Secondary objectives: QoL (MDADI, FACT-HN at baseline, end of RT, 3,6,12,24 and 36 mo), OS, safety, distant metastasis-free survival (DMFS) and locoregional control (LRC). Safety was assessed per CTCAE v5. The trial closed early based on emerging external efficacy data of IO in HN LA setting, enrolling 129 pts overall (80 of the planned 120 in Arm B) with approximately 80% power retained for the primary analysis. **Results:** 129 pts were randomized across 21 Canadian and European sites. Baseline characteristics were well balanced between arms. At the data cutoff (Sep 19, 2025), median follow-up time was 55.7 mo. In both arms, all pts received the planned RT schedule. In Arm A, the median number of cisplatin cycles was 2 (21% received <200m/m^2 and 79%≥ 200 mg/m^2). In arm B, all pts (100%) received durva concurrent to RT. 126 pts were eligible for efficacy analysis. The estimated 3-year EFS in Arm B was 80% (one-sided 90% CI: LB 73%); the prespecified efficacy criterion (LB >83%) was not met. The 3-year EFS in Arm A was 89%. The estimated 3-year OS rates were 92% in both arms. At 3 years, LRC were 97 and 91% in Arms A and B respectively. DMFS was 89% in Arm A and 86% in Arm B. Grade ≥ 3 adverse events any time during trial were similar between Arm B (69%) and Arm A (63%). QoL completion was 96% at baseline and 80%+ throughout; acute worsening during RT followed by gradual recovery (slower in arm B during adjuvant durva), with longer-term persistence of isolated issues (hearing loss, dry mouth) was similar to published experience for drug+RT regimens. **Conclusions:** Durva+RT did not improve 3-year EFS in the overall patient population of intermediate-risk HPV+ OPSCC. No new safety signal was observed. Specific toxicities varied by arm, but overall QoL experience, including swallowing, was similar between arms and with prior trials. Subgroup analysis, blood, tissue and microbiome-based correlates are ongoing. Clinical trial information: NCT03410615. Research Sponsor: Canadian Cancer Society; 707213; AstraZeneca.

Randomized phase I/II trial adjuvant CD40.HVAC, an immunotherapy engaging dendritic cells (DC), in patients with HPV16+ oropharyngeal carcinoma (OPC).

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Background: Up to 70% of OPCs are HPV-mediated predominantly by HPV16. E6/E7 oncoproteins, constitutively expressed in malignant cells, represent optimal immunotherapeutic targets. We evaluated CD40.HVac, a new DC engager combining a humanized IgG4 monoclonal antibody fused to HPV16 E6/E7, designed to target the CD40 receptor on DCs. **Methods:** This trial enrolled OPC HPV16$^+$ patients (pts) in complete remission 16–22weeks (W) post curative treatment. In cohorts 1 (n=11) and 2 (n=11), pts were randomized (5:1) to receive subcutaneously, Hiltonol (1mg) adjuvanted CD40.HVac, 1 and 3 mg, respectively, or placebo, at W0, 4, 24. Dose-limiting toxicity (DLT) was assessed from W0–W6. Blood E6/E7-specific T cells were assessed 2W post-injection using stimulation of PBMCs with vaccine E6/E7 pools of peptides. CD8+T cells were characterized by expression of Activation Induced Markers (AIM). Immune response was defined as a ≥3-fold increase in HPV specific T cell responses over unstimulated controls after in vitro restimulation, or a net increase of ≥ 0.03% reaching at least 0.05% AIM$^+$ T cells compared to baseline. **Results:** Median age was 58 years (IQR 51; 65), 68% were male, 68% were stage I or II, 32% stage III. At entry, 21 pts were lymphopenic (3 grade 3). All pts received the 3 planned injections. Four pts were randomized to placebo, 18 to CD40.HVac. No DLTs nor grade 3-5 adverse events (AEs) were reported. From W0 to W32, all pts treated with CD40.HVac experienced at least 1 vaccine related AE; 5 (28%) experienced at least 1 grade 2 AE while the 13 others experienced only grade 1 AEs. At W6, 77% of pts treated with CD40.HVac in the both 1 mg and 3 mg cohorts exhibited a 27-fold and 42-fold increase from baseline, respectively, in CD4$^+$ T cells producing IL-2, IFNγ and/or TNF. By W26, responses were observed in 100% of pts treated with CD40.HVac in both cohorts, with 35-fold (1 mg) and 83-fold (3 mg) increases from baseline. AIM assays confirmed the induction of HPV specific CD4$^+$ and CD8$^+$ T cell responses. HPV specific CD8$^+$ T cell responses were detected in 50% and 44% of pts treated with CD40.HVac at W6 in the 1 mg and 3 mg cohorts, respectively, and in 71% and 44% at W26. HPV specific CD8$^+$ T cells displayed a polyfunctional cytotoxic phenotype, expressing IFNγ, TNF, granzyme B and CD107a, along with PD-1, consistent with an activated state. Both CD4$^+$ and CD8$^+$ T cell responses were durable and persisted up to1 year post-prime vaccination. Only minimal or no increases in HPV specific responses were observed in pts treated with placebo. After a median follow-up of 1 year, no pt presented disease relapse. HPVct DNA monitoring will be presented at the meeting. **Conclusions:** The safety and immunogenicity of CD40.HVac support further clinical development of this strategy in pts with HPV16+ OPC. Clinical trial information: NCT06007092. Research Sponsor: EnnoDC.

6019 Rapid Oral Abstract Session

Phase II study of izalontamab (SI-B001) in combination with paclitaxel or docetaxel in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).

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Background: Izalontamab is a bispecific antibody targeting EGFR and HER3. Here we present safety and efficacy results from a phase II study on izalontamab in combination with paclitaxel/docetaxel in patients with R/M HNSCC. **Methods:** Patients with R/M HNSCC who had progressed on prior anti-PD-(L)1 therapy, with or without platinum-based chemotherapy, and received no more than two prior lines of treatment were enrolled. Izalontamab was administered at 12mg/kg QW in combination with paclitaxel (80mg/m^2 IV QW) (for patients without prior exposure to paclitaxel) or docetaxel (35mg/m^2 IV D1D8D15 Q4W) (for patients with prior exposure to paclitaxel). Primary endpoint was investigator-assessed ORR. Secondary endpoints included PFS, OS, DCR, and DoR. **Results:** As of Nov 7, 2025, a total of 45 patients (44 HNSCC and 1 sinnonasal) were enrolled, of whom 35 (77.8%) received one prior line of therapy and 10 (22.2%) received two prior lines of therapy. HNSCC patients who received at least one dose of study drug were included in the analysis. Median follow-up was 15.0 months. Overall, ORR was 43.2%, confirmed ORR was 31.8%, median PFS was 4.0 months, and median OS was 10.0 months. In patients treated with izalontamab combo with paclitaxel (n = 34), ORR was 52.9%, confirmed ORR was 41.2%, median PFS was 5.4 months, and median OS was 11.2 months. Grade≥3 TRAEs occurred in 57.8% of patients. The most common grade≥3 TRAE was leukopenia (20.0%), followed by neutropenia (15.6%), rash (13.3%), and anemia (8.9%). One (2.1%) patient discontinued study treatment due to TRAE. No treatment-related death was observed. **Conclusions:** Izalontamab in combination with paclitaxel showed encouraging antitumor activity and a manageable safety profile in patients with R/M HNSCC who were previously treated with anti-PD-(L)1 therapy. Clinical trial information: NCT05054439. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

	Izalontamab+Paclitaxel (N=34)	Izalontamab+ Docetaxel (N=10)	Total (N=44)
ORR, % (95% CI)	52.9 (35.1, 70.2)	10.0 (0.3, 44.5)	43.2 (28.3, 59.0)
cORR, % (95% CI)	41.2 (24.6, 59.3)	0	31.8 (18.6, 47.6)
DCR, % (95% CI)	73.5 (55.6, 87.1)	30.0 (6.7, 65.2)	63.6 (47.8, 77.6)
Median DOR (mo) (95% CI)	5.0 (3.7, 11.0)	NR (NR, NR)	5.0 (3.7, 11.0)
Median PFS (mo) (95% CI)	5.4 (3.9, 6.6)	1.5 (0.4, 3.6)	4.0 (2.8, 5.5)
Median OS (mo) (95% CI)	11.2 (6.6, 19.3)	6.6 (0.4, 13.8)	10.0 (6.6, 13.8)

FID-007 in combination with cetuximab in recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).

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Background: Paclitaxel is commonly used to treat HNSCC but is associated with infusion-related reactions and peripheral neuropathy (PN). Historically, the median progression-free survival (PFS) of standard of care, second line therapy for metastatic HNSCC is 2-3 months (mo). FID-007 is a novel nanoencapsulated paclitaxel utilizing a proprietary poly(2-ethyl-2-oxazoline) polymer excipient. This formulation overcomes the limited water solubility and pharmacodynamics of paclitaxel, enhancing both tumor penetration and retention. **Methods:** FID-007-003 is an ongoing phase 2, randomized, multicenter, open-label study. Patients must have progressed after anti-PD1/PD-L1 therapy and have not received >1 line of prior therapy for R/M HNSCC. Prior cetuximab or taxane in the R/M setting were not allowed. Patients were stratified by p16 status and prior taxane exposure, and randomized 1:1 to one of two doses of FID-007 (Arm A: 75 mg/m^2; Arm B: 125 mg/m^2) IV on days 1, 8, and 15 in combination with cetuximab 500 mg/m^2 IV on days 1 and 15 every 28 days starting with Cycle 2. The primary endpoint was investigator-assessed objective response rate (ORR) by RECIST 1.1. **Results:** As of the preliminary data cut-off date of 20DEC2025, 45 patients were randomized and received ≥ 1 dose of FID-007; 42 patients were efficacy-evaluable (19 in Arm A, 23 in Arm B). Median age was 65 years (range 45-81), 62% (28/45) received prior platinum-based therapy and 67% (30/45) received 1 prior systemic therapy for R/M disease. The median cumulative dose of FID-007 was 825 mg/m^2 in Arm A and 1,450 mg/m^2 in Arm B. The median duration of treatment was 4 mo in Arm A and 4.3 mo in Arm B, with a median follow-up of 4.2 mo. The ORR/complete response (CR) rate was 60%/17% (58%/11% in Arm A, 61%/22% in Arm B), and the median PFS was 7.2 mo [6.7 mo in Arm A (2.0-12.8), and 7.2 mo in Arm B (4.0-NR)]. The median duration of response was 7.4 mo (7.4 mo in Arm A, NR in Arm B) with 56% (14/25) of responders continuing to respond at the time of data cut-off. The overall survival data are immature at present. Treatment-related adverse events (TRAEs) were mostly of grade 1-2. Grade 3-4 TRAEs occurring in ≥ 2 patients included neutropenia (3 in Arm A, 5 in Arm B), anemia (2 in Arm A, 4 in Arm B), leukopenia (3 in Arm B), acneiform dermatitis (2 in Arm A), maculo-papular rash and other rash (2 in Arm B). There was 1 Grade 5 TRAE: pneumonia (Arm B). **Conclusions:** FID-007, administered in combination with cetuximab, demonstrated clinically encouraging and durable anticancer activity at both doses tested in this population of pre-treated R/M HNSCC. Notably, the absence of infusion-related reactions and the lack of grade ≥ 3 PN, along with a tolerable safety profile potentially compares favorably with other taxanes, which may ultimately enable a longer treatment duration and lead to improved therapeutic outcomes. Clinical trial information: NCT06332092. Research Sponsor: Fulgent Pharma.

6021 Rapid Oral Abstract Session

Nivolumab plus lenvatinib for unresectable anaplastic thyroid cancer: Results of the phase 2 NAVIGATION study.

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Background: Anaplastic thyroid cancer (ATC) is one of the most aggressive and lethal malignancies, characterized by limited treatment options and a dismal prognosis. Although lenvatinib has shown some efficacy, its impact remains modest, and no standard systemic therapy has been established for unresectable ATC—particularly for BRAF wild-type (BRAF-negative) disease. **Methods:** The NAVIGATION study (NCT05696548) is an open-label, multicenter, phase 2 trial evaluating the combination of nivolumab and lenvatinib in patients with unresectable ATC. As primary endpoints, Step 1 assessed dose-limiting toxicities (DLTs), while Step 2 evaluated the objective response rate (ORR) by independent radiological central review (IRCR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), best overall response, disease control rate, clinical benefit rate, safety, and quality of life. Eligible patients had histologically confirmed unresectable ATC, measurable disease per RECIST v1.1, adequate organ function, an ECOG performance status of 0–1, and a life expectancy of over 90 days. Lenvatinib was administered orally at 24 mg once daily, and nivolumab intravenously at 240 mg every two weeks, continued until disease progression or unacceptable toxicity. The Step 2 sample size of 48 patients was determined based on a historical ORR of 23.5% and an expected ORR of 44%, providing 80% power with a two-sided α of 0.05, accounting for a 20% dropout rate. ORR was evaluated in the full analysis set of patients with ATC confirmed by independent pathological central review (IPCR). **Results:** Between December 2019 and February 2024, 51 patients were enrolled across 10 sites in Japan (Step 1: n=3; Step 2: n=48). No DLTs were observed in Step 1. In Step 2, the median age was 69.5 years (range, 43-89); 46 patients had metastatic disease, 40 had prior history of surgery, and 42 were pathologically confirmed as ATC by IPCR. The ORR by IRCR was 47.6% (95% CI: 33.4-62.3), meeting the primary endpoint. At a median follow-up of 11.6 months, the median duration of response was 12.9 months (95% CI: 6.28 -27.6), median PFS was 5.6 months (95% CI: 5.5-9.1), and median OS was 14.7 months (95% CI: 10.1-29.2). The 1-year OS rate was 56.9%. In Step 2, grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 38/48 patients (79.2%), serious TRAEs in 20 (41.7%), and there was one treatment-related death (2.1%). **Conclusions:** Nivolumab plus lenvatinib demonstrated a clinically meaningful ORR, meeting the primary endpoint. The combination also achieved favorable PFS and OS with manageable toxicity under appropriate supportive care, suggesting that this regimen may represent a new treatment option for patients with unresectable ATC. Clinical trial information: NCT05696548. Research Sponsor: None.

Whole slide imaging–based prediction of immunohistochemistry markers and surgical pathological features.

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Background: Immunohistochemistry (IHC) marker testing and identification of pathological features are essential tasks in surgical pathology following resection of head and neck cancers. However, IHC testing is time-consuming, and identifying pathologic features typically requires examination of multiple slides. We hypothesized that imaging features from a single H&E-stained whole slide image (WSI) could predict this information using machine learning. **Methods:** We utilized data from the publicly available HANCOCK dataset for machine learning model development and testing. All patients had undergone surgical resection for locoregional head and neck cancer. Image features (embeddings extracted by TITAN, a pretrained vision-language pathology foundation model) from each primary tumor's H&E-stained WSI served as model inputs. Four machine learning algorithms (XGBoost, support vector machine, multilayer perceptron, and random forest) were trained to predict seven IHC markers (CD3, CD8, CD56, CD68, CD163, MHC-I, PD-L1) and three surgical pathological features (tumor grading, lymphovascular invasion, and perineural invasion). IHC marker positivity was determined using DeepLIIF-derived percent-positive staining, with non-PD-L1 markers binarized by median split and PD-L1 positivity defined using a 10% threshold. Surgical pathological features were binary except for tumor grade, which included four classes. All models underwent nested stratified five-fold cross-validation with hyperparameter tuning. Performance was assessed using AUC and F1 score for binary tasks (IHC markers, lymphovascular invasion, perineural invasion), and balanced accuracy and macro-F1 score and for tumor grading. **Results:** Between 685 and 699 cases were available for model development depending on the prediction task. Support vector machine (SVM) was the best-performing model for five tasks, followed by XGBoost (XGB) for three tasks and random forest (RF) for two tasks. Performance metrics for the best-performing models are detailed in the table. **Conclusions:** Our findings demonstrate that IHC markers and surgical pathological features can be predicted with reasonable accuracy from image features extracted from a single H&E-stained WSI. Future work will focus on external validation of these models in independent cohorts and exploration of advanced foundational models to further improve prediction performance. Research Sponsor: None.

Task	Best Model	Metrics
CD3	XGB	AUC: 0.78 ± 0.04 F1: 0.72 ± 0.03
CD8	SVM	AUC: 0.73 ± 0.03 F1: 0.67 ± 0.04
CD56	XGB	AUC: 0.66 ± 0.03 F1: 0.67 ± 0.02
CD68	SVM	AUC: 0.75 ± 0.03 F1: 0.70 ± 0.04
CD163	SVM	AUC: 0.71 ± 0.05 F1: 0.67 ± 0.04
MHC1	SVM	AUC: 0.68 ± 0.05 F1: 0.66 ± 0.03
PDL1	SVM	AUC: 0.73 ± 0.06 Macro F1: 0.54 ± 0.04
Grading	RF	Balanced Acc: 0.71 ± 0.04 Macro F1: 0.70 ± 0.03
Lymphovascular Invasion	RF	AUC: 0.82 ± 0.02 Macro F1: 0.70 ± 0.02
Perineural Invasion	XGB	AUC: 0.78 ± 0.03 Macro F1: 0.67 ± 0.03

Development and multicenter validation of a machine learning framework for predicting severe myelosuppression in nasopharyngeal carcinoma: Evidence from large-scale real-world data and prospective clinical trials.

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Background: Severe treatment-related myelosuppression (Tr-MS) in nasopharyngeal carcinoma (NPC) necessitates dose reductions, compromising survival. Current static models rely on baseline "snapshots," failing to capture dynamic bone marrow fluctuations. We developed a dynamic deep learning system using longitudinal real-world data to predict cycle-specific Tr-MS risk. **Methods:** We analyzed 103,919 longitudinal records from 12,065 NPC patients (Nanfang/SYSUCC). A rolling-window strategy incorporated dynamic pre-dose labs, prior-cycle nadirs, and cumulative exposure to predict Grade ≥3 Tr-MS (CTCAE v6.0). Models (Logistic/XGBoost/LightGBM/TabPFN) were trained (6:3:1 split) and validated in two independent external cohorts (n=197) and three prospective trials (NCT03919552, NCT06767488, NCT06017895; n=173). The model was deployed as an EHR-integrated tool for automated real-time risk stratification. **Results:** Dynamic models demonstrated robust discrimination across all validation hierarchies (Table). In internal validation, AUCs ranged from 0.84 to 0.96. Performance remained stable in external cohorts (AUC 0.75-0.87) and prospective trials (AUC 0.79-0.86). SHAP analysis identified cumulative chemotherapy dosage and prior-cycle nadirs as dominant risk factors. Notably, the HIS-integrated tool successfully automated data retrieval, eliminating manual entry burden. **Conclusions:** This first EHR-integrated, cycle-specific dynamic system for Tr-MS in NPC captures longitudinal marrow exhaustion, enabling a shift from reactive rescue to precise, proactive prevention. Research Sponsor: National Natural Science Foundation of China; NO.82303684; Medical Scientific Research Foundation of Guangdong Province; B2021449; China Postdoctoral Science Foundation; NO. 2023M741560; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503000; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503005; National Natural Science Foundation of China; NO.82272729; China Postdoctoral Science Foundation; NO. 2025M782041; Guangdong Basic and Applied Basic Research Foundation; NO. 2022A1515010509; Guangdong Basic and Applied Basic Research Foundation; NO. 2024A1515010280; Clinical Research Startup Program of Southern Medical University by High-level University Construction Funding of Guangdong Provincial Department of Education; LC2016PY015; Clinical Research Startup Program of Southern Medical University by High-level University Construction Funding of Guangdong Provincial Department of Education; LC2019ZD008; Clinical Research Program of Nanfang Hospital, Southern Medical University; 2018CR021; Clinical Research Program of Nanfang Hospital, Southern Medical University; 2020CR025.

Performance of dynamic prediction models across validation cohorts.

Endpoint	Cohort	AUC (95% CI)	Sens	Spec
Anemia	Internal (n=1,231)	0.96 (0.96-0.98)	0.91	0.91
Anemia	External (n=197)	0.87 (0.85-0.89)	0.89	0.86
Anemia	Prospective (n=173)	0.86 (0.82-0.89)	0.88	0.86
PLT	Internal (n=1,231)	0.90 (0.87-0.92)	0.79	0.84
PLT	External (n=197)	0.80 (0.77-0.81)	0.81	0.82
PLT	Prospective (n=173)	0.81 (0.80-0.83)	0.80	0.83
WBC/Neut	Internal (n=1,231)	0.84 (0.82-0.85)	0.71	0.79
WBC/Neut	External (n=197)	0.75 (0.73-0.77)	0.69	0.77
WBC/Neut	Prospective (n=173)	0.79 (0.77-0.81)	0.69	0.78

Abbreviations: AUC, area under the ROC curve; PLT, thrombocytopenia; WBC/Neut, leukopenia/neutropenia; Sens, sensitivity; Spec, specificity.

6024 Poster Session

AI-powered assessment of tertiary lymphoid structures (TLS) from H&E whole-slide images as a prognostic tool in HNSCC.

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Background: Tertiary lymphoid structures (TLS) are recognized prognostic markers in Head and Neck Squamous Cell Carcinoma (HNSCC), yet manual assessment from H&E whole-slide images (WSI) remains subjective and labor-intensive, limiting clinical utility. This highlights the need for a reproducible and objective AI-based approach to TLS assessment using routine H&E slides. **Methods:** We conducted an integrative analysis by combining transcriptomic and histopathologic data. TCGA HNSCC mRNA expression data (n = 566) were analyzed using xCell to compute enrichment scores for B cells, T cells (CD4+ and CD8+), and dendritic cells. A TLS enrichment score was calculated by averaging the z-standardized aggregate scores of these lineages. Patients in the top and bottom quartiles were labeled 'TLS enriched' and 'non-enriched,' respectively; these labels were used to train a foundation model-based AI using Imagene's OI Suite powered by CanvOI with a 3:1 train–test split. Survival analyses were performed at the patient level in 443 evaluable patients with high-quality H&E whole-slide images and definitive AI-predicted TLS enrichment status. Univariable and multivariable Cox regression evaluated AI-predicted TLS enrichment as an independent predictor of overall survival. **Results:** The AI model demonstrated robust performance for TLS assessment, achieving an AUC of 0.77 in the training set (n = 332, 75%) and AUC of 0.85 in the test set (n = 111, 25%). Kaplan–Meier analysis showed that among 443 patients, the AI-predicted TLS-enriched (TLS+) group (n = 146, 33%) demonstrated improved overall survival compared with the TLS-non-enriched (TLS-) group (n = 297, 67%), with median OS 57.9 vs 35.4 months (HR 0.72; 95% CI 0.53–0.98; log-rank P = 0.039). After adjustment for age, sex, and stage, AI-predicted TLS enrichment remained independently associated with improved overall survival (HR, 0.73; 95% CI, 0.54–1.00; P = 0.0499). These findings suggest that the AI model successfully translates molecular TLS signatures into histological predictors, capturing critical tumor microenvironment (TME) features that refine risk stratification beyond standard clinicopathologic factors. **Conclusions:** AI-based H&E WSI analysis helps identify TLS enrichment as a potential predictor of overall survival in HNSCC. This unbiased computational approach provides a reproducible and objective methodology using H&E slides alone, without the need for additional molecular or immunohistochemical assays, thereby supporting immune risk stratification for precision immunotherapy, particularly in resource-limited settings. Research Sponsor: None.

6025 Poster Session

Volrustomig monotherapy for recurrent/metastatic HNSCC: Substudy 2 of the eVOLVE-02 phase 2 study.

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Background: Inhibition of PD-1 is an important part of standard of care treatment options for patients (pts) with recurrent/metastatic (R/M) HNSCC, but prognosis remains poor and there is a need for novel regimens to improve outcomes. Dual PD-(L)1 and CTLA-4 inhibition has shown a trend towards improved survival vs the EXTREME regimen as first-line (1L) therapy in PD-L1-expressing R/M HNSCC. Volrustomig, a monovalent, bispecific, humanized IgG1 monoclonal antibody, inhibits PD-1 and CTLA-4, with increased CTLA-4 blockade on PD-1-positive activated T cells compared to PD-1-negative resting peripheral T cells. We report safety and efficacy from the planned interim analysis of substudy 2 of the phase 2 eVOLVE-02 (NCT06535607) study, investigating volrustomig monotherapy in pts with R/M HNSCC. **Methods:** Eligible pts had histologically or cytologically confirmed R/M HNSCC of the hypopharynx, oral cavity, larynx, or oropharynx (HP, OC, LX, OP), had ECOG performance status (PS) 0/1, and were either treatment-naïve in the 1L setting with confirmed PD-L1 positivity or had disease progression (PD) on/after a 1L platinum-containing regimen. Pts received IV volrustomig until PD (RECIST v1.1)/discontinuation criteria were met. Primary endpoints: safety and confirmed objective response rate (cORR). Secondary endpoints include progression-free survival (PFS) and overall survival. Data cutoff (DCO): August 15, 2025. **Results:** 23 pts with recurrent (n=12) or metastatic (n=11) HNSCC (7 HP, 8 OC, 4 LX, 4 OP) received volrustomig as 1L (n=12) or 2L (n=11) treatment. Median age was 61 years; 16 pts (69.6%) had PS 1; 19 (82.6%) had a PD-L1 combined positive score (CPS) ≥1. Median duration of exposure was 2.1 months (range 0.7–6.4). Treatment-emergent adverse events (TEAEs) were reported in 91.3% of pts (30.4% grade 3/4, 34.8% serious TEAEs); treatment-related AEs per investigator were reported in 82.6% (8.7% grade 3/4, 4.3% serious AEs). No pts discontinued treatment due to AEs. Grade 5 AEs were reported in 13.0% of pts (none considered related to treatment). At DCO, median follow-up was 5.4 months. In pts with CPS ≥1: 5 had partial responses (3 LX, 1 HP, 1 OC); cORR was 26.3%; disease control rate was 52.6%. Median time to response was 2.6 months (IQR 1.4–2.8); responses were ongoing in 60% of responders at DCO. Blood RNA seq showed increased CTLA-4-associated immune proliferation/activation (Ki67/ICOS gene expression) with volrustomig on cycle 1, day 8 vs at baseline. **Conclusions:** Volrustomig monotherapy showed an acceptable safety profile and encouraging activity in pts with R/M HNSCC, warranting further clinical development. Volrustomig is under investigation in combination with chemotherapy as 1L treatment for R/M HNSCC in the phase 2 eVOLVE-02 substudy 3, and as consolidation monotherapy in locally advanced HNSCC after concurrent chemoradiotherapy in the phase 3 eVOLVE-HNSCC (NCT06129864) study. Clinical trial information: NCT06535607. Research Sponsor: AstraZeneca.

6026 Poster Session

An open-label, randomized phase 2 trial of ramucirumab and pembrolizumab versus pembrolizumab as first-line therapy for PD-L1–positive, recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC).

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Background: Vascular endothelial growth factor (VEGF) is commonly overexpressed in head and neck squamous cell carcinoma (HNSCC). Combination therapies inhibiting VEGF and PD-(L)1 have improved efficacy outcomes compared to PD-(L)1 inhibitors alone in pre-clinical models and in other cancer types. The hypothesis of this randomized phase 2 trial in RM-HNSCC was the objective response rate (ORR) with ramucirumab (a VEGF-2 inhibitor) and pembrolizumab would be higher than pembrolizumab alone. **Methods:** Eligible patients had untreated RM-HNSCC with PD-L1 CPS >1, an ECOG performance status of 0 or 1, and adequate organ function. RM disease within 6 months of curative-intent systemic therapy was permitted. Patients were randomized (stratification factors: HPV status [+ or -] and PD-L1 CPS [1-19 or ≥20]) 2:1 to ramucirumab 10mg/kg and pembrolizumab 200mg (Arm 1) or pembrolizumab (Arm 2) given on Day 1 of each 3-week cycle. The primary endpoint was tumor response as assessed with RECIST v1.1 by BICR. A two-stage group sequential design was used with an O'Brien-Fleming stopping rule to accept the null hypothesis at a one-sided alternative hypothesis. We hypothesized an ORR of ≥50% in Arm 1 and ≤19% in Arm 2. The required sample sizes for stage 1 and stage 2 to obtain 80% power at the type I error of 5% were 36 and 72, respectively. At the end of stage 1, if the standardized Z test statistic was ≥0.453, the study could proceed to stage 2. Otherwise, the study was to be stopped, and the null hypothesis accepted. Secondary endpoints include duration of response (DoR), progression free survival (PFS), overall survival (OS) and adverse events. Here, the results of the interim analysis are reported per protocol. **Results:** Thirty-seven patients were enrolled and treated in stage 1. Median age was 65 years (IQR 60-70), 76% were male, and tumor characteristics (including status of HPV and PD-L1 CPS and prior systemic therapy within 6 months) were balanced between the two arms. The ORR was 28% (7 of 25 patients, 95% CI: 12.1-49.4%) in Arm 1 and 33.3% (4 of 12 patients, 95% CI: 9.9-65.1%) in Arm 2 [z= -0.327]. The null hypothesis was accepted, and the trial did not proceed to stage 2. **Conclusions:** Among patients with previously untreated PD-L1 positive, RM-HNSCC, ramucirumab and pembrolizumab did not result in a higher ORR than pembrolizumab. Clinical trial information: NCT05980000. Research Sponsor: Joseph Sanchez Foundation; Eli Lilly.

Phase 1 basket study of telisotuzumab adizutecan (Temab-A, ABBV-400), a c-Met protein–targeting antibody-drug conjugate: Results from patients with head and neck squamous cell carcinoma (HNSCC).

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Background: c-Met protein is expressed in several tumor types, including HNSCC, and is associated with a poor prognosis. Temab-A comprises a c-Met protein-targeting antibody conjugated to a topoisomerase 1 inhibitor. Phase 1 studies evaluating Temab-A monotherapy in solid tumors showed antitumor activity and a manageable safety profile (NCT05029882, NCT06084481). Here, we report on the efficacy and safety of Temab-A in HNSCC. **Methods:** This phase 1, open-label basket study (NCT06084481) enrolled patients (pts) ≥18 years with histologically/cytologically confirmed locally advanced or recurrent/metastatic, unresectable HNSCC, with Eastern Cooperative Oncology Group performance score ≤1. Pts must have had measurable disease per RECIST v1.1 criteria, and disease progression following ≥1 line of systemic therapy in the advanced/metastatic setting. Pts were platinum-resistant or deemed ineligible/unfit for platinum-based therapy per investigator. Prior checkpoint inhibitor treatment was required, unless contraindicated. Pts received 2.4 or 3.0 mg/kg Temab-A every 3 weeks. Primary objectives were safety and efficacy. **Results:** As of Sept. 11, 2025, 43 pts with HNSCC received Temab-A. The median age was 64 years (range 20–85). Median number of prior lines of systemic therapy was 3 (range 1–12), and median follow-up was 12 months. Objective response rate (ORR) was 21%; duration of response and overall survival were immature at data cutoff. Efficacy data are shown in the Table. The most common treatment-related adverse events (TRAEs) of any Grade (G) included fatigue (51%), anemia (49%), and nausea (40%). TRAEs G ≥3 occurred in 47% of pts. G ≥3 TRAE occurring in ≥10% of pts was anemia (33%). The adjudicated interstitial lung disease/pneumonitis rate was 9.3% (G1, n=2; G2, n=1; G3, n=1). TRAEs led to treatment discontinuation in 12%, dose interruption in 30%, and dose reduction in 26% of pts. There was 1 TRAE that led to death. Exploratory biomarker analyses are ongoing. Pharmacokinetics of Temab-A in HNSCC were consistent with other tumor types. The half-life of the conjugate and payload was 4 and 13 days, respectively. **Conclusions:** Temab-A had a manageable safety profile and showed encouraging antitumor activity in advanced HNSCC. Clinical trial information: NCT06084481. Research Sponsor: AbbVie Inc.

Temab-A efficacy.[a]

Outcome	Pts with HNSCC (N=43)
Best overall response, n (%)	
Complete response	0
Partial response	11 (26)
Stable disease	22 (51)
Progressive disease	7 (16)
Not assessed[b]	3 (7)
Objective response rate[c]**, n (%)**	9 (21)
95% CI	10, 36
Clinical benefit rate[c]**, n (%)**	33 (77)
95% CI	61, 88
Median progression-free survival, months (95% CI)	4.3 (3.8, 5.4)

[a]Responses were assessed by investigators per RECIST v1.1 criteria.
[b]Pts without postbaseline scan.
[c]Confirmed.
CI, confidence interval.

Efficacy and safety of pralsetinib in advanced or metastatic *RET*-altered thyroid cancer (TC): Final analysis of the phase 1/2 ARROW study.

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Background: *RET* alterations are targetable oncogenic drivers in multiple solid tumors and TCs. Pralsetinib is an oral, potent, selective RET inhibitor granted accelerated approval by the FDA for adults and children aged ≥12 y with advanced/metastatic *RET* fusion-positive TC who require systemic therapy and are radioactive iodine-refractory, based on ARROW trial (NCT03037385) results. Accelerated approval for medullary TC (MTC) was withdrawn by the sponsor in 2023 due to recruitment challenges in the confirmatory trial. We report final efficacy and safety in ARROW patients with *RET*-altered TC and MTC. **Methods:** Phase 2 ARROW patients were enrolled from 84 sites in 13 countries. Primary end points were overall response rate (ORR; per RECIST v1.1) and safety. Progression-free survival (PFS), overall survival (OS), and safety were assessed in patients with advanced/metastatic TC and MTC who received ≥1 dose of pralsetinib (Efficacy Population [EP]). ORR and duration of response (DOR) were assessed in the Measurable Disease Population (MDP). **Results:** At the May 20, 2024, data lock, 28 patients with *RET*-altered TC and prior systemic treatment and 145 patients with *RET*-altered MTC received pralsetinib 400 mg/d (median treatment duration: 24.7 mo [TC]; and 35.4 mo [MTC]). In the TC and MTC groups, median age was 58 and 57 y; 39% and 64% were male; median (range) prior lines of treatment was 2 (1, 9) and 1 (1, 6). 53.8% of MTC patients had prior systemic treatment. In TC and MTC patients, ORRs (95% CI) were 91.7% (73.0, 99.0) and 68.2% (59.5, 76.0) (Table). Treatment-related adverse events (TRAEs) occurred in 27 (96%) TC and 142 (98%) MTC patients; 68% and 67% had grade ≥3. TRAEs in ≥35% of TC and MTC patients were increased AST (50% and 38%) and ALT (43% and 30%), decreased white blood cell count (39% and 30%), and anemia (39% each). Death due to a TRAE occurred in 1 TC patient (liver injury) and 1 MTC patient (pneumonia). Safety was consistent with prior reports. **Conclusions:** The final analysis of ARROW confirms that pralsetinib yields clinically meaningful and durable responses in patients with *RET*-altered TC and MTC with a manageable safety profile consistent with prior reports. Clinical trial information: NCT03037385. Research Sponsor: Rigel Pharmaceuticals, Inc.

Efficacy summary.

	All MTC	MTC Prior Cabozantinib/ Vandetanib	MTC Treatment-Naïve	TC Prior Systemic Treatment
MDP, n	132	60	62	24
ORR, % (95% CI)	68.2 (59.5, 76.0)	56.7 (43.2, 69.4)	79.0 (66.8, 88.3)	91.7 (73.0, 99.0)
Complete response, n (%)	12 (9.1)	2 (3.3)	7 (11.3)	4 (16.7)
Partial response, n (%)	78 (59.1)	32 (53.3)	42 (67.7)	18 (75.0)
DOR, median, mo (95% CI)	39.6 (29.4, NE)	21.7 (15.1, 34.8)	NR (36.8, NE)	NR (16.0, NE)
DOR follow-up, median, mo (95% CI)	45.7 (41.0, 48.4)	48.9 (36.9, 58.7)	45.1 (40.4, 47.8)	35.4 (26.9, 40.0)
EP, n	145	67	67	28
OS, median, mo (95% CI)	NR (54.6, NE)	42.2 (31.2, NE)	NR (NE, NE)	NR (25.4, NE)
PFS, median, mo (95% CI)	37.2 (27.5, 55.5)	24.9 (19.9, 35.0)	55.3 (36.8, NE)	NR (14.7, NE)

NE, not evaluable; NR, not reached.

6029 Poster Session

Penpulimab (AK105) combined with cetuximab as first-line treatment in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): A phase II clinical trial.

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Background: Combination therapy with PD-1 and EGFR inhibitors has shown promising efficacy in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). This open-label, single-arm, multicenter phase II study aimed to evaluate the efficacy and safety of penpulimab (an anti-PD-1 monoclonal antibody) plus cetuximab as first-line treatment in this patient population (NCT05260671). **Methods:** Eligible patients had R/M HNSCC with no prior immunotherapy or EGFR inhibitor exposure. Participants were either treatment-naïve for systemic therapy or had received platinum-based neoadjuvant/adjuvant or chemoradiotherapy more than 6 months before enrollment. All patients received cetuximab 500 mg/m^2 intravenously as a lead-in dose on day −14, followed by cetuximab 500 mg/m^2 plus penpulimab 200 mg intravenously on days 1 and 15 of each 28-day cycle. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between March 15, 2022, and January 19, 2026, 31 patients were enrolled. The median follow-up was 20.13 months (95% CI: 15.6–NA). Of these, 29 patients were evaluable for efficacy. The ORR was 44.8% (13/29), and the DCR was 82.8% (24/29). Four patients (13.8%) achieved a complete response (CR). The median DOR was 12.1 months (95% CI: 6.13–NA). For the entire cohort, median PFS was 6.0 months (95% CI: 4.3–18.3), with a 12-month PFS rate of 35.6%. Median OS was 29.1 months (95% CI: 18.2–NA), and the 12-month OS rate was 72.4%. Treatment-related adverse events (TRAEs) occurred in 29 patients (93.5%). Grade ≥3 TRAEs were observed in 4 patients (12.9%), including acneiform rash (6.5%), anemia (3.2%), and oral mucositis (3.2%). No fatal TRAEs were reported. **Conclusions:** The combination of penpulimab and cetuximab demonstrated favorable clinical efficacy and a manageable safety profile in patients with R/M HNSCC, supporting its potential as a first-line treatment option. Trial Registration: NCT05260671. Ethics Approval: This study was approved by the Ethics Committee for Drug Clinical Trials of the Eye & ENT Hospital of Fudan University (Approval No. [20211141-1], 2022). All participants provided written informed consent prior to enrollment. Clinical trial information: NCT05260671. Research Sponsor: Bethune Foundation Colorectal Cancer and Head & Neck Cancer Medical Seed Research Grant.

Real-world efficacy and safety of photoimmunotherapy for recurrent nasopharyngeal carcinoma: A nationwide multicenter study in Japan.

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Background: Treatment options for locally recurrent or residual nasopharyngeal carcinoma (NPC) after definitive radiotherapy remain limited. Salvage surgery is often challenging due to anatomical constraints, while re-irradiation and systemic therapies provide modest efficacy with substantial toxicity. Photoimmunotherapy (PIT) is a light-activated anticancer treatment targeting epidermal growth factor receptor (EGFR) that has been approved in Japan since September 2020 for unresectable locally advanced or locally recurrent head and neck cancers. However, real-world clinical data on PIT for recurrent NPC are limited. We conducted the NPC-PIT Study, a nationwide observational study evaluating the real-world efficacy and safety of PIT in patients with recurrent NPC. **Methods:** Patients with recurrent or residual NPC treated with PIT were enrolled from 26 institutions. Patients with at least 3 months of follow-up after initial PIT were evaluated. Clinical characteristics, prior treatments, PIT illumination techniques, treatment response, overall survival, EBV-DNA levels, and treatment-related adverse events were analyzed. **Results:** As of November 2025, 46 patients were enrolled. The four cases with follow-up <2 months were excluded from the evaluation. The median follow-up duration was 18.6 months. Seventeen patients received one PIT cycle, 14 received two, 6 received three, and 5 received four sessions. Among the 42 evaluable patients, 29 (69.0%) achieved a complete response (CR) lasting ≥ 2 months. Twenty patients remain alive with no evidence of disease. Disease-related deaths occurred in 3 patients, and 2 patients died from carotid artery rupture after treatment. Grade ≥ 3 adverse events were observed in 9 patients (21.4%). The 1-year overall survival rate was 89.7%. Among cases where pre-treatment blood samples were collected, 80% (4/5) showed elevated EBV-DNA levels on Cycle 1 Day 7, suggesting that EBV-DNA levels may reflect biological changes associated with PIT treatment. **Conclusions:** In this nationwide real-world cohort, PIT provided meaningful and long-lasting local control with a manageable safety profile for recurrent NPC. These findings support PIT as a clinically meaningful local treatment option for recurrent NPC and warrant further optimization of patient selection and risk mitigation strategies. Research Sponsor: Rakuten Medical Inc.

Bacteroides sp. DH3716P and mediation of immunotherapy response in oligometastatic nasopharyngeal carcinoma via the gut–nasopharyngeal axis.

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Background: Predictors of benefit from gemcitabine/cisplatin (GP) plus PD-1 blockade in oligometastatic nasopharyngeal carcinoma (OM-NPC) remain limited. We investigated whether baseline gut microbiome features are linked to response through a gut–nasopharyngeal axis. **Methods:** We performed metagenomic sequencing on baseline fecal samples from 69 OM-NPC patients receiving GP chemotherapy combined with PD-1 blockade. β-diversity analyses (PCA, PCoA, NMDS) characterized microbiota compositional differences. LEfSe analysis identified differentially abundant taxa between responders (R) and non-responders (NR). Functional enrichment analyses (KEGG, KO, MetaCyc) determined pathway differences. Co-occurrence network analysis assessed microbiota stability. Single-cell RNA sequencing from 7 tumor specimens was analyzed using SAHMI algorithm to determine bacterial-immune cell interactions. Machine learning models built on microbiota, clinical parameters, and serum biomarkers predicted treatment response. **Results:** Microbiota composition differed significantly between R and NR groups. R group showed significant enrichment of *Enterococcus*, *Megasphaera*, and *Streptococcus*. Functional analysis revealed R group possessed enhanced short-chain fatty acid (SCFA) synthesis, glycolysis, and lipid metabolism pathways. Network analysis demonstrated R group had denser ecological networks with superior stability and functional redundancy compared to NR. At species level, *Bacteroides sp. DH3716P* abundance associated with response and prolonged progression-free survival (PFS). This strain highly expressed SusD/RagB family outer membrane proteins and glycoside hydrolase activities, suggesting xylan degradation pathway activation leading to host glycolysis stimulation and SCFA-mediated immune regulation. scRNA-seq analysis revealed *Bacteroides* predominantly infected CD8+ cells in tumor microenvironment. *Bacteroides+* CD8+ T cells demonstrated enhanced IL-15 pathway activity, activated multiple immune response pathways, and increased sensitivity to ICIs. Cell-cell communication analysis indicated *Bacteroides+* CD8+ T cells recruited proliferative T cell subsets through CCL5-CCR5 axis, promoting sustained CD8+ T-mediated anti-tumor immunity. Integrated machine learning models achieved high accuracy in predicting treatment response (AUC: 0.996, 95% CI: 0.989-1.000). **Conclusions:** *Bacteroides sp. DH3716P* sustains immunotherapy response in OM-NPC through enhanced SCFA production and IL-15-CCL5/CCR5 axis-mediated CD8+ T cell activation and proliferative T cell recruitment in the tumor microenvironment. Our microbiota-derived predictive model (AUC 0.996) establishes a clinically feasible strategy for microbiome-assisted personalized immunotherapy in OM-NPC. Research Sponsor: None.

