LBA6000 **Oral Abstract Session**

Adjuvant PD-1 blockade with camrelizumab in high-risk locoregionally advanced nasopharyngeal carcinoma (DIPPER): A multicenter, open-label, phase 3, randomized controlled trial.

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6001 Oral Abstract Session

Tislelizumab versus placebo combined with induction chemotherapy followed by concurrent chemoradiotherapy and adjuvant tislelizumab or placebo for locoregionally advanced nasopharyngeal carcinoma: Interim analysis of a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial.

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Background: Patients with locoregionally advanced nasopharyngeal carcinoma (LANPC) have a risk of disease relapse after induction chemotherapy (IC)-concurrent chemoradiotherapy (CCRT). Early phase trials indicated that tislelizumab (PD-1 inhibitor) plus IC followed by CCRT have the potential to deepen responses and extend survival in LANPC. Here, we report the interim results of a phase 3 trial to evaluate the efficacy and safety of tislelizumab plus IC, followed by CCRT and adjuvant tislelizumab therapy in LANPC. **Methods:** Patients with high-risk LANPC (stage III-IVa, AJCC 8th Staging System, excluding T3N0, and T3N1 with retropharyngeal lymph nodes +) were randomized (1:1) to receive 200 mg tislelizumab or placebo + gemcitabine and cisplatin (GP) every 3 weeks (Q3W) for 3 cycles, followed by CCRT and adjuvant tislelizumab or placebo Q3W for up to an additional 8 cycles. Stratification factors were center and disease stage (III or IVa). Dual primary endpoints were complete response rate (CRR) after induction therapy and progression-free survival (PFS) per RECIST 1.1 by investigator under blinded review. The planned interim analysis (IA) for evaluating the first primary endpoint, CRR, was scheduled at 4 weeks after the completion of induction therapy to test whether addition of tislelizumab to standard IC significantly improved CRR, with allocated alpha at 0.005. **Results:** Between June 2022, and May 2023, 450 patients were randomized to tislelizumab arm (n = 223) and placebo arm (n = 227). Baseline characteristics were balanced between the two arms. At IA, 93.7% and 93.8% of patients completed 3 cycles of induction therapy in tislelizumab arm and placebo arm, respectively. Significant improvement in CRR was observed in tislelizumab arm vs placebo arm in the intent-to-treat population (ITT) (30.5% vs 16.7%; P = 0.0006). Improvement in CRR in tislelizumab arm vs placebo arm was consistent across key subgroups including disease stage (III [33.8% vs 20.7%]; IVa [28.7% vs 14.5%]), sex (male [28.3 % vs 15.7%]; female [38.0% vs 19.7%]), and ECOG PS (PS of 0 [28.8% vs 16.2%]; PS of 1 [40.6% vs 19.4%]). The ORR was 93.3% in the tislelizumab arm and 90.7% in the placebo arm. In safety population (tislelizumab arm, n=219; placebo arm, n=224), the incidence of Grade ≥3 TEAEs (40.6% vs 39.3%) and SAEs (2.3% vs 1.3%) were similar between two arms. **Conclusions:** The trial met its first primary endpoint with a statistically significant improvement of CRR with the addition of tislelizumab to standard IC in high-risk LANPC. Induction therapy with tislelizumab plus GP was generally well tolerated with manageable safety profile. Continued follow-up is being conducted to assess long-term efficacy and safety. Clinical trial information: NCT05211232. Research Sponsor: None.

6002 Oral Abstract Session

Endostar combined with concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone for locoregionally advanced nasopharyngeal carcinoma (LA-NPC): A phase III, prospective, randomised-controlled, multicenter clinical trial.

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Background: Cisplatin-based concurrent chemoradiotherapy (CCRT) has long been regarded as standard treatment for LA-NPC. However, approximately 30% of patients still fail to obtain a satisfactory effect. Endostar (Rh-endostatin), an anti-angiogenesis inhibitor, is well-tolerated and has been reported as a promising complement to CCRT. This trial aimed to evaluate the efficacy and safety of adding Endostar to CCRT for LA-NPC. **Methods:** In this prospective, randomized phase III study, patients with LA-NPC (stage III-IVb, 7^{th} edition) were enrolled at 6 centers in China, and randomly assigned (1:1) to receive Endostar plus CCRT (CCRT+E group, n=150) or CCRT alone (CCRT group, n=150). Endostar (7.5 mg/m2/day, days 1-10, 15 days/cycle) was given continuously intravenously for 5 cycles (3 concurrent from 5 days before radiotherapy, and 2 adjuvant from the first day after the completion of radiotherapy). The primary endpoint was the progress-free survival (PFS) rate. The secondary endpoints included overall survival (OS), distant metastasis-free survival (DMFS), local-regional relapse-free survival (LRRFS), the rate of complete response (CR) at 3 months after RT, and safety. **Results:** Between November 2016 and July 2020, 300 patients with LA-NPC were randomized (CCRT+E group, 150; CCRT group, 150). As of the data cutoff (December 2023), the median follow-up was 66 months. Intention-to-treat analysis showed that patients in the CCRT+E group achieved better CR rate at 3 months after RT (90.0% vs 80.7%, P=0.022). The 3-year PFS was 84.8% in the CCRT+E group, and 75.1% in the CCRT group (HR, 0.544; 95% CI, 0.336-0.879; $P_