Stereotactic body radiotherapy combined with chemotherapy and PD-1 inhibitor in oligometastatic nasopharyngeal carcinoma (STOMP): A prospective phase II clinical trial.

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Background: To evaluate the efficacy and safety of stereotactic body radiation therapy (SBRT) combined with gemcitibine plus cisplatin (GP) chemotherapy and PD-1 inhibitor in patients with oligometastatic nasopharyngeal carcinoma (NPC), registered on clincialtrials.gov (NCT05524168). **Methods:** Main eligibility criteria included diagnosed as oligometastasis NPC (≤5 lesions), and have ≥1 measurable lesion meeting the RECIST 1.1 criteria. Patients firstly receive SBRT for oligometastatic lesions (6-8Gy/fraction × 3-5 fractions), then receive GP+PD-1 inhibitor for 4-6 cycles followed by PD-1 inhibitor maintenance for 1 year. For patients with primary metastasis, the primary lesion and regional metastatic lymph nodes are given radiotherapy (RT) after completing 4-6 cycles of GP+PD-1 inhibitor. The primary endpoint was the 1-year progression-free survival (PFS) rate. **Results:** Between Nov 2022 to Jun 2025, 41 oligometastasis NPC patients were recruited (Table 1). 23 patients were primary metastases, and 17 had distant metastasis (DM) after receiving chemo-radiotherapy, and 1 had regional relapse and DM. All patients finished SBRT for metastatic lesions followed by GP+PD-1, and 23 patients with primary metastasis also received RT for primary lesions after 6 cycles of GP+PD-1. Then 17 received ≥1 year PD-1 maintenance, 3 discontinued for PD, 1 requested to withdraw, and 20 still under PD-1 maintenance. With the median follow-up time of 17.3 (IQR, 12.9-21.8) months, all these metastatic lesions receiving SBRT controlled well; 7 patients had disease progression, including 1 regional relapse, 4 DM, and 2 loco-regional relapse and DM, and all these lesions were newly developed metastatic lesions except one regional relapse which didn't receive SBRT. The primary endpoint 1-year PFS rate was 92.2% (95%CI, 77.6-97.4%), and the secondary survival endpoints 1-year OS, DMFS and LRRFS rate were 100.0% (95%CI, 100-100%), 92.2% (95%CI, 77.6-97.4%), and 97.5% (95%CI, 83.5-99.6%), respectively. The best objective response rate (ORR) and disease control rate (DCR) before starting PD-1 maintenance were 92.7% and 100%, with 27 got complete response, 11 got partial response and 3 got stable disease. The median value of EBV DNA copies pretreatment was 743 (IQR, 151.5-5331.0) copies/ml, then decreased to 0 (IQR, 0-0) copies/ml post 6 cycles of GP+PD-1. No grade 5 therapeutic toxicity was observed in this trial. **Conclusions:** Patients with oligometastatic NPC who receive SBRT for metastatic lesions combined with GP and PD-1 inhibitor could achieve good therapeutic effects with acceptable toxicities. Clinical trial information: NCT05524168. Research Sponsor: Young Talents Program of Sun Yat-sen University Cancer Center; Sun Yat-sen University Cancer Center 308 Program.

Basic information.

Characteristic		N (%)
Median age (IQR), year		48 (39-54)
Sex	Female	13 (31.7)
	Male	28 (68.3)
ECOG, points	0	4 (9.8)
	1	37 (90.2)
Number of metastases lesions	1-2	33 (80.5)
	3-4	8 (19.5)
Number of metastases organs	1	31 (75.6)
	2	10 (24.4)

6033 Poster Session

Cadonilimab in combination with chemotherapy versus chemotherapy alone in patients with immunotherapy-refractory recurrent or metastatic nasopharyngeal carcinoma: A multicenter, randomized, phase III trial the CONQUEST trial).

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Background: Chemotherapy combined with immune checkpoint inhibitors (ICIs) is the standard first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC); however, resistance is common. In the post-ICI setting, prospective trials have demonstrated limited efficacy, with objective response rates (ORRs) ranging from 4.2% to 34.3%. A prior phase II study of nab-paclitaxel, cisplatin, and capecitabine (TPC) plus cadonilimab demonstrated a promising ORR of 68% in ICI-refractory patients, providing the rationale for this phase III trial comparing TPC plus cadonilimab versus TPC alone in this population. **Methods:** In this randomized, multicenter, phase III trial, patients were assigned (1:1) to receive TPC plus cadonilimab or TPC alone. TPC consisted of nab-paclitaxel 200 mg/m² d1, cisplatin 60 mg/m² d1, and capecitabine 1000 mg/m² BID d1–14 (Q3W). In the experimental arm, cadonilimab (10 mg/kg d1) was added. Maintenance with capecitabine plus cadonilimab (experimental) or capecitabine alone (control) continued until disease progression, unacceptable toxicity, or 2 years. The primary endpoint was progression-free survival (PFS), defined as the time from randomization to disease progression or death from any cause. Secondary endpoints included overall survival (OS), ORR (defined as the best overall response), and safety. **Results:** A total of 84 patients were randomized (n=42/arm) at three hospitals. Baseline prior therapies were balanced (P=0.533): 35 (83.3%) patients in the experimental arm and 37 (88.1%) in the control arm had received 1-3 prior lines of therapy, while 7 (16.7%) and 5 (11.9%) had received >3 prior lines, respectively. After a median follow-up of 10.2 months, PFS was significantly prolonged in the experimental arm versus the control arm (8.9 months [95% CI 6.3-11.4] vs. 5.1 months [95% CI 3.2-6.9]; HR 0.47, 95% CI 0.28-0.80; P=0.004). The ORR was 61.9% in the experimental arm versus 52.4% in the control arm, showing no statistically significant difference (P=0.378). Median OS was not reached. All patients experienced adverse events (AEs). Grade 3-4 AEs occurred in 19 (45.2%) patients in the experimental arm versus 23 (54.8%) in the control arm (P=0.383). The most common Grade 3-4 AEs were anemia (31.0% vs. 21.4%), neutropenia (21.4% vs. 21.4%), and leukopenia (16.7% vs. 14.3%). Immune-related AEs (irAEs) were more frequent in the experimental arm (34 [82.9%] vs. 25 [58.1%]; P=0.013); however, no Grade 3-4 irAEs were observed in either arm. **Conclusions:** TPC chemotherapy combined with cadonilimab demonstrated a statistically significant improvement in PFS compared with TPC alone in heavily pretreated, ICI-refractory R/M NPC patients, with a manageable safety profile (NCT06664983). Clinical trial information: NCT06664983. Research Sponsor: None.

Reirradiation with NBTXR3/SBRT in combination with nivolumab or pembrolizumab for the treatment of patients with recurrent or metastatic head & neck squamous cell carcinoma (HNSCC) in the phase I trial study 1100.

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Background: HNSCC reirradiation with stereotactic body radiation therapy (SBRT) has emerged as a potential option for the management of locoregionally recurrent (R) or metastatic (M) HNSCC, however treatment toxicity remains a limiting factor. NBTXR3 is a novel intratumoral radioenhancer composed of functionalized hafnium oxide nanoparticles which locally amplifies radiation therapy (RT). In pre-clinical models, NBTXR3/RT has demonstrated an ability to generate cell killing effects at low RT doses as well as trigger local and systemic immune responses. Here we report outcomes in pts with R or R+M HNSCC who were treated with reirradiation with NBTXR3/SBRT followed by immune checkpoint inhibitors (ICIs). **Methods:** A phase I dose escalation/expansion trial [NCT03589339] evaluating NBTXR3/SBRT followed by ICI (nivolumab or pembrolizumab) included a subgroup with R or R+M HNSCC that were either naïve or resistant to prior ICI. Pts received an intra-tumoral NBTXR3 injection at dose of 22% or 33% of gross tumor volume (GTV), SBRT (35 Gy in 5 fractions), and ICI. Primary objective was safety and establishing RP2D of NBTXR3/SBRT/anti-PD-1 combination. The expansion part tested the RP2D (33% of GTV). Secondary objectives include efficacy. **Results:** From June 2019 to February 2025, 30 pts were treated: 16 ICI naïve, 14 ICI resistant with median age of 67 years, 90% ECOG 0-1, and 55% HPV negative. 20 pts (66.7%) had R disease, 10 (33.3%) pts had R+M disease. All injected lesions were in a previously irradiated H&N field. Median time from end of prior radiotherapy to NBTXR3 injection was 21.3 [5-229] months. Median GTV was 16.1 [3-110] mL. 4 pts (13.3%) experienced G≥3 injection-related AEs, 8 (26.7%) G≥3 RT-related AEs, and 6 (20%) G≥3 NBTXR3-related AEs. Carotid injury was not observed. Most frequent injection or NBTXR3-related AEs were injection site pain (10%), oropharyngeal pain (6.7%), tumor pain (6.7%), dysphagia (6.7%), and soft tissue necrosis (6.7%). 27 pts (90%) were evaluable for efficacy. For all disease (i.e. injected and non-injected), the objective response rate (ORR) was 48.1% (13/27) and disease control rate (DCR) was 77.8% (21/27). In R pts, ORR was 64.7% (11/17) and DCR was 88.2% (15/17). In R+M pts, ORR was 20% (2/10) and DCR was 60% (6/10). Survival outcomes in reirradiation pts with R and R+M HNSCC will be presented. **Conclusions:** Reirradiation with NBTXR3 with SBRT and anti-PD1 was feasible in R or R+M HNSCC with an adverse effect profile expected for this clinical setting. Encouraging preliminary efficacy outcomes have been observed, thus warranting further investigation. Clinical trial information: NCT03589339.
Research Sponsor: None.

6035 Poster Session

Trends in end-of-life immunotherapy use in metastatic head and neck squamous cell carcinoma: A National Cancer Database analysis.

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Background: Aggressive systemic cancer treatment near the end of life (EOL) rarely benefits patients and is an established marker of low-quality healthcare. While EOL chemotherapy use has substantially declined over time, EOL immunotherapy administration has increased in the era of immune checkpoint inhibitors (ICIs). For metastatic head and neck squamous cell carcinoma (mHNSCC), a high-burden disease with rapidly expanding approvals, ICIs have emerged as a compelling mainstay of treatment. However, these expansions may have increased nonbeneficial ICI use among end-stage patients, contributing to quality impacts like decreased hospice enrollment and high financial burden. Given recent evolutions in head and neck cancer care, we conducted a retrospective cohort study to examine temporal trends and factors associated with EOL immunotherapy initiation in mHNSCC. **Methods:** Patients diagnosed with mHNSCC who received first-course immunotherapy between 2016-2022 were identified in the National Cancer Database. EOL-initiated immunotherapy was defined as initiation within 1 month of death. Two-sample t- or χ^2 testing was used for comparison of means and proportions, respectively, between EOL and non-EOL immunotherapy initiation groups. Multivariable logistic regression with *a priori* covariate selection was used to identify factors associated with EOL immunotherapy initiation. Sensitivity analyses were conducted with 2 and 3-month EOL thresholds. **Results:** Among 8806 included patients, 29.3% received immunotherapy, rising from 17.7% in 2016 to 40.9% in 2022 following first-line FDA ICI approvals. By 2021, EOL-initiated immunotherapy occurred among 6.7%, 13.0%, and 16.4% of treated patients at 1-, 2-, and 3-month EOL thresholds, with possible upward trends after 2019 (2021 vs 2019, 1-month EOL, $p=0.114$; 2-month EOL, $p<0.05$, χ^2 test). In regression analysis, predictors of one-month EOL initiation included female sex (odds ratio [OR]=2.09, 95% CI=1.33–3.27), disadvantaged insurance status (Medicaid/other governmental OR=2.27, 95% CI=1.18–4.35; uninsured/unknown OR=5.09, 95% CI=2.33–11.12), high metastatic burden ($\geq$3 sites OR=8.77, 95% CI=2.94–26.12), and surgical treatment (OR=2.12, 95% CI=1.19–3.79). Protective factors included academic setting (OR=0.60, 95% CI=0.40–0.90), oropharyngeal primary site (OR=0.54, 95% CI=0.32–0.92), and concurrent radiotherapy (OR=0.53, 95% CI=0.35–0.79) or chemotherapy (OR=0.48, 95% CI=0.31–0.73). **Conclusions:** EOL-initiated immunotherapy occurs among a small but notable proportion of mHNSCC patients and is associated with various indicators of clinical and demographic vulnerability. As ICI use expands, our findings underscore the importance of optimizing patient selection, EOL treatment guidelines, and system-level practices to ensure judicious use of immunotherapy in terminal settings. Research Sponsor: U.S. National Institutes of Health; 5R25CA281789-03.

Penpulimab plus oral anlotinib and capecitabine as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC): A multicenter, single-arm, phase 2 clinical trial.

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Background: Patients (pts) with NPC progressing after intensive radical treatment often have limited treatment tolerance and poor prognosis. Incorporation of oral agents into triple therapy combining chemotherapy, immunotherapy, and targeted therapy may improve efficacy while reducing toxicity. **Methods:** This multicenter, single-arm, phase 2 trial evaluated first-line penpulimab (a PD-1 blockade) plus oral anlotinib (a tyrosine kinase inhibitor) and capecitabine in pts with R/M NPC previously treated with radical chemo/radiotherapy for non-metastatic disease. Pts from 4 academic hospitals in China received 4–6 cycles of penpulimab 200 mg IV d1, anlotinib 10 mg PO qd d1–14, and capecitabine 650 mg/m^2 PO bid d1–21 q3w, followed by penpulimab-capecitabine maintenance until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), safety, and quality-of-life (QoL; assessed by the EORTC and FACT surveys). This trial was to be considered positive if the median PFS significantly reached an expected value of 11 mo than a historical threshold of 7 mo, with a 1-sided α of 2.5% and 80% power. This trial was registered with ClinicalTrials.gov (NCT05807880) and is now ongoing. **Results:** Between Sept. 2023 and July 2025, 59 eligible pts (median [IQR] age, 50 [40–58] yrs; 33.9% women) were included, of which 23 (38.9%) and 41 (69.5%) pts had recurrent and metastatic diseases, respectively. Overall, 74.6% (44/59) of pts completed at least the required 4 cycles of the triple therapy. After a median follow-up of 10 mo (data cutoff: Nov. 14, 2025), the median PFS was 13.5 mo (95% CI, 13.1–not reached [NR]) and the 12-mo PFS was 64.4% (95% CI, 50.3–78.5%). The median OS was NR, and the 12-mo OS was 87.8% (95% CI, 78.4–97.2%). The ORR was 71.4% in 56 pts with available assessments, including complete and partial responses in 5 (8.9%) and 35 (62.5%) pts, respectively. Pts with baseline EBV DNA $\leq$ 4000 copies/mL had higher median PFS (NR *vs* 6.0 mo) and 12-mo PFS rate (71.3% *vs*41.7%) than those with EBV DNA $>$ 4000 copies/mL (p = 0.024). Twelve (20.3%) pts had grade 3–4 acute treatment-related adverse events (trAEs), with the most frequent trAE of palmar–plantar erythrodysesthesia (5.1%). Fifty-seven (96.6%) pts had all-grade trAEs, mainly including palmar–plantar erythrodysesthesia (39.0%), hypothyroidism (37.3%), stomatitis (33.9%), sore throat (32.2%), anemia (27.1%), and leukopenia (23.7%). Two treatment-related deaths were observed. Twenty-nine of 37 QoL domains (78.4%) remained stable or showed clinically meaningful improvement. **Conclusions:** First-line therapy of penpulimab plus oral anlotinib and capecitabine provides promising antitumor efficacy, low toxicity, and favorable QoL for pts with R/M NPC. Clinical trial information: NCT05807880. Research Sponsor: Chia Tai Tian Qing Pharmaceutical Group Co., Ltd.

Safety and efficacy of dostarlimab monotherapy as first-line treatment in programmed cell death-ligand 1–positive recurrent/metastatic head and neck squamous cell carcinoma: Results from a phase 2 trial.

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Background: The use of immune checkpoint inhibitors (ICIs) in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) has improved patient outcomes and showed benefit in the perioperative setting. The GALAXIES H&N-202 study (NCT06062420) evaluated novel immunotherapy combinations versus dostarlimab monotherapy in patients with R/M programmed cell death-ligand 1 (PD-L1)-positive HNSCC. Here, we present updated safety and efficacy results for patients who received dostarlimab monotherapy. **Methods:** GALAXIES H&N-202 is a multicenter, open-label, randomized, Phase 2 study assessing immunotherapy as monotherapy or in combination as first-line treatment (1L) in adults with R/M PD-L1-positive (combined positive score [CPS] ≥1) HNSCC. The dostarlimab monotherapy arm comprised patients randomized to receive dostarlimab 500 mg every 3 weeks until progression, unacceptable toxicity, death, or withdrawal. Investigator-confirmed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was the primary endpoint, and safety was a secondary endpoint. Outcomes were analyzed descriptively. **Results:** At data cutoff (July 14, 2025), 66 patients were enrolled in the dostarlimab monotherapy arm. All patients had ≥4.5 months of follow-up from first dose. The mean patient age was 64.7 years, 80% were male, and 53% had lung metastases. After a median treatment duration of 19.0 weeks (range: 3.0–69.0), ORR was 27.3% (95% confidence interval [CI]: 17.0, 39.6) overall and 42.4% (25.5, 60.8) for those with a CPS ≥20 (Table), and median PFS (95% CI) was 4.2 (2.7, 5.8) and 7.8 (3.0, NE) months, respectively. Treatment-emergent adverse events (TEAEs) occurred in 59 (91%) patients and treatment-related adverse events (TRAEs) in 33 (51%) patients. Three (5%) patients discontinued treatment due to TEAEs. Grade ≥3 TEAEs were reported in 21 (32%) patients and Grade ≥3 TRAEs in 3 (5%) patients. Seventeen (26%) patients experienced serious adverse events (SAEs) and 3 (5%) experienced treatment-related SAEs. Fatal SAEs were reported in 7 (11%) patients; none were treatment related. **Conclusions:** Dostarlimab monotherapy showed encouraging antitumor activity, particularly in patients with a CPS ≥20, and a consistent safety profile in 1L R/M HNSCC that is comparable to other ICIs in HNSCC. Clinical trial information: NCT06062420. Research Sponsor: This study (NCT06062420; GSK Study 219885) was funded by GSK.

Efficacy outcomes.

Confirmed ORR per RECIST v1.1, n (%) [95% CI]	n=66
CPS ≥20 (n=33)	14 (42.4) [25.5, 60.8]
CPS 1–19 (n=33)	4 (12.1) [3.4, 28.2]
Overall	18 (27.3) [17.0, 39.6]
Best response, n (%)	**n=66**
Complete response	1 (1.5)
Partial response	17 (25.8)
Stable disease	23 (34.8)
Progressive disease	17 (25.8)
Not evaluable	8 (12.1)

CI, confidence interval; CPS, combined positive score; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

6038 Poster Session

Real-world treatment patterns and overall survival in recurrent/metastatic head and neck squamous cell carcinoma following treatment with immune checkpoint inhibitor and platinum-based chemotherapy.

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Background: Treatments for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) include immune checkpoint inhibitors (ICI) and/or platinum-based chemotherapy, yet most patients (pts) will experience disease progression, with poor survival and limited therapeutic options in later-line settings. Real-world evidence in R/M HNSCC after ICI and platinum-based chemotherapy is limited. We characterize real-world treatments and survival outcomes in pts with heavily pretreated R/M HNSCC. **Methods:** This retrospective analysis used electronic medical records from the US Flatiron Health Advanced EDM (71% community centers, 22% academic centers, 7% both). Study period was 1 Jan 2015 to 31 Mar 2025 (date of data cutoff). All identified pts had R/M HNSCC and had received prior PD-1 inhibitor and platinum-based chemotherapy. Demographics, baseline disease characteristics, and treatment patterns were analyzed descriptively. Kaplan-Meier method was used to evaluate real-world overall survival (rwOS), defined as time from index date (first date of treatment after PD-1 inhibitor and platinum-based chemotherapy) until date of recorded death. Subgroups by HPV-unrelated (oral cavity, larynx, hypopharynx, HPV-negative oropharyngeal) and HPV-related (HPV-positive oropharyngeal) HNSCC were evaluated. **Results:** In total, 2105 pts with R/M HNSCC were identified from the Flatiron database as previously treated with PD-1 inhibitor and platinum-based chemotherapy. There were 1271 pts who did not receive any subsequent treatment, while 834 pts received an index line of therapy after PD-1 inhibitor and platinum-based chemotherapy and were eligible for analysis. Among those eligible, primary tumor site distribution was 55% oropharynx (81% HPV-positive / 19% HPV-negative), 21% larynx, 18% oral cavity, and 6% hypopharynx. Most pts had an ECOG score of 0 or 1 (77%). Most common regimens in the index line of therapy included chemotherapy, anti-EGFR, and/or PD-(L)1 agents. Among the 834 pts identified, rwOS was 7.8 months (95% CI, 7.0–8.4). There were 373 and 461 pts identified with HPV-related and HPV-unrelated disease, respectively. Median rwOS was significantly longer for the HPV-related vs HPV-unrelated group (9.3 months [95% CI, 8.2–10.9] vs 6.8 months [95% CI, 6.1–7.3]; HR, 0.85 [95% CI, 0.73–0.99]; P=0.036). The 6-month rwOS rate was 65% vs 55%, respectively. Of note, a substantial portion of pts died prior to receiving another line of therapy (39% for HPV-related and 49% for HPV-unrelated). **Conclusions:** Median rwOS is poor in R/M HNSCC following treatment with PD-1 inhibitor and platinum-based chemotherapy, and particularly poor for HPV-unrelated disease, with nearly half dying by 6 months. These results highlight the pressing need for innovative treatments to improve survival in R/M HNSCC. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

6039 Poster Session

Defining the role of locoregional radiotherapy for de novo metastatic nasopharyngeal carcinoma in the immunotherapy era: A systematic review and meta-analysis.

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Background: In the pre-immunotherapy era, a phase 3 randomized controlled trial (NCT02111460) confirmed locoregional radiotherapy (LRRT) combined with palliative chemotherapy improved overall survival (OS) and progression-free survival (PFS) in de novo metastatic nasopharyngeal carcinoma (dmNPC). Consequently, this strategy has been adopted by major clinical practice guidelines, including NCCN, CSCO, and ESMO. However, with immunotherapy now integrated into first-line treatment, the contemporary role of LRRT and the definition of patients most likely to benefit from it are uncertain and necessitate further exploration. **Methods:** This meta-analysis was conducted in accordance with PRISMA guidelines. A comprehensive search was conducted in electronic databases including PubMed, Cochrane Library, and Web of Science from their inception to December 31, 2025, to identify eligible studies comparing immunochemotherapy with or without LRRT in dmNPC. The primary outcomes were PFS and OS. Meta-analysis was performed using OnlineMeta V1.1. **Results:** A total of six clinical trials were rated as high-quality and included in this meta-analysis. Our meta-analysis results showed that the palliative immunochemotherapy (PICT) plus LRRT group achieved significantly longer PFS (HRs: 0.560, 95%CIs: 0.431-0.727) and OS (HRs: 0.502, 95%CIs: 0.289-0.869) than the PICT alone group. Additionally, single-arm meta-analysis results demonstrated that the 1-year, 2-year, and 3-year PFS rates (with 95% CIs) in the PICT plus LRRT group were 80.5% (76.3%-84.2%), 56.3% (53.7%-58.9%), and 37.6% (28.6%-47.5%), compared with 62.7% (56.2%-68.8%), 26.3% (16.8%-38.7%), and 7.6% (2.4%-21.6%) in the PICT group. Regarding OS, the 1-year, 2-year, and 3-year rates (with 95% CIs) were 97.1% (95.3%-98.2%), 84.2% (72.3%-91.6%), and 76.0% (47.4%-91.7%) in the PICT plus LRRT group, whereas those in the PICT group were 76.9% (33.5%-95.7%), 55.8% (13.7%-90.9%), and 39.7% (1.7%-88.4%). Sensitivity analysis confirmed the stability of the results, and no significant publication bias was detected. Subgroup analyses indicated that dmNPC patients achieved greater PFS benefit from LRRT when they had partial or complete response to PICT (HRs: 0.509, 95%CIs: 0.368-0.704), undetectable post-treatment EBV DNA (HRs: 0.541, 95%CIs: 0.378-0.774), or oligometastatic disease (HRs: 0.349, 95%CIs: 0.193-0.634). **Conclusions:** In the immunotherapy era, LRRT combined with PICT confers significant and durable survival benefits for dmNPC patients, with pronounced efficacy among those achieving PR/CR to PICT, harboring undetectable post-treatment EBV DNA, or presenting with oligometastatic disease. Research Sponsor: None.

Depth and durability of response with TGF-β trapping in recurrent or metastatic (R/M) HPV-negative head and neck squamous cell carcinoma (HNSCC): Long-term results from two expansion cohorts of a phase 1/1b study of ficerafusp alfa plus pembrolizumab.

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Background: In HPV-negative HNSCC, TGF-β overexpression creates fibrotic barriers within the tumor microenvironment that limit tumor penetration and drive resistance to anti-EGFR and anti-PD1 therapy. Ficerafusp alfa is the first and only bifunctional EGFR-directed antibody designed to trap TGF-β, enabling tumor penetration of immune cells and driving deep and durable responses for potential overall survival (OS) benefit. **Methods:** Two dose-expansion cohorts of an ongoing phase 1/1b study (NCT04429542) enrolled adults with 1L R/M HNSCC with PD-L1 CPS ≥1. Patients received ficerafusp alfa 750 or 1500 mg IV on D1, 8, and 15 plus pembrolizumab (pembro) 200 mg IV Q3W. Assessments included objective response rate (ORR), duration of response (DOR), and progression free survival (PFS) per RECIST v1.1; OS; safety; and pharmacodynamic (PD) and pharmacokinetic analyses. This is the first report of long-term efficacy follow-up across two cohorts of ficerafusp alfa. **Results:** As of December 16, 2025, 61 HPV-neg pts were treated in two cohorts (750 mg, n=31; 1500 mg, n=30); 58 pts were efficacy evaluable. Exposure increased in an approximately dose-proportional manner with manageable safety observed in both cohorts. A higher proportion of pts had exposure levels associated with meaningful efficacy with 1500 mg vs 750 mg dosing. Improved outcomes were observed in the 1500 mg vs 750 mg cohort, including deep responses (≥80% tumor shrinkage in 80% vs 47% of responders) and mPFS (9.9 mo vs 6.9 mo), along with increased markers of TGF-β inhibition and tumor penetration in paired biopsies, and increased pro-inflammatory cytokines in blood (Table). **Conclusions:** Deeper and more durable tumor responses were observed with ficerafusp alfa 1500 mg vs 750 mg. Exposure and PD markers of TGF-β inhibition demonstrated dose-related trends consistent with mechanism of action. Together, these data suggest that TGF-β inhibition with ficerafusp alfa facilitates T-cell infiltration, enhancing immunologic activity, contributing to deep and durable responses for patients with HPV-neg HNSCC. These findings support the rationale for FORTIFI-HN01, an ongoing phase 2/3 trial evaluating this combination in 1L PD-L1 pos, HPV-neg, R/M HNSCC (NCT06788990). 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).

Endpoint (efficacy set)	Ficerafusp alfa 750 mg + pembro N=30	Ficerafusp alfa 1500 mg + pembro N=28
Confirmed ORR/complete response rate, n (%)	17 (57)/4 (13)	15 (54)/6 (21)
Responders with ≥80% shrinkage, n (%)	8/17 (47)	12/15 (80)
Median DOR, mo	NR	21.7
Proportion of responses >12 mo, n (%)	9/17 (53)	9/15 (60)
Median PFS, mo	6.9	9.9
Median OS, mo	NR	21.3
Tumor TGF-β inhibition: mean change from baseline in pSMAD2, %	−16.4 (n=5)	−33.2 (n=7)
Immune activation: mean change from baseline in blood TNF-α/IFN-γ, %	25.6/163, (n=24)	64.9/346 (n=20)

6041 Poster Session

First-in-class Trop2-targeted PET imaging with ^{68}Ga-MY6349 for diagnostic accuracy and altered management in recurrent/metastatic thyroid cancer compared to standard ^{18}F-FDG PET/CT.

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Background: Accurate, non-invasive detection of recurrent and metastatic thyroid cancer remains an unmet clinical need due to the limitations of conventional imaging and biopsy. Trop2 is a tumor-associated antigen that frequently overexpressed in thyroid cancer, it represents a promising molecular target for imaging. This study aimed to evaluate the diagnostic accuracy of Trop2-targeted PET/CT using the novel nanobody tracer, ^{68}Ga-MY6349, the results were compared with those of ^{18}F-FDG PET/CT. **Methods:** In this prospective, single-center, single-arm trial conducted at the First Affiliated Hospital of Xiamen University (Xiamen, China), adults with suspected or confirmed recurrent or metastatic thyroid cancer were enrolled between January and December 2024. Each participant underwent both ^{68}Ga-MY6349 and ^{18}F-FDG PET/CT scans within one week. Three independent, blinded readers assessed the PET/CT images. The primary endpoints were patient-based sensitivity and specificity, using histopathology or clinical follow-up as the reference standard. The full analysis set included patients with evaluable PET/CT imaging and a confirmed final diagnosis. The trial is registered with ClinicalTrials.gov, NCT06465017 and is closed to enrollment. **Results:** Of 161 screened participants, 143 were finally included in the primary analysis. Papillary thyroid cancer (PTC) was the most common pathological subtype (115/143, 80%). The median clinical follow-up duration was 19 months (IQR: 14-22 months). In the overall cohort, the sensitivity and specificity of ^{68}Ga-MY6349 PET/CT was 90% (95% CI 83-94) and 91% (95% CI 76-97), respectively. Among participants with PTC, its sensitivity and specificity were 94% (95% CI, 87–98) and 96% (95% CI, 79–100), respectively. Additionally, ^{68}Ga-MY6349 PET/CT demonstrated superior diagnostic accuracy in participants with thyroglobulin-elevated negative iodine scintigraphy (TENIS), with sensitivity of 92% (95% CI 82-97) and accuracy of 93% (95% CI 84-97), respectively. Further details are presenting in the Table. No grade 2 or higher adverse event was observed during study. **Conclusions:** ^{68}Ga-MY6349 PET/CT is a safe and highly accurate imaging modality for detecting recurrent and metastatic thyroid cancer, particularly in PTC and patients with TENIS. These findings suggest it could significantly influence clinical practice and may become a standard imaging option in this setting. Further multicenter studies are warranted to validate its diagnostic accuracy and assess its long-term impact on patient management and outcomes. Clinical trial information: NCT06465017. Research Sponsor: None.

First-line HLX07 vs placebo combined with serplulimab and chemotherapy for nasopharyngeal carcinoma: A randomized, double-blind, multicenter phase 2 study.

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Background: Programmed cell death protein 1 (PD-1) blockade with chemotherapy confers significant survival benefit compared to chemotherapy alone and is the standard first-line therapy for recurrent or metastatic nasopharyngeal carcinoma (R/M-NPC). Epidermal growth factor receptor (EGFR) is overexpressed in approximately 85% of all NPCs and associated with poor outcomes, suggesting a potential target for improved efficacies. This study explores the efficacy of HLX07 (a novel humanized anti-EGFR antibody) versus placebo, in combination with serplulimab (PD-1 inhibitor) and chemotherapy as first-line treatment for R/M-NPC. **Methods:** This is a randomized, double-blind, multicenter phase 2 study. Patients with histopathologically confirmed, unresectable, R/M NPC that is not amenable to local or radical treatment and had no prior systemic therapy were randomized 2:1 to receive either HLX07 at 1000 mg (HLX07 group) or placebo (placebo group), along with serplulimab (300 mg) and chemotherapy (gemcitabine and cisplatin) Q3W intravenously. Primary endpoint was blinded independent central review (BICR)-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included other efficacy endpoints, safety, pharmacokinetics and biomarker explorations. **Results:** As of December 24, 2025, 75 patients were randomized to the HLX07 group (n=50) or placebo group (n=25). Efficacy results are reported for the per-protocol set (n = 72), which excluded two patients who violated the enrolment criteria and one with no post-baseline tumor assessment in the HLX07 group. With 26.0 months of follow-up, BICR-assessed confirmed ORR was 74.5% vs. 72.0% for the two groups. Overall, a trend of an improved median progression-free survival (PFS) was observed with HLX07 (17.3 months vs. 9.4 months, stratified hazard ratio [HR] 0.79, 95% CI 0.40–1.56). Median overall survival was not reached vs. 27.9 months (stratified HR 0.40, 95% CI 0.16–0.99) for the respective groups. Subgroup analysis revealed a trend of improved PFS in the HLX07 group compared to the placebo group for patients with PD-L1 CPS <10 (median PFS, 8.1 vs. 6.8 months, HR 0.54, 95% CI 0.19–1.56) as well as for patients with EGFR H-score ≥ 200 (median PFS, not reached vs. 7.8 months, HR 0.30, 95% CI 0.08–1.15). 74 (98.7%) patients experienced treatment-emergent adverse events (TEAEs), with grade ≥ 3 TEAEs reported in 60 (80.0%) patients. TEAEs led to treatment discontinuation occurred in 14 (18.7%) patients. Deaths due to TEAEs were reported in 5 (6.7%) patients, with 1 (1.3%) in the HLX07 group that was treatment related. **Conclusions:** The addition of HLX07 to serplulimab and chemotherapy showed encouraging efficacy along with a manageable safety profile in patients with treatment-naïve R/M-NPC. Further investigation of this treatment regimen is warranted. Clinical trial information: NCT05513573. Research Sponsor: Shanghai Henlius Biotech, Inc.

6043 Poster Session

Expansion of circulating NKG7⁺ cytotoxic CD4⁺ T cells as a predictor of response to PD-1 blockade in recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC): A prospective phase II study with translational analysis.

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Background: Nivolumab has demonstrated meaningful survival benefit in patients with refractory R/M HNSCC. Nevertheless, reliable predictive biomarkers remain scarce—particularly those capable of identifying long-term survivors—underscoring the need for translational studies to uncover immune correlates of durable response. In this prospective phase II study (NCT04603248), we sought to define dynamic circulating immune cell–based biomarkers predicting durable clinical outcomes with nivolumab in patients with R/M HNSCC. **Methods:** Patients with R/M HNSCC who had prior failure of or intolerance to platinum-based chemotherapy were treated with nivolumab (3 mg/kg) intravenously every 2 weeks until disease progression or unacceptable toxicity occurred. Clinical outcomes were correlated with single-cell transcriptomic profiles of circulating immune cells at baseline (cycle 1 day 1) and on-treatment (cycle 2 day 1). To validate the transcriptomic findings at the protein level, mass cytometry by time-of-flight (CyTOF) analysis was additionally performed. **Results:** A total of 48 patients were enrolled. The objective response rate was 22.9%, and the disease control rate was 62.5%. The median progression-free survival (PFS) and overall survival (OS) were 4.4 and 13.3 months, respectively. Single-cell transcriptomic analysis revealed a significant expansion of circulating NKG7⁺ cytotoxic CD4⁺ T cells in long-term responders (PFS $>$ 48 months; n=6) compared with early progressors (PFS $<$ 2 months; n=6) at cycle 2 day 1. T cell receptor analysis further demonstrated that nivolumab induced marked clonal expansion of these NKG7⁺ cytotoxic CD4⁺ T cells, particularly in long-term responders. Their sustained presence was confirmed in blood samples collected one year after treatment initiation in long-term responders. CyTOF analysis (n=37) revealed that expansion of NKG7⁺ cytotoxic CD4⁺ T cells at cycle 2 day 1 was significantly associated with both PFS and OS, supporting their potential role as predictive biomarkers of response to PD-1 blockade. **Conclusions:** Expansion and clonal amplification of circulating NKG7⁺ cytotoxic CD4⁺ T cells represent a key immune correlate of favorable outcomes with nivolumab in refractory R/M HNSCC. These findings highlight their potential as predictive biomarkers of durable response to PD-1 blockade in R/M HNSCC and implicate this immune subset as a promising target for future immunotherapeutic strategies. Clinical trial information: NCT04603248. Research Sponsor: None.

Cytokine dynamics in a phase II trial of metronomic carboplatin/paclitaxel combined with cemiplimab in recurrent/metastatic head and neck squamous cell carcinoma.

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Background: Standard-dose chemotherapy combined with immunotherapy improves response rates in recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC), but its use is often constrained by significant toxicity. Metronomic chemotherapy (MCT) offers a potentially better-tolerated alternative while preserving immune-modulatory properties. We evaluated cytokine profiles and their longitudinal dynamics to investigate the relationship between immune-mediated mechanisms and clinical outcomes in patients treated with MCT plus cemiplimab. **Methods:** Single- arm phase II trial (NCT04862650). R/M HNSCC pts received first-line cemiplimab 350 mg IV Q3W ($\leq$35 cycles) plus weekly carboplatin (AUC1) and paclitaxel (25 mg/m^2) for 24 weeks. Primary endpoint was overall response rate (ORR) per RECIST v1.1 at week 12. Forty immune-modulatory cytokines were assessed at baseline, week 3, and week 6 using the Luminex xMAP platform. **Results:** From Nov 2021 to Dec 2024, 40 evaluable patients were enrolled (median age was 66 years, 82.5% were male; 35% were HPV-positive). Median follow-up was 10 months (range 1–28). ORR was 42.5% (15% CR) and Median OS was 14.8 months (95% CI, 10.3–23.9). Responders had significantly higher IFN-β at all timepoints (P=.008–.04). Elevated IL-4, IL-5, and IL-10 at baseline were associated with improved ORR. Overall, LIGHT, FasL and TGF-α decreased while PD-L1 increased over time (all q<0.001). Compared to baseline, on week 6, responders showed decreased VEGF-A, TSLP, FasL, and IL-4 (P < .03), while non-responders exhibited increased IFN-γ, PD-L1, and IL-6Rα (P < .04). Changes in IFN-γ (HR 3.23, P=.006) and IL-4Rα (HR 3.06, P=.008) from baseline to week 3 were associated with worse overall survival. **Conclusions:** MCT combined with cemiplimab demonstrated clinically meaningful antitumor activity. Alterations in plasma concentrations of select cytokines were associated with therapeutic response and overall survival. These results are hypothesis-generating and support the need for prospective validation. Clinical trial information: NCT04862650. Research Sponsor: Regeneron Pharmaceuticals; Internal founds from The Ohio State University.

6045 Poster Session

Updated results of benmelstobart combined with anlotinib and chemotherapy as neoadjuvant therapy for locally advanced head and neck squamous cell carcinoma: A single-arm, open-label phase II clinical trial.

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Background: Locally advanced head and neck squamous cell carcinoma (HNSCC) is characterized by high risks of local recurrence and distant metastasis, resulting in poor prognosis. Neoadjuvant therapy has the potential to improve survival outcomes in these patients. This study aimed to evaluate the safety and efficacy of benmelstobart in combination with anlotinib and chemotherapy as neoadjuvant therapy for resectable locally advanced HNSCC. Preliminary results were presented at the 2025 ESMO Congress (Abstract 1454eP), and updated consecutive results are reported herein. **Methods:** This single-center, phase II clinical trial enrolled patients with stage III/IVA HNSCC who met predefined eligibility criteria. Patients underwent neoadjuvant therapy with benmelstobart (1200mg), anlotinib (10mg), cisplatin (60mg/m^2), and nab-paclitaxel (125mg/m^2, d1, d8) for three 21-day cycles. Surgical resection was performed within two weeks after neoadjuvant therapy completion, with tumor specimens collected for pathological evaluation. The primary endpoint was major pathological response (MPR) rate. Postoperative adjuvant therapy was administered based on risk assessment. Secondary endpoints included objective response rate (ORR), pathological complete response (pCR) rate, 2-year disease-free survival (DFS), 2-year locoregional recurrence-free survival (LRFS), 2-year distant metastasis-free survival (DMFS), 2-year overall survival (OS), and safety assessment. **Results:** As of Jan 9, 2026, a total of 36 patients who met the inclusion and exclusion criteria were enrolled. The median age was 61 years (range: 38-77), with males accounted for 91.7%. ECOG performance status 0 was observed in 80.5% of patients, and hypopharyngeal carcinoma was the most common primary tumor site (50.0%). Stage III and IVA disease accounted for 25.0% and 75.0% of patients, respectively. At the data cut-off date, 32 patients completed neoadjuvant therapy, achieving an ORR of 96.9% and a disease control rate (DCR) of 100%. Among them, 27 patients underwent surgery and completed histopathological assessment. MPR was achieved in 23 cases (including 20 with pCR), resulting in an MPR rate of 85.2% (95% CI: 66.3%-95.8%). The incidence of all grade treatment-emergent adverse events (TEAEs) was 86.1% (31/36). The incidence of grade≥3 TEAEs was 8.3% (3/36), most commonly myelosuppression (5.6%) and renal impairment (2.8%). **Conclusions:** The combination of benmelstobart, anlotinib, and chemotherapy demonstrated promising efficacy as neoadjuvant therapy for resectable HNSCC, with high ORR and MPR rates, along with an acceptable safety profile. These updated results support further evaluation of this combination in randomized controlled trials. Clinical trial information: NCT0669949. Research Sponsor: None.

Second-line cetuximab plus immune checkpoint inhibitor (ICI) versus cetuximab plus carboplatin and paclitaxel following ICI-containing regimen in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC).

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Background: ICI-containing regimens are the standard first-line therapies for R/M HNSCC. However, the optimal therapeutic regimen after progression on ICI-containing therapies remains uncertain. This study compares outcomes among patients (pts) who received either second-line cetuximab plus ICI (CICI) or cetuximab plus weekly carboplatin and paclitaxel (CPT). **Methods:** We performed a retrospective analysis of R/M HNSCC pts treated at our institution between 2018 and 2025 who received cetuximab combination therapy after progressing on first-line ICI alone or ICI with chemotherapy. Pts with ECOG 0-2 were included. All pts received cetuximab 400 mg/m^2 followed by 250 mg/m^2 weekly as tolerated, concurrently with either pembrolizumab (200 mg every 3 weeks) or chemotherapy (carboplatin AUC 1.5 and paclitaxel 45 mg/m^2 weekly). The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), disease control rate (DCR; SD+PR+CR), objective response rate (ORR; CR+PR), and rate of treatment modification. Time-to-event outcomes were estimated using the Kaplan-Meier method and compared using log-rank tests and Cox proportional hazards models. Fisher's exact test was used to compare binary outcomes. Results were deemed significant when $p<0.05$. Subgroup analyses were considered exploratory. **Results:** Out of 100 pts included, 31 received CICI, and 69 received CPT. Median age at the start of cetuximab was 65 years (range 34-93), 79% were male, 95% were Caucasian, and 38% had HPV-related disease. Primary tumor sites included oropharynx (47%), oral cavity (26%), and larynx (19%). 9% had CPS 0, 30% had CPS 1-19, and 43% had CPS $\geq$ 20. For first-line treatment, 41% had received an ICI alone, and 59% had received an ICI with chemotherapy. Median follow-up was 7.6 months (range 3.8-13.4) with CICI and 38.8 months (range 4.3-71.5) with CPT. DCR was 77.4% with CICI and 60.6% with CPT (p=0.12). ORR was 51.6% versus 34.8%, respectively (p=0.13). Median PFS was 7.6 months (95% CI 4.1-NR) with CICI and 2.7 months (95% CI 2.0-4.4) with CPT (HR 0.48, 95% CI 0.29-0.82, $p<0.01$). Median OS was 11.3 months (95% CI 9.1-NA) with CICI and 9.4 months (95% CI 8.2-10.5) with CPT (HR 0.78, p=0.10). Subgroup analyses showed favorable PFS with CICI in select groups: age $\leq$ 65 (p=0.037), male sex (p=0.009), ECOG 0-1 (p=0.024), and prior ICI plus chemotherapy ($p<0.001$). No clear differences were found within subgroups with CPS 1-19 or CPS $\geq$ 20. There was no difference in the rates of treatment modification (p=1.00). **Conclusions:** In this retrospective cohort of R/M HNSCC pts, CICI was associated with a longer PFS than CPT. This effect remained significant in pts who previously received first-line ICI plus chemotherapy. A longer follow-up is planned to evaluate for differences in OS. Research Sponsor: None.

6047 Poster Session

An open-label, single-center phase II trial of mitoxantrone hydrochloride liposome combined with programmed death-1 (PD-1) inhibitors for pretreated recurrent or metastatic nasopharyngeal carcinoma.

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Background: Liposomal mitoxantrone (Lipo-MIT) in combination with programmed death-1 (PD-1) inhibitors exhibits potential synergistic antitumor effects. This study aimed to evaluate the efficacy and safety of this regimen in patients with pretreated recurrent/metastatic nasopharyngeal carcinoma (R/M NPC). **Methods:** This was a single-arm, Simon two-stage clinical study enrolling patients with R/M NPC who were refractory to platinum-based chemotherapy and PD-1 inhibitors. Patients received intravenous infusion of Lipo-MIT (20 mg/m^2) combined with a PD-1 inhibitor on Day 1 of each 21-day treatment cycle, for a maximum of 6 cycles. Subsequent maintenance therapy with PD-1 inhibitors alone was administered until disease progression, occurrence of intolerable toxicity, or completion of 2-year treatment. The primary endpoint was objective response rate (ORR). Key secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety profile. **Results:** A total of 32 patients were enrolled between February 3, 2024, and July 21, 2025, all of whom were included in the efficacy and safety analysis sets. The ORR was 40.6% (95% confidence interval [CI], 24.2–59.2), and the DCR was 78.1% (95% CI, 59.6–90.1). With a median follow-up duration of 8.1 months (range, 4.7–17.2 months), the median OS was not reached and the median PFS was 7.4 months (95% CI, 6.0–not reached [NR]). Grade 3 or higher treatment-related adverse events (TRAEs) were observed in 18 patients (56.3%), and the most common TRAEs were leukopenia (25.0%), anemia (21.9%), neutropenia (18.8%), pneumonia (15.6%), and thrombocytopenia (12.5%). No treatment-related deaths were observed. **Conclusions:** Lipo-MIT combined with PD-1 inhibitors demonstrates promising antitumor activity with manageable toxicities in patients with pretreated R/M NPC. Long-term survival data are pending as follow-up is still ongoing. Clinical trial information: NCT06472713. Research Sponsor: None.

A prospective, single-arm, phase II exploratory clinical study on the efficacy and safety of neoadjuvant adebrelimab combined with cisplatin and docetaxel in patients with clinical stage IVB oral squamous cell carcinoma.

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Background: Oral squamous cell carcinoma (OSCC) is one of the most common malignant tumors of the head and neck. Stage IVB OSCC had long been considered unresectable with extremely poor prognosis, and mainstream guidelines encourage exploring new therapies via clinical trials. This study aimed to evaluate the efficacy and safety of adebrelimab plus cisplatin/docetaxel as neoadjuvant therapy for stage IVB OSCC (NCT06277791). **Methods:** IVB OSCC patients aged 18–75 years were enrolled and received 2 cycles of neoadjuvant immunochemotherapy (adebrelimab 1200 mg + cisplatin 75 mg/m^2/docetaxel 75 mg/m^2, q3w). Three weeks after neoadjuvant treatment, patients underwent extended primary tumor resection and radical neck dissection, followed by adjuvant radiotherapy/chemoradiotherapy. The primary endpoint was pathological response rate (pCR+MPR); secondary endpoints included radiographic response, R0 resection rate, and safety. **Results:** 28 patients were enrolled between June 2023 and January 2026. The mean age was 47.8 years, with a male predominance (25, 89.3%). Primary tumors were mainly located in the buccal mucosa (14, 50.0%) and tongue (10, 35.7%). Smoking, alcohol consumption, and betel nut chewing histories were noted in 75.0%, 42.9%, and 64.3% of patients, respectively. Most had an ECOG performance status of 1 (75.0%). 8 cases (28.6%) were classified as cT4b and 20 cases (71.4%) as cN3b at baseline. Three patients (10.7%) were excluded from efficacy analysis due to insufficient data. In the evaluable population (n=25), no complete response (CR) was observed; 8 (28.6%) achieved partial response (PR), 14 (50.0%) stable disease (SD), and 3 (10.7%) progressive disease (PD), with an overall objective response rate (ORR) of 32.0% (8/25). Subgroup ORRs were 33.3% (2/6) for cT4b and 31.6% (6/19) for cN3b. Pathological assessment was available for 25 patients: based on the combined pathological assessment of the primary tumor and lymph nodes, 15 (60.0%) achieved MPR, 1 (4.0%) pCR, resulting in a 64.0% pathological response rate. For subgroups, the pathological response rate was 50.0% in 6 evaluable cT4b (2 MPR, 1 pCR) and 68.4% in 19 evaluable cN3b (13 MPR, no pCR). The R0 resection rate was 100% among 25 surgical patients. Treatment-related adverse events (TRAEs) were mostly grade 1–2. Grade 3 TRAEs occurred in 2 cases (7.2%), with no grade 4/5 events. At data cutoff (median follow-up: 12.0 months), 3 deaths occurred. The estimated 1-year OS rate was 87.9%, with subgroup rates of 89.1% for cN3b (median follow-up: 12.0 months) and 87.5% for cT4b (median follow-up: 19.4 months). **Conclusions:** Neoadjuvant adebrelimab combined with chemotherapy achieves a high pathological response rate in stage IVB OSCC, with manageable adverse events and favorable safety. Clinical trial information: NCT06277791. Research Sponsor: None.

6049 Poster Session

Evaluation of autologous tumor-infiltrating lymphocytes (GT201) plus toripalimab in recurrent or metastatic head and neck cancer.

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Background: Immune checkpoint inhibitors (ICIs) are the standard treatment for recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (HNC) after failure of platinum-based chemotherapy; however, the clinical benefit remains limited, with reported overall response rate (ORR) of approximately 13% and median progression-free survival (PFS) of about 2 months in the second line setting. GT201 is an autologous TIL therapy engineered to express membrane-bound IL-15 (mbIL-15), which may enhance immune activation in the tumor microenvironment and promote durable response. We report preliminary safety and efficacy results from an open-label, single-arm study evaluating GT201 in combination with the PD-1 inhibitor toripalimab in patients with R/M HNC (NCT06190275). **Methods:** The primary endpoint was safety, including treatment-emergent adverse events (TEAEs) graded per CTCAE v5.0. Secondary endpoints included ORR, disease control rate (DCR), PFS, duration of response (DOR), and overall survival (OS), assessed per RECIST v1.1. **Results:** As of November 30, 2025, 6 patients with R/M HNC were treated (median age of 57 years; median 1 prior line of therapy). Histology indicated 5 squamous cell carcinoma and 1 lymphoepithelial carcinoma. All patients received 1–2 cycles of bridge therapy, followed by lymphodepletion (low-dose in 5 patients; intermediated-dose in 1 patient), GT201 infusion (5×10^9-5×10^{10} viable cells), and high-dose IL-2 (600,000 IU/Kg; 4-6 doses). Five patients subsequently received toripalimab; one patient progressed prior to PD-1 inhibitor treatment. Maximum follow-up was 15.5 months. Most of AEs were Grade 1-2. Grade $\geq$ 3 AEs were primarily related to lymphodepletion and IL-2, and included cytopenia, neutropenia, lymphocytopenia, monocytopenia, hypokalemia, rash, and increased bilirubin; all resolved or improved to Grade $\leq$ 2 within 14 days. The ORR was 66.7% (4/6), including 2 complete response (CR) and 2 partial response(PR); DCR was 83.3% (5/6). One patient with CR remains progress-free exceeding 12 months. Median PFS and OS have not yet been reached. GT201 cells expanded robustly and persisted in peripheral blood for at least 6 months post-infusion. **Conclusions:** GT201 combined with toripalimab demonstrated a manageable safety profile and encouraging antitumor activity in heavily pre-treated R/M HNC, supporting further clinical development of this combination. Clinical trial information: NCT06190275. Research Sponsor: Grit Biotechnology. Research Sponsor: None.

6050 Poster Session

Defining a long-term benefit phenotype to PD-1 inhibitors in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): A multicentre retrospective study.

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Background: Limited data exists on predictors of durable benefit to PD-1 inhibitors in R/M HNSCC. We aimed to identify clinical characteristics associated with long-term benefit from anti-PD-1 therapy in R/M HNSCC. **Methods:** We reviewed clinical data from patients with R/M HNSCC treated with PD-1 inhibitors between December 2018 and August 2025, at Princess Margaret Cancer Centre (an academic hospital) or within the William Osler Healthy System (a community hospital). Eligible patients received pembrolizumab or nivolumab, either alone or with chemotherapy (for pembrolizumab), and had available tissue for planned biomarker studies. Patients were grouped by progression-free survival (PFS): (A) PFS $\geq$ 24 months (m), (B) PFS 12-24 m and (C) best response of progressive disease (PD). Best response was determined from treating physician documentation based on clinical and radiographic assessment. PFS was estimated with the Kaplan-Meier method. Univariate analysis used Kruskal-Wallis test for continuous variables and Fisher's exact or Chi-square tests for categorical variables. **Results:** A total of 150 patients were included: 31 in group A (PFS $\geq$ 24 months), 28 in group B (PFS 12-24 months) and 91 in group C (PD as best response). We observed significantly more immune-related adverse events (irAEs) (61% vs 16%, OR 8.0, 95% CI 3.2-19.9, $p<0.001$) and corticosteroid use (32% vs 8.8%, OR 4.9, 95% CI 1.7-14.1, p= 0.002) in group A compared to group C. There was a trend toward a higher proportion of patients with lung-only metastases in group A compared to C (39% vs 21%, OR 2.4, 95% CI 1.0-5.8, p= 0.052). Similar associations were found for irAEs ($p<0.001$), corticosteroid use (p= 0.011) and lung-only metastases (p= 0.054) in group B compared with group C. Additionally, we found more active smokers (p=0.010) and ex-smokers (p= 0.036) in group B compared to group C, as well as more active smokers in group B compared to group A (p= 0.042), whereas smoking rates were similar in groups A and C. Interestingly, there was no significant difference in Charlson Comorbidity Index (CCI) scores, albumin levels or neutrophil-to-lymphocyte ratios (NLR) between the three groups. The mean CCI scores were 7.3, 7.3 and 7.1; albumin levels 39.1, 40.1 and 39.7 and NLR 6.8, 6.5 and 8.7 for groups A, B and C respectively. P16 status and PD-L1 CPS were distributed similarly between the groups, although PD-L1 testing was not available in 25% of patients. **Conclusions:** IrAEs, corticosteroids and lung-only metastases are associated with PFS $\geq$ 12 m in patients with R/M HNSCC treated with anti-PD-1 agents. Smoking is associated with PFS 12-24 m but not with PFS $\geq$ 24 m, suggesting a potential role in acquired resistance. Further molecular analysis in this population is underway to identify biomarkers of long-term benefit. Research Sponsor: Canadian Association of Medical Oncologists (J.P.); Princess Margaret Cancer Centre Drug Development Fellowship Program (J.P.).

6051 Poster Session

Preliminary efficacy and safety of intratumoral long-acting cisplatin-SRGel (TumoCure) in refractory locally advanced head and neck squamous cell carcinoma: Phase Ib CLPR-001.

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Background: Refractory LA-HNSCC progressing despite standard therapies is associated substantial locoregional disease driven morbidity and limited effective salvage therapies that achieve modest response rates and are poorly tolerated. Intratumoral (IT) therapies enabling high and durable drug exposure at the site of disease with minimal systemic toxicity may address this unmet need. TumoCure is a long acting injectable IT cisplatin formulation (100mg/mL) incorporated in SRGel, a solvent free biodegradable matrix designed to provide IT cisplatin release for up to 2 months, aiming to maximize locoregional cisplatin exposure with minimal systemic exposure. **Methods:** CLPR-001 is an open-label, multicenter Phase I/Ib study evaluating IT TumoCure in patients with chemo and/or radio resistant LA-HNSCC with no available curative or effective standard treatment options. TumoCure is administered as a single IT injection; individualized based on tumor dimensions to optimize IT dispersion. The primary endpoint is safety and tolerability. Secondary endpoints include locoregional response by RECIST v1.1, PK and QoL assessment. **Results:** Eight patients received IT TumoCure (5 males and 3 females) with a mean age of 66y. Patients were in average 7y from diagnosis and were heavily pretreated: 7/8 (87.5%) had prior surgery and 7/8 (87.5%) were platinum-resistant or refractory. The mean number of prior systemic treatment lines (including RT and IO) was 3. Target lesions reflected substantial locoregional tumor burden (longest diameter 30-98 mm). Administration was feasible across tumor sizes, with injection volumes of 0.4-1.0 mL. Treatment was generally well tolerated. Procedure related AEs were uncommon and limited to injection site pain. No systemic cisplatin related AEs were reported. Early clinical activity was observed, with 3 months best response of 45% and 37% reductions in tumor diameter and corresponding volumetric reductions of 75% and 36% respectively. Patients also experienced clinically meaningful improvement in tumor bulk related manifestations. Preliminary PK analyses demonstrated systemic platinum exposure at least one order of magnitude lower than historical systemic cisplatin exposure. **Conclusions:** In heavily pretreated, platinum-resistant/refractory patients, TumoCure treatment was safe and well tolerated. Early signals of tumor regression and improvement in tumor bulk-related symptoms were observed, supported by markedly reduced systemic platinum exposure. These findings support continued development of TumoCure as treatment for refractory LA-HNSCC. A subsequent study is planned to evaluate TumoCure + IMRT in cisplatin ineligible patients, addressing an unmet need where current chemoradiation regimens remain suboptimal, with the goal of improving outcome while minimizing toxicity. Clinical trial information: NCT05200650. Research Sponsor: None.

First-line lenvatinib versus dabrafenib plus trametinib (D+T) in *BRAF*-mutated differentiated thyroid cancer (DTC): Insights from real-world data.

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Background: *BRAF* mutations are present in approximately 40%–60% of patients with DTC. Lenvatinib is the NCCN Category 1 preferred first-line (1L) systemic therapy for progressive radioiodine-refractory (RAI-R) DTC—including *BRAF*-mutated disease. For patients with *BRAF* V600E–positive, RAI-R DTC, *BRAF*-targeted therapy is recommended for those unsuitable for lenvatinib or as a 2L agent for patients after disease progression or intolerance to one or more prior multikinase inhibitors. This analysis compares real-world effectiveness of 1L treatment with lenvatinib versus D+T in patients with *BRAF*-mutated tumors. **Methods:** Patients with DTC who initiated lenvatinib monotherapy (n=319; Dec 2014–Jul 2025) or D+T (n=131; June 2016–Sept 2025) were identified from the Tempus multimodal real-world database. Among them, 88 patients were treated with lenvatinib and 54 patients were treated with D+T as 1L therapy for DTC harboring *BRAF* V600E and/or K601E mutations. Retrospective analyses in this patient cohort (n=142) were performed to compare real-world progression-free survival (rwPFS) and overall survival (exploratory; rwOS) between patients treated with 1L lenvatinib and those treated with 1L D+T in *BRAF*-mutated DTC. **Results:** Of the 142 patients in the study cohort who were treated with lenvatinib or D+T, the median age was 66 years (interquartile range: 57–74); 45% of patients were female and 55% were male. The majority (75%) of patients were White, 5.7% were Asian, 3.4% were African American, and 16% had their race categorized as "Other." Papillary, follicular, and Hürthle histology accounted for 92%, 0.7%, and 1.4% of patients, respectively, while the remaining 6% had uncommon or unspecified histology. Demographics and clinical characteristics were balanced between patients treated with 1L lenvatinib or D+T. At median follow-up of 33.6 months, median rwPFS indexed from treatment initiation dates was 17.0 months (95% confidence interval [CI], 12.2–27.8) in patients treated with lenvatinib and 6.2 months (95% CI, 4.9–8.7) in patients treated with D+T (hazard ratio [HR] for lenvatinib vs D+T, 0.44 [95% CI, 0.28–0.69]. Median rwOS was 70.7 months (95% CI, 51.8 – 90.8) in patients treated with lenvatinib, and 37.8 months (95% CI, 16.4–66.4) in patients treated with D+T (HR for lenvatinib vs D+T, 0.34 [95% CI, 0.18–0.62]). Sensitivity analyses showed that rwPFS and rwOS benefits associated with lenvatinib were maintained irrespective of age, sex, or race. **Conclusions:** In this retrospective study of real-world data, 1L therapy with lenvatinib demonstrated longer rwPFS and rwOS compared with 1L D+T in patients with DTC harboring *BRAF* mutations. While recognizing the inherent limitations of real-world data, this study has implications regarding the sequencing of agents used to treat patients with *BRAF*-mutated RAI-R DTC. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

The association of nutritional factors on disease control and survival in patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M-HNSCC) treated with anti–PD-1 monoclonal antibody.

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Background: Anti-PD-1 mAb therapy is standard of care for systemic treatment for R/M-HNSCC. These patients (pts) also face significant issues with malnutrition. Therefore, we evaluated whether there was any association between outcomes with anti-PD-1 treatment and nutritional markers including BMI, prognostic nutritional index (PNI), and serum albumin. **Methods:** We collected baseline serum albumin, PNI [(10 × serum albumin (g/dL)) + (0.005 × total lymphocyte count)], BMI, and initial BMI trend (baseline to 3 months), on pts with R/M-HNSCC treated with anti-PD-1 at our institution and evaluated association with disease control (CR/PR/SD vs. PD), PFS, and OS. Baseline BMI was analyzed as a continuous variable and binarily [<18.5 vs. ≥18.5, and median split (23.85)]. Associations of explanatory variables with disease control were evaluated using multivariable logistic regression, reported as odds ratios (ORs) and 95% confidence intervals (CIs) and with PFS and OS using Cox proportional hazards regression, reported as hazard ratios (HRs) and 95% CIs. All analyses were conducted using R version 4.5.2. **Results:** In our retrospective cohort (n = 124), the median age was 68 and primary sites included oral cavity (39%), larynx (16%), hypopharynx (5%), oropharynx (34%; 64% p16+), and other (6%). 43% of patients received anti-PD-1 for platinum failure and 57% for frontline. On univariate analysis, higher PNI was significantly associated with increased disease control (OR = 1.11; 95% CI: 1.04–1.21; p = 0.007), PFS (HR = 0.96; 95% CI: 0.94-0.98; p < 0.001), and OS (HR = 0.97; 95% CI: 0.95–0.99; p = 0.002). Higher albumin was significantly associated with increased PFS (HR = 0.45; 95% CI: 0.24-0.85; p = 0.014) and OS (HR = 0.25; 95% CI: 0.13-0.48; p < 0.001). Evaluation of baseline characteristics showed platinum failure was significantly associated with worse efficacy and therefore multivariate analysis was conducted, adjusting for platinum failure status. PNI was still significantly associated with increased disease control (OR = 1.09; 95% CI: 1.03–1.18; p = 0.016) and PFS (HR = 0.97; 95% CI: 0.95–0.99; p <0.001). Higher serum albumin was only significantly associated with increased OS (HR = 0.29; 95% CI: 0.14–0.57; p <0.001). Neither baseline nor trend in BMI was associated with efficacy. **Conclusions:** In our cohort of anti-PD-1 treated R/M-HNSCC pts, higher baseline albumin was associated with increased OS while higher baseline prognostic nutritional index was associated with increased disease control and PFS, including in multivariate analysis. While BMI has been associated with efficacy of anti-PD-1 in other solid tumors, it was not in our cohort. Our data suggests that markers that factor in nutritional and immune status may be more relevant in R/M-HNSCC. Further study is warranted. Research Sponsor: None.

6054 Poster Session

Four-year landmark survival analysis of low-dose nivolumab added to metronomic chemotherapy in advanced head and neck squamous cell carcinoma: A phase III randomized trial.

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Background: In advanced head and neck squamous cell carcinoma (HNSCC), the addition of low-dose nivolumab to triple metronomic chemotherapy (TMC-I) previously demonstrated an overall survival (OS) benefit versus triple metronomic chemotherapy (TMC) alone. We report extended follow-up with a 4-year landmark survival analysis to assess the durability of benefit. **Methods:** This was an open-label, randomised, phase III superiority trial enrolling 151 adult patients (≥18 years) with relapsed–recurrent or newly diagnosed advanced HNSCC with ECOG performance status 0–1, and adequate organ function. Patients were randomized 1:1 to receive oral TMC comprising of Methotrexate 9 mg/m² weekly, Celecoxib 200 mg twice daily and Erlotinib 150 mg daily, with (TMC-I) or without (TMC) nivolumab 20 mg intravenously every 3 weeks. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was OS. Survival outcomes were analyzed using Kaplan–Meier methods, log-rank tests, and Cox proportional hazards models. A 4-year landmark analysis was performed. **Results:** At a median follow-up of 55.6 months (95% CI, 45.0–66.2), the median OS was 6.60 months (95% CI, 5.74–7.47) in the TMC arm and 9.33 months (95% CI, 8.00–10.66) in the TMC-I arm (p = 0.045). Treatment with TMC-I was associated with a 29% reduction in the risk of death [hazard ratio (HR), 0.709; 95% CI, 0.506–0.994; p = 0.046]. At 3 years, OS was 5.1% (95% CI, 1.7–12.3) with TMC versus 13.6% (95% CI, 9.7–26.3) with TMC-I [HR 0.686; 95% CI, 0.485–0.971; p = 0.033]. On 4-year landmark analysis, overall survival curve separation was maintained, with OS remaining superior in the TMC-I arm. The median PFS was 4.50 months (95% CI, 3.89–5.12) with TMC and 6.47 months (95% CI, 4.02–8.93) with TMC-I (p = 0.007). The OS benefit with TMC-I was consistent across pre-specified subgroups including age, gender, ECOG performance status, disease site, prior platinum exposure, and tumour programmed death ligand (PD-L1) expression. **Conclusions:** With extended follow-up exceeding 4.5 years, the addition of low dose nivolumab to triple metronomic chemotherapy demonstrates a clinically meaningful, durable and statistically significant survival advantage at a 4-year landmark in a predominantly relapsed/refractory advanced HNSCC population compared with TMC alone, confirming the long-term clinical benefit of this strategy in the palliative setting. Clinical trial information: CTRI/2020/11/028953. Research Sponsor: None.

6055 Poster Session

Second-line cetuximab monotherapy following PD-1 inhibitor treatments in patients with recurrent/metastatic head and neck carcinoma.

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Background: PD-1 inhibitors, alone or in combination with chemotherapy, are standard first-line therapy for recurrent/metastatic head and neck squamous cell cancer (R/M HNSCC). No established second-line standard exists for majority of patients who progress on immunotherapy. Cetuximab, the only approved targeted biologic agent in HNSCC, has historically shown modest activity as monotherapy, with a 13% response rate. We hypothesized that cetuximab administered after PD-1 inhibitors may demonstrate enhanced efficacy due to potentially synergistic, immunomodulatory effects. **Methods:** This non-randomized single-institution study included patients with R/M HNSCC who experienced disease progression or intolerance to PD-1 inhibitor therapy, with or without chemotherapy, and were subsequently treated with cetuximab monotherapy. Imaging was performed every 6 weeks, and response was assessed per RECIST v1.1. Outcomes included best overall response (BOR), progression-free survival (PFS), overall survival (OS), and toxicity. Survival outcomes were estimated using Kaplan–Meier methods. **Results:** Twenty-seven patients (8 female, 19 male) were included; 5 were HPV-positive. All HPV-positives had metastatic disease, while all HPV-negatives had recurrent disease. Two patients experienced anaphylaxis with the first cetuximab infusion, and two died from tumor-related complications prior to first restaging; all were included in outcome analyses. Nine patients (33.3%) achieved a partial response (PR), while 18 (66.7%) were non-responders, including 10 (37.0%) with stable disease (SD), 4 (14.8%) with progressive disease (PD), and 4 (14.8%) non-evaluable. Median follow-up was 32.4 mos, with 21 deaths observed. Median OS was 11.6 mos (95% CI, 8.0–21.0) in all patients, 15.5 mos (95% CI, 4.2–24.9) in responders and 11.4 mos (95% CI, 5.3–25.0) in non-responders, with 18.0 mos (95% CI, 4.4–32.0) in patients with SD. Median PFS was 4.4 mos overall, 5.3 mos (2.7 to 11.5) in responders, and 4.4 mos (2.6 to 6.2) in non-responders, with 5.9 mos (2.5 to 7.0) in patients with SD. Median OS was 32.0 mos (11.7 to NE) in HPV-positive patients and 10.8 mos (5.3 to 18.0) in HPV-negatives. Two patients experienced anaphylactic reaction with the initial cetuximab administration. All treated patients developed acneiform skin rash, with 17 (68%) experiencing grade 3, necessitating oral antibiotics. **Conclusions:** Cetuximab monotherapy following PD-1 inhibitor therapy demonstrated encouraging clinical activity in patients with R/M HNSCC, with improved outcomes compared with historical cetuximab monotherapy. These findings suggest that sequential targeting of immune-mediated pathways may provide clinical benefit after an immunotherapy failure. Larger prospective studies are warranted to validate these results and to better define response patterns in the immunotherapy setting. Clinical trial information: NCT04375384. Research Sponsor: None.

6056 Poster Session

Evaluation of the impact of regional lymph node depletion on response to immune checkpoint blockade in recurrent and metastatic head and neck squamous cell carcinoma.

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Background: Lymphadenectomy remains a central component of definitive treatment for head and neck squamous cell carcinoma (HNSCC). However, lymphadenectomy disrupts the draining regional lymph node basin where anti-tumor immune cell priming can occur. We hypothesized that history of regional lymph node depletion may be associated with decreased efficacy of immune checkpoint blockade (ICB) in patients who suffer recurrent or metastatic (R/M) HNSCC. **Methods:** This was a single-institution retrospective cohort study including all patients treated with ICB (anti-PD-1 mAb) for R/M HNSCC from 2015 - 2025. Patients with distant metastatic disease at presentation were excluded. Demographic, clinicopathologic, and treatment history prior to ICB were collated and summarized for each patient. We defined regional lymph node depletion (LN depletion) as history (at any time prior to ICB initiation) of bilateral lymphadenectomy, >4 levels dissected, or ≥ 18 lymph nodes excised. We then examined history of LN depletion as a predictor of ICB disease control rate (DCR: SD, PR, or CR) and progression-free survival (PFS) after ICB with Kaplan-Meier method and Cox models alone and controlling for tumor HPV status. **Results:** Our cohort was comprised of 100 patients (median age 72 years, 71% male). Primary tumor sites included oral cavity (n=38) p16+ oropharynx (n=23), larynx (n=21), p16- oropharynx (n=13) and sinonasal (n = 5). Forty-six were treated with first-line ICB, while 54 were treated after platinum chemotherapy failure. Sixty had a history of lymphadenectomy prior to ICB. Of these 60 patients, 51 (85%) had a history of radiation prior to ICB. History of regional LN depletion was significantly associated with lower DCR with ICB when considering bilateral lymphadenectomy (25.9% vs 54.8%, $p = 0.03$), >4 levels dissected (25.0% vs. 54.8%, $p = 0.02$), or ≥ 18 lymph nodes excised (25.0% vs. 84.6%, $p < 0.0001$) analyzed alone and on bivariate analysis controlling for HPV status. In patients meeting all three criteria for LN depletion (n = 24), DCR was the lowest at 16% compared to 75% for patients meeting none of the criteria. On bivariate analyses controlling for HPV status, history of bilateral lymphadenectomy (HR: 2.04 [95% CI 1.1 – 3.8] $p = 0.02$), >4 levels dissected (HR: 1.82 [95% CI: 1.0 – 3.3] $p = 0.05$, and ≥ 18 lymph nodes excised (HR: 3.35 [95% CI: 1.4 – 8.1] $p < 0.01$) were independently associated with poorer PFS after ICB. **Conclusions:** In patients with R/M HNSCC, prior regional LN depletion was associated with lower DCR and PFS after ICB. This suggests that greater surgical disruption of draining regional lymph node basins prior to ICB may affect immune response. Research Sponsor: None.

6057 Poster Session

Neoadjuvant and adjuvant pembrolizumab (pembro) plus standard of care (SOC) for resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): Efficacy by surgical outcomes in the phase 3 KEYNOTE-689 trial.

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Background: In the phase 3 KEYNOTE-689 trial (NCT03765918), neoadjuvant and adjuvant pembro plus SOC (surgery and postoperative [chemo]radiotherapy) significantly improved EFS versus SOC in participants (pts) with resectable LA HNSCC. We present results from an exploratory analysis of EFS by surgical outcomes in KEYNOTE-689. **Methods:** Adults with newly diagnosed resectable LA HNSCC were randomly assigned to receive 2 cycles neoadjuvant pembro 200 mg followed by surgery and 15 cycles adjuvant pembro starting concurrently with postoperative (chemo)radiotherapy (pembro arm) versus surgery and postoperative (chemo) radiotherapy only (control arm). This exploratory analysis evaluated EFS in pts with R0 resection (negative [≥5mm] or close [1-5mm] margin) by local assessment, and postoperative presence or absence of extranodal extension (ENE) or positive (<1mm) surgical margins by BIPR in the PD-L1 CPS ≥1 and total populations of the study. Median study follow-up (data cutoff date: July 25, 2024) was 38.3 months (range, 9.0-66.5). **Results:** Of 714 total pts, 630 underwent surgery (n = 322, pembro arm; n = 308, control arm). Among 630 who underwent surgery, 307 in the pembro arm and 294 in the control arm had tumors with PD-L1 CPS ≥1. EFS in subgroups by surgical outcome is shown in the table. **Conclusions:** In this exploratory analysis of the KEYNOTE-689 study, EFS benefit with neoadjuvant and adjuvant pembro added to surgery and postoperative (chemo)radiotherapy occurred in all subgroups by surgical outcome, consistent with the primary analysis population. Fewer pts in the pembro arm had ENE or positive margins post-surgery indicating downstaging due to neoadjuvant pembro. ENE presence or positive margins were associated with a poorer EFS prognosis; however, EFS was better in the pembro arm vs control in pts with or without these high-risk pathological features. Results further support the addition of neoadjuvant and adjuvant pembro to SOC for resectable LA HNSCC. Clinical trial information: NCT03765918. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	R0 by local assessment		ENE present by BIPR		ENE absent by BIPR		Positive surgical margins by BIPR		Negative surgical margins by BIPR	
All pts	**Pembro n = 287**	**Control n = 261**	**Pembro n = 82**	**Control n = 112**	**Pembro n = 228**	**Control n = 188**	**Pembro n = 64**	**Control n = 92**	**Pembro n = 249**	**Control n = 209**
Median EFS, mo	NR	40.2	25.2	12.6	NR	57.0	50.3	13.8	NR	51.5
HR (95% CI)	0.67 (0.50-0.88)		0.77 (0.52-1.15)		0.74 (0.53-1.05)		0.58 (0.36-0.93)		0.78 (0.57-1.07)	
36-mo rate, %	64.0	51.1	41.3	33.8	68.4	58.5	58.0	36.8	63.0	55.6
CPS ≥1	**Pembro n = 275**	**Control n = 249**	**Pembro n = 76**	**Control n = 109**	**Pembro n = 220**	**Control n = 178**	**Pembro n = 58**	**Control n = 89**	**Pembro n = 242**	**Control n = 198**
Median EFS, mo	NR	35.3	25.2	12.6	NR	57.0	50.3	13.8	NR	50.1
HR (95% CI)	0.62 (0.47-0.83)		0.74 (0.49-1.12)		0.71 (0.51-1.01)		0.60 (0.37-0.98)		0.72 (0.53-1.00)	
36-mo rate, %	65.1	49.5	42.3	33.9	68.5	56.6	55.0	36.0	64.2	53.9

6058 Poster Session

The impact of depth of response on long-term clinical outcomes: Exploratory analyses from multiple expansion cohorts of a phase 1/1b study of ficerafusp alfa plus pembrolizumab in first-line recurrent/metastatic (R/M) HPV-negative head and neck carcinoma (HNSCC).

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Background: Ficerafusp alfa is the first and only bifunctional EGFR-directed antibody designed to trap TGF-β, enabling tumor penetration of immune cells and driving deep and durable responses. Depth of response has been shown to correlate with prolonged progression free survival (PFS) and overall survival (OS) in several solid tumors. However, such data are limited in R/M HPV-negative HNSCC. Here we performed exploratory analyses to evaluate whether depth of response achieved with ficerafusp alfa and pembrolizumab is associated with prolonged duration of response (DOR), PFS and OS. **Methods:** Three cohorts of a phase 1/1b study (NCT04429542) in 1L, R/M HNSCC, with PD-L1 CPS ≥1 evaluated ficerafusp alfa (750mg QW,1500 mg QW, or 2000 mg Q2W) IV combined with pembrolizumab IV. Objective response rate (ORR) per RECIST v1.1, DOR, PFS, and OS were assessed. In the pooled efficacy evaluable set from the three cohorts, we explored if the magnitude of tumor regression, comparing tumor regression ≥80% regression (defined as a deep response) vs. tumor regression 0 to <80%, is predictive of longer-term clinical outcomes (DOR, PFS, OS). **Results:** As of December 16, 2025, 85 patients with HPV-negative disease were efficacy evaluable across three cohorts (n=30, n=28, and n=27 at 750mg, 1500mg, and 2000mg doses of ficerafusp alfa, respectively). Among these, the confirmed ORRs were 57%, 54%, and 48%, respectively, including 47%, 80%, and 77% of responders achieving a deep response. In the pooled efficacy evaluable set the percentage of patients with a deep response was 36%, with tumor regression 0 to <80% was 46%, and no tumor regression was 18%. mDOR was longer for patients with a deep response compared to patients with tumor regression 0 to <80% (21.9 mo vs 8.2 mo, HR 0.27). mPFS was also longer in patients with a deep response compared to patients with tumor regression 0 to <80% (26.4 mo vs 6.5 mo, HR 0.19). mOS was not reached (NR) in patients with deep response and 14.9 mo in patients with tumor regression 0 to <80% (NR vs 14.9 mo, HR 0.17). **Conclusions:** Ficerafusp alfa plus pembrolizumab demonstrated deep responses across multiple dose levels. Deep responses were associated with improved long-term efficacy outcomes, including DOR, PFS, and OS. This suggests that depth of response may represent a clinically meaningful surrogate for understanding long-term efficacy outcomes in HPV-negative 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).

	Tumor Regression 0 to <80% N=39	Tumor Regression ≥ 80% (Deep Response) N=31
mDoR (mo)	8.2	21.9
HR [vs < 80% tumor regression] (95% CI)	N/A	0.27 [0.10, 0.71]
mPFS (mo)	6.5	26.4
HR [vs No DR] (95% CI)	N/A	0.19 [0.09, 0.40]
mOS (mo)	14.9	NR
HR [vs No DR] (95% CI)	N/A	0.17 [0.07, 0.41]

6059 Poster Session

Outcomes of PD-(L)1 inhibitor continuation or rechallenge after first-line progression in recurrent or metastatic head and neck squamous cell carcinoma.

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Background: PD-(L)1 inhibitors are a standard first-line (1L) backbone for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, many patients progress after 1L PD-(L)1–based therapy, and optimal post-progression strategies remain undefined. In particular, the benefit of continuing or rechallenging PD-(L)1 inhibitors beyond progression is unclear. **Methods:** In this multicenter retrospective study, we included patients diagnosed with R/M HNSCC (oral cavity, oropharynx, larynx, and hypopharynx) between 2016 and May 2025 at Samsung Medical Center and Mass General Brigham. Eligible patients received 1L PD-(L)1–containing regimen, experienced disease progression, and underwent subsequent second-line systemic therapy. Patients were categorized by post-progression strategy: continuation or rechallenge with PD-(L)1 inhibitors versus non–PD-(L)1–based therapy. Overall survival (OS) was defined as the time from initiation of 1L therapy to death from any cause. **Results:** A total of 252 patients with R/M HNSCC met eligibility criteria. Median age was 64; 191 (76%) were male; 68 (27.0%) were HPV-positive; and 217 (86%) were PD-L1 positive (CPS ≥1). Twenty-six patients (10.3%) received anti-PD-(L)1 monotherapy, and 84 (33%) remained on 1L therapy for ≥6 months. Median OS for the entire cohort was 18 months (95% CI, 15.9-20.1). Median OS was 21.1 months among patients who continued or were rechallenged with PD-(L)1 inhibitor (n = 112) versus 14.4 months in those who were not (n = 140) ($p < 0.001$). On multivariable analysis including post-progression PD-(L)1 continuation/rechallenge, HPV status, PD-L1 expression, age, sex, ECOG performance status, and duration of 1L PD-(L)1 therapy, continuation or rechallenge with PD-(L)1 inhibitors (HR 0.583, p=0.003) and 1L PD-(L)1 duration ≥6 months (HR 0.487, $p<0.001$) were independently associated with improved OS. **Conclusions:** In this study, continuation or rechallenge with PD-(L)1 inhibitors after progression on 1L therapy was associated with improved OS in patients with R/M HNSCC, independent of PD-L1 expression or HPV status. Prolonged benefit from 1L PD-(L)1 therapy was also independently associated with favorable survival. These findings suggest that selected patients may derive continued clinical benefit from anti-PD-(L)1–based strategies beyond progression and support prospective studies to refine patient selection and optimize post-progression treatment strategies. Research Sponsor: None.

6060 Poster Session

Efficacy and safety of HLX43 (an anti–PD-L1 ADC) in previously treated recurrent/metastatic nasopharyngeal carcinoma: A multicenter, randomized phase 2 study.

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Background: Treatment options are limited and clinical outcomes remain unsatisfactory for patients with recurrent/metastatic nasopharyngeal carcinoma (r/m NPC) in the later-line setting. HLX43 is a novel anti-programmed cell death-ligand 1 (PD-L1) antibody-drug conjugate with promising antitumor activity in advanced tumors. Here we present results from a phase 2 study evaluating HLX43 in previously treated r/m NPC. **Methods:** This randomized, multicenter trial enrolled patients with histologically or cytologically confirmed r/m NPC who had received at least second-line chemotherapy (including one prior line of platinum-based chemotherapy) and progressed on or were intolerant to programmed death (ligand) 1 (PD-[L]1) inhibitor. Patients were randomized 1:1:1 to receive 2 mg/kg, 2.5 mg/kg, or 3 mg/kg of intravenous HLX43 every 3 weeks. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS) per investigator's assessments. **Results:** As of September 18, 2025, 30 patients were randomized to the 2, 2.5, or 3 mg/kg group (n = 10 for each group). The median follow-up duration was 2.8 months (range 2.1–5.6). Twenty-six patients (86.7%) had performance status 1; 27 (90.0%) had prior radiotherapy. The median line of prior systemic therapy was 3 (range 2–8). ORR was 36.7%, with partial responses (PRs) in 11 patients. ORR in the three dose groups was 20.0%, 20.0% and 70.0% (all confirmed by December 2025), respectively; disease control rate (DCR) was 50.0%, 50.0% and 80.0%. PFS data were immature. Overall, treatment-emergent adverse events (TEAEs) occurred in 29 patients (96.7%; grade ≥3, 50.0%). TEAE incidence was 90.0%, 100% and 100% in the three dose groups, respectively. TEAE leading to dose reduction was reported in 3 patients (30.0%) in the 3 mg/kg group only. TEAE leading to treatment discontinuation occurred in 1 (10.0%) each in the 2.5 mg/kg and 3 mg/kg groups. There was no death due to TEAE. The efficacy and safety findings are detailed in Table 1. **Conclusions:** HLX43 showed promising efficacy with a manageable safety profile in r/m NPC patients who had progressed after second-line or later chemotherapy and PD-(L)1 inhibitors. Further investigation is warranted. Clinical trial information: NCT06839066. Research Sponsor: Shanghai Henlius Biotech, Inc.

Efficacy and safety.

	2.0 mg/kg N=10	2.5 mg/kg N=10	3.0 mg/kg N=10	Total N=30
PR	2 (20.0)	2 (20.0)	7 (70.0)	11 (36.7)
SD	3 (30.0)	3 (30.0)	1 (10.0)	7 (23.3)
PD/NE	5 (50.0)	5 (50.0)	2 (20.0)	12 (40.0)
ORR, 95% CI (%)	20.0 (2.5, 55.6)	20.0 (2.5, 55.6)	70.0 (34.8, 93.3)	36.7 (19.9, 56.1)
DCR, 95% CI (%)	50.0 (18.7, 81.3)	50.0 (18.7, 81.3)	80.0 (44.4, 97.5)	60.0 (40.6, 77.3)
TEAEs	9 (90.0)	10 (100)	10 (100)	29 (96.7)
Grade ≥3 TEAEs	2 (20.0)	7 (70.0)	6 (60.0)	15 (50.0)
TEAE leading to dose reduction	0	0	3 (30.0)	3 (10.0)
TEAE leading to treatment discontinuation	0	1 (10.0)	1 (10.0)	2 (6.7)

NE, not evaluable. PD, progressive disease. SD, stable disease.

6061 Poster Session

A prospective phase II clinical study of different time-delivered drugs combined with intensity-modulated radiotherapy for locally advanced nasopharyngeal carcinoma.

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Background: To compare the effects of combining intensity-modulated radiotherapy administered at different times on the toxic side effects, quality of life (QoL) and long-term survival of patients with locally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** A total of 160 patients with LA- NPC were randomized into the experimental group and the control group of 80 patients each, both groups received 2 cycles of TPF (docetaxel, cisplatin, and 5- fluorouracil) induced chemotherapy sequential synchronous radiochemotherapy, the experimental group received chrono- chemotherapy, while the control group received conventional chemotherapy. Primary study endpoints included Grade $\geq$ 3 acute adverse reactions, Secondary study endpoints included quality of life and 8- year overall survival (OS), progression- free survival (PFS), distant metastasis- free survival (DMFS), and local recurrence- free survival (LRFS). **Results:** As of October 10, 2024, the incidence rates of grade $\geq$ 3 acute vomiting, oral mucositis, leukopenia, and neutropenia in the experimental group were 3.75%, 6.25%, 27.5%, and 35.0%, while those in the control group were 15.0%, 16.25%, 47.5%, and 52.5%, and the differences were statistically significant ($P < 0.05$). In the experimental group, the incidence rates of Grade 1- 2 xenosomia and hearing impairment were 63.2% and 23.5%, respectively, compared to 80% and 48.6% in the control group, with a statistically significant difference ($P < 0.05$), and no Grade 3- 4 late toxicities were reported in either group. The experimental group demonstrated significantly higher overall QoL scores compared to the conventional group, with statistically significant differences in vomiting, general health status, and quality of life scores between the two groups ($P < 0.05$). However, no statistically significant differences were observed in 8-year OS, PFS, DMFS, or LRFS between the groups ($P > 0.05$). **Conclusions:** The integration of chronotherapy with IMRT significantly reduced adverse reactions and improved quality of life with LA-NPC, without compromising long-term survival outcomes. Clinical trial information: NCT02937519. Research Sponsor: None.

6062 Poster Session

A phase 1/2 study of the next-generation nectin-4–targeting antibody-drug conjugate CRB-701 (SYS6002) in patients with recurrent or metastatic head and neck squamous cell carcinoma.

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Background: CRB-701 is a next-generation Nectin-4–targeted monomethyl auristatin E (MMAE)-based antibody–drug conjugate with differentiated safety, efficacy and pharmacokinetics compared with other agents in the same class. As previously reported, CRB-701 demonstrated antitumor responses independent of Nectin-4 expression levels in solid tumors, notably in patients with heavily pretreated head and neck squamous cell carcinoma (HNSCC) and cervical cancer, as well as urothelial carcinoma. Here, we provide data from this phase 1/2 trial in patients with recurrent or metastatic (R/M) HNSCC enrolled in dose escalation (part A) and dose optimization (part B) (NCT06265727). **Methods:** Patients with R/M HNSCC who had received ≥ 1 line of therapy were enrolled. Part A employed a Bayesian Optimal Interval design with four doses (1.8, 2.7, 3.6 and 4.5 mg/kg; each every 3 weeks [Q3W]) to determine the maximum tolerated dose. In part B, the pharmacologically active dose range identified in part A was evaluated using a time-to-event Bayesian optimal phase 2 design. Patients were randomized 1:1 to receive CRB-701 at 2.7 or 3.6 mg/kg Q3W. The primary endpoints for parts A and B were dose-limiting toxicities and objective response rate (ORR), respectively. A scan ≥ 4 weeks after the initial response was required to confirm partial and complete responses. Safety, tolerability and pharmacokinetics were also assessed. Nectin-4 expression and human papilloma virus (HPV)/p16 status were evaluated retrospectively. **Results:** As of September 2025, 60 patients with HNSCC were enrolled across parts A and B. The median (range) number of previous therapies was 3.0 (1–9) in the 2.7 mg/kg group and 3.0 (1–8) in the 3.6 mg/kg group; 85% of patients were refractory to immunotherapy and platinum-based regimens. The confirmed ORR was 33.3% (4/12 patients; unconfirmed ORR also 33.3%) at the 2.7 mg/kg dose, and 33.3% (7/21 patients; unconfirmed ORR, 47.6% [10/21 patients]) at the 3.6 mg/kg dose. Responses were observed regardless of HPV/p16 status. The safety profile of CRB-701 was broadly consistent with earlier findings: keratitis, fatigue, alopecia, dysgeusia and anemia were the most frequently reported treatment-emergent adverse events (≥ 15% of overall solid tumor population [N = 167]). An expanded efficacy analysis reporting an additional 6 months of follow-up, including ORR, duration of response and progression-free survival will be presented at the congress. Subgroup analyses by HPV status, treatment history and disease extent will also be presented. **Conclusions:** CRB-701 has shown promising efficacy in patients with heavily pretreated R/M HNSCC, along with a favorable safety profile compared with other MMAE-based therapies. Further investigation of CRB-701 is warranted in this difficult-to-treat patient population. Clinical trial information: NCT06265727. Research Sponsor: Corbus Pharmaceuticals, Inc.

6063 Poster Session

PD-L1 CPS ≥10 population subgroup analysis of KEYNOTE-412: Pembrolizumab plus chemoradiotherapy versus placebo plus chemoradiotherapy for unresected locally advanced head and neck squamous cell carcinoma.

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Background: At the end-of-trial analysis of the randomized, double-blind, phase 3 KEYNOTE-412 trial (NCT03040999) in participants with unresected locally advanced (LA) head and neck squamous cell carcinoma (HNSCC), pembrolizumab plus chemoradiotherapy (CRT) was associated with a clinically meaningful event-free survival (EFS) benefit over placebo plus CRT (HR 0.79; 95% CI, 0.65-0.96) in the total population, and in participants whose tumors expressed PD-L1 CPS ≥1 (HR 0.80; 95% CI 0.64-0.98) and CPS ≥20 (HR 0.70; 95% CI, 0.49-1.00). We conducted a post hoc analysis of outcomes in the PD-L1 CPS ≥10 population. **Methods:** Adults with high-risk unresected LA HNSCC (T3-4 N0-3 or T1-4 N2a-3 laryngeal/hypopharyngeal/oral cavity/p16-negative oropharyngeal SCC, or T4 or N3 p16-positive oropharyngeal SCC) were randomly assigned to receive definitive CRT plus 17 cycles of pembrolizumab 200 mg or placebo intravenously every 3 weeks concurrently and after CRT. This exploratory analysis evaluated EFS and overall survival (OS) in the PD-L1 CPS ≥10 population. **Results:** Of 804 total participants, 382 had tumors expressing PD-L1 CPS ≥10 (n = 194, pembrolizumab group; n = 188, placebo group). As of data cutoff date (August 21, 2024), median study follow-up in the PD-L1 CPS ≥10 population was 74.1 months (range, 63.8-88.1). Median EFS was not reached (NR) in the pembrolizumab group and 61.4 months in the placebo group (HR 0.71; 95% CI, 0.53-0.97). The 60-month EFS rates were 62.4% and 50.3%, respectively. Median OS was not reached in either the pembrolizumab or the placebo group; the 60-month OS rates were 70.7% and 60.9%, respectively (HR 0.75 [95% CI, 0.53-1.04]). **Conclusions:** Results from this post hoc analysis of the KEYNOTE-412 trial with over 2 years of additional follow-up were consistent with those of the end-of-trial analysis in the overall population. For participants whose tumors expressed PD-L1 with a CPS ≥10, we observed a clinically meaningful EFS and OS benefit for pembrolizumab plus CRT over placebo plus CRT, with a numerically lower HR than reported for the overall population. Clinical trial information: NCT03040999. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

6064 Poster Session

Clonal hematopoiesis in head and neck carcinomas receiving immunotherapy.

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Background: Clonal hematopoiesis (CH) is an age-related accumulation of somatic genetic alterations in hematopoietic stem cells. It is implicated in the evolution of myeloid neoplasms and has been associated with poor prognosis in patients with solid tumors. Immunotherapy (ITx) has become the standard of care in the treatment of recurrent/metastatic head and neck cancer (R/M HNSCC), however, response rate corresponds to 20% of total population and relies in a robust innate host immunity. This study aims to identify the presence of CH among ITx-treated R/M HNSCC patients and its potential association with treatment outcomes. **Methods:** Matched pre-treatment peripheral blood (PB) and tumor tissue samples of 32 ITx-treated R/M HNSCC patients were used for DNA extraction. The ten most commonly mutated CH genes were sequenced using a custom NGS Qiagen panel with unique molecular identifiers. Low confidence and synonymous variants were excluded. Pathogenic, likely pathogenic and conflicting with moderate or high annotation impact variants based on the ClinVar database were investigated for associations with progression-free (PFS) and overall survival (OS) as well as for differences in expression between blood and tissue. The same gene alterations and their correlation with survival in HNSCC were also explored in three public datasets (TCGA, GENIE, MSKCC) as an external validation of our findings. **Results:** A total of 2,088 variants were detected with 1,222 silent variants. After filtering,105 pathogenic, likely pathogenic and conflicting interpretation variants were retained. Mutations in CH related genes were identified in 18 out of 32 PB samples (56%). In tissue samples, (excluding *TP53*) mutations were identified in 12 out of 32 samples (37%). *TP53*mutations were significantly higher in tissue samples versus PB (P=0.028). *PPM1D* mutations in PB were correlated with shorter PFS (P=0.003) and OS (P=0.0116), while *TP53* mutations in tissue showed a trend for decreased OS (P =0.097). TCGA and MSKCC analysis confirmed a negative association of *TP53* mutations in tissue with OS (P=0.0020, P=0.0001, respectively). **Conclusions:** CH was frequently detected in PB and tumor tissue of R/M HNSCC patients. CH-related *PPM1D* mutations in PB and *TP53* in tumor tissue, were associated with shorter PFS and OS to ITx, suggesting a potential association between both peripheral and intratumoral immune contexture and clinical outcomes. Research Sponsor: None.

6065 Poster Session

Prognostic impact of tumor suppressor and DNA damage repair gene mutations in oral cavity squamous cell carcinoma: A clinico-genomic analysis from a real-world database.

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Background: Oral cavity squamous cell carcinoma (OCSCC) has unique genomic features, yet molecular biomarkers predicting prognosis remain poorly defined. Prior surgical series and TCGA analyses demonstrated TP53 and TERT promoter mutations associate with worse outcomes, while DDR pathways may influence immunotherapy response. However, no study has systematically evaluated these mutations with linked treatment and survival data. This is the first real-world clinico-genomic analysis addressing this gap in OCSCC. **Methods:** Using a prespecified protocol with IRB approval, we analyzed 381 OCSCC patients from the Flatiron Health-Foundation Medicine Clinico-Genomic Database. Inclusion required confirmed OCSCC, genomic profiling (~300 genes), and survival data. We evaluated tumor suppressors (TP53, CDKN2A), TERT promoter, PIK3CA, and DDR genes (BRCA1/BRCA2/PRKDC). IPTW adjusted for age, sex, stage, smoking, advanced disease, and TMB. A 90-day landmark eliminated immortal time bias. Complete case analysis handled missing data. IO cohort (n=213, 56%) received checkpoint inhibitors. Primary endpoint: OS from diagnosis; secondary: OS from IO initiation. **Results:** Stage IV was the strongest clinical prognostic factor (HR 1.64, 95%CI 1.29-2.08, p<0.0001). In IO-treated patients, TMB-high showed improved survival (HR 0.54, p=0.035). DDR pathway mutations were associated with markedly inferior outcomes from IO initiation (HR 2.34, 95%CI 1.00-5.49, p=0.049; median OS 5.7 vs 13.8 months; 12-month OS 17.4% vs 50.4%). TP53+CDKN2A co-mutation showed a trend toward worse survival versus TP53 alone (HR 1.50, 95%CI 0.99-2.27, p=0.056; median OS 9.8 vs 12.8 months; 12-month OS 34.7% vs 51.5%). **Conclusions:** In this first real-world clinico-genomic analysis of OCSCC, TP53 mutation was associated with worse OS, and TP53+CDKN2A co-mutation identified an even higher-risk subset with nearly halved median survival (20.9 vs 44.5 months) compared to wild-type. CDKN2A co-occurred with TP53 in 95% of cases. TERT promoter mutations confirmed their adverse prognostic role. Notably, PIK3CA mutation showed favorable prognosis (HR 0.59), potentially relevant for targeted therapeutics. DDR pathway mutations predicted particularly poor outcomes following immunotherapy. These findings provide a molecular framework for risk stratification in OCSCC and warrant prospective validation. Research Sponsor: None.

Prognostic impact of gene mutations on overall survival in oral cavity cancer.

Genes	HR (95%CI)	p-value	Median OS (MT vs WT)	12-mo OS (from diagnosis)
TP53+CDKN2A co-mutation	1.83 (1.23-2.72)	0.003	20.9 vs 44.5 mo	76.5% vs 83.9%
TP53	1.72 (1.20-2.47)	0.003	26.0 vs 44.5 mo	80.6% vs 85.1%
CDKN2A	1.34 (1.04-1.73)	0.024	20.9 vs 34.2 mo	77.3% vs 83.6%
TERT promoter	1.35 (1.01-1.80)	0.041	24.4 vs 38.0 mo	77.6% vs 88.8%
PIK3CA	0.59 (0.42-0.85)	0.004	51.3 vs 25.7 mo	83.5% vs 81.0%

6066 Poster Session

Clinical validation of ultra-sensitive WGS-based MRD detection in head and neck squamous cell carcinoma: Results from MONSTAR-SCREEN-3.

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Background: Circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) detection has shown promise across various malignancies, yet limited data exist for Head and Neck Squamous Cell Carcinoma (HNSCC). The prospective, multicenter MONSTAR-SCREEN-3 study evaluates an ultra-sensitive whole-genome sequencing (WGS)-based MRD assay in patients with resectable solid tumors undergoing curative-intent therapy. Here, we report preliminary results from patients with resectable HNSCC enrolled in the definitive cohort (target n=1,100). **Methods:** Personalized ctDNA panels were generated using a WGS-based tumor-informed platform (Myriad Genetics), incorporating up to 1,000 tumor-specific variants identified through WGS of matched tumor tissue. Serial plasma samples were collected at baseline, 1 month post-surgery, quarterly during the first year, and biannually thereafter for up to two years. **Results:** As of November 2025, 44 patients with resectable HNSCC were enrolled; MRD results were available for 139 samples from 34 patients. Median age was 65 years (range: 39-87), with male predominance (65.7%). Clinical staging included Stage III (15.6%), IVA (75.0%), and IVB (9.4%). All patients underwent upfront radical surgery. Personalized panel creation succeeded in 100% of patients (34/34), identifying a median of 6,119 highly confident tumor-specific alterations per patient (range: 1,288-15,418) and yielding bespoke panels containing 717-1,000 alterations. Customized panels were created with 97.7% SNVs and 2.3% indels. The assay demonstrated 100% baseline ctDNA detection (34/34), with 5.9% detected at ultra-sensitive levels (tumor fraction <100 parts per million [ppm]; minimum detection: 83.3 ppm). MRD positivity at 1 month, 3 months, and 6 months was at ultrasensitive levels in 10/14 (71.4%), 6/16 (37.5%), and 4/5 (80%) patients, respectively. Among 10 patients who developed radiological recurrence, median lead time was 2.7 months (range: 0-4.6 months). MRD-positive patients at 1 month after surgery had poorer disease-free survival than MRD-negative patients (HR 18.9, 95% CI 2.4–148.9; log-rank P<0.0001). Nine of the 13 patients who were ctDNA-positive at 1 month experienced recurrence, whereas only 1 of the 20 ctDNA-negative patients recurred. **Conclusions:** The WGS-based personalized ctDNA assay achieved high technical feasibility in HNSCC, with comprehensive customized variant panels highlighting the critical importance of ultra-sensitive platforms. These results suggest potential clinical utility for recurrence surveillance in HNSCC. Updated results will be presented. Clinical trial information: UMIN000053975. Research Sponsor: None.

6067 Poster Session

Integrated proteogenomic profiling to reveal prognostic subtypes and actionable targets in adenoid cystic carcinoma.

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Background: Adenoid cystic carcinoma (ACC) is a rare head and neck malignancy characterized by highly variable clinical outcomes and a lack of validated biomarkers to guide risk stratification or therapeutic decision-making. Despite a generally low tumor mutational burden, patients frequently experience late recurrence and distant metastasis, underscoring the need for biologically informed prognostic models. Existing genomic and transcriptomic classifiers have failed to adequately explain this heterogeneity. We therefore performed integrated multi-omic profiling to define biologically grounded prognostic subtypes and clinically actionable biomarkers in ACC. **Methods:** We established a multi-omics cohort of 55 surgically resected ACC tumors, including salivary gland–derived and pulmonary ACC, with matched adjacent normal tissues. Whole-exome sequencing, RNA sequencing, quantitative proteomics, and phosphoproteomics were performed. Cross-omics concordance and driver-anchored pathway effects were assessed. Transcriptomic and proteomic data were integrated using Similarity Network Fusion (SNF) to derive molecular subtypes. Prognostic proteins were evaluated using Cox regression. Targeted quantitative mass spectrometry was applied for orthogonal validation and for quantifying antibody–drug conjugate (ADC) targets and pathway stoichiometry. **Results:** ACC exhibited a low-mutational genomic landscape but profound proteomic and phosphoproteomic remodeling, with systematic activation of replication, cell-cycle, chromatin remodeling, and receptor tyrosine kinase–adhesion pathways, accompanied by suppression of immune-associated signaling. Driver effects were more consistently captured at the protein level than at the RNA level, indicating a proteome-driven tumor biology. SNF-based multi-omic integration identified three molecular subtypes with significantly different disease-free survival (DFS; log-rank P=0.0064), outperforming the conventional ACC-I/II classifier. These subtypes formed a biological continuum defined by metabolic robustness and cell-cycle competence. A compact three-protein signature independently stratified DFS. Quantitative profiling demonstrated broad and functionally relevant expression of ADC targets, including TROP2 and B7-H3, and identified ratio-based functional indices (e.g., IGF2/IGF1R and TP63/NOTCH1) associated with risk groups. **Conclusions:** ACC is a proteome-driven malignancy in which post-transcriptional regulation and signaling stoichiometry dominate clinical behavior. Integrated multi-omic analysis redefines ACC prognostic architecture and yields quantitative, translatable biomarkers that may inform precision risk stratification and therapeutic strategies in this rare head and neck cancer. Research Sponsor: Bio-insight Biotechnology (Hangzhou) Co., LTD; The National Key Research and Development Program of China; 2023YFC2508500; National Natural Science Foundation of China; 82272951, 82272953; CAMS Innovation Fund for Medical Sciences (CIFM); 2024-I2M-TS-005.

6068 Poster Session

Baseline spatial tumor microenvironment states to define response and primary resistance to immune checkpoint inhibition in recurrent/metastatic head and neck squamous cell carcinoma.

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Background: Despite the clinical impact of immune checkpoint inhibitors (ICIs) in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC), durable benefit is limited to a minority of patients and robust predictive biomarkers are lacking. PD-L1 combined positive score incompletely captures response heterogeneity, likely due to the spatial complexity of the tumor microenvironment (TME). We used spatial transcriptomics to identify baseline TME architectures associated with ICI response. **Methods:** Pre-treatment primary tumor samples from 12 patients with R/M HNSCC treated with ICIs were profiled using high-resolution spatial transcriptomics (Xenium In Situ, 10x Genomics; 380-gene immuno-oncology panel). Exceptional responders (ER) were defined by progression-free survival (PFS) $\geq$20 months, while poor responders (PR) had PFS $\leq$3 months. Differential gene expression and Gene Ontology (GO) enrichment were integrated with cell-type–resolved analyses to map transcriptional programs to cellular compartments. **Results:** Distinct baseline TME architectures separated ER and PR. ER tumors showed coordinated upregulation of interferon-related and immune activation genes (STAT1, MX1, CD274) together with cell-cycle-associated genes (MKI67, CDK1). Functional enrichment highlighted immune signaling, chemokine-mediated recruitment, and vascular remodeling, consistent with an immune-inflamed and spatially permissive microenvironment. In contrast, PR tumors exhibited dominant fibroblast-driven extracellular matrix and inflammatory programs, with enrichment of FN1, SPARC, LUM, VCAN and IGFBP7. GO enrichment in PR highlighted integrin-mediated processes, PDGFR-centered signaling, TGF-β–related pathways, and platelet-related signaling programs. Cell-type–resolved spatial mapping showed that fibroblast/ECM programs in PR were predominantly localized to fibroblast-enriched stromal compartments, whereas interferon-response programs in ER were distributed across both tumor and immune compartments. **Conclusions:** Baseline spatially organized TME states are associated with ICI outcomes in R/M HNSCC. ER exhibit an interferon-enriched, immune-permissive architecture, whereas primary resistance is linked to a fibroblast-dominated, ECM-rich and immune-restrictive niche. Proteomic validation of key spatial signals is ongoing to prioritize candidate predictive biomarkers for evaluation in a larger cohort. Enrichment of integrin-mediated processes and PDGFR-centered signaling in PR highlights actionable stromal vulnerabilities warranting translational investigation. Research Sponsor: Institutional research funds from the Catholic University of the Sacred Heart (Università Cattolica del Sacro Cuore), Rome, Italy (non-profit,investigator-initiated; no commercial sponsorship).

6069 Poster Session

Circulating HPV DNA for early detection of minimal residual disease after definitive therapy in oropharyngeal cancer: A phase II biomarker-driven study.

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Background: Persistent detection of circulating HPV DNA (cfHPVDNA) in plasma following definitive therapy for HPV-positive oropharyngeal squamous cell carcinoma (HPV+OPSCC) is strongly associated with inferior outcomes, including increased risk of relapse and distant metastasis, and defines a high-risk patient population. Immune checkpoint blockade targeting the PD-1 pathway has demonstrated clinically meaningful activity in both curative and palliative settings. We hypothesize that balstilimab, an anti–PD-1 antibody, can induce cfHPVDNA clearance in patients (pts) with persistent ctHPVDNA after definitive treatment and improve long-term disease control. **Methods:** Eligible pts had HPV+OPSCC, stage I–III per AJCC 8th edition (excluding T1–2N0 and T1–2N1 with lymph nodes <3 cm), and baseline ctHPVDNA (>20 copies/ml) per our institution digital droplet PCR assay. After completion of definitive standard-of-care therapy, ctHPVDNA was assessed at 3- and 6-months. Pts with positive ctHPVDNA test in the absence of radiographic evidence of disease were eligible to receive balstilimab (AGEN2034) at 3 mg/kg intravenously every 2 weeks for 6 months. The primary endpoint was cfHPVDNA clearance rate. Secondary endpoints included time to cfHPV DNA clearance, recurrence-free survival, overall survival, and safety. The study was designed to enroll up to 20 pts using a Bayesian optimal phase II design considering an expected clearance rate of 30%. In order to treat 20 pts, 140 pts would needed to be pre-screened with a baseline positive ctHPVDNA (15% of expected minimal residual disease). **Results:** A total of 168 pts were pre-screened, of whom 139 were eligible to proceed; disease stage was I, II, and III in 46% (N=64), 28% (N=39), and 26% (N=36) of pts, respectively. The median baseline ctHPVDNA level was 614 copies/mL (range, 26–239,111). A total of 130 of 139 pts had the 3-month ctHPVDNA assessment, as nine have been excluded (loss of follow-up or withdraw consent). Five had a positive ctHPVDNA result, all of whom had radiographic evidence of disease recurrence (3 local, 1 distant, and 1 both local and distant). Among the remaining 125 pts, 100 have completed the 6-month ctHPVDNA assessment. One pt had a positive ctHPVDNA result with radiographic evidence of local recurrence. One patient had a qualitative positive test (<20 copies/ml) without evidence of disease, but the following test prior to trial enrollment was negative. To date, no pts has been allocated to receive balstilimab. **Conclusions:** Persistent ctHPV DNA positivity without radiographic evidence of disease has not been observed following definitive therapy. These findings suggest that cfHPVDNA surveillance may have limited utility for early detection of minimal residual disease in this setting, thereby challenging the feasibility of ctHPVDNA–guided post-definitive intervention strategies. Clinical trial information: NCT05363709. Research Sponsor: Charles and Daneen Stiefel MD Anderson Oropharyngeal Cancer Fund; Agenus Inc; Cancer Moonshot NCI.

6070 Poster Session

Identification of tumor repopulating–like epithelial cells and a repair-dominant niche in pathological responders after neoadjuvant chemo-immunotherapy for HNSCC.

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Background: Neoadjuvant PD-1 blockade plus chemotherapy can induce deep pathologic responses in HNSCC. However, pCR is an imperfect surrogate for OS, and the prior study showed that >50% of patients achieving CR after neoadjuvant chemo-immunotherapy relapse rapidly without local therapy, suggesting post-treatment ecosystems may retain programs supporting residual cell persistence and relapse. **Methods:** We profiled tumors from treatment-naïve patients and from patients receiving neoadjuvant taxane/platinum (TP) plus PD-1 blockade with partial response or pCR using scRNA-seq and Xenium spatial transcriptomics. Integrated computational analyses mapped residual epithelial/microenvironmental programs and spatial organization, with validation by immunoblotting, flow cytometry, and mIHC. Translational strategies were evaluated in a 4NQO-induced murine model and a PD-1–resistant murine tongue cancer line. **Results:** We identified a KRT15+IL1R2+ stem-like epithelial population enriched after therapy, most prominent in pCR (61/78 patients), localized to post-treatment regression beds but not discernible on H&E. They were viable and quiescent, lacking DNA damage and cell-death activation; CytoTRACE indicated high differentiation potential, suggesting tumor-repopulating cells. Concerning the microenvironment, across the response continuum from treatment-naïve to partial pathologic response to pCR, scRNA-seq revealed stepwise enrichment of infiltrating non-exhausted cytotoxic CD8 effector T cells, consistent with progressively strengthened tumoricidal immunity. In contrast, deep responders displayed a shift toward a repair-dominant niche: macrophages progressively transitioned from CXCL9+ inflammatory monocytes to SPP1+ macrophages with reduced antigen-presentation programs and enhanced tissue-remodeling features, accompanied by enrichment of multiple repair-associated fibroblast states. Xenium further supported spatial proximity and putative interactions among IL1R2+ epithelium, macrophages, and fibroblasts, which may limited T cell–tumor contact. IL1R2 upregulation was also observed in a PD-1–resistant murine tongue cancer line. In vivo, IL-1β co-administration with PD-1 blockade attenuated treatment efficacy, whereas anti–IL-1β antibody combined with PD-1 blockade enhanced efficacy. **Conclusions:** Deep responses to neoadjuvant chemo-immunotherapy are coupled with a paradoxical repair program and enrichment of IL1R2+ stem-like epithelium that may permit residual persistence and recurrence. The IL-1β–IL1R2 axis is a translationally actionable lever to improve durability and mitigate relapse. Given residual risk even after pCR, de-escalation of local therapy (such as reducing surgical extent or altering definitive treatment strategies) warrants caution. Research Sponsor: National Natural Science Foundation of China; 82303881; 82573603.

6071 Poster Session

Inferring optimal detection of homozygous loss (homozygous deletion) in head and neck cancer: Associations with HPV status, primary disease site, and clinical outcomes.

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Background: Validated detection of homozygous loss is becoming increasingly important in clinical practice. Examples include targeting the AKT pathway in breast cancer with *PTEN* loss and ongoing multi-tumor trials of PRMT5 and MAT2A inhibitors, with *MTAP* loss serving as a key biomarker. Homozygous losses are challenging to detect and require intentional next-generation sequencing assay design and validation. We evaluated the prevalence of the most common homozygous losses in advanced head and neck squamous cell carcinoma (HNSCC) and their associations with HPV status, primary site, and clinical outcomes on standard first-line (1L) therapies. **Methods:** This study used the nationwide (US-based) de-identified Flatiron Health–Foundation Medicine head and neck cancer clinico-genomic database (FH-FMI CGDB), originating from approximately 280 US cancer clinics (~800 sites of care). Patients with advanced HNSCC who underwent tissue-based genomic profiling with FoundationOneCDx were included. First-line therapy included chemotherapy alone or in combination with cetuximab or immune checkpoint inhibitors (ICIs). Logistic regression assessed the associations of prior treatment, HPV status, and primary disease site with homozygous losses. Clinical outcomes were evaluated with Cox proportional hazards models. **Results:** Among 969 HNSCC specimens, homozygous losses were most frequent in *CDKN2A* (22.1%), *CDKN2B* (17.8%), *MTAP* (9.4%), and *PTEN* (5.3%). *CDKN2A, CDKN2B and MTAP* losses were enriched in tumors arising from the larynx and hypopharynx compared with the oral cavity and oropharynx and were largely mutually exclusive with HPV positivity. *PTEN* loss was most common in the oropharynx and was enriched in HPV-positive tumors and in metastatic liver biopsies. In univariable analysis, homozygous losses were not associated with outcomes after 1L therapy. In multivariable analysis, HPV negativity and higher ECOG scoring, but not PD-L1 status, were independently associated with worse overall survival. **Conclusions:** Using an assay that is FDA-approved to detect and report copy-number (CN) losses, homozygous losses of *CDKN2A*, *CDKN2B*, *MTAP*, and *PTEN* were frequently observed in HNSCC. These alterations were not directly associated with outcomes following 1L therapy. Similar to *CDKN2A/B* loss, *MTAP* loss was enriched in HPV-negative tumors and defines a clinically relevant subset of HNSCC (~10%) potentially eligible for emerging MTAP-targeted therapies. Research Sponsor: None.

6072 Poster Session

Comprehensive genomic profiling of adenoid cystic carcinoma using the AACR Genie Database.

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Background: Adenoid cystic carcinoma (ACC) is a rare neoplasm of the secretory glands, comprising <1% of head and neck tumors. While most commonly arising in salivary glands, ACC has also been reported in the skin, breasts, prostate, and female genital tract. Despite multimodal treatment, no standardized therapeutic approach exists, and prognosis remains poor, with a 5-year survival rate of 50-60%. This study utilizes the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database to characterize the genomic landscape of ACC and identify prognostic biomarkers and therapeutic targets. **Methods:** The AACR GENIE database was accessed via cBioPortal (v18.0-public) on December 12, 2025, to identify ACC cases. Frequently mutated genes, demographic associations, and patterns of mutual exclusivity were evaluated using two-sided t-tests and non-parametric analyses with Benjamini-Hochberg false discovery rate correction. **Results:** A total of 540 samples from 500 patients were analyzed, of whom 229 (45.8%) were male, and 266 (53.2%) were female. The cohort included 334 (66.8%) non-Hispanic patients and 39 (7.8%) Hispanic patients. By race, 334 (66.8%) were White, 46 (9.2%) Asian, and 42 (8.4%) Black. Most tumor samples were metastatic (293, 54.3%), followed by primary tumors (217, 40.2%). The most frequently mutated genes were *NOTCH1* (n=152; 28.1%), *KDM6A* (n=59; 10.9%), *ARID1A* (n=54; 10.0%), *BCOR* (n=52; 9.6%), *KMT2C* (n=44; 8.1%), and *KMT2D* (n=42; 7.7%). Sex-stratified analysis demonstrated *FH* mutations occurring exclusively in females (n=4, $p<0.001$), and a higher prevalence of *KMT2C* in female patients (n=25 vs n=8, $p<0.001$). *TET2* alterations were more frequent in males (n=8 vs n=1). Race-based analysis identified *GATA3* mutations exclusively in Asian patients (n=2; p=0.002) and a higher frequency of *FGFR3* alterations in Asians compared with non-Asian patients (n=2 vs n=1; p=0.0447). Co-occurrence was observed between *NOTCH1* and *ARID1A* (n=21/106; $p<0.001$), *CREBBP* (n=17/98; $p<0.001$), and *KDM6A* (n=22/117; p=0.003). Additional co-occurrence was noted between *KDM6A* and *ARID1A* (n=14/80; $p<0.001$), and *CREBBP* with *PIK3CA* (n=8/50; p=0.001). Mutations in *APC* (n=6; $p<0.001$), *CDK12* (n=4; p=0.05), *ELF3* (n=4; $p<0.05$), *MDM2* (n=4; $p<0.05$), and *JAK2* (n=4; $p<0.05$) were observed exclusively in primary tumors. **Conclusions:** To our knowledge, this is the first comprehensive analysis of ACC using the GENIE database. Our findings corroborate prior reports implicating *CREBBP*, *NOTCH1*, and *KDM6A* in ACC while identifying a novel demographic association with GATA3 mutations exclusive to Asian patients. These findings highlight *CREBBP*, *NOTCH1*, *KDM6A*, and *GATA3* as potential targets for future therapeutic development. Research Sponsor: None.

6073 Poster Session

Environmental exposure and prevalence of papillary thyroid cancer in West Virginia: An ecological analysis of per and polyfluoroalkyl substances (PFAS)–impacted regions.

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Background: Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants with widespread exposure through contaminated surface water, groundwater, and drinking water systems. In West Virginia, PFAS contamination has been documented across counties within the Ohio River basin and inland regions affected by industrial activity, waste disposal, and groundwater contamination. This project aimed to study the prevalence of papillary thyroid cancer at a county-level to assess geographic clustering in relation to PFAS-impacted regions and compare statewide incidence with national benchmarks. **Methods:** We conducted a statewide, county-level ecological analysis using Epic electronic health record-driven data to identify papillary thyroid cancer cases diagnosed between 2015 and 2025. County specific prevalence rates were calculated using averaged county population denominators. Relative risks (RR) with 95% confidence intervals were calculated for each county relative to the statewide thyroid cancer prevalence using Poisson-based methods. Spatial patterns were evaluated in relation to counties within the Ohio River basin, including the Monongahela and Kanawha sub-basins, as well as counties with documented or suspected PFAS-related groundwater contamination. Statewide thyroid cancer incidence was contextualized using U.S. Cancer Statistics (1999-2022). **Results:** Papillary thyroid cancer prevalence demonstrated marked geographic heterogeneity across WV, with spatial clustering observed in multiple PFAS-impacted counties. Counties with elevated prevalence demonstrated RRs ranging from approximately 1.75 to 2.75, with the highest RR observed in Harrison (RR 2.75 CI 2.35-3.22), Marion (RR 2.33 CI 1.94-2.79), Braxton (RR 2.30 CI 1.58-3.33), Barbour (RR 2.13 CI 1.50-3.00) and Webster (RR 1.98 CI 1.21-3.24) counties. All associations were statistically significant ($p < 0.05$). Many counties outside PFAS-impacted regions demonstrated RR approximating or below 1.0. At the population level, WV demonstrated a higher thyroid cancer incidence than the U.S. overall (20.5 vs 17.4 per 100,000, age-adjusted). **Conclusions:** Papillary thyroid cancer in West Virginia has a spatial clustering pattern in PFAS-impacted counties and a higher statewide incidence compared with national benchmarks. Experimental evidence provides biologic plausibility, as perfluorooctanoic acid disrupts thyroid-stimulating hormone receptor signaling, impairs N-glycosylation, and promotes pro-tumorigenic cellular pathways. Although causal inference is limited by the ecologic design, the convergence of geographic clustering and elevated statewide incidence warrants further investigation of PFAS-related papillary thyroid cancer risk using exposure-resolved individual-level analytic approaches. Research Sponsor: None.

6074 Poster Session

Discovery of gene set–based biomarkers and therapeutic targets for papillary thyroid cancer based on circulating DNA and tissue RNA.

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Background: Mutations in pathways known to promote oncogenesis in Papillary Thyroid Carcinoma (PTC) have been demonstrated in cell-free DNA (cfDNA) samples from patients with PTC, and at higher levels in patients with advanced and de-differentiated disease such as anaplastic thyroid cancer (ATC). In our study, the most frequent cfDNA mutations were associated with activation of *BRAF*-independent pathways and epigenetic regulation, suggesting a prominent role as drivers of disease in some patients. Also observed were mutations more frequently associated with dedifferentiated thyroid cancer, such as *TP53* at 10% (5/49) in cfDNA vs 2% (1/47) in tissue samples. We hypothesized that nucleosome pattern analysis on cfDNA samples from a *BRAF*-independent subgroup would reveal evidence of heightened epigenetic signaling. **Methods:** We classified PTC into two subtypes based on cfDNA mutation profiles: *BRAF*-independent pathway (BI, 35% of patients with ≥1 mutation in *KMT2A*, *ATM*, or *TP53*) and *BRAF*/alternate-mediated pathway (B/a, 65% with *ARID1A*, *BRAF*, or others). These two gene groups were mutually exclusive by co-mutation and protein interaction networks. Chromatin structure was inferred from cfDNA fragment patterns using LIQUORICE. Gene signatures and pathway scores were then analyzed via GSEA and GSVA on the tissue RNA-seq data. **Results:** Significantly higher H3K4me1 signal ($p = 0.047$) was detected in cfDNA from the BI subgroup, indicating active epigenetic enhancer states. Additional gene expression analysis on tumor tissue revealed a unique six-gene signature (FDR = 0.089) enriched in the maternal-to-zygotic transition (MZT) pathway, with GSVA scores differing markedly between BI and B/a groups ($p = 0.004$). Cross-referencing these patients with the PTC cohort data from The Cancer Genome Atlas (TCGA) showed worse disease-free survival in the BI group ($p = 0.008$) but no difference in overall survival ($p = 0.580$) between the two groups, possibly due to early-stage diagnosis. **Conclusions:** Mutations in *TP53*/*ATM*/*KMT2A*, associated with *BRAF*-independent pathways, correlate with active epigenetic states in PTC. This supports the hypothesis that epigenetic mechanisms are important drivers of progression in PTC. This study also supports a therapeutic strategy which targets these pathways, such as HDAC inhibitors previously validated in ATC cell lines and PDX models. Finally, six MZT-related genes may serve as biomarkers and regulators of epigenetic and transcriptional reprogramming important to the evolution of cancer in PTC patients. Research Sponsor: Atrium Health Foundation Grant Keep Pounding Fund.

6075 Poster Session

Intrapatient comparative analysis of tumor-informed ctDNA and ctHPV-DNA in patients with HPV-driven OPSCC.

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Background: The rising incidence of oropharyngeal squamous cell carcinoma (OPSCC) is largely attributable to human papillomavirus associated (HPV+) disease, which accounts for ~70% of OPSCC cases. Circulating tumor (ct)DNA has the potential to enable more accurate treatment response assessment, guide response-adaptive management, and detect minimal residual disease to indicate persistence or recurrence. Both mutation-based tumor-informed ctDNA and ctHPV-DNA testing have demonstrated utility in HPV+ disease, but prospective intra-patient evaluations remain limited. A direct comparison of these approaches is essential to determine redundancy versus complementarity and to guide optimal integration into OPSCC patient management. **Methods:** In an ongoing prospective study, serial plasma samples were obtained from patients with stages I-IV OPSCC undergoing curative intent treatment. Up to 50 patient specific somatic variants were selected based on tumor whole exome sequencing to develop a personalized tumor-informed next generation sequencing (NGS) ctDNA assay (Haystack MRD) for plasma analysis. In patients with HPV+ disease (determined via ISH, IHC, and/or NGS), plasma was also analyzed using an NGS-based assay interrogating 13 high-risk HPV strains (Haystack HPV). Paired intrapatient samples were analyzed using percent agreement with 95% confidence intervals and Cohen's kappa; concordance of dynamic changes was assessed using Spearman's correlation. **Results:** As of January 2026, ctDNA results were available for 111 serial timepoints from 26 patients. The median number of timepoints per patient was 4 (range 1-9). Seventeen patients (65%) had HPV+, and 9 (35%) had HPV− disease. In HPV+ patients, across 85 longitudinal samples collected during multimodal treatment and post-treatment surveillance, mutation-based ctDNA and ctHPV demonstrated high concordance (91%; 95% CI, 82.5−95.2; κ=0.80). Of 30 ctDNA+ samples, 28 were ctHPV+ (93%; 95% CI, 78.7−98.2%), while 49 of 55 ctDNA- samples were ctHPV- (89%; 95% CI, 78.2−94.9%). Discordance was infrequent (8/85, 9.4%), predominantly ctHPV+/ctDNA- (6/85, 7.1%). All ctHPV+/ctDNA- cases occurred during neoadjuvant treatment monitoring and reflected earlier clearance of ctDNA, with ctHPV clearance lagging by several weeks to months. Two low-level (<100 parts per million) ctDNA+/ctHPV- cases were observed in the adjuvant setting. When both analytes were present, dynamic changes in ctDNA and ctHPV levels were highly concordant (Spearman's ρ=0.94), although ctHPV was consistently detected at higher absolute levels. **Conclusions:** In HPV-driven OPSCC, tumor-informed ctDNA and ctHPV show high longitudinal concordance and distinct clearance kinetics, with earlier ctDNA clearance. Ongoing analyses will define how these assays can be optimally integrated into response assessment, treatment adaptation, and surveillance strategies. Research Sponsor: U.S. National Institutes of Health; U01CA230691; Cancer Research Foundation; University of Chicago Comprehensive Cancer Center (UCCCC).

Biologic and clinical implications of HPV genome state variation in oropharyngeal cancers.

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Background: HPV integration enhances carcinogenesis by ensuring viral DNA retention and increasing E6/E7 expression. Though HPV usually integrates in cervical cancer, DNA episomes persist in ~50% of HPV+ oropharyngeal cancers (OPCs), and prior studies relating integration to clinical outcomes are contradictory. Defining molecular traits and clinical behavior of episomal vs. integrated OPCs is impeded by the complexity of HPV genome states, which defy classification by any one assay. Here we classified HPV states based on concordance between HPV-host fusion mRNA detection (suggesting integration) and E6/E7 levels. Gene expression and clinical outcomes were compared among groups to seek biomarkers allowing therapeutic personalization. **Methods:** Samples were curated from 851 therapy-naïve HPV+ OPCs receiving robotic surgery at a single institution (2007-2020). RNA sequencing was performed on 50 HPV+ OPCs that later recurred (cases) and 50 that were cured (controls). Groups were matched for stage, smoking, and adjuvant therapy. OPCs were deemed likely episomal if absence of HPV-host fusion mRNA was accompanied by E6/E7 levels in the bottom tertile and likely integrated if fusion mRNA presence coincided with E6/E7 in the top tertile. These two OPC subsets were defined as E6/E7-concordant and the rest as E6/E7-discordant. Molecular traits were analyzed as previously (Sannigrahi MK et.al, *JNCI* 2025 117:7) using GSEA of Hallmark pathways and by two scores derived by GSVA of host mRNAs that potently stratified recurrence risk across multiple HPV+ OPC cohorts: (1) an immune suppression score (ISS) measuring reduced anti-tumor immunity and (2) a *t*umor progression score (*TPS*) capturing aggressive tumor cell-intrinsic traits. **Results:** In the overall cohort (n=100), the fusion (+) OPCs (n=49) had increased risk of recurrence (OR 2.90, 95% CI=1.27-6.64, p=.01). Whereas E6/E7 levels alone did not stratify recurrence risk, combining it with fusion status optimized prediction: the likely integrated OPCs (n=23) had high recurrence risk vs. likely episomal OPCs (n=24) (OR=3.81, 95% CI=1.13-12.82, p=.03) despite similar clinical characteristics in both groups. Time to recurrence was also shorter in likely integrated vs. episomal subsets (p=.02). By contrast, fusion read status did not stratify recurrence risk in the E6/E7-disconcordant OPCs (n=53). Adverse gene expression features were upregulated in likely integrated vs. likely episomal OPCs, as reflected in increased TPS (p=.04) and ISS (p=.04). These differences were absent in fusion (+) tumors of the E6/E7-discordant group. **Conclusions:** Our findings offer the most compelling evidence to date supporting independent association of HPV integration with adverse tumor biology and recurrence risk in OPCs. Jointly considering HPV-host fusion mRNAs and E6/E7 levels may guide the molecular biomarker development needed to personalize therapy based on HPV genome state. Research Sponsor: U.S. National Institutes of Health; R01DE034056; U.S. National Institutes of Health; UH2CA2675022.

Validation of Immunoscore for prognostic stratification in HPV-associated oropharyngeal cancer: An international multicenter study.

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Background: Treatment optimization in HPV-associated oropharyngeal cancer (OPSCC) remains challenging due to the limited results of de-escalation trials. Existing patient selection criteria, mainly based on smoking history and TNM classification are insufficient and highlight the urgent need for standardized prognostic biomarkers. Herein, we present the first validation of the Immunoscore (IS) as a prognostic stratification tool in HPV-associated OPSCC. **Methods:** A cohort of 191 HPV-associated ($p16^+$ and HPV DNA/RNA^+) OPSCC patients treated between 2015–2024 was analyzed, including a French training cohort (N = 48) and three independent validation cohorts: a French retrospective monocentric (N = 48), a French prospective multicenter (N = 50) and a US retrospective multicenter cohort (N = 45). IS, an IHC-based standardized clinical digital pathology assay, quantifies $CD3^+$ and $CD8^+$ cell densities in tumor cores and invasive margins of FFPE sections. IS cut-offs were defined using the 25^{th} percentile of immune cell density in the training cohort and subsequently validated across all cohorts. Associations with disease-free survival (DFS), time to recurrence (TTR), and overall survival (OS) were assessed, along with immune profiling by 3′RNA-seq and sequential immunofluorescence. **Results:** Median age 65; 80% male; 74% smokers; 66% T1-2; 82% N0-1 (AJCC 8^{th}). Treatments included surgery only (9%), radiotherapy ± chemotherapy (27%) and surgery + radiotherapy ± chemotherapy (64%). 52.4% were IS-High (N = 100) and 47.6% IS-Low (N = 91). IS-High patients showed significantly improved DFS, consistently across the training and validation cohorts 1-3 (log-rank P = 0.0004, 0.003, 0.006, and 0.001, respectively). Multivariable analysis identified IS-Low as the strongest independent risk factor for DFS (HR 9.27; 95% CI: 4.14-20.76; $P < 0.001$), outperforming smoking status, T/N stage, and treatment modality. The model combining IS with clinical factors showed higher predictive accuracy for DFS (C-index 0.82) than clinical variables alone (0.70; $P < 0.0001$). Similar strong prognostic value of IS was observed for TTR (HR 7.64; 95% CI: 3.37-17.33; $P < 0.001$) and OS (HR 7.26; 95% CI: 2.77-18.99; $P < 0.001$). IS-High tumors showed enrichment of lymphoid and myeloid immune cell populations, contrasting with immune-poor signatures in IS-Low tumors (all $P < 0.05$). **Conclusions:** IS is a robust biomarker that outperforms standard clinical variables in both prognostic and predictive accuracy. The enriched cytotoxic immune infiltrate in IS-High tumors explains favorable outcomes and supports their potential suitability for treatment de-escalation. Prospective validation in future trials is warranted. Research Sponsor: None.

Prognostic value and role in guiding individualized treatment of imaging extranodal extension (iENE) in nasopharyngeal carcinoma.

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Background: Imaging extranodal extension (iENE) is a critical prognostic factor in nasopharyngeal carcinoma (NPC). While international consensus has standardized iENE grading, its prognostic value in NPC remains to be validated. Furthermore, evidence is lacking regarding the utility of iENE-based risk stratification in guiding individualized treatment, particularly for identifying candidates benefiting from adjuvant chemotherapy (AC). **Methods:** A total of 694 non-metastatic NPC patients with cervical lymph node metastasis who received intensity-modulated radiotherapy (IMRT) at Sun Yat-sen University Cancer Center from 2016 to 2017 were included. iENE was graded based on international group consensus by two radiologists through a consensus reading protocol: G0 (no extranodal extension), G1 (infiltration of perinodal fat), G2 (matted nodes), and G3 (invasion of adjacent structures including muscles and neurovascular bundles). Progression-free survival and overall survival were analyzed using the Kaplan–Meier method and log-rank test. Multivariable Cox proportional hazards models were applied to adjust for confounders. Time-dependent receiver operating characteristic (TD-ROC) curve analysis was used to evaluate the predictive performance of clinical variables. Stratified analysis for prognosis was performed based on treatment strategies including concurrent chemoradiotherapy(CCRT), induction chemotherapy plus CCRT(IC+CCRT), and IC+CCRT followed by adjuvant chemotherapy (IC+CCRT+AC). **Results:** The cohort included 257 (37.0%) G0, 117 (16.9%) G1, 216 (31.1%) G2, and 104 (15.0%) G3 patients. Survival analysis for OS, PFS, DMFS, and LRRFS revealed that G1 patients showed a comparable prognosis to G0 patients(5-year PFS: 82.1% vs. 89.1%, $P > 0.05$), whereas G2 and G3 patients exhibited significantly worse outcomes; therefore, G0 and G1 were combined into a low-risk subgroup. Multivariable analysis adjusting for T stage, N stage, volume of maximal lymph node, clinical stage, and treatment regimens confirmed that the refined iENE grading was an independent prognostic factor for PFS (G2 vs. G0/1: HR 1.77, 95% CI 1.25–2.51, $P = 0.001$; G3 vs. G0/1: HR 1.90, 95% CI 1.08–3.36, $P = 0.027$). TD-ROC curve demonstrated that the predictive performance of iENE for 1-, 3-, and 5-year PFS and OS was superior to that of T stage and pre-treatment EBV DNA. Most importantly, subgroup analysis indicated that the addition of AC significantly improved PFS outcomes in the G2/G3 subgroup ($P = 0.006$ and $P = 0.009$, respectively), whereas no survival benefit was observed in the low-risk G0/G1 subgroup ($P = 0.133$). **Conclusions:** The refined iENE grading system provides robust risk stratification for NPC. This system outperforms traditional biomarkers like EBV DNA, better distinguishing prognostic outcomes in patients and effectively guiding the application of intensified treatment. Research Sponsor: None.

Prognostic significance of imaging-detected extranodal extension (iENE) in pathological ENE-negative head and neck squamous cell carcinoma.

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Background: Advances in perioperative systemic therapy for head and neck squamous cell carcinoma (HNSCC) (e.g., KEYNOTE-689) have increased the need to tailor postoperative management, balancing oncologic benefit against toxicity and resource constraints. Imaging-detected extranodal extension (iENE) has been incorporated as a potential prognostic factor in the UICC TNM 9th edition. However, the prognostic impact of iENE among patients without pathological extranodal extension (pENE) remains unclear. We evaluated the association between iENE status and clinical outcomes in pENE-negative HNSCC. **Methods:** We retrospectively reviewed patients with HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx, radiologically suspected lymph node metastasis, and underwent primary surgery with neck dissection without adjuvant therapy, between 2012 and 2021. Eligible patients had pathologically confirmed lymph node metastasis, negative surgical margins, and no evidence of pENE. Preoperative iENE status was assessed by board-certified radiologists. Survival endpoints included event-free survival (EFS) and overall survival (OS). Patients were stratified into low-risk (non-candidates for adjuvant therapy) and intermediate-risk (candidates for postoperative radiotherapy alone) groups according to NCCN guidelines. **Results:** Of 3,771 screened patients, 133 met the eligibility criteria (low-risk: 20, intermediate-risk: 113), of whom 41 (30.8%) were iENE-positive. At a median follow-up of 60.6 months, iENE-positive patients demonstrated poorer outcomes than iENE-negative patients, including shorter EFS (5-year: 33.1% vs 55.4%; hazard ratio [HR], 1.69; p=0.029). The association between iENE positivity and inferior EFS was observed consistently across both risk strata. Overall survival also favored iENE-negative patients (5-year: 80.4% vs. 68.7%). On multivariate analysis, iENE positivity, ECOG Performance Status ≥1, and lower baseline serum albumin were independently associated with poorer EFS. Patients meeting none of the three factors had excellent outcomes despite omission of adjuvant therapy (5-year EFS: 69.8%, 5-year OS: 88.0%). **Conclusions:** iENE may help identify an unfavorable-prognosis subset among pENE-negative HNSCC patients. The study cohort predates the routine use of perioperative immunotherapy, and the generalizability of these findings in contemporary treatment settings requires prospective validation. Research Sponsor: None.

Five-year EFS by iENE status: Overall and by risk group.

Group	iENE status	5y-EFS	HR (95% CI)	P-value
ALL (n = 133)	Positive	33.1%	1.69 (1.05-2.71)	0.029
	Negative	55.4%	Ref.	
Intermediate risk (n = 113)	Positive	34.2%	1.57 (0.94-2.63)	0.08
	Negative	51.9%	Ref.	
Low risk (n = 20)	Positive	28.6%	3.57 (0.85-15.04)	0.06
	Negative	76.9%	Ref.	

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A phase 3, randomized, double-arm, open-label, controlled study of ASP-1929 photoimmunotherapy (PIT) versus physician's choice standard of care (SOC) for patients with locoregional, recurrent head and neck squamous cell carcinoma (HNSCC).

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Background: Locoregional recurrence is the main cause of morbidity and mortality in HNSCC, yet therapeutic choices are limited by sequelae of previous treatment and the potential for significant loss of function. ASP-1929 PIT is a novel cancer-targeted technology, utilizing an anti-EGFR monoclonal antibody conjugated to the dye IR700, that is activated by 690 nm light to induce rapid selective tumor cell destruction and trigger immune response. **Methods:** This global phase 3 study was conducted at 40 study centers located in the US, Taiwan, Japan, India, and Ukraine. Patients with locoregionally recurrent HNSCC who had failed or progressed on or after at least 2 lines of therapy were randomized 2:1 to the PIT arm or SOC. The planned sample size was 275. In the PIT arm, each cycle consisted of ASP-1929 infusion (640 mg/m^2) on Day 1, followed 24 ± 4 hours later by illumination (50 J/cm^2 superficial and/or 100 J/cm interstitial). Retreatment occurred ≥4 weeks apart, based on tumor response, for up to 8 cycles. In the control arm, patients received the physician's choice of standard of care (docetaxel, cetuximab, methotrexate, or paclitaxel) until disease progression, intolerable adverse effects, or discontinuation of study treatment. Safety and efficacy outcomes were evaluated, with a data cutoff of 30 April 2025. **Results:** Active patient enrollment was discontinued due to challenges in patient recruitment and changes in the SOC landscape. As of 17 December 2024, 135 patients had been enrolled, with 68 patients experiencing progression or death and 36 patients in the ongoing long-term survival follow-up phase of the study. Median age was 62.0 years; 80.7% were male. In PIT and SOC arms, 64.0% and 63.0% of patients had received ≥ 3 prior therapy lines. Despite similar progression-free survival (HR 0.91; 95% CI 0.24 - 3.45), median overall survival was 15.7 months in the PIT arm compared to 9.6 months in the SOC arm (HR 0.83; 95% CI 0.50 - 1.36). Objective response rate was 25.8% in the PIT arm and 15.2% in the SOC arm, and disease control rate was 68.5% and 43.5%, respectively. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 58.3% of patients in the PIT arm and 36.4% of patients in SOC; however, fewer TEAEs led to dose modification, delay, or interruption in the PIT arm (15.5% vs 30.3%). **Conclusions:** Considering the limitations of the study data, these results support ASP-1929 PIT as a tolerable and clinically active treatment option for locoregional, recurrent HNSCC and its ongoing evaluation in the current randomized global Phase 3 ASP-1929-381 study. Clinical trial information: NCT03769506. Research Sponsor: Rakuten Medical Inc.

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Efficacy of neoadjuvant immunochemotherapy followed by surgery in locally advanced buccal squamous cell carcinoma: A single-center real-world study.

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Background: The 5-year overall survival (OS) rate for locally advanced (stage III–IV) buccal squamous cell carcinoma (LA BSCC) is under 50%. In stage IV disease, the 2-year OS rate is under 45%, and the 5-year OS rate is under 30% (29.3% for the anterior buccal and only 18.7% for the posterior buccal). Evidence is limited regarding whether betel nut chewing and tumor subsites influence the efficacy of neoadjuvant immunochemotherapy. **Methods:** Retrospective analysis of 115 patients with LA BSCC received neoadjuvant therapy at Hunan Cancer Hospital between August 2021 and October 2024. Treatment regimen: Neoadjuvant albumin-bound paclitaxel plus cisplatin or carboplatin combined with a PD-1 inhibitor, followed by definitive surgery. Postoperative adjuvant radiotherapy or chemoradiotherapy was administered based on pathological findings. Primary endpoint: Pathological complete response and major pathological response (pCR/MPR) rate; Secondary endpoints: Overall survival (OS) and disease free survival (DFS) at 1 and 2 years; Subgroup analyses: Outcomes were evaluated by betel nut chewing history, tumor subsite, and TNM stage. **Results:** Of 113 evaluable patients, 16% had stage III and 84% had stage IV disease. A history of betel nut chewing was present in 71.9%. The objective response rate to neoadjuvant therapy was 83.5%, including a 28.3% clinical complete response rate. 98 patients proceeded to surgery; the pCR/MPR rate was 27.6%, and the partial pathological response (pPR) rate was 52.0%. With a median follow-up of 29 months (15-53 months), 1-year OS and DFS rates were 80.5% and 74.3%, respectively; 2-year OS and DFS rates were 70.0% and 67.5%, respectively. 2-year OS did not differ significantly by betel nut chewing (P=0.8578) or by tumor subsite (anterior vs posterior buccal; P=0.5568). More advanced TNM stage was associated with poorer survival (P=0.0352). Patients achieving pCR or MPR had significantly better 2-year OS and DFS than those who did not (P=0.0386 and P=0.0102, respectively). Grade≥3 adverse events occurred in 18% of patients and no treatment-related deaths were observed. **Conclusions:** Neoadjuvant immunochemotherapy increased the 2-year OS rate of LA BSCC to 70%, with the 27.6% pCR/MPR rate. Treatment efficacy did not differ by betel nut chewing or by tumor subsite, whereas TNM stage remained an independent prognostic factor. Deep pathological response (pCR/MPR) was associated with superior long-term outcomes. Research Sponsor: None.

	Number	2-yr OS rate(%)	p value	2-yr DFS rate(%)	p value
Tumor stage					
III	18/113	88.89	0.1558	78.75	0.0352
IVa	64/113	71.12		66.54	
IVb	31/113	54.17		39.13	
Tumor subsite					
Anterior buccal	88/113	69.85	0.5568	60.30	0.9963
Posterior buccal	25/113	64.29		60.00	
Pathological response rate					
pCR+MPR	27/98	78.95	0.0386	78.95	0.0102
pPR	51/98	83.43		72.66	
SD+PD	21/98	54.55		47.37	
Betel nut use					
+	82/113	69.22	0.8578	60.02	0.9238
-	31/113	67.88		60.87	

Phase II randomised controlled trial on postoperative radiotherapy, in high-risk, resected, non-medullary, non-anaplastic thyroid cancers (THYRO-RT).

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Background: Locally advanced thyroid cancers have high rates of locoregional recurrence after standard treatment with surgery and radioactive iodine (RAI). Repeated surgery and RAI in recurrent disease contributes to significant morbidity. Retrospective studies have shown that the addition of adjuvant external beam radiotherapy (EBRT) may improve locoregional control in selected high-risk patients. This randomized phase II trial evaluated the role of adjuvant EBRT in reducing locoregional recurrence (LRR) in high-risk resected thyroid cancer. **Methods:** This was a phase II randomized controlled trial comparing surgery with RAI versus surgery with RAI plus EBRT in high-risk resected thyroid cancers. Patients with resected non-medullary, non-anaplastic thyroid cancer and predefined high-risk features were randomized (1:1) between July 2013 and April 2021. Patients randomized to EBRT received 6-MV IMRT with daily IGRT to a dose of 60 Gy in 30 fractions over six weeks. The primary endpoint was locoregional recurrence. Secondary endpoints included acute and late toxicity (LENT-SOMA scale) and quality of life. **Results:** Seventy-two patients were randomized, with 36 assigned to each arm; five patients withdrew consent. Overall, 86.6% had pathological T4a disease and 89.6% had pathological N1a/b disease. Further, 71.6% demonstrated extracapsular nodal extension and R1/R2 resection was seen in 49.3% of the patients. With a median follow-up of 102 months, on an intention to treat analysis, LRR occurred in 19.4% of patients in the surgery + RAI arm (OR 1.376, 95% CI 0.852-2.222), and 9.7% in the Surgery+RAI+EBRT arm (OR 0.611, 95% CI 0.299-1.632). This difference was not statistically significant (p = 0.263). Logistic regression analysis did not identify any factor significantly associated with LRR. There was no significant difference in 10 year-locoregional recurrence free survival between the two arms. Grade 3 acute radiation induced toxicity was observed in two patients. At last follow up, there was one death in the entire cohort, which was non-cancer related. **Conclusions:** In this very high-risk, resected thyroid cancer cohort, the addition of adjuvant EBRT to surgery and RAI did not significantly decrease locoregional recurrence. The overall acute toxicity was low and if adjuvant EBRT is indicated, it can be delivered with acceptable toxicity. Clinical trial information: NCT03669432. Research Sponsor: Department of Atomic Energy- Clinical Trials Unit, Government of India.

C-POST study of adjuvant cemiplimab for high-risk cutaneous squamous cell carcinoma (CSCC): Disease-free survival (DFS) analyses per high-risk criteria and per start time after radiotherapy.

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Background: C-POST, a phase 3 trial (NCT03969004) in patients (pts) with high risk CSCC after surgery and radiotherapy (RT), demonstrated superior disease-free survival (DFS) for adjuvant cemiplimab (cemi) vs placebo (pbo) (HR, 0.32; $P<0.0001$); treatment discontinuation due to adverse events occurred in 9.8% vs 1.5% of pts (Rischin, et al. *N Engl J Med*. 2025). With approximately 6 months of additional follow-up, we present exploratory analyses of DFS per high-risk criteria and per the interval between completion of prior RT and study randomization (2-6 wk vs >6 wk). These additional analyses provide key data to understand the importance of risk factors and the impact of time post RT. **Methods:** Pts were randomized 1:1 (N=415) to adjuvant cemi or pbo (350 mg cemi or pbo Q3W for 12 wk, then 700 mg cemi or pbo Q6W for 36 wk). All pts had nodal high-risk disease (with extracapsular extension [ECE] and ≥1 node ≥20 mm, or ≥3 nodes regardless of ECE) and/or non-nodal high-risk disease (in-transit metastases, perineural invasion, T4 lesions, or recurrent CSCC with ≥1 other feature). Tumors could meet ≥1 high-risk criteria. Randomization occurred within 2-11 wk after completion of RT. Data cutoff was April 7, 2025. **Results:** Among 415 pts (209/206 cemi/pbo) randomized, the DFS HR was 0.35 (95% CI, 0.23-0.55) at a median follow-up of 30 months. The most common high-risk criterion was nodal ECE, present in 48.4% of pts (201/415). DFS was improved with cemi vs pbo across all high-risk features, including both nodal and non-nodal criteria (Table 1). A consistent benefit was observed regardless of whether the interval between prior RT completion and study randomization was 2-6 wk (DFS events, 17/117 [14.5%] vs 37/112 [33.0%]; HR, 0.39; 95% CI, 0.22-0.70) or >6 wk (DFS events, 12/91 [13.2%] vs 31/93 [33.3%]; HR, 0.36; 95% CI, 0.19-0.71). **Conclusions:** In this phase 3 study, adjuvant cemi demonstrated a DFS benefit vs pbo across all high-risk features and regardless of the interval between prior RT completion and randomization. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals Inc. and Sanofi.

DFS with cemi vs pbo: Analyses per high-risk criteria.

Criteria[a]	Met high risk criteria, n/N (%)	DFS events in cemi arm, n/N (%)	DFS events in pbo arm, n/N (%)	DFS HR (95% CI)
Nodal high risk				
ECE with ≥1 node ≥20 mm	201/415 (48.4)	14/105 (13.3)	27/96 (28.1)	0.44 (0.23-0.84)
≥3 nodes	71/415 (17.1)	7/34 (20.6)	18/37 (48.6)	0.34 (0.13-0.92)
Non-nodal high risk				
In-transit metastases	41/415 (9.9)	2/20 (10.0)	9/21 (42.9)	0.07 (0.01-0.58)
T4 lesion	33/415 (8.0)	6/17 (35.3)	5/16 (31.3)	0.58 (0.16-2.11)
Perineural invasion	64/415 (15.4)	3/32 (9.4)	8/32 (25.0)	0.27 (0.07-1.04)
Recurrent CSCC with ≥1 additional high-risk criteria	105/415 (25.3)	9/55 (16.4)	22/50 (44.0)	0.19 (0.08-0.45)

[a]Tumors could meet ≥1 high-risk criteria.

6084 Poster Session

Evaluation of a tissue-free genome-wide methylome enrichment assay for detecting molecular residual disease (MRD) in patients with head and neck squamous cell carcinoma (HNSCC).

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Background: Squamous cell carcinomas comprise ~90% of head and neck cancers (HNCs). Although ~80% of patients with HNSCC are eligible for curative therapy, an estimated 20% to 35% will develop recurrence, typically within 2 years. Recurrence is associated with poor survival, but early detection may enable salvage therapy. We previously reported clinical validation of a tissue-free, genome-wide methylome enrichment MRD assay for recurrence detection in HNC. Here we present performance of an updated classifier in a subset of patients with HNSCC. **Methods:** Test performance was evaluated using blood samples collected at ~3 (landmark), 12, and 24 mo after curative-intent treatment from patients with stage I-IVb HNSCC. MRD testing was performed using an assay based on cell-free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq) as previously described (Liu et al. *Ann Oncol.* 2025;36(1):108-117). To improve test performance and clinical actionability, we evaluated the effect of defining an *indeterminate* test category near the classifier threshold. An updated classifier defining 5% of training samples as *indeterminate* was analyzed in a training set, followed by a pre-specified clinical validation analysis. The primary endpoint was recurrence-free survival (RFS), comparing patients with MRD detected vs not detected. RFS was estimated using the Kaplan-Meier method, with differences assessed by the 2-sided log-rank test. Hazard ratios (HR) were estimated using the Cox proportional hazards model. **Results:** Among 117 patients in the validation set, median follow-up was 65.3 mo. MRD detection during surveillance was strongly associated with inferior RFS (HR, 54.5 [95% CI, 18.4-161.2]), an improvement over the previously reported HR of 35.7. Lead time between MRD detection and clinical recurrence was up to 10.8 mo (mean, 3.3 mo). MRD detection was also prognostic for OS (HR, 89.3 [11.8-676.4]). The updated classifier showed improved performance, with a sensitivity of 86.7% (26/30) and a specificity of 97.7% (85/87) for recurrence detection. Positive predictive value was 92.9% (26/28); negative predictive value was 95.5% (85/89). Performance was similar (P=0.24) among patients with HPV-positive oropharyngeal carcinoma (n=52) vs HPV-negative disease (n=65), patients with stage I-II (n=72) vs stage III-IVb (n=45) disease (P=0.20), and patients with surgery (n=34) vs non-surgical (n=83) definitive treatment (P=0.37). **Conclusions:** This study demonstrates that tissue-free, blood-based MRD testing using a genome-wide methylome enrichment platform is prognostic for recurrence in patients with HNSCC treated with curative intent, regardless of stage, HPV status, or treatment modality. The platform offers a robust, sensitive approach for early detection of recurrence in a broad patient population. Research Sponsor: Adela, Inc.

6085 Poster Session

Neoadjuvant chemotherapy with/without PD-1i in locally advanced laryngeal/hypopharyngeal cancer: A multicentered retrospective study.

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Background: The efficacy of adding programmed death-1 (PD-1) inhibitors to neoadjuvant chemotherapy (NACT) for improving survival in locally advanced laryngeal/hypopharyngeal carcinoma remains unclear. This study aimed to compare progression-free survival (PFS) between patients receiving NACT with or without a PD-1 inhibitor (NACT+PD-1i). **Methods:** This multicenter retrospective study enrolled 267 patients with T2-4N0-3M0 laryngeal/hypopharyngeal squamous cell carcinoma who received NACT with (n=165) or without (n=102) a PD-1 inhibitor, followed by definitive radiotherapy, between 2019 and 2024, from Fudan University Shanghai Cancer Center, Fujian Cancer Hospital and Sun Yat-sen University Cancer Center. The primary endpoint was PFS. Inverse probability of treatment weighting (IPTW) was used to adjust for baseline imbalances. **Results:** The NACT+PD-1i group demonstrated significantly improved PFS versus NACT alone (median PFS: not reached vs. 33.0 months; hazard ratio [HR]=0.61, 95% confidence interval [CI]: 0.41–0.90; p=0.012). The 2-year PFS rates were 70.2% and 56.5%, respectively. This PFS benefit persisted after IPTW (p=0.012). PD-1 inhibition was an independent favorable factor for PFS in multivariable analysis (unadjusted, HR=0.54, p=0.005; IPTW-adjusted, HR= 0.63, p=0.040). Notably, the NACT+PD-1i group showed superior regional recurrence-free survival (RRFS) (2-year RRFS: 92.1% vs. 81.0%; HR=0.31, p=0.001) and higher objective response rate (ORR) (93.9% vs. 85.9%, p=0.027), particularly for cervical lymph nodes (94.2% vs. 81.6%, p=0.002). Achieving an ORR after neoadjuvant therapy was a strong predictor for improved outcome, either in unadjusted PFS (HR=0.40, p=0.0005) or in IPTW-adjusted PFS (HR=0.49, p=0.0005). **Conclusions:** In this real-world analysis, adding a PD-1 inhibitor to NACT significantly improved ORR and PFS in locally advanced laryngeal/hypopharyngeal carcinoma, supporting its further evaluation in neoadjuvant strategies. Research Sponsor: None.

Induction toripalimab and chemotherapy for organ preservation in locally advanced laryngeal and hypopharyngeal cancer: 3-year follow-up of the INSIGHT study.

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Background: This phase II study evaluated the efficacy and larynx-preservation potential of induction chemotherapy combined with the toripalimab in patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma (LA-L/HPSCC). Primary and 1-year survival outcomes were previously reported; here we present the 3-year follow-up results. **Methods:** This is a single-arm phase II study. Patients with histopathologic confirmed, resectable LA-L/HPSCC and ECOG PS 0-1 were eligible. Three cycles of induction chemotherapy (paclitaxel 175mg/m^2 d1, cisplatin 25mg/m^2 d1-3) combined with toripalimab (240mg d0) were administered. Response assessment was performed after induction chemoimmunotherapy using RECIST 1.1 criteria. Patients with CR/PR of primary tumor received concurrent chemoradiation, followed by maintenance therapy of toripalimab. Otherwise, patients were referred to surgery, followed by adjuvant (chemo)radiation, and maintenance therapy of toripalimab. The primary endpoint is larynx-preservation rate at three months post-radiation. Secondary endpoints included overall survival (OS), progression-free survival (PFS), larynx preservation rate, and larynx-preservation survival (LPS), etc. **Results:** Twenty-seven patients were enrolled. Most cases exhibited stage IV disease (81.5%), with T4 representing 37.0%. Five patients underwent pretreatment tracheostomy. The date of data cut-off was Jan 23, 2026. With a median follow-up of 36.4 [95%CI: 33.4-39.4] months, 3-year OS rate, PFS rate, larynx preservation rate and LPS rate was 73.5%, 61.1%, 84.3% and 73.6%, respectively. Excluding patients with pretreatment tracheostomy, these rates improved to 86.4%, 70.8%, 90.2% and 81.1%. The 3-year larynx preservation rate for T2/3 and T4 disease was 92.9% and 70.0%, respectively (p=0.081). All patients with preserved larynx at last follow-up maintained functional laryngeal status, free from tracheostomy or feeding tube dependence. **Conclusions:** Induction toripalimab combined with chemotherapy provided promising and durable larynx preservation rate in this cohort of extensively LA-L/HPSCC. Clinical trial information: NCT04995120. Research Sponsor: National Natural Science Foundation of China; 82072951; Chinese Society of Clinical Oncology Foundation; Y-Young2021-0127.

Comparison of patients enrollment and survival among pivotal clinical trials.

Study	Phase	Clinical Stage	Larynx preservation rate at 3 year	Progression-free rate at 3 year
GORTEC 2000-01	III	Stage III, IV Hypopharynx 54.0%, larynx 46.0%	70.1% for TPF and 57.5% for PF	58% for TPF and 44% for PF
Subgroup analysis of TAX324	II	Stage III 26.5% Stage IV 73.5%, Hypopharynx 46.4%, larynx I 64.5%	Not available	43% for TPF and 29% for PF
This study	II	Stage III 18.5% Stage IVa 33.3% Stage IVb 48.1% Hypopharynx 66.7%, larynx 33.3%	84.3% for whole cohort and 90.2% when excluding patients with pretreatment tracheostomy	61.1% for whole cohort and 70.8% when excluding patients with pretreatment tracheostomy

6087 Poster Session

A prospective trial of single-dose neoadjuvant PD-1 blockade with or without a CD40 agonist in HPV-negative HNSCC.

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Background: Neoadjuvant PD-1 blockade is approved for resectable locally advanced HPV-negative HNSCC, but major pathologic response rates are <10%, underscoring the need for effective combination strategies. Agonists of the TNF receptor superfamily member CD40 can reverse dendritic cell dysfunction, a key mediator of immune resistance, and may combine with PD-1 blockade to enhance anti-tumor T cell recruitment. We investigated the safety and immunologic effects of combination neoadjuvant PD-1 blockade with CD40 agonism. **Methods:** We enrolled 20 patients with resectable HPV-negative HNSCC; 10 received a single intravenous dose of PD-1 inhibitor (LVGN3616, 300mg), and 10 received a PD-1 inhibitor (LVGN3616, 300mg) in combination with a CD40 agonist (LVGN7409, 1mg/kg), administered prior to surgical resection (window, 4-28 days). Pre-treatment biopsies, post-treatment surgical specimens, and peripheral blood samples were collected. The primary endpoint was safety, with secondary endpoints including pharmacodynamic immune changes and pathologic responses. **Results:** Median age was 65 years (range, 39-79); 16 (80%) were male; 16 (80%) were White; 18 (90%) had oral cavity cancer (2 larynx); and 17 (85%) had PD-L1 CPS ≥1. Baseline demographics and PD-L1 were well-balanced between arms. Neoadjuvant immunotherapy was administered a median of 9 days (range, 5-19) before surgery, with no surgical delays observed. Treatment was well tolerated; grade 3/4 events occurred in 12/20 patients, nearly all attributable to post-surgical complications and unrelated to study drug. The only treatment-related grade 3/4 events were transient elevations in liver enzymes seen in two patients in the PD-1+CD40 arm. With a minimum of 6 months' follow-up, 3/20 patients (1 in PD1 arm, 2 in PD1+CD40 arm) had progressed. Serum analyses revealed that combined PD-1 and CD40 agonist therapy induced significant increases in multiple cytokines including IL-15 ($p=0.0084$), IP-10 ($p=0.0379$), MCP-1 ($p=0.0002$), MDC ($p<0.0001$), and MIG ($p=0.0178$) at 24 hours, indicating enhanced immune activation. A biomarker-driven inflammatory score based on baseline LCN2 and SAA levels predicted pathological response with 85% accuracy, 71.4% sensitivity, and 92.3% specificity (Fisher's exact $p=0.0072$). Pathologic tumor response (pTR) was observed in 3/10 patients in the PD-1 arm (pTR1, 10-49%) and 4/10 patients in the PD-1+CD40 arm (including one pTR2 with 85% regression. Multiplex IHC was performed on tissue samples using CD3, Ki67, PD-L1, CD8, FOXP3, CD68, and panCK markers; quantitative spatial analyses are ongoing and results will be presented. **Conclusions:** Single-dose neoadjuvant PD-1 blockade combined with a CD40 agonist for HPV-negative HNSCC was safe, did not delay surgery, and produced modestly improved pathologic regressions that correlated with a cytokine-based baseline inflammatory score. Clinical trial information: NCT06159621. Research Sponsor: Conquer Cancer, the ASCO Foundation; Abramson Cancer Center.

6088 Poster Session

Baseline skeletal muscle index as an independent prognostic factor in locally advanced head and neck squamous cell carcinoma: A post hoc analysis of the REACH trial.

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Background: The prognosis for locally advanced squamous cell carcinoma of the head and neck (LAHNSCC) is heterogeneous. A low skeletal muscle mass index (SMI) assessed by computed tomography reflects sarcopenia and is associated with a poor prognosis. However, evidence-based data on HNSCC remain scarce. Moreover, the prognostic value of SMI in patients treated with radiotherapy combined with different systemic treatments remains unclear. **Methods:** This is a post hoc analysis of the REACH trial (NCT02999087), conducted between 2017 and 2020, which treated LAHNSCC in two cohorts. Patients eligible (fit) for cisplatin were randomized between radiotherapy with cisplatin and radiotherapy with cetuximab-avelumab; those ineligible for cisplatin (unfit) were randomized between radiotherapy with cetuximab and radiotherapy with cetuximab-avelumab. Baseline SMI was assessed on a C3 vertebral slice using radiotherapy planning computed tomography and analyzed as a continuous variable. Associations of SMI with disease-free survival (DFS) and overall survival (OS) were assessed using Cox proportional hazards models, with multivariable adjustment for performance status, age, stage, p16 status, treatment and cisplatin fit/unfit status. Model performance was internally validated using bootstrapping. **Results:** Among the 694 patients included in REACH, SMI analysis was available for 623 patients (90%). Only the analyses performed for the 507 men are presented. Among them, 312 (62%) were eligible for cisplatin and 195 (38%) were ineligible. Median SMI was 47 (range 32-66) kg/m^2, with no difference according to the fit/unfit status and treatment received. A higher SMI was observed in patients with ECOG 0 (vs 1, $p<0.0001$), younger patients (<65y, $p=0.01$) but not according to tumor stage (III vs IV). There was a linear relationship between SMI and DFS with a better DFS as SMI rises in both univariate (HR 0.81 every 5 SMI units, $p<0.0001$) and multivariate analyses (HR 0.88/5 units, $p=0.013$). Comparable results were observed for OS, with a significant linear relationship between SMI and OS (HR of death 0.76/5 units, $p<0.0001$, univariate analysis; HR 0.86/5 units, $p=0.015$, multivariate analysis). Other independent factors associated with improved OS were a p16+ oropharynx tumor, ECOG 0 (vs 1), Stage III tumor (vs IV) and eligibility for cisplatin. The prognostic impact of SMI was consistent across fit/unfit cohorts and treatment arms, with no significant interaction detected. **Conclusions:** Baseline SMI determined on C3 is a strong and independent prognostic factor for DFS and OS in patients with LAHNSCC treated with radiotherapy with cisplatin, radiotherapy with cetuximab, or radiotherapy with cetuximab and avelumab. The association between SMI and clinical outcomes is linear, arguing against the use of arbitrary prognostic thresholds for SMI. Research Sponsor: None.

6089 Poster Session

Four cycles of tislelizumab plus GP regimen as neoadjuvant therapy for high-risk (T4/N3) locally advanced nasopharyngeal carcinoma.

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Background: The efficacy of standard chemoradiotherapy for locally advanced nasopharyngeal carcinoma (LANPC) is still unmet need, especially for stage IVa(T4/N3, AJCC 8th) NPC. The efficacy and safety of the 4 cycles neoadjuvant chemotherapy strategy in stage N2-3 LANPC has been confirmed. Meanwhile, immunotherapy has showed favorable tumor response and survival benefit for patients with LANPC. Therefore, this study investigated the efficacy and safety of four cycles tislelizumab plus GP regimen as neoadjuvant therapy for high-risk LANPC. **Methods:** Patients with stage IVa (T4/N3, AJCC 8th) NPC were enrolled and treated with neoadjuvant therapy (gemcitabine, 1000 mg/m^2, on days 1 and 8, cisplatin, 80 mg/m^2, on day 1, tislelizumab 200mg, on day 1) every 3 weeks for 4 cycles followed by standard concurrent chemoradiotherapy. The primary endpoint was complete response (CR) rate after neoadjuvant therapy. Secondary endpoints included overall response rate (ORR) after neoadjuvant therapy, disease-free survival, overall survival, and tolerance. **Results:** From February 2022 to June 2022, 25 patients were enrolled and 24 evaluable patients (median age 49 years old; 15 men [62.5%]) completed protocol-specified 4 cycles neoadjuvant therapy without delaying radiotherapy. 1 patient was withdrawn from the trial due to treatment of acute viral parotitis. The CR rate was 50% (12/24), achieving the predefined endpoint. The ORR of all evaluable patients was 91.7%. By the cut-off date of Jan 15th 2026, the median follow-up time was 44.8 months. The median disease-free survival was not reached and 36-month disease-free survival was 91.7%(95% CI 70.6%–97.8%). Two patients died of diseases not related to nasopharyngeal carcinoma and treatment, while the other patients still have no disease progression. 13 (52%) of 25 patients had grade 3-4 acute treatment-related adverse events (TRAE). Grade 1-2 immune-related adverse events (irAE) was recorded in 18 patients (72%). No grade 3-4 irAEs occurred. 3 (12%) of 25 patients had long-term TRAEs. **Conclusions:** Four cycles of tislelizumab plus GP regimen as neoadjuvant therapy demonstrated promising tumor response, long-term survival benefit and manageable safety profile in high-risk LANPC patients. Clinical trial information: ChiCTR2200056941. Research Sponsor: None.

Mandibular preservation with neoadjuvant tislelizumab plus platinum-doublet chemotherapy in locally advanced resectable oral squamous cell carcinoma: A prospective phase II trial.

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Background: Segmental mandibulectomy for locally advanced oral squamous cell carcinoma (OSCC) severely compromises quality of life. In patients without radiographic mandibular invasion but still requiring mandibulectomy to achieve negative margins, effective tumor downstaging strategies that enable mandibular preservation are of major clinical importance. Neoadjuvant chemo-immunotherapy may reduce tumor burden, potentially enabling less radical resection and mandibular preservation. This study aimed to evaluate the efficacy and safety of mandibular preservation using neoadjuvant tislelizumab plus platinum-doublet chemotherapy in resectable locally advanced OSCC. **Methods:** This phase II, open-label, single-arm trial enrolled previously untreated patients with locally advanced, resectable OSCC (stage III-IVB, T3-T4N0-3M0) necessitating mandibulectomy based on conventional surgical criteria despite the absence of definitive clinicoradiologic mandibular invasion. Neoadjuvant treatment consisted of tislelizumab (200 mg), docetaxel (75 mg/m^2) and cisplatin (60 mg/m^2) on day 1 of each 21-day cycle for three cycles. All patients then proceeded to surgery. The primary endpoint was mandibular preservation rate. Secondary endpoints included pathological complete response (pCR), major pathological response (MPR), margin-negative resection (R0) rate, objective response rate (ORR), progression-free survival, disease-free survival, overall survival and treatment-related adverse events (TRAEs). **Results:** Between October 2023 and September 2025, a total of 53 patients were enrolled, and 49 were evaluable. All 49 patients completed three cycles of neoadjuvant therapy and underwent surgery. The mandibular preservation rate was 95.9% (47/49), and all patients achieved R0 resection. The ORR was 79.6% (39/49) and the pCR rate was 51.0% (25/49). TRAEs occurred in 100% (49/49) of patients. Grade 3 TRAEs were reported in 10.2% (5/49), including leukopenia, fatigue, and hypertension. No grade 4–5 TRAEs were observed. **Conclusions:** Neoadjuvant tislelizumab combined with platinum-doublet chemotherapy achieved a high mandibular preservation rate and a favorable pathological response profile with manageable toxicity in patients with locally advanced, resectable OSCC. This strategy represents a promising organ-preserving approach. Longer follow-up is ongoing to determine long-term survival outcomes. Clinical trial information: NCT06130007. Research Sponsor: None.

Neoadjuvant immunotherapy in combination with chemotherapy in resectable locally advanced head and neck squamous cell carcinoma: Updated efficacy and safety data from a randomized phase II trial.

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Background: Neoadjuvant immunotherapy combined with chemotherapy is a promising strategy for resectable LAHNSCC. While most regimens employ single-target PD-1 inhibitors, dual-target agents (PD-1/CTLA-4 or PD-1/VEGF) have shown superior efficacy in recurrent/metastatic HNSCC. Building on our preliminary data (ASCO 2025) which suggested high pathological response rates, this ongoing randomized phase II trial aims to compare single- versus dual-target NAI regimens in an expanded cohort to identify the optimal treatment strategy. **Methods:** This is an ongoing randomized, open-label, phase II trial. Eligible pts were randomized (1:1:1) to receive 3 cycles of neoadjuvant therapy as follows: Cohort 1 will receive ivonescimab (PD-1/VEGF bispecific antibody, 10 mg/kg every 3 weeks), Cohort 2 will receive cadonilimab (PD-1/CTLA-4 bispecific antibody, 6 mg/kg every 3 weeks), and Cohort 3 will receive penpulimab (PD-1 antibody, 200 mg every 3 weeks), all in combination with cisplatin and nab-paclitaxel. After neoadjuvant treatment, Surgery was performed with the surgical margins based on pre-treatment (baseline) evaluation. Pts with pCR received adjuvant immunotherapy for up to 16 cycles. Pts without pCR received adjuvant radiotherapy or chemoradiotherapy, followed by 16 cycles of adjuvant immunotherapy. **Results:** Up to Dec. 2025, all 59 pts completed 3 cycles of neoadjuvant therapy and were evaluable, with a median follow-up of 12 months. The pCR rates were 60% (12/20) in Cohort 1, 42.1% (8/19) in Cohort 2, and 40% (8/20) in Cohort 3. The major pathologic response (MPR) rates were 75% (15/20), 57.9% (11/19), and 55% (11/20) in Cohort 1, 2, and 3, respectively. The ORR was 95% in Cohort 1 (CR: 8/20, PR: 11/20) and 84.2% in Cohort 2 (CR: 5/19, PR: 11/19), while Cohort 3 had an ORR of 80% (CR: 4/20, PR: 12/20). To date, pts have received a median of 6 cycles of adjuvant immunotherapy. The most common treatment-related adverse events (TRAEs) (>20%) were: leukopenia, anemia, neutropenia, thrombocytopenia, lymphocytopenia, hypothyroidism, hypertriglyceridemia, radiation dermatitis, stomatitis, vomiting, decreased appetite, and fatigue. **Conclusions:** Neoadjuvant dual-target (PD-1/VEGF) immunotherapy combined with chemotherapy demonstrated a higher pCR rate compared to dual-target (PD-1/CTLA-4) and single-target PD-1 regimens in resectable LAHNSCC. The treatment was well-tolerated, with all pts completing the intended neoadjuvant therapy and the observed most common TRAEs consistent with expected chemotherapy and radiotherapy profiles. Further analyses are ongoing with continued enrollment. Clinical trial information: NCT06444009. Research Sponsor: None.

RECIST and pathologic response.

	RECIST				Pathologic Response			
	CR	PR	SD	PD	pCR (RVT=0)	MPR (0<RVT<10%)	pPR (RVT:10-49%)	pNR (RVT:≥50%)
Cohort 1 (n=20)	8	11	1		12	3	2	3
Cohort 2 (n=19)	5	11	3		8	3	2	6
Cohort 3 (n=20)	4	12	4		8	3	0	9

Adjuvant nivolumab in addition to postoperative radiation therapy in locally advanced head and neck cancer: Results of the phase II NadiHN trial.

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Background: The benefit of adding immune checkpoint inhibition to standard postoperative adjuvant radiotherapy in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) with an intermediate risk of recurrence remains unclear. **Methods:** The phase II, open-label, randomized, multicenter national NadiHN trial (EudraCT 2016-004787-20) enrolled participants with resected locally advanced HNSCC (R0 resection with ≥5 mm margins; no extracapsular nodal extension). Patients were stratified by primary site (oropharyngeal vs non-oropharyngeal), p16 status (for oropharyngeal tumors), centrally assessed PD-L1 tumor cell (TC) score (≥1% vs <1%), and center, and were randomized 1:1 to receive nivolumab before, during, and after postoperative radiotherapy (PORT) or PORT alone. Nivolumab (10 cycles of 240 mg q2w, followed by 10 cycles of 480 mg q4w) started 2 weeks prior to PORT. The primary endpoint was disease-free survival (DFS) in the intention-to-treat population. The planned sample size of 176 patients was designed to provide 80% power to detect a significant DFS improvement (log-rank test). Key secondary endpoints included overall survival (OS) and safety. Enrollment remained below target. During the trial, an adaptive interim analysis was implemented and led to early study termination upon Data Monitoring Committee recommendation due to futility. **Results:** Between 2017 and 2022, 84 participants were randomized (42 per arm). After a median follow-up of 37.3 months, median DFS was not reached in either group. The 2-year DFS rate was numerically higher with nivolumab + PORT (80%) than with PORT alone (69%), but the difference was not statistically significant (HR 0.934; 95% CI 0.408–2.140; p = 0.7301). Censoring deaths without documented recurrence yielded similar results. OS also did not differ significantly (HR 2.618; 95% CI 0.892–7.684; p = 0.0827). Grade ≥3 treatment-emergent adverse events occurred in 80.6% of patients in the nivolumab arm and 52.5% in the control arm. One treatment-related death occurred in the nivolumab + PORT arm. **Conclusions:** Interpretation of the trial is limited by early termination, small sample size, and fewer-than-expected DFS events. Adjuvant nivolumab added to standard PORT numerically—but not significantly—improved DFS in locally advanced HNSCC. Signals of potential benefit were observed in the PD-L1–positive subgroup (2y-DFS 82.4 vs. 76.2%) and lymph-node–positive subgroups (2y-DFS 84.2% vs. 70.7%). No new safety signals were identified. Funding: The trial was sponsored by the University Hospital Bonn with financial support from Bristol Myers Squibb. Clinical trial information: EudraCT 2016-004787-20. Research Sponsor: University Hospital Bonn; Bristol Myers Squibb.

6094 Poster Session

Real-world evidence on definitive chemoradiotherapy following neoadjuvant chemoimmunotherapy in locally advanced head and neck squamous cell carcinoma.

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Background: Real-world evidence regarding the efficacy and safety of neoadjuvant chemoimmunotherapy (NACI) in the treatment of curable head and neck squamous cell carcinoma (HNSCC) is currently limited. This multi-center study aimed to evaluate the outcomes of NACI in China. **Methods:** This retrospective study examined stage II-IVB HNSCC patients who underwent NACI followed by radical surgery (Group A) or definitive concurrent chemoradiotherapy (CCRT) (Group B) at four medical centers in China from 2019 to 2025. Propensity score matching was employed to balance baseline covariates between the groups. The primary endpoint was progression-free survival (PFS), while key secondary endpoints included complete pathological response (pCR), major pathological response (MPR), overall survival (OS), and treatment-related adverse events (TRAEs), which were graded according to the CTCAE v5.0 criteria. Survival analyses were conducted using Kaplan-Meier/log-rank tests and Cox proportional hazards models. **Results:** After matching (n=756), baseline characteristics were well-balanced (|SMD|$<$0.1). Group A (NACI + surgery, n=457) showed a 67% radiological response and MPR rate, with a 38% pCR, while Group B (NACI + CCRT, n=299) achieved a higher 76% radiological response rate. Regimens were similar (taxane-platinum-immunotherapy), but Group A received fewer chemotherapy cycles (3-4 cycles: 66% vs. 90%). Post-NACI progression was lower in Group B (0.7%). Group B demonstrated significantly longer PFS (hazard ratio [HR] 0.68; p=0.036) and markedly improved OS (HR 0.20; p$<$0.001). Multivariate analysis confirmed NACI + CCRT (Group B) as a significant independent predictor of improved OS (HR=0.20, 95% CI 0.07–0.59; p=0.003), considering factors such as betel nut use, tumor location, and T and N staging. Common grade 3-4 TRAEs were neutropenia and transaminase elevations; among grade 3 immune-related AEs, thyroid dysfunction predominated. **Conclusions:** This multicenter real-world study highlights that the combination of NACI and CCRT (Group B) results in significantly better PFS and OS outcomes compared to the NACI and surgical intervention (Group A), despite a pCR rate of 38% in Group A. These findings support the potential benefit of concurrent chemoradiotherapy as a consolidative approach following NACI. However, it is important to recognize that the observational nature of this study prevents definitive conclusions about causality. Therefore, prospective randomized controlled trials are essential to confirm these findings and to ascertain the optimal consolidative strategy. Additionally, further investigation into biomarker-driven patient selection is vital for enhancing treatment precision and effectiveness. Research Sponsor: None.

Larynx preservation via chemotherapy-free neoadjuvant sintilimab-cetuximab-SBRT and response-adapted treatment in locally advanced laryngeal cancer: A phase II, single-arm clinical trial (the NeoVOICE study).

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Background: The current standard of care for locally advanced laryngeal squamous cell carcinoma (LA-LSCC), including surgery and chemoradiotherapy, might cause long-term toxicities and laryngeal dysfunctions. The study aims to investigate the efficacy and safety of neoadjuvant cetuximab, sintilimab and stereotactic body radiation therapy (SBRT) treating patients with LA-LSCC for larynx preservation. **Methods:** In this phase II, single-arm trial, patients with LA-LSCC (cT2N1-3M0 or cT3-4aN0-3M0, AJCC 8.0th) were recruited. Eligible patients received SBRT (8 Gy $\times$ 3 fractions), followed by sintilimab (200mg, Q3W, 2 cycles) and cetuximab (a loading dose of 400 mg/m^2, followed by 250 mg/m^2, QW, 6 cycles). Further treatment was determined by a radiographic evaluation per RECIST 1.1: patients who reached CR or PR would receive intensity modulated radiation therapy (The initial IMRT dose to the primary tumor was 46 Gy in 23 fractions, with a pre-specified plan to reduce the dose to 37.8 Gy based on early tolerance data from the cohort.) or minimally invasive surgery, while ones with SD or PD would receive radical surgery. The primary endpoint was the larynx-preservation rate (LPR) at 1-year post-radiation. **Results:** Between July 1, 2024 and June 30, 2025, 20 patients were enrolled. 15 (75%) were clinical stage III and 5 were stage IVa. 19 finished neoadjuvant SBRT, sintilimab and cetuximab (one withdrawn due to personal reasons after SBRT), with the ORR of 100% (12 had CR and 7 had PR). Then 18 patients received sequential IMRT, with a median dose of 37.8 Gy (one refused and chose active surveillance). During the whole treatment, grade 3 TRAEs occurred in 5/20 patients (25%), including 3 cases of post-radiation pharyngitis, 1 myocarditis and 1 rash. All 3 cases of grade 3 pharyngitis occurred in the first 6 patients with 46 Gy IMRT. Following a protocol amendment, subsequent patients (n=12) received a reduced dose of 37.8 Gy. In the reduced-dose cohort, no further grade 3+ pharyngitis was observed, while the LPR remained high. After a median follow-up of 7.4 months, 3 patients failed to larynx preservation, including 2 cases with tracheotomies due to pharyngitis and 1 receiving total laryngectomy due to tumor recurrence. Based on results of EORTC QLQ-H&N35 questionnaires, compared to the baseline, most patients reported similar or improved symptoms, including pain, speech and dry mouth, at 6 months post-radiation. **Conclusions:** Neoadjuvant combination of immunotherapy, targeted therapy and SBRT showed excellent efficacy and tolerant toxicity for patients with LA-LSCC. Importantly, dose reduction of sequential IMRT appears to mitigate severe toxicity without compromising laryngeal preservation, outlining a promising de-escalation strategy for future practice. Clinical trial information: ChiCTR2500100185. Research Sponsor: None.

Niraparib and dostarlimab in locally advanced head and neck squamous cell carcinoma (LA-HNSCC) treated with (chemo)radiotherapy (CRT): Results from the phase IB-II TTCC-2022-01 RADIAN trial.

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Background: Treatment intensification with antiPD-(L)1 agents given concurrently to definitive CRT in LA-HNSCC have failed to improve survival. Beyond radiation sensitization, PARP inhibition is predicted to trigger immune responses via STING pathway activation and synergize with anti-PD-(L)1 agents. TTCC-2022-01 RADIAN Trial evaluates niraparib and dostarlimab in LA-HNSCC patients (pts) treated with CRT (cohort A) or RT alone (Cohort B-cisplatin ineligible) (Oliva M et al ASCO 2024). Results of cohort A are presented. **Methods:** Investigator-initiated, non-randomized phase 1b/II study of niraparib and dostarlimab in LA-HNSCC pts candidates for definitive CRT or RT alone conducted in 7 Spanish sites. In cohort A, pts received 500 mg dostarlimab intravenously on week (w)-3 prior to RT and 200-300 mg/day niraparib from w-2 until 48h before start of CRT (70Gy/35 fractions plus cisplatin 100mg/m^2 w1,4 and 7). Maintenance dostarlimab (500 mg/3w) plus daily niraparib started 4w post-CRT for up to 14 cycles. Eligibility criteria: newly-diagnosed stage III-IVA-IVB HPV-negative oro-hipopharyngeal or laryngeal SCC and stage III HPV-related oropharyngeal, ECOG 0-1, centrally-confirmed PD-L1 CPS≥1, and with no cisplatin/dostarlimab/niraparib contraindications. Primary endpoint was 1-year disease-free survival (1y-DFS). Secondary objectives include safety; overall response rate (ORR) and ctDNA dynamics. 17 pts per cohort were planned. Experimental treatment was expected to increase 1y-DFS up to 75.9 % vs 65% historical control. **Results:** From Dec 23 to Jun 25, 17 pts were enrolled: median age 65 y (41-68); 71% male; 88% smokers; larynx/hypopharynx/oropharynx (HPV-related)= 53/6/41% (43%); stage III/IVA/IVB=29/53/18%. All pts completed dostarlimab and niraparib pre-CRT with no serious or Grade(G) 3-4 treatment-related adverse events (TRAEs); 15/17 completed CRT: 2 pts died during this phase (1 G5 febrile neutropenia cisplatin-niraparib-related; 1 unknown cause); 14/17 pts started maintenance: 2 completed, 7 ongoing and 5 (36%) discontinued due to TRAEs. The most common grade ≥3 TRAEs were neutropenia (71%), lymphopenia and dysphagia (29% each). Niraparib dose reductions/interruptions occurred in 12 (71%) pts. Most common TRAEs leading to dostarlimab+niraparib maintenance discontinuation were immune-mediated pneumonitis (18%) and respiratory tract edema (12%). ORR was 100% (14 complete+1 partial response) in 15 evaluable pts. With a median follow-up of 8.5 months (95% CI: 8.3-11.1), 15/17 were alive with no disease recurrence or progression. Intention-to-treat 1y-DFS was 88% (95% CI:74.1-100). **Conclusions:** Dostarlimab and niraparib with CRT showed promising efficacy results in this preliminary analysis. Maintenance post-CRT was poorly tolerated leading to high rate of discontinuation. Clinical trial information: NCT05784012. Research Sponsor: GlaxoSmithKline Research& Development Limited.

6097 Poster Session

Neoadjuvant HPV16-specific viral immunotherapy (HB200) plus chemotherapy with response-adapted de-escalation in HPV16+ oropharyngeal squamous cell carcinoma: TARGET-HPV trial.

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Background: Neoadjuvant immunotherapy is an emerging strategy in head and neck squamous cell carcinoma to enhance systemic antitumor immunity and enable response-adapted de-escalation. In HPV associated oropharyngeal squamous cell carcinoma (OPSCC), virally encoded oncoproteins represent shared, tumor-specific antigens and a rational immunologic target well suited for the neoadjuvant setting in the presence of intact tumor antigen. We conducted a phase I/II trial evaluating neoadjuvant HPV16-specific viral immunotherapy (HB200; HB201 and HB202 HPV16 therapeutic vaccines) plus chemotherapy followed by response-adapted definitive treatment in non-metastatic HPV16+ OPSCC (NCT05108870). **Methods:** This investigator-initiated phase I/II trial enrolled patients with previously untreated, non-metastatic HPV16+ OPSCC (N1-3 or T3-4; smokers permitted). All patients received three cycles of neoadjuvant HB200 (HB201 alone or alternating HB202/201) with carboplatin/paclitaxel, followed by radiographic response assessment. Patients with T1-2 tonsil or well-lateralized base of tongue tumors achieving ≥50% tumor shrinkage underwent transoral robotic surgery (TORS) alone. Remaining patients received response and risk adapted radiotherapy (50-70Gy based on risk/response) with or without cisplatin. The primary endpoint was deep response rate (DRR; ≥50% tumor shrinkage). Secondary endpoints included survival and toxicity. Exploratory endpoints included circulating tumor HPV-DNA (ctHPV-DNA), HPV16-specific immunity, and spatial transcriptomics. **Results:** Thirty-five patients were enrolled (median age 58; 89% male); Twelve patients (34%) received HB201 alone and 23 (66%) received alternating HB202/201. Nineteen patients (54%) were current or former smokers, and 49% had stage II-III (AJCC 8th edition). The DRR was 87.9% (95% CI, 71.8-96.6). Thirty (86%) received de-escalated definitive therapy. At a median follow-up of 23 months, 2-year PFS and OS were 86% and 100% respectively. Most common AEs during neoadjuvant HB200/chemo were fatigue (97%), nausea (91%), and fever (76%). Detectable ctHPV-DNA following treatment was significantly associated with disease recurrence ($p<0.01$). HPV16-specific immune responses and spatial transcriptomic analyses will be presented. **Conclusions:** Neoadjuvant HB200 combined with chemotherapy resulted in high deep response rates, frequent treatment de-escalation, and excellent survival outcomes in locoregionally advanced HPV16+ OPSCC. These findings support further evaluation of HPV directed immune therapy in neoadjuvant setting. Clinical trial information: NCT05108870. Research Sponsor: HOOKIPA Pharma, Inc.; University of Chicago Cancer Center.

6098 Poster Session

Patterns of tumor regression after neoadjuvant immunochemotherapy in oral squamous cell carcinoma and their surgical margin implications.

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Background: Neoadjuvant immunochemotherapy (nICT) has been increasingly applied in locally advanced oral squamous cell carcinoma (OSCC), demonstrating promising tumor downstaging and improved pathological response rates. However, the spatial patterns of tumor regression after nICT and their implications for surgical margin design and potential de-escalation of surgery remain poorly defined. **Methods:** We retrospectively analyzed 36 hemiglossectomy specimens from OSCC patients treated with nICT. All specimens were entirely embedded and evaluated using large-format histopathology. Tumor regression patterns were classified based on the distribution of residual viable tumor into central necrotic regression, peripheral regression, and patchy ablation types, each with distinct morphological subtypes. The relationship between pathological residual tumor foci, margin distance (1 mm vs 5 mm), and multicentricity was systematically assessed. **Results:** Distinct tumor regression patterns were observed following nICT. Most cases exhibited predominantly unicentric residual disease, while a small proportion demonstrated multicentric pathological residuals. Using a 1-mm pathological distance threshold, 1 cases were classified as multicentric, whereas no case met multicentric criteria using a 5-mm threshold. Notably, cases achieving major pathological response (MPR) or near pathological response (NPR) showed minimal residual tumor burden, though isolated satellite foci were occasionally detected. These findings suggest that regression morphology directly influences margin risk distribution and surgical safety. **Conclusions:** Tumor regression patterns after nICT in OSCC are heterogeneous and play a critical role in determining optimal surgical resection boundaries. While surgical de-escalation may be feasible in selected responders, careful assessment of residual tumor distribution is essential to ensure oncologic safety. Our findings support the development of an integrated preoperative regression assessment and postoperative margin reconstruction framework to guide individualized, function-preserving surgical strategies in OSCC. Research Sponsor: None.

6099 Poster Session

GDF-15 levels and clinical correlates in head and neck cancer patients: Developing a risk model for cachexia.

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Background: Cachexia is a challenging complication of cancer and its treatment, associated with an increased risk of death. Growth differentiation factor 15 (GDF15) is a known driver of cachexia in lung, pancreatic and colorectal cancer. However, we lack information about GDF15 role and temporal dynamics in patients with head and neck squamous cell carcinoma (HNSCC) receiving curative treatments. Here, we aimed to quantify circulating GDF15 in HNC patients and determine the relationship with indicators of cachexia and other prominent clinical correlates, namely oral mucositis (OM). **Methods:** Adults diagnosed with HNSCC, scheduled to receive definitive platinum based chemoradiotherapy (CRT), were recruited from four tertiary hospitals in Australia and Italy. Cachexia was determined using a variety of clinical parameters, including weight, grip strength, and upper arm circumference (UAC). OM was assessed using the World Health Organization (WHO) mucositis scale (grade 0-4). GDF15 was quantified in serially-collected serum using a commercial ELISA. All measures were assessed at baseline, week 3, end of treatment (EOT) and 3 months after treatment end. **Results:** Fifty-nine patients (pts) were enrolled, predominantly male (71%) with a mean age of 64+/-8 years. Main subsite of disease was oropharynx (44 cases, 75%), of whom 68% were HPV positive. Treatment was delivered with definitive intent in 90% of the cases. Median dose of RT was 70 Gy (66-70). At EOT, 77.3% of the pts met the diagnostic criteria for cachexia, with an average weight loss of 8.6% over the course of treatment. This was accompanied by a 7.7% and 5.6% average reduction in grip strength and UAC, respectively. Notably, these reductions continued beyond treatment cessation, with an average baseline weight loss of 9.8% after 3 months. Aligning with these outcomes, serum GDF15 levels were highly elevated following CRT compared to baseline (2.6 fold, $P<0.0001$), and correlated with reductions in weight ($R^2=0.168$, $P=0.0002$), UAC ($R^2=0.1516$, $P<0.0001$), grip strength ($R^2=0.1332$, $P<0.0001$), as well as OM severity ($R^2=0.1013$, $P<0.0009$). **Conclusions:** These data reveal that highly elevated GDF15 production correlates with OM and cachexia, providing strong clinical rationale to explore the biological basis of this new symptom cluster, as well as identifying a new clinical cohort that may benefit from GDF15 targeting agents. Research Sponsor: None.

A multicenter, randomized controlled phase III trial of TPF induction chemotherapy versus PF adjuvant chemotherapy combined with concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: Long-term follow-up analysis.

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Background: To investigate whether TPF induction chemotherapy combined with concurrent chemoradiotherapy (CCRT) can provide greater survival benefits compared to CCRT followed by PF adjuvant chemotherapy. **Methods:** Patients with newly diagnosed locally advanced (Stage III–IVA) nasopharyngeal carcinoma (NPC) treated at the Affiliated Tumor Hospital of Guizhou Medical University, the Second Affiliated Hospital of Guizhou Medical University, the Second Affiliated Hospital of Zunyi Medical University, and Guiyang Hospital of Guizhou Aviation from May 2018 to July 2021 were enrolled. Each group included 133 patients. The experimental group received 3 cycles of TPF induction chemotherapy (docetaxel 75mg/m^2,intravenous infusion, Day 1; cisplatin 75mg/m^2,continuous intravenous infusion over 5 days,10:00–22:00 daily; fluorouracil 750mg/m^2/day, continuous intravenous infusion over 5 days, 22:00–10:00 daily) followed by 2–3 cycles of concurrent chemotherapy (cisplatin 100mg/m^2, continuous intravenous infusion over 2 days, 10:00–22:00 daily). The control group received PF adjuvant chemotherapy (cisplatin 80mg/m^2, continuous intravenous infusion over 5 days,10:00–22:00 daily; fluorouracil 800mg/m^2/day, continuous intravenous infusion over 5 days, 22:00–10:00 daily) combined with 2–3 cycles of concurrent chemotherapy (same as induction chemotherapy).Both groups underwent intensity-modulated radiotherapy (IMRT),with total doses of 69.96 Gy for T1–T2 primary lesions, 72.6 Gy for T3–T4 lesions, and 69.96 Gy for positive lymph nodes. Data were analyzed using SPSS 26.0.Differences in 5-year PFS, OS, LRFS, DMFS, and adverse events were compared between the two groups. **Results:** No significant differences were observed between the two groups in age, sex, Karnofsky Performance Status (KPS) score, T stage, N stage, or overall stage ($P > 0.05$).At a median follow-up of 58 months, the 5-year PFS in both the intention-to-treat and per-protocol populations was similar between the induction chemotherapy (IC) and adjuvant chemotherapy (AC) groups (66.6% vs 66.0%, P= 0.589; 75.3% vs 69.9%, P=0.471). The 5-year OS, LRFS, and DMFS rates were 73.0% vs 71.3% (P=0.582), 87.4% vs 90.8% (P=0.508), and 76.9% vs 72.6% (P=0.267), respectively, with no significant differences. **Conclusions:** Both groups had similar 5-year PFS, OS, LRFS, DMFS, and long-term toxicity profiles. Clinical trial information: NCT03574324. Research Sponsor: None.

5-year observation indicators for two groups.

Observation indicators	IC+CCRT	CCRT+AC	P value	Risk ratio(95% CI)
PFS				
ITT Population	66.6%	66.0%	0.589	0.89 (0.58-1.36)
PP Population	75.3%	69.9%	0.471	0.85 (0.55-1.33)
OS	73.0%	71.3%	0.582	0.88 (0.55-1.39)
LRFS	87.4%	90.8%	0.508	1.30 (0.60-2.80)
DMFS	76.9%	72.6%	0.267	0.75 (0.45-1.25)

OS, LRFS, and DMFS were all calculated in the ITT population.

6101 Poster Session

Comparison of efficacy between 2 and 3 cycles of neoadjuvant immunotherapy combined with chemotherapy for LA HNSCC.

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Background: To compare efficacy, safety and long-term survival of 2 vs 3 cycles of neoadjuvant PD-1 inhibitor plus chemotherapy for LA HNSCC, providing evidence for optimizing treatment cycles. **Methods:** Retrospective analysis of LA HNSCC patients treated with the above neoadjuvant regimen at Beijing Tongren Hospital (Jan 2022-Dec 2024) was performed. Initially 76 (2-cycle) and 102 (3-cycle) cases were enrolled. Propensity score matching (1:1) balanced baseline differences, resulting in 65 cases per group. Chi-square, Kappa, Kaplan-Meier and Log-rank tests were used for comparisons, consistency analysis and survival assessment. Stratified analyses focused on HPV-negative and poorly differentiated subgroups. **Results:** After matching, 3-cycle group had higher ORR (95.4% vs 80.0%, P=0.008) and pCR rate (72.3% vs 55.4%, P=0.045). Subgroup analyses showed superior pCR in 3-cycle group for HPV-negative (68.9% vs 42.1%, P=0.014) and poorly differentiated (82.6% vs 35.7%, P=0.004) patients. Weak consistency existed between imaging and pathology (Kappa=0.176, P=0.044). Immune-related adverse events were more common in 3-cycle group (24.6% vs 10.8%, P=0.039). No significant 1-/2-year PFS/OS differences were noted, but 3-cycle group showed favorable numerical trend. **Conclusions:** Three cycles of the regimen significantly improve ORR and pCR in LA HNSCC, especially in HPV-negative and poorly differentiated subgroups. Despite higher immune-related adverse events, it is clinically preferable. Multi-dimensional evaluation is needed due to poor imaging-pathology consistency, with longer follow-up required for definitive prognosis assessment. Research Sponsor: None.

6102 Poster Session

Five-year follow-up of neoadjuvant chemoimmunotherapy in locally advanced head and neck squamous cell carcinoma.

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Background: Neoadjuvant chemoimmunotherapy has shown high rates of pathological response in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). However, its long-term survival outcomes, the predictive value of pathological complete response (pCR), and patterns of late failure remain unclear. **Methods:** In this single-arm phase II trial, 30 patients with resectable LA-HNSCC received three cycles of nab-paclitaxel (or docetaxel) plus cisplatin and camrelizumab, followed by surgery and adjuvant radiotherapy. The primary endpoint was pCR rate. With follow-up until January 2026, the median follow-up was 60 months. Analyses included overall survival (OS), recurrence patterns, and incidence of second primary tumors. **Results:** The pCR rate was 37.0% (10/27). Key Finding 1: This study represents the first report of 5-year long-term survival data for this regimen, with a 5-year OS rate of 76.7%. Key Finding 2: None of the patients who achieved pCR and completed adjuvant radiotherapy experienced local recurrence (0/7), whereas the recurrence rate was 33.3% (1/3) among those who did not receive radiotherapy, underscoring the role of radiotherapy even in pCR patients. Key Finding 3: Six patients (20%) developed second or third primary tumors during long-term follow-up (sites included larynx, esophagus, and lung), with incidence increasing over time. Key Finding 4: Two patients developed osteoradionecrosis of the jaw more than two years after radiotherapy, leading to malnutrition and subsequent death, highlighting the importance of long-term toxicity management. **Conclusions:** Neoadjuvant chemoimmunotherapy provides durable survival benefit in LA-HNSCC. pCR is associated with minimal local recurrence. However, with prolonged survival, the risk of second primary tumors becomes significant, and late radiation toxicities can impact outcomes. These findings emphasize the need for establishing lifelong surveillance protocols for multiple primary cancers and systematic management of late toxicities in this population. Clinical trial information: ChiCTR1900025303. Research Sponsor: None.

6103 Poster Session

Induction chemotherapy response–guided selection for hypoxia-directed major radiation de-escalation in T3–T4 HPV-positive oropharyngeal cancer.

Eric Jeffrey Sherman, Nadeem Riaz, Winston Wong, James Vincent Fetten, Lara Dunn, Anuja Kriplani, Daphna Y. Gelblum, Yao Yu, Achraf Shamseddine, Alan Loh Ho, Nancy Y. Lee; Memorial Sloan Kettering Cancer Center, New York, NY

Background: De-escalation trials in human papillomavirus associated oropharyngeal carcinoma (HPV+ OPC) often exclude patients with very locally advanced disease. We previously demonstrated in several Phase II study that for patients with T1-T2 HPV+OPC, de-escalation to 30Gy of definitive chemoradiation based on lack of hypoxia on ^{18}F-FMISO (fluoromisonidazole) PET (30-ROC Study) is associated with excellent outcomes (JNCI 2021; JCO 2024). Here, we hypothesized that induction chemotherapy (ICT) response could be used to select appropriate locally advanced (T3-T4) HPV+OPC for de-escalation while simultaneously improving tumor hypoxia. **Methods:** We conducted a pilot study in HPV+ OPC patients with AJCC v7 T3-T4 and/or large volume N2b-N2c-N3 disease (who were ineligible for 30-ROC Study (NCT03323563)). ICT – carboplatin (AUC2), paclitaxel (90 mg/m2), and cetuximab (250 mg/m2 after 400 mg/m2 loading dose) weekly for 6 weeks. To be eligible for de-escalation (30-ROC), after ICT, patients needed to be down-staged (<=T2 and <=N3 disease). ^{18}F-FMISO PET scan done prior to ICT, after ICT, and, if eligible for ROC study, about 2 weeks after start of radiation therapy. If an ^{18}F-FMISO PET scan showed no hypoxia prior to the start of chemoradiation, no further scans were necessary and patients received 30Gy of radiation therapy with 2 cycles of chemotherapy concurrently. Primary outcome is 2-year local control rate in 20 evaluable patients. **Results:** 20 patients were accrued 3/2023-12/2023. Median age - 70 years old (46-88); Male – 95%; ECOG PS 0 – 80%. Tumor stage – T3 (70%); T4a (30%); N2b (70%); N2c (30%). All 20 patients had pretreatment hypoxia by ^{18}F-FMISO. All 20 patients had sufficient downstaging to be treated by 30-ROC Study and converted to no hypoxia by ^{18}F-FMISO. The estimated progression free survival and local control rate at 2 years is 90% (95% CI 76.9%-100%). There were no distant failures. The median follow up is 23 months (range 12-29 months). All patients were alive and without evidence of disease at last follow up. **Conclusions:** Preliminary results suggest that ICT can allow more advanced tumors (T3/T4), that are typically excluded from de-escalation studies, to be de-escalated and may eliminate tumor hypoxia in a large proportion of cases. This small pilot study shows similar results seen in the larger ROC studies published to date, but a larger study is needed to confirm these results and is currently ongoing. Clinical trial information: NCT05491512. Research Sponsor: None.

6104 Poster Session

Zopapogene imadenovec-drba, a novel non-replicating adenoviral vector-based immunotherapy: Effects on complete and durable responses in recurrent respiratory papillomatosis pivotal trial.

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Background: Recurrent respiratory papillomatosis (RRP) is a rare, neoplastic disorder caused by chronic human papillomavirus (HPV) type 6 or 11 infection. Significant morbidity can occur due to airway obstruction and transformation into malignant cancer. Repeat surgical debulking has historically been the most common treatment for RRP symptom management. Zopapogene imadenovec-drba (zopa), a novel adenoviral vector-based immunotherapy, is the first and only FDA-approved treatment for adults with RRP. Zopa is now recommended as the first-line treatment for adults with RRP in an RRP Foundation position statement authored by 16 key opinion leaders (Best *et al.* Laryngoscope 2026). **Methods:** The pivotal trial (NCT04724980) evaluated zopa in patients with RRP requiring ≥3 clinically indicated interventions 12 months (m) prior to treatment. 12m follow-up data was reported and demonstrated that 4 subcutaneous injections of zopa ($5x10^{11}$ particle units per injection; n=35) were well-tolerated, with no serious adverse events, no grade >2 treatment-related adverse events, and no early treatment discontinuations. The most common adverse events were injection-site reaction, fatigue, chills, fever, and myalgia. Robust efficacy was observed following zopa treatment with 51% (34 to 69; 95% CI) of patients achieving a complete response (CR), defined as no requirement for interventions in the 12m following treatment, and 86% (30/35) of patients experiencing a decrease in interventions in the year following treatment as compared to the year prior to treatment. Here we present data up to 51m of follow-up. **Results:** As of December 15, 2025, 83% (15/18) of patients who achieved a CR at 12m remain in CR with no recurrence of papilloma requiring surgical or medical intervention. The median duration of follow-up for patients in CR was 36m (range: 30-51m), with 3 patients having a response lasting more than 4 years. No new safety events were observed during long-term follow-up. **Conclusions:** Zopa treatment demonstrated significant clinical benefit with the vast majority of CR patients experiencing ongoing durable complete responses for up to 4 years with excellent long-term safety. Updated follow-up results for all patients achieving CR will be available at the time of presentation. Clinical trial information: NCT04724980. Research Sponsor: Precigen Inc.

6105 Poster Session

Omitting postoperative radiotherapy after pathologic complete response to neoadjuvant immunochemotherapy for patients with locally advanced head and neck squamous cell carcinoma: Survival and patient-reported outcomes.

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Background: Neoadjuvant immunochemotherapy (NICT) results in high pathologic response rates in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). However, whether it is safe to omit postoperative radiotherapy (PORT) for patients who achieved pathologic complete response (pCR) after NICT and surgery remains unclear. We assessed the survival and patient-reported outcomes (PROs) for LA-HNSCC patients who achieved pCR to NICT. **Methods:** This retrospective cohort study included LA-HNSCC patients who achieved pCR to NICT between July 2019 and June 2025. Patients were categorized into two groups based on whether they received PORT. Propensity score matching (PSM) was performed to minimize confounding and balance baseline characteristics. Kaplan-Meier survival analysis was performed to estimate local recurrence-free survival (LRFS), locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and overall survival (OS). EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires before NICT, preoperatively, and at month 1, 3, and 12 postoperatively were collected. Least-squares mean (LS mean) changes from baseline were estimated using linear mixed-effects models for repeated measures (group, time, and group-$\times$time), adjusting for baseline scores. **Results:** A total of 236 HNSCC patients who achieved pCR after NICT and surgery were included (non-PORT, n = 98; PORT, n = 138). After 1:1 PSM to balance baseline characteristics, 164 patients (82 matched pairs) with comparable baseline characteristics were analyzed. With a median follow-up of 31.67 months (95% CI, 29.57-35.35), survival analysis showed no significant differences between the non-PORT and PORT groups in 2-year LRFS, LRRFS, DMFS or OS (all $p > 0.05$). Longitudinal EORTC QLQ-C30 global health/QOL analyses showed poorer recovery in the PORT group. PORT was associated with significantly greater postoperative QOL decline at 1 and 3 months postoperatively, with a persistent deficit at 12 months , while non-PORT improved above baseline by 12 months whereas PORT remained slightly reduced. On the EORTC QLQ-HN35, PORT was associated with persistently higher symptom burden, peaking at 3 months postoperatively and remaining elevated up to 1 year compared with non-PORT, suggesting potential QOL benefits of omitting PORT in pCR patients. **Conclusions:** In this propensity score-matched cohort of LA-HNSCC patients achieving pCR after NICT and surgery, omitting PORT was associated with comparable 2-year disease control and survival but better recovery of multidimensional QOL and lower symptom burden on head and neck-specific PROs. These findings favor omission of PORT for this patient population, while prospective validation and longer follow-up are warranted. Research Sponsor: None.

Neoadjuvant adebrelimab plus chemotherapy in untreated locally advanced head and neck squamous cell carcinoma: Efficacy and biomarker insights from a single-arm phase 2 trial.

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Background: Improving outcomes for locally advanced head and neck squamous cell carcinoma (LA-HNSCC) requires novel strategies. This phase 2 trial evaluated the efficacy and safety of neoadjuvant adebrelimab (a PD-L1 inhibitor) combined with chemotherapy in untreated, resectable LA-HNSCC. **Methods:** In this single-center, single-arm study, eligible patients had newly diagnosed, resectable stage III-IVA/B LA-HNSCC. Patients received three cycles of neoadjuvant adebrelimab (1200 mg), nab-paclitaxel (260 mg/m^2), and carboplatin (AUC 5) every 21 days. The primary endpoint was objective response rate (ORR, RECIST v1.1). Secondary endpoints included safety, pathologic response, larynx preservation, and biomarker analysis. **Results:** Twenty-four patients were enrolled (median age 61.5 years; 91.7% male; 70.8% hypopharynx primary). Twenty-three completed all three cycles of neoadjuvant therapy and were evaluated. The ORR was 87.5% (21/24) in the intention-to-treat population and 91.3% (21/23) in the per-protocol population, including 5 complete and 16 partial responses. The larynx preservation rate was 95.8%. Pathologic complete response was observed in 3 of 7 surgical patients (42.9%). Significant downstaging occurred in T-stage (66.7%), N-stage (70.8%), and overall stage (54.2%). All patients with p16-positive tumors (8/8) and those with PD-L1 combined positive score ≥20 (8/8) achieved an objective response. Grade 3 adverse events occurred in 41.7% of patients (primarily hematologic toxicities), with no grade 4/5 events. **Conclusion:** Neoadjuvant adebrelimab plus chemotherapy demonstrated high response rates, promising organ preservation, and manageable toxicity in resectable LA-HNSCC. Biomarker analysis suggests p16 positivity and high PD-L1 expression may correlate with better response. Clinical trial information: ChiCTR2400091171. Research Sponsor: National Natural Science Foundation of China; 82473271.

Efficacy outcomes based on full analysis set (FAS).

Efficacy Parameter	Overall (N=24)	Larynx (n=4)	Hypopharynx (n=17)	Oropharynx (n=3)
Best Overall Response, n (%)				
CR	5 (20.8)	1 (25.0)	4 (23.5)	0 (0.0)
PR	16 (66.7)	3 (75.0)	10 (58.8)	3 (100.0)
SD	3 (12.5)	0 (0.0)	3 (17.6)	0 (0.0)
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ORR	21 (87.5,)	4 (100.0)	14 (82.4)	3 (100.0)
(95% CI)	(67.6 - 97.3)	(39.8 - 100.0)	(56.6 - 96.2)	(29.2 - 100.0)
(95% CI)	(48.9 - 87.4)	(19.4 - 99.4)	(38.3 - 85.8)	(29.2 - 100.0)
Larynx Preservation Rate	23 (95.8)	4 (100.0)	16 (94.1)	3 (100.0)
(95% CI)	(78.9 - 99.9)	(39.8 - 100.0)	(71.3 - 99.9)	(29.2 - 100.0)
DCR	24 (100.0)	4 (100.0)	17 (100.0)	3 (100.0)
(95% CI)	(85.8 - 100.0)	(39.8 - 100.0)	(80.5 - 100.0)	(29.2 - 100.0)

Data are n (%, 95% CI). FAS: full analysis set (all enrolled patients receiving at least one treatment cycle); ORR: objective response rate (CR + PR); DCR: disease control rate (CR + PR + SD). Antitumor response was assessed according to RECIST v1.1.

Long term functional survivorship in oral cavity cancer: Quality of life (QOL) outcomes by return to work (RTW) status.

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Background: Long-term survivors of oral cavity cancer (OCC) often experience persistent physical, functional, and psychosocial impairments despite disease control. Return to work (RTW) reflects real-world functional recovery and social reintegration. We evaluated whether health-related quality of life (QOL) differs between OCC survivors who returned to work and those who did not. **Methods:** This prospective cohort study included OCC survivors ≤65 years who underwent definitive surgery between 2016 and 2023 and were disease-free for ≥2 years. Health-related QOL was assessed using EORTC QLQ-C30, EORTC QLQ-HN43, and UW-QOL questionnaires. QOL domains were compared between survivors who returned to work and those who did not. **Results:** Three hundred OCC survivors were evaluated at a median of 28.5 months after treatment. Survivors who returned to work demonstrated significantly higher global health status and superior physical, role, emotional, cognitive, and social functioning on EORTC QLQ-C30 compared with non-working survivors (all $p<0.0001$). Non-working survivors had substantially greater head-and-neck–specific symptom burden on EORTC QLQ-HN43, including swallowing difficulty, speech problems, shoulder dysfunction, pain, dry mouth, body-image disturbance, social eating limitations, and fear of progression (all $p<0.0001$). UW-QOL confirmed significantly worse pain, activity, recreation, swallowing, chewing, speech, shoulder function, mood, anxiety, and overall health-related QOL in survivors who did not return to work (all $p<0.0001$). **Conclusions:** Return to work is strongly associated with superior multidimensional quality of life in oral cavity cancer survivors. Survivors who do not resume work experience profound physical, functional, and psychosocial impairment, highlighting the need for rehabilitation-centered survivorship care to restore meaningful functional recovery beyond oncologic cure. Research Sponsor: None.

Quality of life scores for European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 43 (EORTC QLQ HN 43).

EORTC QLQ HN 43	Total patients (Overall population)	Returned to work at the time of survey (Mean + SD)	Did not return to work at the time of survey (Mean + SD)	P Value
Pain in the mouth	34.2 + 15.8	10.3+ 13.2	33.2 + 13.5	p<0.0001
Swallowing issue	10.8 + 12.5	7.8 + 8.7	25.5 + 16.9	p<0.0001
Problems with teeth	17.8 + 19.2	14.1 + 17.2	35.7 + 18.6	p<0.0001
Dry mouth and sticky saliva	23.4 + 21.9	19.5 + 19.1	42.8 + 24.3	p<0.0001
Problems with senses	18.1 + 18.9	14.2 + 16.6	36.9 + 18.0	p<0.0001
Speech issues	15.9 + 18.8	11.6 + 15.4	44.9 + 17.2	p<0.0001
Body image issues	18.0 + 19.7	12.5 + 15.2	41.3 + 20.1	p<0.0001
Social eating issues	17.0 + 19.9	12.0 + 15.7	47.1 + 22.5	p<0.0001
Sexuality problem	18.1 + 22.7	12.2 + 17.6	46.4 + 18.3	p<0.0001
Problems with shoulder	18.6 + 22.0	12.9 + 17.9	46.4 + 18.3	p<0.0001
Skin Problems	13.5 + 18.5	9.0 + 14.7	35.7 + 19.4	p<0.0001

Barriers and variability in lymphedema therapy for head and neck cancer survivors: Secondary analysis from a randomized trial.

Cristina Kline-Quiroz, Barbara Murphy, Sheila H. Ridner, Derek Smith; Vanderbilt University Medical Center, Nashville, TN; Vanderbilt University, Nashville, TN; University of Iowa College of Dentistry, Iowa City, IA

Background: Secondary lymphedema is a significant underrecognized sequela of head and neck cancer (HNC) and its treatments. Lymphedema may impact external structures (head, face, neck) and internal structures (larynx, pharynx), leading to functional impairments impacting breathing, speaking and swallowing resulting in disability, and reduced quality of life. Although therapist guided lymphedema treatment (TGLT) is effective, timely access is frequently limited by financial constraints, geographic barriers, systemic inefficiencies, and shortages of trained therapists. This study evaluates accessibility, implementation, and barriers to TGLT in HNC survivors. **Methods:** This prospective cohort study was nested within a multi-site randomized trial comparing usual care to an advanced pneumatic compression device (APCD). Eligible participants (N=117) were HNC survivors with lymphedema and at least one lymphedema-associated symptom rated ≥4/10. Therapy notes and patient data were abstracted to assess referral patterns, therapy timelines, lymphedema treatment characteristics, documented therapeutic goals, and reported barriers. Descriptive statistics were obtained to depict trends in therapy initiation, implementation, and barriers. **Results:** Of 117 participants referred for therapy, 77 (66%) were evaluated by a therapist. Of these, 11 failed to return for a second visit (56%). Median time from referral to evaluation was 17 days. Median time from evaluation to last recorded visit was 72.5 days (median 10 visits). Many patients experienced protracted wait times (Figure 1) and treatment breaks. Therapy delivery varied substantially; By last documented visit, recommendations included home manual lymphatic drainage (82%), compression garments (65%), APCD (33%), and written self-care instructions (26%). 28% achieved all therapy goals. Documentation inconsistencies and gaps in provider communication hindered effective therapy implementation. Barriers included geographic distance, financial constraints, and therapist shortages. **Conclusions:** Significant variability, limited care access, and delays in TGLT exist for HNC survivors. Standardized protocols, telemedicine, and adjunctive technologies such as APCDs may improve accessibility, adherence, and outcomes. Future studies should focus on optimizing care models including self-care and reducing disparities in therapy delivery. Clinical trial information: NCT04797390. Research Sponsor: Tactile Medical.

Timeframe of therapy implementation in days.

	Provider Referral to Therapy Evaluation	Therapy Evaluation to Second Visit	Provider Referral to Second Visit	Therapy Evaluation to Last Visit
Average	23.7	9.0	32.7	80.0
Standard deviation	21.9	6.8	23.3	44.9
Median	17.0	7.0	27.0	72.5
Minimum	0.0	1.0	1.0	7.0
Maximum	93.0	31.0	108.0	175.0
25th percentile	8.0	4.0	16.3	48.0
75th percentile	31.8	14.0	44.5	103.5

6109 Poster Session

Impact of advanced pneumatic compression devices and usual care on psychosocial outcomes in head and neck cancer survivors with lymphedema.

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Background: Head and neck cancer (HNC)-associated lymphedema impairs quality of life (QOL) in survivors, affecting body image, self-management efficacy, work productivity, and psychosocial functioning. Data supports therapist guided lymphedema therapy (TGLT) and technologies such as advanced pneumatic compression devices (APCD) reduce swelling. There is a lack of data on psychosocial and QOL outcomes. This randomized clinical trial compared psychosocial outcomes of TGLT and APCD in treatment-naïve HNC survivors with symptomatic lymphedema over 6 months. **Methods:** Participants (N=236) with HNC-associated lymphedema were randomized 1:1 to receive either TGLT (117) or APCD (119) for 6 months. Psychosocial outcomes were assessed at baseline, 2, 4, and 6 months using validated instruments: the Work Productivity and Activity Impairment Questionnaire (WPAIQ), Perceived Medical Condition Self-Management Scale (PMCSMS), Body Image Quality of Life Inventory (BIQLI), and Linear Analog Self-Assessment (LASA) for QOL. Longitudinal mixed-effects models evaluated within- and between-group changes over time. **Results:** Both treatment groups experienced improvements in psychosocial outcomes over time. Self-management efficacy improved in both arms. The APCD group demonstrated significantly greater self-efficacy managing lymphedema at 6 months (p=0.004). Work and activity impairment decreased in both groups, with no significant between-group differences. BIQLI scores improved across timepoints in both arms, reflecting enhanced body image-related QOL. LASA scores for overall QOL and emotional, physical, and spiritual well-being also improved similarly in both groups. No significant time-by-treatment interactions were observed, indicating comparable trajectories of psychosocial recovery. **Conclusions:** Both TGLT and APCD were associated with meaningful improvement in psychosocial outcomes, including self-management efficacy, body image, and QOL, among HNC survivors with lymphedema. APCD offers ongoing access to a convenient, home-based treatment which may enhance fidelity and self-efficacy through ongoing instrumental support. These findings underscore the value of accessible, patient-centered lymphedema interventions to enhance survivorship care. Future research should explore long-term adherence, cost-effectiveness, and integration of psychosocial support into treatment pathways. Clinical trial information: NCT04797390. Research Sponsor: Tactile Medical.

GDF-15 in oropharyngeal squamous cell carcinoma (OPSCC): Association of an HPV-dependent biomarker with malnutrition and low skeletal muscle.

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Background: GDF15 is a stress-response cytokine implicated in systemic inflammation and cancer-related wasting. We assessed whether baseline circulating GDF15 captures an HPV-stratified nutritional/body composition phenotype and whether longitudinal GDF15 changes relate to treatment outcome in OPSCC. **Methods:** We analyzed a prospective cohort of OPSCC patients (pts) undergoing curative intent treatment (CIT; surgery and radiotherapy [RT]-based) with available baseline plasma GDF15. HPV status was defined by dual detection ($p16^{INK4a}$ and HPV DNA). Baseline nutritional status (Patient Generated Subjective Global Assessment), symptom burden (nutrition-impact composite score), body mass index (BMI), and CT-derived skeletal muscle index (SMI) were analyzed when available. Response assessment was performed 8-12 weeks after CIT, classifying cases as no evidence of disease (NED) vs evidence of disease (ED). Longitudinal GDF15 was analyzed using linear mixed-effects models (LMEN) (random intercept) including interactions of time with response status and induction chemotherapy. **Results:** We included 138 pts (HPVnegative [−] n=82; HPVpositive [+] n=56). Stage III–IV was more frequent in HPV- vs HPV+ (85.4% vs 30.4%; $p<0.001$) and ECOG 0 less common (9.8% vs 51.8%; $p<0.0001$). RT-based treatment predominated (85.5%) mainly chemoradiotherapy ± induction (82.6%). Baseline GDF15 was higher in HPV- vs HPV+ (median 1591 vs 803 pg/mL; $p<0.001$). HPV− pts showed worse nutritional phenotype: lower BMI (22.7 vs 27.2 kg /m^2; p=0.001), more severe malnutrition (37.8% vs 7.1%; $p<0.001$), higher symptom burden (1.90±0.94 vs 1.39±0.71; p=0.002) and higher sarcopenia (34.1% vs 16.1%; p=0.029). In pts with CT body composition (n=89), SMI was lower in HPV− vs HPV+ (45.6 vs 53.6 cm^2/m^2; p=0.010). Baseline GDF15 differed by nutritional status (p=0.014) and was associated with symptom burden and SMI (both $p<0.05$). In LMEN, GDF15 increased significantly from baseline to end of treatment (β=2264 pg/mL; $p<0.001$). Baseline HPV positivity was independently associated with lower GDF15 (β=−980 pg/mL; $p<0.001$). At the end of treatment, NED was associated with lower GDF15 compared with ED (β=−1141 pg/mL; p=0.011). Induction chemotherapy showed no significant effect on GDF15 change (β=−448 pg/mL at end of treatment; p=0.22). No significant interaction between time and baseline HPV status was observed (p=0.26) indicating comparable longitudinal trajectories of GDF15 in HPV+ and HPV-pts. **Conclusions:** Baseline GDF15 is strongly HPV-dependent and reflects a multidimensional nutritional and muscle phenotype. GDF15 increases during CIT and lower end-of-treatment GDF15 is independently associated with NED, whereas induction chemotherapy does not significantly modify GDF15 change. Research Sponsor: None.

6111 Poster Session

Nonoperative management of locally advanced resectable cutaneous squamous cell cancer of the head and neck with PD-1 blockade.

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Background: Head and neck cutaneous squamous cell carcinoma (cSCC) is common, increasing in incidence, and highly immunogenic. Neoadjuvant PD-1 blockade with cemiplimab has demonstrated substantial efficacy prior to surgery; however, its role as a definitive nonoperative strategy in resectable disease remains poorly defined. **Methods:** We conducted a single-institution retrospective study (2018–2023) of patients with locally advanced, resectable stage III/IV head and neck cSCC treated with cemiplimab. Patients received either neoadjuvant cemiplimab followed by surgery or cemiplimab monotherapy without surgery. The primary endpoint was objective clinical and radiologic response rate. Secondary endpoints included disease-specific survival (DSS), progression-free probability (PFP), histopathologic response, and exploratory genomic biomarkers. **Results:** Seventy-three patients were included: 52 received cemiplimab monotherapy (median age, 78.8 years) and 21 received neoadjuvant cemiplimab (median age, 73 years). In the monotherapy cohort, complete response occurred in 68.6%, partial response in 9.8%, stable disease in 5.9%, and progression in 15.7% (median treatment duration, 10 months). Two-year DSS and PFP were 90% (95% CI, 80–100) and 82% (95% CI, 72–94), respectively. In the neoadjuvant cohort, radiographic response was observed in 66.7% and pathologic complete response in 38.1%. Two-year DSS and PFP were 95% (95% CI, 86–100) and 78% (95% CI, 62–100), respectively. DSS and PFP did not differ significantly between cohorts. Tumor-infiltrating lymphocytes (TILs) were higher in complete and partial responders than in patients with stable or progressive disease (p=0.005, q=0.02), with absent TILs more frequent in non-responders. Tumor mutational burden (TMB) was greater in complete (55.7) and partial responders (14.9) than in patients with progressive disease (4.9; p=0.02, q=0.04). **Conclusions:** In the largest reported series to date, cemiplimab monotherapy achieved durable disease control and oncologic outcomes comparable to neoadjuvant cemiplimab in selected patients with resectable, locally advanced head and neck cSCC, supporting further study of definitive immunotherapy as an organ-preserving strategy. Research Sponsor: None.

Dynamic biological and metabolic response by EBV DNA and ^{18}F-FDG-PET-CT to induction chemotherapy (IC) to enhance prognostication in endemic nasopharyngeal carcinoma (NPC).

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Background: IC followed by concurrent chemoradiotherapy (CCRT) is the current standard of care for locoregionally-advanced NPC (LA-NPC). Nonetheless, evidence suggests that IC response is a strong predictor for risk of relapse in LA-NPC. Here, we characterized the dynamic metabolic and biological responses to IC, and investigated their associations with survival in patients with high-risk LA-NPC. **Methods:** Newly diagnosed patients with non-metastatic, biopsy-proven NPC were enrolled into two prospective ongoing studies (NCT04340024 and NCT06093061). For this analysis, patients who received 2-3 cycles of gemcitabine-cisplatin/carboplatin IC were included; all patients had plasma EBV DNA assessed following every IC cycle, and ^{18}F-FDG-PET-CT performed pre-IC and 1 week before the end of IC. For the latter, standardized uptake values (SUVs) were recorded for the primary tumor (SUVp) and individual nodal lesion(s) (SUVn). Biological (bCR) and metabolic complete response (mCR) were defined as EBV DNA =0 copy/mL and SUV ≤2.5, respectively. Prediction accuracy of 2y disease-free survival (DFS) was assessed by area under the receiver operating characteristic curve (AUC). **Results:** 117 patients diagnosed between Jan 2019 to Apr 2025 were included in this analysis; of these, 112 and 106 had SUVp and SUVn at pre- and post-IC. For SUVn, we performed lesion-level analysis for 259 LNs. Median follow-up was 20.5 (interquartile range [IQR]: 11.6-41.3) mo and TNM-8 stage distribution for stage III and IVA were 43% (50/117) and 57% (67/117), respectively. Median SUVp and SUVn pre-IC were 15.0 (IQR: 10.4-18.2) and 8.5 (IQR: 4.5-12.3), respectively, while median EBV DNA level was 4800 (IQR: 914-20598) copies/mL. Post-IC, we recorded mCR at the primary tumor and LNs for 33/112 (29%) and 49/106 (46%), respectively; while 14/117 (12%), 30/117 (26%) and 40/117 (34%) patients manifested bCR post-IC1, IC2, and IC3, respectively. Metabolic response was not correlated with biological response; of 33 patients with primary tumor mCR, 20/33 (61%) had bCR; while for LNs, only 25/49 (51%) patients with mCR manifested bCR post-IC. Additionally, we observed significant intrapatient heterogeneity of mCR between LN lesions post-IC; in 57/106 patients with non-mCR for ≥1 of the LNs, SUVn ranged between 0-12.9. Finally, incorporating both post-IC bCR and mCR to TNM-8 stage and pre-IC EBV DNA enhanced AUC of 2y DFS prediction; from 0.58 (95%CI:0.44-0.73) [TNM-8+pre-IC EBV DNA] to 0.77 (95%CI:0.60-0.94). **Conclusions:** Metabolic and biological responses to IC provide unique information on response phenotypes of patients with LA-NPC, and improved the prediction accuracy of 2y DFS compared with TNM-8 stage and pre-IC EBV DNA. Combinatorial ^{18}F-FDG-PET-CT and EBV DNA post-IC may enhance the selection of these patients for treatment intensification. Research Sponsor: National Medical Research Council Singapore; NMRC/OFLCG21jun-0013; National Medical Research Council Singapore; NMRC/CSAINV20nov-0021.

Chrono-chemotherapy combined with IMRT in locoregionally advanced nasopharyngeal carcinoma: A prospective randomized study.

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Background: Induction chemotherapy followed by radiotherapy with concurrent cisplatin is a standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC). The TPF induction regimen combined with intensity-modulated radiation therapy (IMRT) improves tumor control but causes substantial toxicity. Circadian rhythms regulate tumor biology and drug metabolism. Docetaxel, cisplatin, and 5-fluorouracil show circadian-dependent pharmacologic properties. Chrono-chemotherapy aligns drug administration with circadian rhythms and may reduce toxicity. This study compared long-term outcomes and late adverse events between chrono-chemotherapy and conventional chemotherapy combined with IMRT in LA-NPC. **Methods:** This single-center, prospective, randomized clinical trial was registered at ClinicalTrials.gov (NCT03196869). Between April 2017 and May 2018, 128 patients with newly diagnosed stage III–IVa nasopharyngeal carcinoma were randomly assigned to chrono-chemotherapy or conventional chemotherapy. All patients received three cycles of TPF induction chemotherapy, followed by IMRT with two cycles of concurrent cisplatin chemotherapy. Survival outcomes were analyzed using the Kaplan–Meier method and compared by log-rank test. Late toxicities were graded using CTCAE v5.0. Quality of life was assessed with the EORTC QLQ-C30 questionnaire. **Results:** A total of 124 patients were included in the survival analysis. No significant differences were observed between groups in 5-year overall survival (P=0.709), progression-free survival (P=0.492), distant metastasis-free survival (P=0.467), or locoregional recurrence-free survival (P=0.697). The chrono-chemotherapy group showed lower rates of xerostomia (P=0.034) and dysphagia (P=0.019). No grade ≥4 late toxicities were observed. Global health status scores were higher in the chrono-chemotherapy group (P=0.043). **Conclusions:** Chrono-chemotherapy combined with IMRT achieved long-term survival outcomes comparable to conventional chemotherapy in LA-NPC. This approach reduced selected late toxicities and improved overall health status. Chrono-chemotherapy may represent a toxicity-sparing treatment option. Clinical trial information: NCT03196869. Research Sponsor: None.

Late toxicities and quality of life.

Outcome	Conventional Chemotherapy	Chrono-chemotherapy	P value
Xerostomia, n (%)	24/36 (66.7)	16/38 (42.1)	0.034
Dysphagia, n (%)	24/36 (66.7)	15/38 (39.5)	0.019
Global health status score*	58.33 (50.00–72.92)	75.00 (50.00–83.33)	0.043

*Scores derived from the EORTC QLQ-C30 questionnaire; values are presented as median (interquartile range).

Survival implications of context-dependent oncogenic *PIK3CA* mutations in HNSCC.

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Background: Head and neck squamous cell carcinoma (HNSCC) is a heterogenous disease that generally lacks clinically useful stratification methods beyond anatomy and HPV status. *PIK3CA* is the most frequently mutated oncogene in HNSCC, and previous studies have linked *PIK3CA* mutations to survival in HNSCC. Thus, we aimed to investigate overall survival (OS) in a large multi-center cohort of HNSCC as a function of specific *PIK3CA* mutation hotspots to better understand the molecular drivers of risk and prognosis in HNSCC. **Methods:** A subset of oral cavity (OC, n=606) and oropharyngeal (OP, n=480) tumors from the VOYAGER consortium underwent exon sequencing in 1,109 cancer related genes and whole HPV16/18 genomes. Mutations in *PIK3CA* were analyzed using a somatic variant calling and filtering pipeline, and driver alterations were annotated based on gain-of-function variants at recurrent hotspots in specific functional protein domains. HPV status was defined using serology, p16 IHC, RNA ISH, and viral genomics. Multivariable Cox proportional hazards models were used to assess the relationship between *PIK3CA* mutations and five-year OS adjusted for age, sex, HPV status, tumor type, and TNM staging. **Results:** In OP tumors, 289 were HPV(+) and 174 were HPV(-), while only 13 of OC tumors were HPV(+). The overall *PIK3CA*mutation rate was 18% (13% of OC vs 24% of OPs), and among OP cases, *PIK3CA* mutations occurred in 28% of HPV(+) vs 18% of HPV(-) tumors. Of the nine recurrent hotspots in *PIK3CA*, the most common were the APOBEC-associated ones in the helical domain, *p.E545K* (3% OC vs 12% OP) and *p.E542K* (2% OC vs 5% OP), as well as smoking-associated kinase domain mutations at *p.H1047R* (3% OC vs 2% OP). In OC and OP cases combined, tumors harboring *PIK3CA* driver alterations in one of the nine hotspots showed a statistically significant improvement in OS that was independent of age, sex, staging, tumor type, and HPV status (HR 0.72, P=0.048). Among all HPV(+) tumors, driver mutations in *PIK3CA* conferred significantly better OS in the adjusted model (HR 0.42, P=0.02). Likewise, in all OP tumors, *PIK3CA* driver mutations were significantly associated with improved OS in the multivariate models (HR 0.60, P=0.04) and when stratified by HPV status this effect was particularly strong for HPV(+) OP tumors only (HR 0.45, P=0.04). Among the hotspots, *p.E545K* was the only one with improved survival in a univariable analysis of the full cohort (Log-rank P=0.01), but this was not significant in the adjusted model (HR 0.62, P=0.07). **Conclusions:** Our findings validate previously described associations between *PIK3CA* mutation and OS in HNSCC that are dependent on anatomic site and HPV status. Moreover, we provide a new perspective by analyzing OS as a function of recurrent mutation hotspots in *PIK3CA*, which may signify distinct pathologic processes among HNSCCs and thus may be clinically useful for patient stratification with prognostic or therapeutic intent. Research Sponsor: None.

Survival outcomes with contemporary treatments including immunotherapy for poorly differentiated neuroendocrine carcinomas of the head and neck.

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Background: Poorly differentiated Neuroendocrine Carcinomas of the Head and Neck (HN-NECs) are rare aggressive malignancies with limited data guiding therapeutic approaches, particularly in the metastatic setting, with cytotoxic chemotherapy (chemo) comprising the backbone of management. Despite the widespread use of immune checkpoint inhibitors/immunotherapy (IO) in advanced lung NECs, evidence regarding their utility in the extrapulmonary setting, particularly for HN-NECs, is scarce. We explored real-world outcomes with various therapeutic strategies, including IO, in patients with metastatic HN-NECs, using the National Cancer Database (NCDB). **Methods:** Patients with metastatic HN-NECs diagnosed between 2018 to 2023 were identified. Overall survival (OS) was analyzed using Kaplan-Meier estimations and Cox proportional hazards regression. **Results:** A total of 275 patients with metastatic HN-NECs were identified. Primary sites included larynx (n = 75, 27.3%), pharynx (n = 72, 26.2%), nasal cavity + paranasal sinuses (n = 67, 24.4%), and oral cavity (n = 61, 22.2%). Most common metastatic sites were liver (n = 128, 46.5%) and bone (N = 272; n = 116, 42.6%). Of these 275 patients, 212 (77.1%) received chemo, 95 (34.5%) received IO, 122 (44.4%) received radiotherapy (RT), and 46 (16.7%) underwent primary site surgery (surg). Among patients with available survival data (N = 227), receipt of chemo (n = 174) and/or IO (n = 78) were associated with prolonged OS vs. no chemo ($p < 0.001$) and/or no IO ($p = 0.005$), respectively. Use of RT (n = 105; $p = 0.17$) and surg (n = 39; $p = 0.18$) were not significantly associated with OS (Table). Among 174 patients who received chemo, concurrent IO (chemoIO; n = 73) was associated with significantly prolonged OS vs. chemo alone (14.1 months [m] vs. 9.9 m; HR, 0.67; 95% CI, 0.47 – 0.96; $p = 0.03$). On multivariable analysis adjusting for bone metastatic disease (the only other significant prognostic covariate on univariable regression), chemoIO remained associated with reduced mortality risk vs. chemo alone (HR 0.57; 95% CI, 0.39 – 0.82; $p = 0.003$). **Conclusions:** Akin to lung NECs, IO may improve OS in HN-NECs. Despite NCDB limitations, chemoIO was associated with prolonged OS over chemo alone. Further prospective evaluations are warranted, and results from ongoing studies (e.g., NCT05058651) are awaited. Research Sponsor: None.

Survival comparisons with univariable Cox proportional hazards regression.

Treatment Group	Median OS in months (95% CI)	HR (95% CI)	p
Chemo (vs. No Chemo)	11.3 (9.5 – 14.2) vs. 3.4 (2.7 – 6.2)	0.53 (0.38 – 0.74)	<0.001
IO (vs. No IO)	13.0 (10.8 – 17.1) vs. 8.1 (6.2 – 10.3)	0.63 (0.46 – 0.87)	0.005
RT (vs. No RT)	10.8 (8.8 – 14.6) vs. 8.5 (6.4 – 11.7)	0.81 (0.60 – 1.09)	0.17
Primary Site Surgery (vs. No Surgery)	12.5 (8.7 – 28.5) vs. 9.0 (7.7 – 11.7)	0.76 (0.51 – 1.14)	0.18
ChemoIO (vs. Chemo alone)	14.1 (11.1 – 19.3) vs. 9.9 (8.3 – 13.7)	0.67 (0.47 – 0.96)	0.03

$CCL3^{+}$ neutrophil signature as a predictor of response to neoadjuvant toripalimab plus chemotherapy in hypopharyngeal squamous cell carcinoma: A phase II trial.

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Background: Hypopharyngeal squamous cell carcinoma (HPSCC) has a poor prognosis. Although neoadjuvant chemoimmunotherapy (nCIT) is promising, responses are heterogeneous and PD-L1 combined positive score (CPS) inadequately stratifies benefit. We sought biomarkers to guide patient selection. **Methods:** In this prospective, single-center, single-arm phase II trial, patients with resectable locally advanced HPSCC received two cycles of neoadjuvant toripalimab, albumin-bound paclitaxel, and nedaplatin. The primary endpoint was the pathological complete response (pCR) rate. Pre-treatment tumor biopsies from a subset of patients (n=13) were analyzed by single-cell RNA sequencing (scRNA-seq) to identify determinants of response. Findings were validated in a larger cohort (n=60) using bulk RNA sequencing and immunohistochemistry. **Results:** Among 70 evaluable patients, the objective response rate was 82.7%. Of the 64 patients who underwent surgery, the pCR rate was 29.7% (95% CI, 18.9%–42.7%). Baseline PD-L1 CPS was not associated with pathological response (P=0.313). Single-cell analysis revealed that the pre-treatment tumor microenvironment of responders was significantly enriched with a pro-inflammatory neutrophil subset characterized by high expression of CCL3 (Neu_CCL3). A gene signature score derived from this subset was a strong and independent predictor of pCR (AUC = 0.788), significantly outperforming PD-L1 CPS (AUC = 0.621). **Conclusions:** The efficacy of nCIT in HPSCC is predetermined by a baseline immune architecture orchestrated by a CCL3+ neutrophil subset. The Neu_CCL3 gene signature is a promising, clinically translatable biomarker that can fill a critical gap in precision immunotherapy for HPSCC. Clinical trial information: ChiCTR2400081826. Research Sponsor: None.

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Palliative neck radiation therapy (RT) in combination with lenvatinib/pembrolizumab (L/P) in BRAF wild-type anaplastic thyroid cancer (BRAF-WT ATC).

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Background: BRAF-WT ATC carries a poor prognosis due to limited effective therapies and rapid, often fatal locoregional (LR) progression. Although L/P has shown some efficacy, response rates remain modest (36-52%). Prior studies have shown that complete surgical resection of the primary tumor significantly improves overall survival (OS). **Methods:** We retrospectively reviewed patients with BRAF-WT ATC treated with palliative neck RT (PNRT, ≤45 Gy) administered five days before to 21 days after first-line L/P, between January 2016 and August 2025. Primary objective was to evaluate the efficacy and safety of PNRT combined with L/P. Primary endpoints were progression-free survival (PFS), locoregional PFS (LPFS), and OS, defined from RT start, and estimated using Kaplan-Meier method. Secondary endpoints were overall response rate (ORR) and neck response per RECIST v1.1, changes in surgical morbidity assessed by the Thyroid Neck Morbidity and Complexity (TNMC) score, and proportion of patients proceeding to surgery. **Results:** Twenty-six patients met inclusion criteria. Median age was 66 years (range, 36-82) and 14 were male (54%). 23/26 (88%) had stage IVC disease. 21/26 (81%) received 'Quadshot' regimen (14Gy in 4 fractions), two 20 Gy in 5 fractions and three 30 Gy in 10 fractions. Median time from RT to L/P start was 2 days (range, −4 to 21). Median follow-up was 18.5 months (95% CI, 11.7-25.4). After PNRT and L/P, ORR was 72%, and 72% achieved a complete or partial response in the neck. Median OS and PFS were 10.0 (95% CI, 3.4-16.7) and 7.6 (95% CI, 4.4-10.8) months respectively. Median LPFS was not reached. Median TNMC score (0-4 scale, 4=unresectable) decreased from 4 (range, 2-4) at baseline to 3 (range, 0-4) at time of best response with a mean reduction of 1 point (range, 0-3). Ten patients (38%) proceeded to R0/R1 neck surgery after a median of 5.4 months (range, 1.6-9.5) from RT, with absence of residual ATC in the surgical specimens in 70% (7/10). OS and PFS were significantly longer in patients who underwent surgery compared with those who did not, with median OS 22.8 vs 6.1 months (p=0.002) and median PFS 12.7 vs 3.9 months (p=0.034). Seventeen patients (68%) had disease recurrence/progression: 1 LR, 10 distant, and 6 both LR and distant. All but one (6/7) LR recurrences were in patients who did not undergo surgery. PNRT combined with L/P was well tolerated, with most adverse events grade ≤ 2. One patient had a fistula 3 months after RT requiring emergency tracheostomy. **Conclusions:** Palliative neck RT combined with L/P for BRAF-WT ATC appears safe and may improve surgical resectability in patients with initially unresectable disease or high baseline surgical morbidity. Patients who proceeded to neck surgery had high pathologic complete response rate (70%) and significantly prolonged OS and PFS with low rate of locoregional relapse. Research Sponsor: None.

Detection, quantification, and subtyping of adenoid cystic carcinoma (ACC) using methylation from liquid biopsies.

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Background: Despite the common indolent behavior of ACC, some patients will experience aggressive disease with short survival. These distinct clinical behaviors have been linked to two transcriptional profiles: ACC-I, defined by NOTCH1 activation, solid histology, and more aggressiveness, and ACC-II, characterized by predominant myoepithelial p63 expression and generally indolent behavior. DNA methylation has been widely used for tumor identification and subtyping; however, their relevance in distinguishing ACC-I and ACC-II has not yet been explored. **Methods:** Forty-one ACC tissue samples from the original subtype development cohort (41/54) and twenty-three cfDNA samples from a phase II trial of axitinib and avelumab in recurrent/metastatic ACC (NCT03990571) were profiled through target-enriched enzymatic methylation sequencing. ACC subtypes (ACC-I/II) in tissue samples were validated with unsupervised clustering of highly variable regions. To translate these signatures to liquid biopsy, we used the METER (METhylome AnalysER) pipeline to identify tumor-specific differentially methylated sites (DMS) and regions (DMRs) relative to 22 healthy donors, enabling ctDNA detection (METER-positive), tumor proportion score (TPS) quantification, and ACC subtype assignment in cfDNA. Methylation-derived TPS were validated with ichorCNA (copy number alterations) estimates, and cfDNA-assigned subtypes were benchmarked against matched tissue transcriptional signatures. Finally, we investigated if METER detection was associated with progression-free survival (PFS). **Results:** ACC tissue methylation identified two clusters that perfectly matched reference transcriptional subtypes (17/17 ACC-I and 24/24 ACC-II). ACC-I tumors were hypermethylated compared to ACC-II (11,205 hyper and 1,804 hypo DMR, $p<0.05$). Of 23 cfDNA samples, 15 (65.2%) were deemed as METER positive with a higher rate among ACC-I (8/9, 88.9%) compared to ACC-II (7/14, 50.0%), consistent with the more aggressive subtype of ACC-I. The median (range) estimated TPS among METER positive samples was (3.86%; range 0.7%-82%), with a numerical higher TPS among ACC-I (14.8% vs 2.0%, p=0.073). TPS had strong correlation with ctDNA estimation by ichorCNA (spearman 0.86, $p<0.001$). METER subtyping correctly identified ACC-subtypes in 15/15 (100%) METER positive and 4/8 (50%) METER negative samples. METER-positive patients had shorter PFS (HR = 4.32; 95%CI, 1.49–12.5, p=0.007), including among ACC-II patients (HR = 4.84; 95%CI, 1.20–19.5, p=0.026). **Conclusions:** Methylation-based subtyping of ACC is highly concordant with transcriptional profiles and enables detection and subtyping of ACC in liquid biopsies. Beyond subtyping, cfDNA detection may serve as an additional prognostic marker, identifying patients at high risk for progression even within traditionally indolent subgroups. Clinical trial information: NCT03990571. Research Sponsor: U.S. National Institutes of Health; 1R01CA292385-01.

6119 Poster Session

Window of opportunity study of the Notch inhibitor AL101 in Notch1 activated adenoid cystic carcinoma (ACC): Biological effects and biomarker correlates.

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Background: ACC with NOTCH1 pathway activation (ACC-N1) is associated with aggressive clinical behavior and poor outcomes. AL101, an inhibitor of gamma secretase-mediated Notch signaling, previously demonstrated modest clinical activity in metastatic *NOTCH*-mutant ACC. We conducted a window-of-opportunity study to evaluate the biological effects of AL101 in ACC-N1 and to identify biomarkers to inform rational combination strategies. **Methods:** Patients with ACC-N1 received AL101 (4 mg weekly) for 4 to 8 weeks prior to surgery. Eligibility required Notch1 pathway activation by cleaved Notch (NICD1) immunohistochemistry ($\geq$ 70% nuclear staining). Treatment-related adverse events (AEs) were assessed per CTCAE v5.0 and radiographic response per RECIST v1.1. Whole-exome sequencing and RNA sequencing were performed on baseline samples, with paired analysis (pre- and post-treatment) in 12 patients. This report focuses on biomarker analysis; clinical endpoints and feasibility were previously presented. **Results:** 13 patients were enrolled between Nov/21 and Dec/23; 8 were newly diagnosed. The median number of AL101 doses were 6 (range: 4–7), the most common primary site was maxillary sinus (n=4). There were no grade 3-5 AEs. One patient achieved a partial response (ORR 7.7%), 11 had stable disease (including 2 with >20% tumor shrinkage), and one had progression in a non-target lesion. Post-treatment NICD1 expression was not significantly reduced (p=0.8). Genomic profiling revealed *NOTCH1* activating mutations in 9/13 tumors and MYB-NFIB fusions in 8/13, with co-occurrence in 6 patients. *MYB-NFIB* fusion with *MYB* overexpression, irrespective of *NOTCH1* mutation status, was associated with tumor shrinkage (p=0.02). Higher baseline NOTCH signaling activity by RNA sequencing (NOTCH signaling signature) correlated with greater tumor shrinkage (p=0.025). Although NICD1 IHC levels did not significantly change, AL101 treatment resulted in significant downregulation of NOTCH signaling activity, and the magnitude of signature reduction correlated with tumor shrinkage (p=0.037). Post-treatment transcriptomic analysis demonstrated upregulation of potentially druggable oncogenic pathways, providing biologic rationale for future combination therapeutic strategies. **Conclusions:** In this first window-of-opportunity study in ACC, AL101 demonstrated biological target modulation. Importantly, *MYB* overexpression and NOTCH signaling activity rather than NICD1 modulation or *NOTCH1* mutation correlated with tumor shrinkage. These findings provide translational insights and support biomarker-driven development of rational combination strategies in NOTCH1-activated ACC. Clinical trial information: NCT04973683. Research Sponsor: U.S. Department of Defense.

Long-term outcomes of SINTART 1 and SINTART 2: Two phase II trials of multimodal treatments in patients with locally advanced sinonasal carcinomas.

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Background: Sinonasal carcinomas (SNCs) are rare malignancies with poor prognosis. Multimodal treatments including induction chemotherapy (ICT), surgery and radiotherapy (RT) - modulated by histology and response to ICT - are often used, aiming to improve oncological outcome in terms of local control and survival. Two phase II clinical studies published in 2023 assessed the role of ICT in SNCs, SINTART1 and 2 for resectable and unresectable tumors, respectively [PMIDs: 37164774, 37163806]. The current work aims at reporting the long-term follow-up (FUP) data for both trials. **Methods:** The FUP was updated as of January 2026 for patients enrolled in both clinical studies. Median FUP was estimated with reverse Kaplan-Meier method. The following survival times were analyzed with Kaplan-Meier method in each cohort: overall survival (OS), disease-free survival (DFS), loco-regional-free survival (LRFS), distant metastasis-free survival (DMFS). **Results:** The updated median (m) survival times (in months) with their 95% confidence intervals (CI) and the event rates are detailed in Table 1. Pooling together the 2 studies, 30% of patients (18/60) were alive at last follow-up. **Conclusions:** SINTART 1 and 2 represent, to date, the largest prospective cohorts with long-term survival data in SNCs. With a median FUP exceeding 9 years, these results provide a robust benchmark for ICT-based multimodal strategies in this setting. Survival outcomes remain consistent with the initial reports, indicating that prognosis is largely determined within the first 2-3 years, when most deaths occur (approximately 70%). The near-overlap of mDFS and mLRFS identifies loco-regional failure as the predominant pattern of recurrence. Moreover, the short interval between relapse and death underscores the limited opportunity for salvage. These findings collectively emphasize the need for more effective local-intensification approaches and novel systemic agents. Additional analyses are underway to identify prognostic and predictive factors. Clinical trial information: NCT02099175; NCT02099188. Research Sponsor: None.

	Resectable (SINTART1) N=35	Unresectable (SINTART2) N=25
mFUP (95% CI)	108.26 (97.37-129.84)	103.22 (91.68-NR)
mOS (95% CI)	37.53 (21.97-98.36)	27.07 (11.28-65.03)
Events	66%	76%
mDFS (95% CI)	26.25 (15.43-80.43)	17.1 (7.89-37.76)
Events	71%	80%
mLRFS (95% CI)	26.25 (15.43-80.43)	18.95 (7.89-39.05)
Events	71%	80%
mDMFS (95% CI)	34.47 (21.84-96.32)	26.88 (9.31-46.78)
Events	69%	76%

Clinicopathologic characteristics and treatment outcomes of adenoid cystic carcinoma (ACC) by different primary sites.

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Background: Although ACC commonly arises in the salivary glands, nearly 40% arise at extra-salivary sites and are often managed as site-specific malignancies rather than as a unified histologic entity. Population-based data suggest that thoracic and head and neck ACC are associated with poorer survival compared with breast ACC; however, the factors underlying these differences remain poorly understood. **Methods:** We retrospectively identified all patients (pts) with ACC, irrespective of primary site, who were followed at a large cancer center between 2011 and 2024. Collected data included staging at diagnosis, primary site, local treatment (i.e. surgery, radiation), histologic subtype (solid, cribriform or tubular), lymphovascular invasion (LVI), perineural invasion (PNI), margin status (R0, R1), and clinical outcomes including local recurrence-free survival (LRFS), distant metastasis free-survival (DMFS), and overall survival (OS). Primary sites were grouped as major salivary glands (MASG), oral cavity or oropharynx (OCOP), sinonasal region (SINO), breast (BRST), thorax-lung (THLU), lacrimal gland (LCGL), and others (i.e., skin OTHR). Clinicopathologic characteristics were compared using Fisher tests, and associations between primary site and clinical outcomes were evaluated with multivariable Cox models comparing each site versus all others combined adjusted for local treatment type, margins, and solid histology, defined a priori following a causal inference framework. **Results:** Of 220 pts, 151 (69%) were female, and 199 (90.5%) had localized or locally advanced disease at diagnosis. The most common primary site was OCOP (n=67, 30%), followed by MASG (n=60, 27%), SINO (n=25, 11%), THLU (n=22, 10%), BRST (n=20, 9.1%), LCGL (n=6, 2.7%), and OTHR (n=20, 9.1%). Among 210 pts that received local treatment, 41 (19%) had surgery only, 134 (61%) surgery plus radiation, and 35 (16%) radiation alone. Patients with THLU primary had less up-front surgery (50% vs 76-100%, $p<0.001$). Among surgical cases, 58% had R1 resections; PNI was present in 48%. BRST pts had lower rates of positive margins (R1 7.7%, p=0.04) and PNI (28% vs 35-83%, p=0.019). Histologic subtype was reported in 108 (49%) pts with 72 (78%) cribriform, 58 (54%) solid, and 49 (45%) tubular. Median LRFS, DMFS, and OS were 103 months [mo] (95%CI 77-141), 87 mo (95%CI 70-131), and 153 mo (95% CI 124-222) respectively. Pts with SINO experience worse LRFS (HR 2.01, p=0.03), DMFS (HR 2.07, p=0.02), and OS (HR 3.51, $p<0.001$) while MASG had potentially improved DMFS (HR 0.63, p=0.07) and THLU OS (HR 0.31, p=0.07) in adjusted models. **Conclusions:** Primary site-specific clinical outcomes in ACC are not fully explained by treatment approach or histologic features. These findings suggest biological heterogeneity across ACC by primary site and underscore the need for molecular characterization of site-specific disease drivers. Research Sponsor: None.

Artificial intelligence–powered spatial analysis of endothelial cells and tumor-infiltrating lymphocytes to predict response to axitinib in adenoid cystic carcinoma.

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Background: Despite the limited systemic options for adenoid cystic carcinoma (ACC), VEGFR inhibitors remain a clinical mainstay. Although high stromal tumor-infiltrating lymphocyte (TIL) density has been identified as a predictive biomarker for improved progression-free survival (PFS), its predictive power remains to be fully optimized. We hypothesized that baseline vascular architecture, represented by endothelial cell (EC) density, might modulate the efficacy of axitinib. **Methods:** We performed a post-hoc exploratory analysis on H&E-stained whole-slide images (WSI) from 27 patients with R/M ACC treated with axitinib in a multicenter phase II trial (NCT02859012). An updated AI-powered analyzer (Lunit SCOPE IO), capable of multiple component TME profiling, was used to quantify the density (cells/mm^2) of TILs and ECs within the tumor epithelium and stroma. Patients were stratified into subgroups based on the median values. The clinical impact of integrated immune and vascular architecture was evaluated by analyzing PFS and OS. **Results:** The analyzed cohort (N=27) had a best objective response of stable disease in 25 patients (92.6%) while 16 patients showed tumor shrinkage (59.3%). Stratification revealed that patients with concurrent High EC and High TIL density in the tumor stroma (n=9) derived exceptional clinical benefit compared to all other patients (N=18). The High EC/High TIL subgroup achieved a median PFS of 19.6 months compared to 11.1 months in the comparator group (HR 0.30; 95% CI: 0.11–0.87; P=0.026). Furthermore, this subgroup demonstrated significantly prolonged OS (median NR vs. 24.4 months; HR 0.12; 95% CI: 0.02–0.95; P=0.044). Stratification based on intratumoral densities of EC and TILs showed a similar trend with the High EC/High TIL subgroup (n=10) reporting prolonged PFS (HR 0.32; 95% CI: 0.12-0.87; P=0.025) but not OS (HR 0.46; 95% CI: 0.12-1.74; P=0.251). The individual biomarkers based on median TIL and EC showed a trend towards prolonged survival but were not statistically significant. **Conclusions:** The co-enrichment of stromal ECs and TIL is associated with significantly prolonged PFS and OS, suggesting that this unique TME architecture may identify R/M ACC patients who derive greater clinical benefit from axitinib. This AI-based spatial analysis using H&E slides offers a practical, scalable biomarker strategy to guide treatment selection in this rare cancer. Research Sponsor: National Cancer Center, Republic of Korea; HA22C0011.

6123 Poster Session

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

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Background: Pemetrexed (PTX) is safe and tolerable with responses reported in pts with R/M SGC. 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 adenoid cystic carcinoma (ACC). **Methods:** MC200708 is a single arm phase II study of PTX and PMB in pts with R/M SGC (NCT04895735) with 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) for Cohort A but was amended to clinical benefit rate (CBR=SD+PR+CR) due to prolonged SD in several pts. Secondary endpoints: progression free survival (PFS), overall survival (OS), and toxicity. Exploratory analyses in Cohort A1 (post-amendment pts) included PSMA PET imaging and circulating PSMA extravesicles (EVs) as a biomarker. All pts received PTX 500 mg/m2 IV + PMB 200 mg IV q3 weeks until progression or treatment intolerance. Imaging was q3 cycles. **Results:** 20 pts (11 Cohort A + 9 Cohort A1) were enrolled from August 2021-Feb 2025. All 20 patients were eligible and received ≥ 1 cycle of treatment. Median age was 60.5 yrs, 50% male, performance status 0 (80%) or 1 (20%). 11 pts had no prior therapies (55.0%). The remaining pts had 1 (35%) or 2 (10%) prior lines of therapy. 75% of pts had no prior ICI. In Cohort A, the ORR was 0% (0 of 11). Cohort A1 met criteria for success based on CBR with 1 PR (12.5%) and 5 SD (62.5%) in the first 8 pts. For the whole cohort of 20 patients, the ORR was 5% (95% CI: 0.1-24.9) and the CBR rate was 75% (95% CI: 51-91) with 1 PR and 14 pts with SD. The duration of response for the 1 PR patient was 12.4 months. The median duration of response for the 15 pts with SD was 7.5 (2.0-29.7) months. 3 pts (15%) had PD and 2 pts (10%) went off prior to response assessment. Median cycles of treatment was 4 (2-30). In the 17 pts who discontinued, treatment was stopped in 9 (53%) for PD, 4 (23.5%) due to adverse events (AE), and 4 (23.5%) due to physician/patient preference. With a median follow-up of 14.5 months (1.5-39.2), the 1-year PFS rate is 52.1% (32.6 – 83.2%) and the OS rate is 82.1% (95% CI: 65.6 – 100%). The overall grade 3+ AE rate regardless of attribution was 80% (16/20). The most common grade 3 AEs were lymphocyte count decrease (40%), hypertension (20%), fatigue (10%), and pneumonitis (10%). 2 pts had a grade 4 AE (lymphocyte count decrease and thrombotic thrombocytopenic purpura). There were no treatment-related deaths. Analysis of correlative studies for Cohort A1 with PSMA imaging and EV biomarker ongoing. **Conclusions:** PTX and PMB has modest activity in pts with R/M ACC with CBR of 75% and prolonged benefit for some patients. Clinical trial information: NCT04895735. Research Sponsor: Merck.

Anti–PD-1 immunotherapy with chemotherapy for poorly chemo-responsive thyroid and salivary gland tumors: The iPRIME study.

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Background: Clinical trial data guiding treatment of unresectable or metastatic salivary and thyroid gland cancers are limited. While targeted therapies have advanced management for selected patients, chemotherapy remains a treatment strategy for those with aggressive disease biology. Anti-PD1 therapy has shown antitumor activity in advanced, PD-L1 positive salivary and thyroid gland cancers, underscoring the need to evaluate the synergistic activity of PD-1 blockade with cytotoxic chemotherapies in these neoplasms. **Methods:** The iPRIME (NCT03360890) is a single center, parallel two cohort trial evaluating pembrolizumab with cytotoxic chemotherapy in patients with advanced salivary gland and thyroid cancers. Eligible patients had histologically confirmed disease that was unresectable and not amenable to curative intent therapy. Patients received pembrolizumab 200 mg IV with docetaxel or doxorubicin 75 mg/m2 for 2-6 cycles, followed by pembrolizumab monotherapy for up to 2 years. Docetaxel or doxorubicin could be reintroduced upon disease progression while on pembrolizumab or after the 2-year treatment period. The primary endpoint was response rate. Secondary endpoints included progression free survival (PFS), overall survival (OS), disease control rate, and adverse events. **Results:** A total of 39 patients (27 salivary and 12 thyroid cancer) were enrolled between 2018-2022. Mean age was 61 in salivary and 71 in the thyroid cancer, with 48% and 58% female patients, respectively. Salivary gland cancer histologies included adenoid cystic 15/27 (56%), ex-pleomorphic 18%, mucoepidermoid 7.4%, acinic cell 7.4%, salivary duct 7.4%, basaloid adenocarcinoma 3.7%. In the salivary gland group, the overall response rate was 25.6% (7/27; 90% CI 12.9%-43.2%), and the disease control rate was 89% (24/27; 90% CI 73.7%-96.9%). The overall response rate in the adenoid cystic patients was 27% (4/15). Median PFS was 8.6 months (90% CI: 6.0 to 12.4), including 8 months in adenoid cystic patients (90% CI: 6.0-16.7%) and 7.8 months in the non-adenoid cystic cases (90% CI: 3.8-14.6), with one and two-year PFS rates of 37% and 8.2%, respectively. Median OS was 25.5 months in the adenoid group (90% CI:8.5-32) and 22.9 months in the non-adenoid group (90% CI: 7.8-78) (p=0.26). One, two, and five-year OS rates in the salivary cohort were 66%, 50%, and 23%, respectively. In the thyroid cohort, the response rate was 16.7% (2/12), with both PR. Grade 4 events occurred in nine patients salivary patients and one grade 5 event was observed. **Conclusions:** The combination of pembrolizumab and cytotoxic chemotherapy did not substantially change antitumor control activity relative to historical controls in patients with advanced salivary or thyroid cancers. There were no statistically significant differences in PFS and OS between adenoid cystic and non-adenoid cystic subtypes. Clinical trial information: NCT03360890. Research Sponsor: Merck.

TPS6125 Poster Session

Phase III randomized trial of tislelizumab plus gemcitabine/capecitabine (GX) versus tislelizumab plus gemcitabine/cisplatin (GP) as first-line therapy for recurrent/metastatic nasopharyngeal carcinoma: A prospective multicenter study (PROGRESS).

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Background: Nasopharyngeal carcinoma (NPC) is a prevalent malignancy in Southeast Asia and Southern China. Around 10% of pts have distant metastasis at initial diagnosis, and ~30% of those initially without metastasis will develop distant metastasis after radical treatment. These recurrent/metastatic (R/M) NPC pts have poor prognosis with a 5-year survival rate of only 20–30%. The RATIONALE-309 study established tislelizumab plus GP as a standard first-line therapy for R/M NPC, but most pts still experience disease progression in 2 years. Furthermore, in real-world clinical practice, a lot of pts are either platinum-intolerant or platinum-refractory recurrent, underscoring the urgent need for novel treatments. Recent studies suggest that first-line treatment regimens incorporating capecitabine may provide longer progression-free survival (PFS) compared to the GP regimen with a more favorable safety profile. Additionally, a retrospective study demonstrated that tislelizumab plus GX achieved notable tumor responses and PFS benefits in R/M NPC pts who have relapsed immunotherapy.
Methods: This is a prospective, multicenter, randomized, controlled Phase III trial evaluating the efficacy and safety of tislelizumab + GX vs. tislelizumab + GP as first-line therapy in R/M NPC. 266 pts will be randomly assigned to the experimental or the control group. The experimental group will receive tislelizumab plus GX (gemcitabine 1g/m^2 D1,8 + capecitabine 1000 mg/m^2 BID D1-14) for 4–6 cycles, followed by tislelizumab plus capecitabine maintenance. The control group will receive tislelizumab plus GP (gemcitabine 1 g/m^2 D1,8 + cisplatin 80mg/m^2 D1) for 4–6 cycles, followed by tislelizumab monotherapy. Treatment will continue until disease progression or intolerable toxicity. The primary endpoint is PFS. Secondary endpoints include objective response rate, duration of response, overall survival, etc. Adverse events will be monitored and graded according to NCI CTCAE v5.0. Patient enrollment began in December 2023 across 10 centers in China, with 168 pts enrolled by December 2025. Clinical trial information: NCT06177301. Research Sponsor: None.

TPS6126 Poster Session

MC240701: Decentralized pilot study of triple oral metronomic chemotherapy in recurrent/metastatic oral cavity cancer.

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Background: Oral cavity cancers (OCC) are a rare subtype of head and neck cancer (HNC) with poor outcomes and limited second-line treatment options in the recurrent or metastatic (R/M) setting. Treatment-related morbidity and repeated local recurrences in OCC result in significant impairment of function and quality of life. Rural OCC patients comprise a sizable portion (50%) of our practice and are usually of lower socioeconomic status with lack of access to specialist care. They also have multiple barriers to treatment access and ancillary services, translating to poorer clinical outcomes. There is a critical need for effective and accessible therapies for R/M OCC in rural patients. Triple oral metronomic chemotherapy (TOMC) with Methotrexate, Erlotinib and Celecoxib (MEC) suppresses angiogenesis and activates antitumor microenvironment in HNC. Studies using TOMC in R/M OCC outside the US show reasonable efficacy (6-month OS 52.9%), better safety and lower cost compared to standard second line options. We hypothesize that a decentralized clinical trial with TOMC in R/M OCC is feasible, safe and effective in addition to being economical and accessible for rural patients. **Methods:** MC240701 is a single institution, open label, decentralized, single arm pilot study of MEC in patients with R/M OCC. Eligible pts must be ≥18 years old, have pathologically confirmed R/M OCC not amenable to curative-intent therapy, ECOG 0-2 and adequate organ function. At least 1 measurable lesion by RECIST 1.1 OR non-measurable disease (evident mucosal lesions, CNS/bone disease, lesions not meeting RECIST criteria) is permitted. Patients must have received standard first line immunotherapy with or without chemotherapy OR should be unable/unwilling to receive first line treatment. Key exclusion criteria include patients unable to take pills by mouth, serious medical co-morbidity or autoimmune disease, immunocompromised patients and other active malignancy. Primary endpoint is to demonstrate feasibility of decentralized clinical trials, secondary outcomes include overall response rate, progression free and overall survival and toxicity. Additional goals are to evaluate patient impact of decentralized treatment through surveys and interviews After initial screening and evaluation, patients are remotely consented and will receive study drugs by mail. All patients will receive the same treatment of Methotrexate 9mg/m^2 PO weekly, Erlotinib 150 mg PO daily, and Celecoxib 200 mg PO BID, each cycle will be 28 days. Treatment will continue until disease progression or treatment tolerance, study duration is for 2 years. All subsequent clinical and laboratory monitoring and response assessments (every 3 cycles) will be remotely performed or have an option for local testing. Enrollment began July 2025 and 4 out of planned 25 patients have been accrued. FDA IND: 174540. Clinical trial information: NCT06997068. Research Sponsor: Mayo Clinic Comprehensive Cancer Center.

TPS6127 Poster Session

OrigAMI-5: A randomized, phase 3 study of amivantamab plus pembrolizumab and carboplatin vs standard of care pembrolizumab plus platinum and 5-fluorouracil as first-line treatment in recurrent/metastatic head and neck cancer.

Robert I. Haddad, Renata Ferrarotto, Ye Guo, Kevin Joseph Harrington, Lisa F. L. Licitra, Nabil F. Saba, Makoto Tahara, Pablo Nenclares, Irene Brana, John Xie, Pei-Ling Chu, Mariah Ennis, Jessica Dobbs, Brooke Diorio, Priya Kim, Sujay Shah, Barbara Burtness; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Shanghai East Hospital, Shanghai, China; The Institute of Cancer Research/Royal Marsden Hospital, London, United Kingdom; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Winship Cancer Institute, Emory University, Atlanta, GA; National Cancer Center Hospital East, Kashiwa, Japan; The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, London, United Kingdom; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Johnson & Johnson, Raritan, NJ; Johnson & Johnson, Titusville, NJ; Johnson & Johnson, Bridgewater, NJ; Johnson & Johnson, Spring House, PA; Yale School of Medicine / Yale Cancer Center, New Haven, CT

Background: Recurrent and/or metastatic head and neck squamous cell cancer (R/M HNSCC) is associated with significant morbidity and mortality. Current first-line standard of care regimens, including combinations of pembrolizumab with platinum-based chemotherapy with/without 5-fluorouracil (5-FU), yield low response rates and poor long-term outcomes, with a median survival of approximately 1 year. Many patients with R/M HNSCC exhibit EGFR and MET overexpression. Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity that is FDA-approved in *EGFR*-mutated advanced non-small cell lung cancer. In a prior report of the phase 1b/2 OrigAMI-4 study (NCT06385080), subcutaneous (SC) amivantamab monotherapy demonstrated a confirmed objective response rate of 45% among participants with HPV-unrelated R/M HNSCC whose disease had previously progressed on immune checkpoint inhibitor and platinum-based chemotherapy (Harrington *Oral Oncology* 2025). The objective of this phase 3 randomized study is to assess the efficacy of SC amivantamab in addition to pembrolizumab and carboplatin, as compared to the standard of care (pembrolizumab plus carboplatin or cisplatin and 5-FU) as first-line therapy for participants with R/M HNSCC. **Methods:** The ongoing multicenter, global OrigAMI-5 study (ClinicalTrials.gov identifier: NCT07276399) is planned to open in approximately 205 sites in 22 countries. Eligible participants will have HPV-unrelated R/M HNSCC (primary tumor locations: oral cavity, oropharynx, hypopharynx, or larynx); all primary oropharyngeal tumors must be human papillomavirus (HPV)-negative. All participants, regardless of combined positive score (CPS), are eligible but must have local testing results to determine CPS for stratification and be treatment-naïve in the R/M setting; systemic therapy in the locally advanced setting is allowed if completed >6 months prior. Prior exposure to EGFR or MET targeting agents is exclusionary. Approximately 500 participants will be randomly assigned 1:1 to receive SC amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) with pembrolizumab and carboplatin, or 5-FU plus pembrolizumab and investigator's choice of carboplatin or cisplatin. Randomization will be stratified by programmed cell death ligand 1 (PD-L1) CPS (<1, $1–19$, ≥ 20) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). The primary endpoints will be objective response rate and overall survival. Secondary endpoints include progression-free survival, duration of response, and patient-reported outcomes. Safety assessments will include adverse event monitoring and laboratory abnormalities. Clinical trial information: NCT07276399. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

TPS6128 **Poster Session**

NRG-HN015: A phase II randomized trial of neoadjuvant chemotherapy or chemo-immunotherapy in patients with recurrent/persistent PD-L1–positive squamous cell carcinoma of the head and neck undergoing salvage surgery.

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Background: Treatment for locoregionally recurrent squamous cell carcinoma of the head and neck (SCCHN) remains a challenge. 30-40% of patients treated with definitive-intent therapy will recur, the majority locoregionally (Ang 2010, Galloway 2016, Tan 2010). Despite improvements in the effectiveness of palliative systemic therapy over the last decade (Vermorken 2008), salvage surgery (SS) remains the modality of choice to achieve cure in patients with locally recurrent disease particularly in patients who have previously received radiation. Thus, there is a pressing need to improve the therapeutic ratio by increasing the benefit of SS and improving oncologic outcomes. One promising means would be early introduction of systemic therapy with or without immune checkpoint inhibition for patients who are candidates for SS. NRG-HN015 proposes to investigate the effect on event-free survival (EFS) of pre-operative chemotherapy or chemo-immunotherapy in comparison to the standard SS approach. **Methods:** NRG-HN015 (NEOPOLIS) is a randomized, multicenter, controlled, 3-arm, superiority phase II study of neoadjuvant chemotherapy or chemo-immunotherapy in patients with recurrent/persistent PD-L1 enriched SCCHN who have planned SS. The primary objective is to compare investigator-assessed EFS of patients treated with neoadjuvant chemotherapy or chemo-immunotherapy prior to SS versus SS alone. The primary hypothesis is that neoadjuvant chemotherapy or chemo-immunotherapy added to SS will improve EFS. Enrolled patients will be randomized 1:1:1 to receive SS (Arm 1 - control), chemotherapy + SS (Arm 2), or chemo-immunotherapy + SS (Arm 3). Prior to randomization, patients will be stratified by primary tumor site (Oropharynx or oral cavity vs. larynx or hypopharynx, stage (rT4a or rN3a vs. other), and prior use of iPD1/PDL1 inhibitors in the definitive setting. Patients must have locally recurrent or persistent SCCHN arising within the oral cavity, oropharynx, larynx, or hypopharynx and are deemed candidates for salvage surgery. P16-positive oropharynx patients with T2, T3, T4, N0, N1, N2 and all other patients with T2, T3, T4a, N0, N1, N2a, N2b, N2c, N3a are eligible. Patients must have PDL1-positive and measurable disease, with no major vascular involvement (>180° involvement of the common carotid or internal carotid artery), jugular foramen involvement, or prevertebral, paraspinous muscle involvement precluding a curative resection. Patients who are candidates for salvage laryngectomy to treat recurrent laryngeal cancer and who are having SS for curative intent are eligible. The trial is opened to enrollment. Clinical trial information: NCT071953734. Research Sponsor: National Cancer Institute; NRG-HN015.

TPS6129 **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 HPV-negative, PD-L1–positive, recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): FORTIFI-HN01.

Renata Ferrarotto, John M. Kaczmar, David R. Spigel, Christine H. Chung, Dan Paul Zandberg, Irene Brana, Caroline Even, Kevin Joseph Harrington, Lisa F. L. Licitra, Bhumsuk Keam, Danny Rischin, Melvin L.K. Chua, Ralf Reiners, Rita Dalal, Glenn J. Hanna; The University of Texas MD Anderson Cancer Center, Houston, TX; Hollings Cancer Center, The Medical University of South Carolina, Charleston, SC; Sarah Cannon Research Institute Oncology Partners, Nashville, TN; Moffitt Cancer Center and Research Institute, Tampa, FL; UPMC Hillman Cancer Center, Pittsburgh, PA; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Gustave Roussy, Villejuif, France; The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust, London, United Kingdom; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Seoul National University Hospital, Seoul, NA, South Korea; Peter MacCallum Cancer Centre, Melbourne, Australia; National Cancer Centre Singapore, Singapore, Singapore; Bicara Therapeutics, Boston, MA; Harvard Medical School, Boston, MA

Background: HPV-negative HNSCC is an aggressive disease characterized by high rates of recurrence, metastasis, and resistance to standard treatments. Most HPV-negative HNSCC tumors overexpress tumorigenic factors EGFR and TGF-β. In a phase 1/1b trial (NCT04429542), ficerafusp alfa demonstrated promising efficacy and a manageable safety profile in first-line R/M HNSCC. FORTIFI-HN01 (NCT06788990) is an ongoing randomized, double-blind, placebo-controlled, phase 2/3 trial designed to assess the efficacy and safety of ficerafusp alfa combined with pembrolizumab vs 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 HPV-negative OPSCC confirmed by central laboratory testing. Additional eligibility criteria include no prior systemic therapy for R/M disease, PD-L1-positive tumor (CPS ≥1), measurable disease per RECIST v1.1, and ECOG performance status 0 or 1. The phase 2 objective was to determine the optimal biological dose (OBD) of ficerafusp alfa through an integrated analysis of safety, tolerability, PK, PD, and efficacy. Following OBD determination (1500 mg QW), the trial transitioned seamlessly into the phase 3 portion with 2:1 randomization (ficerafusp alfa:control). Randomization is stratified by PD-L1 CPS (1–19 vs ≥20) and disease extent (local/regional recurrence only, distant metastasis only, or both). Patients receive pembrolizumab (200 mg IV every 3 weeks for up to 35 cycles) and either ficerafusp alfa or placebo IV QW until disease progression or unacceptable toxicity. Tumor imaging occurs every 6 weeks during the first year and every 9 weeks thereafter. The primary endpoints are objective response rate (ORR) per RECIST v1.1 (blind independent committee review) and overall survival. An interim analysis evaluating ORR is planned. Secondary endpoints include safety, duration of response, progression free survival, clinical benefit rate, and patient-reported outcomes. The trial is actively recruiting, with planned enrollment of ~650 subjects. Clinical trial information: NCT06788990. Research Sponsor: Study funded by Bicara Therapeutics Inc.

TPS6130 **Poster Session**

Becotatug vedotin plus pucotenlimab as first-line therapy in patients with recurrent or metastatic nasopharyngeal carcinoma: A phase II clinical trial.

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Background: Epidermal growth factor receptor (EGFR) is highly expressed in approximately 85% of nasopharyngeal carcinoma (NPC) cases and plays a critical role in tumor cell proliferation. Becotatug vedotin (MRG003) is a novel EGFR-targeted antibody-drug conjugate (ADC) with promising anti-tumor activity in NPC. Pucotenlimab is a recombinant humanized programmed cell death protein-1 (PD-1) inhibitor. Although platinum-based chemotherapy combined with a PD-1 inhibitor represents the current standard first-line treatment for recurrent or metastatic (R/M) NPC, treatment-related toxicities and suboptimal efficacy remain significant challenges. Preclinical and early clinical data have demonstrated synergistic anti-tumor activity of MRG003 combined with pucotenlimab in platinum-refractory R/M NPC. However, the efficacy and safety of this platinum-free combination as a first-line therapy for R/M NPC remain uncertain. This study aims to evaluate the efficacy and safety of becotatug vedotin plus pucotenlimab as a novel first-line treatment for patients with R/M NPC. **Methods:** This is an open-label, single-arm, phase II trial enrolling patients with R/M NPC eligible for first-line systemic therapy. Inclusion criteria include: age 18 to 75 years; ECOG performance status score of 0 or 1; histologically or cytologically confirmed NPC; stage IVB (UICC/AJCC 8th edition) or locoregional recurrence not amenable to curative local therapy; at least one measurable lesion per RECIST v1.1; and adequate organ function. Key exclusion criteria include severe uncontrolled pulmonary disease, active autoimmune disease, or a history of autoimmune disease requiring systemic immunosuppressive therapy. Eligible patients receive becotatug vedotin (2.0 mg/kg, IV, D1, Q3W) and pucotenlimab (200 mg, IV, D1, Q3W) until disease progression, unacceptable toxicity, or death. Dose adjustments are permitted based on toxicities. The primary endpoint is progression-free survival (PFS), defined as the time from treatment initiation to disease progression or death from any cause. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), duration of response (DoR), overall survival (OS), treatment-related safety, and predictive biomarkers. Research Sponsor: Lepu Biopharma Co., Ltd. Clinical trial information: NCT07381699. Research Sponsor: None.

TPS6131 Poster Session

ERBIOTAX (TTCC-2022-02): A phase II, multicenter, randomized study of cetuximab with or without weekly paclitaxel after progression on first-line pembrolizumab plus platinum/5-FU in recurrent or metastatic head and neck squamous cell carcinoma.

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Background: Pembrolizumab, with or without platinum–5FU (PF), is the current first-line (1L) standard of care for PD-L1–positive recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). However, no established standard of care exists after progression on immune checkpoint inhibitors (ICI). Emerging evidence suggests that cetuximab administered post-ICI achieves higher objective response rates (ORR) and longer progression-free (PFS) and overall survival (OS) compared with historical second-line (2L) cetuximab outcomes from the pre-ICI era. We hypothesize that 2L treatment with cetuximab +/- paclitaxel may be more effective after ICI failure than previously observed in the pre-ICI era. **Methods:** This is a multicenter, open-label, randomized, non-comparative, two-arm, investigator-initiated phase 2 trial. Patients will be randomized (2:1) to cetuximab plus paclitaxel (Arm A: ERBITAX) or cetuximab monotherapy (Arm B), administered on Days 1, 8 and 15 of 21-day cycles for 4 cycles, followed in both arms by biweekly cetuximab monotherapy until disease progression, death, unacceptable toxicity, or withdrawal of consent. A total of 65 evaluable patients will be enrolled: 41 in Arm A (H0: ORR 25%, H1: 45%, 80% power, two-sided alpha 0.05) and 24 in Arm B (H0: ORR 10%, H1: 30%, 80% power, two-sided alpha 0.05). The primary endpoint is ORR in each arm. Secondary endpoints include disease control rate (DCR), PFS, OS, health-related quality of life (EORTC QLQ-C30, EORTC QLQ-H&N35 and EuroQol EQ-5D) and safety. Baseline tumor tissue (all patients) and on-treatment samples (between cycles 2-5 in 50% of patients; optionally at progression), as well as serial plasma samples will be collected for translational exploratory studies. Patients must have histologically confirmed SCCHN of oral cavity, oropharynx (HPV-positive or HPV-negative), hypopharynx, or larynx, with confirmed progression per RECIST 1.1. on or after 1L pembro + PF. The study started enrollment in June 2025, with 7 patients enrolled by December 23, 2025. The total accrual period is 18 months. Clinical trial identifiers: NCT06856213; EUDRACT 2024-514953-31-00. Trial supported by Merck, S.L.U., Madrid, Spain, an affiliate of Merck KGaA, Darmstadt, Germany, providing study medication and financial support. Clinical trial information: NCT06856213. Research Sponsor: Merck, S.L.U., Madrid, Spain, an affiliate of Merck KGaA, Darmstadt, Germany,.

TPS6132 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 those with HPV positive disease and current treatment 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 and 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 (p16 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 received 2 or fewer prior lines of anticancer therapy in the R/M setting; and have had 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 is ongoing to select the optimal dose. 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 (Eli Lilly provided cetuximab in N. America and Merck KGaA, Darmstadt, Germany in Europe, United Kingdom and Asia-Pacific). 1. JITC. 2019;7:184. 2. JCO. 2023. 41:3851. Clinical trial information: NCT06064877. Research Sponsor: AVEO Pharmaceuticals, Inc.

TPS6133 Poster Session

A phase III multicenter randomized non-inferiority trial comparing selective versus modified neck dissection in node-positive oral squamous cell carcinoma (SND vs MND).

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Background: Neck dissection is a critical component in the management of oral squamous cell carcinoma (OSCC) with nodal involvement. While modified neck dissection (MND) is widely practised in node-positive disease, selective neck dissection (SND) may offer comparable oncologic outcomes with reduced morbidity. Retrospective studies and meta-analyses suggest similar survival and regional control with SND in selected patients; however, high-quality prospective randomized evidence is lacking. This trial aims to evaluate whether SND is non-inferior to MND in terms of disease-free survival in treatment-naïve, node-positive OSCC patients. **Methods:** This is a prospective, multicenter, randomized, non-inferiority controlled trial enrolling patients aged 18–70 years with clinically and radiologically confirmed node-positive OSCC (T1–T4, N+), ECOG performance status 0–1, and adequate organ function. Eligible participants are randomized 1:1 to undergo primary tumor resection with either selective neck dissection (Arm A) or modified neck dissection (Arm B). Adjuvant radiotherapy or chemoradiotherapy is administered according to adverse pathological features, including extracapsular extension and positive margins. Randomization is stratified by participating centres. The planned accrual period is 3 years, followed by 2 years of follow-up. The study is conducted at four tertiary cancer centres in India. The primary endpoint is disease-free survival. Secondary endpoints include overall survival, regional recurrence rate, treatment-related morbidity, and quality of life assessed using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. Statistical Considerations: Assuming a 24-month DFS of 85% in the MND arm and a non-inferiority margin of 10%, a total of 432 patients (216 per arm) provides 80% power with a one-sided alpha of 0.05. Non-inferiority will be concluded if the upper bound of the 90% confidence interval for the hazard ratio is less than 1.5. Survival analyses will be performed using Kaplan–Meier methods and Cox proportional hazards models. The study has received institutional ethics approvals at participating centres and is registered with the Clinical Trials Registry of India. Patient recruitment is ongoing. This trial will provide prospective evidence regarding the oncologic equivalence of selective and modified neck dissection in node-positive OSCC and may help define a less morbid standard surgical approach. This trial will provide prospective evidence regarding the oncologic equivalence of selective and modified neck dissection in node-positive OSCC and may help define a less morbid standard surgical approach. Clinical trial information: CTRI/2024/11/076784. Research Sponsor: None.

TPS6134 Poster Session

Phase 1 study of VLPONC-01, a novel IL-12–encoding saRNA viral replicon particle, alone and in combination with pembrolizumab in head and neck cancer patients: Protocol summary.

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Background: Head and neck squamous cell carcinoma (HNSCC) has high recurrence rates despite standard perioperative treatments such as surgery with adjuvant radiotherapy and/or chemotherapy, with about 35% of patients relapsing. Neoadjuvant immune checkpoint therapy has shown promise: in the Phase III KEYNOTE-689 trial, adding perioperative pembrolizumab to standard care significantly improved median event-free survival (51.8 vs 30.4 months), leading to FDA approval in June 2025. However, only 9.4% of patients achieved a major pathologic response, a key predictor of reduced relapse and a surrogate for long-term benefit in other cancers. This low response rate underscores the need for more effective strategies to expand and deepen durable immune-mediated tumor responses in HNSCC. Our strategy is to develop a combination immunotherapy/gene therapy targeting the immunosuppressive myeloid populations such as tumor-associated macrophages (TAMs) and neutrophils (TANs), which are increasingly recognized as key mediators of immune evasion and poor outcomes. VLPONC-01 is a novel, non-replicating, viral particle-based therapy to target TAMs and TANs. VLPONC-01 efficiently delivers self-amplifying RNA (saRNA) encoding an engineered human Interleukin 12 (IL-12) gene into cells in the tumor microenvironment (TME), leveraging the natural tropism of Venezuelan equine encephalitis virus (VEEV). Within transfected cells, the RNA amplifies itself and directs the cell to produce and secrete IL-12 protein. The released IL-12 is expected to concentrate in the TME, where it activates immune cells and enhances their ability to attack cancer cells. **Methods:** This is a first-in-human, phase 1, open-label trial evaluating the safety and early efficacy of intratumoral administration of VLPONC-01 in patients with HNSCC, focusing on its ability to reduce tumor burden and lessen surgical morbidity. Furthermore, it will characterize IL-12-driven alterations in the tumor microenvironment and determine the synergistic potential of combining this approach with anti-PD-1 immunotherapy. The study includes two cohorts: Cohort A tests weekly intratumoral injection in recurrent and/or metastatic tumor patients to assess safety and determine dose levels, while Cohort C randomizes patients with resectable tumors into three groups to receive low-dose VLPONC-01 plus pembrolizumab, high-dose VLPONC-01 plus pembrolizumab, or pembrolizumab alone, prior to surgery. Outcomes include dose-limiting toxicities, surgical delays, systemic cytokine responses, and tumor response assessed by imaging and pathology. Clinical trial information: NCT06736379. Research Sponsor: None.

TPS6135 Poster Session

A randomized, non-comparative, multicenter phase II trial of neoadjuvant becotatug vedotin alone or combined with immune checkpoint inhibitors (penpulimab/ivonescimab) in resectable locally advanced head and neck squamous cell carcinoma.

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Background: The efficacy and safety of neoadjuvant therapy for resectable locally advanced head and neck squamous cell carcinoma (LAHNSCC) remain uncertain, and optimal treatment protocols needs further explored. Epidermal growth factor receptor (EGFR) is overexpressed in 90% of head and neck squamous cell cancers (HNSCC) and plays a critical role in tumor proliferation and survival. Antibody drug conjugates (ADCs) represent an emerging class of cancer therapeutics that combines several mechanisms of action to improve efficacy and reduce the systemic toxicity. Becotatug Vedotin is a novel ADC molecule of an anti-EGFR humanized immunoglobulin G1 (IgG1) monoclonal antibody conjugated with monomethyl auristatin E via a valine-citrulline linker. Studies have shown that combining immunotherapy with an Anti-EGFR monoclonal antibody may produces a synergistic anti-tumor effect. This study aims to assess the efficacy and safety of neoadjuvant Becotatug Vedotin, alone or in combination with immune checkpoint inhibitors Penpulimab, an anti-PD-1 monoclonal antibody, or Ivonescimab, a bispecific anti-PD-1/VEGF-A antibody, in patients with resectable LAHNSCC.
Methods: This is a randomized, non-comparative, multicenter phase II clinical trial. Key eligible patients aged 18–70 years with previously untreated, pathologically confirmed LAHNSCC (oral, laryngeal, hypopharyngeal, and oropharyngeal carcinoma), resectable and ECOG 0–1 will be enrolled. Main exclusions include active autoimmune diseases, use of immunosuppressive drugs, or systemic corticosteroids. Patients will be allocated to 3 cohorts, and all will receive three preoperative cycles of Becotatug Vedotin(2.3 mg/kg, ivgtt, Q3W) with or without immune checkpoint inhibitors: Cohort 1 (monotherapy); Cohort 2 (combined with Penpulimab, 200 mg, ivgtt, Q3W); Cohort 3 (combined with Ivonescimab, 10 mg/kg, ivgtt, Q3W). Surgery will be scheduled 2 to 4 weeks after the completion of neoadjuvant therapy, followed by adjuvant radiotherapy or chemoradiotherapy based on risk factors. Subjects in Cohorts 2 and 3 will continue immune checkpoint inhibitor therapy for 14 cycles following the completion of radiotherapy. Dose adjustments are permitted based on toxicity. The primary endpoint is Pathologic Complete Response (PCR).Secondary endpoints include major Pathological Response (MPR), objective Response Rate (ORR), 1-year Event-Free Survival (EFS) Rate, 2-year Overall Survival (OS) Rate, treatment-related safety, and predictive biomarkers. Research Sponsor: Lepu Biopharma Co., Ltd. Clinical trial information: NCT07381075. Research Sponsor: None.

TPS6136 Poster Session

Neoadjuvant cemiplimab plus cetuximab prior to salvage surgery for recurrent oral cavity squamous cell carcinoma.

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Background: Locoregional recurrence of oral cavity squamous cell carcinoma (OCSCC) after curative-intent therapy remains a major cause of morbidity and mortality. Salvage surgery is the standard of care when feasible but is associated with substantial functional impairment. The combination of PD-1 blockade and EGFR inhibition has demonstrated promising activity in the recurrent/metastatic setting. We hypothesize that the combination of cemiplimab and cetuximab will elicit a robust antitumor response in patients with resectable recurrent OCSCC that will lead to improved clinical outcomes. **Methods:** This is an open-label, single-center, phase II trial designed to assess the efficacy and safety of cemiplimab plus cetuximab in patients with recurrent, resectable OCSCC irrespective of PD-L1 status (NCT06448026). Key eligibility criteria include histologically confirmed locoregional recurrence at least 3 months after prior curative-intent therapy, including surgery and postoperative radiation, ECOG performance status 0–1, measurable disease per RECIST v1.1, and adequate organ function. Eligible participants receive neoadjuvant cemiplimab 350 mg intravenously every 3 weeks for two cycles combined with weekly cetuximab (loading dose 400 mg/m^2 followed by 250 mg/m^2 for up to 6 weeks), followed by salvage surgery. Patients achieving ≥50% pathologic tumor response are eligible to receive adjuvant cemiplimab for up to one year. Blood and tumor tissue for correlative analyses are collected at baseline, during treatment, and at the time of surgery. The primary endpoint is the rate of pathologic tumor response ≥50% (pTR-2) assessed in the surgical specimens local and/or regional. Secondary endpoints include objective response rate per RECIST v1.1, pathologic response rate, disease-free survival, overall survival, and safety. The planned sample size is 17 patients based on a Simon two-stage design. The study is active and accruing; to date, 9 of 17 planned patients have been enrolled. Clinical trial information: NCT06448026. Research Sponsor: Regeneron Pharmaceuticals.

TPS6137 Poster Session

GP regimen chronomodulated induction chemotherapy combined with concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma: A phase III, multicenter, randomized controlled study.

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Background: Radiotherapy is the primary treatment for nasopharyngeal carcinoma (NPC). Currently, induction chemotherapy combined with concurrent chemoradiotherapy has become a Category I recommendation for NPC treatment. Studies show that the GP regimen is one of the most effective induction chemotherapy protocols for locally advanced NPC. However, the incidence of grade 3-4 acute toxicities with the GP regimen is as high as 75.7%, severely affecting patient treatment compliance. To reduce toxicity while maintaining efficacy, this study focuses on a "chronomodulated chemotherapy" strategy, which adjusts drug administration timing based on biological rhythms to minimize damage to normal tissues. **Methods:** Clinical Data: 1. Sample Size Calculation: This study is a randomized controlled trial with a non-inferiority design. Based on a 3-year recurrence-free survival rate of 85.3% in the conventional group, a non-inferiority margin (δ) of 10%, a one-sided α of 0.025, a power (1-β) of 0.8, equal group sizes, and accounting for a 10% dropout rate, the calculated total sample size is 434 subjects. 2. Inclusion Criteria: Treatment-naïve patients with Stage III or IVa non-keratinizing nasopharyngeal carcinoma (UICC/AJCC 8th edition). 3. Exclusion Criteria: History of prior malignancy, prior radiotherapy, or presence of other severe diseases. 4. Withdrawal Criteria: Occurrence of severe adverse events or intolerable toxicities during the study. Treatment Protocol: 1. Induction Chemotherapy Phase: Experimental Group: Gemcitabine 1000 mg/m^2, IV infusion over 30 min on days 1 & 8, administered between 08:00-09:30; Cisplatin 80 mg/m^2, continuous IV infusion (civ) on day 1, delivered evenly over 12 h from 10:00 to 22:00. Repeated every 3 weeks (Q3W) for 3 cycles. Control Group: Gemcitabine 1000 mg/m^2, IV infusion over 30 min on days 1 & 8; Cisplatin 80 mg/m^2, IV infusion over 2-3 h on day 1. Q3W for 3 cycles. 2. Concurrent Chemoradiotherapy Phase: Concurrent Cisplatin Regimen: Experimental Group: Cisplatin 100 mg/m^2, civ on day 1, delivered evenly over 12 h from 10:00 to 22:00. Q3W for 3 courses. Control Group: Cisplatin 100 mg/m^2, IV infusion over 2-3 h on day 1. Q3W for 3 courses. 3. Radiotherapy: Intensity-Modulated Radiation Therapy (IMRT) was used, with a total dose of 69.96-72.6 Gy delivered in 33 fractions. Innovation: Therapeutic efficacy for nasopharyngeal carcinoma has reached a plateau, making “toxicity reduction” a key research focus. The toxicity-reducing approach of chronomodulated chemotherapy holds promising application prospects for locally advanced nasopharyngeal carcinoma. Current Status: To date, 122 patients have been enrolled. Clinical trial information: ChiCTR2400086032. Research Sponsor: None.

TPS6138 Poster Session

NRG-HN006: Randomized phase II/III trial of sentinel lymph node biopsy versus elective neck dissection for early-stage oral cavity cancer.

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Background: Patients with early-stage oral cavity cancer (OCC; T1-2N0M0; AJCC 8th edition) have a 20-30% risk of occult nodal metastases despite clinical and radiographic evaluations. Standard-of-care treatment for most patients includes elective neck dissection (END), which requires surgical removal of the regional cervical lymph nodes, even though 70-80% of these necks are disease-free. Sentinel lymph node biopsy (SLN Bx), a less invasive procedure, could assess the first echelon lymph nodes as an alternative to END, potentially reducing morbidity and costs. A pivotal clinical trial comparing SLN Bx to END (NCT#04333537) is underway to inform efforts to establish optimal disease management for early-stage OCC. **Methods:** To assess the efficacy of SLN Bx in this population, we activated an international, multi-institutional, prospective phase II/III trial in July 2020, randomizing patients to two surgical arms: SLN Bx and END. A node-negative ^{18}F-FDG PET/CT imaging biomarker study with centralized read was required before randomization. OCC patients with a positive PET/CT remained in a registry to compare imaging findings with final neck pathology. Given the current evidence on morbidity for SLN Bx versus END, the phase II was designed to determine whether the change in patient-reported neck and shoulder function and related quality of life (QOL) from baseline to 6 months after surgery, using the Neck Dissection Impairment Index (NDII), showed a signal of superiority of SLN Bx compared to END (minimum important difference ^{3} 7.5; one-sided a = 0.10; 90% power). As of December 2024, 261 patients had been randomized and 203 were analyzed for the "Go/No-Go" decision to move forward into phase III. The phase III portion is a non-inferiority (NI) trial with disease-free survival (DFS) as the primary endpoint (NI margin hazard ratio 1.34 based on a 5% absolute difference in 2-year DFS; one-sided a = 0.05; 80% power, and two interim looks). The change in NDII from baseline to 6 months after surgery is a hierarchical co-primary endpoint for phase III. Phase III opened in October 2025 upon receiving a "Go" signal from phase II. Target accrual for phase III is 686 node-negative PET/CT patients, including those randomized in phase II (425 additional patients). In addition to sites requiring radiotherapy and imaging credentialing, quality assurance will include central pathology review of all negative SLN Bx cases and surgeon credentialing through an education course with SLN Bx and END case review by the surgical co-chairs. A surgical quality assurance working group will review all trial SLN Bx and END procedures. As of 01/12/26, 351 patients have been screened, and 273 of the planned 686 have been randomized. Clinical trial information: NCT#04333537. Research Sponsor: National Cancer Institute and Cardinal Health; UG1CA189867, U10CA180822, U10CA180868.

TPS6139 **Poster Session**

Neoadjuvant therapy for head and neck squamous cell carcinoma based on hyperprogression genotyping: Cetuximab beta combined with chemotherapy with or without camrelizumab.

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Background: Surgery remains the preferred treatment option for locally advanced head and neck squamous cell carcinoma (LA HNSCC). However, its efficacy is still unsatisfactory, with local recurrence and distant metastasis rates as high as 20% and a 5-year survival rate of only about 50%. Immune checkpoint inhibitors (ICIs) have achieved success in recurrent/metastatic HNSCC (R/M HNSCC), laying the foundation for the application of immunotherapy in earlier-stage patients. Cetuximab, an anti-Epidermal Growth Factor Receptor (EGFR) antibody, is a standard treatment for both LA HNSCC and R/M HNSCC. Patients who experience Hyper-progressive Disease (HPD) have a poor prognosis, and various genetic mutations have been shown to predict the occurrence of HPD. **Methods:** This study was designed as a prospective, open label, multicenter, phase II trial (ChiCTR2500108701), and the primary endpoint was the postoperative pathological complete response (pCR) rate. The secondary endpoints included the objective response rate (ORR), major pathological response (MPR) rate, 1-year and 2-year event-free survival (EFS) rates, and 2-year overall survival (OS) rate. Eligible patients (pts) were over 18 years old with histologically or cytologically confirmed SCCHN (excluding naso-pharyngeal carcinoma); had T1N2-3M0, T2N1-3M0, or T3/T4aNanyM0, according to the 8th Edition of the American Joint Committee on Cancer (AJCC) staging guidelines; had resectability of the tumor was evaluated by a head and neck surgeon; had no previous local and systemic treatment for SCCHN; had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST 1.1). All enrolled 40 pts received whole exome sequencing (WES), and were assigned to Cohort A (n=25, HPD-gene-negative) and Cohort B (n=15, HPD-gene-positive), respectively. All treatment was administered intravenously in 21-day cycles. Patients in Cohort A were given albumin-bound paclitaxel (260 mg/m^2, d1), cisplatin (25 mg/m^2, d1-d3), camrelizumab (200 mg, d1) and cetuximab (250 mg/m^2, d1;500 mg/m^2, d8). Patients who successfully completed 2~4 cycles of neoadjuvant treatment returned for surgical intervention 28~42 Endpoints days after the last cycle, and adjuvant radiotherapy was administered followed by 2~4 cycles of camrelizumab (200 mg, d1) and cetuximab (250 mg/m^2, d1;500 mg/m^2, d8) as adjuvant treatment.Cohort B received the same treatment regimen as Cohort A, excluding camrelizumab. Clinical trial information: ChiCTR2500108701. Research Sponsor: None.

TPS6140 **Poster Session**

EA3231: A randomized phase III study of BRAF-targeted therapy vs cabozantinib in RAI-refractory differentiated thyroid cancer with *BRAF* V600Em.

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Background: About half of patients with RAIR advanced differentiated thyroid cancer (DTC) harbor a mutation in BRAF V600E. Although multiple systemic therapies are now approved, optimal treatment sequencing remains undefined for patients with BRAF V600Em RAIR DTC. Given the indolent natural history of this disease and often prolonged exposure to oral therapies with significant toxicity, comparative data on efficacy and tolerability of second-line therapy is a clear unmet need. **Methods:** EA3231 (NCT06475989) is a NCTN cooperative group randomized phase III study in patients with BRAF V600Em RAIR DTC who have progressed on prior multikinase inhibitor therapy such as lenvatinib or sorafenib. Patients will be randomized 1:1 to BRAF-targeted therapy (dabrafenib and trametinib) or cabozantinib, all of which are FDA-approved agents in this setting. The primary objective is to compare progression-free survival (PFS) between dabrafenib/trametinib vs cabozantinib, with secondary objectives including overall response rate, overall survival, PFS2, and safety and tolerability. We hypothesize that BRAF-directed therapy will be associated with improved PFS and tolerability compared to cabozantinib. Our target accrual is 120 patients; this sample size will provide 83% power to detect a HR of 0.60 (corresponding to a median PFS of 12 months) compared to an estimated median PFS of 7.2 months in the cabozantinib arm. This study was activated in late 2024, and has enrolled 8/120 patients as of 1/2026. Clinical trial information: NCT06475989. Research Sponsor: None.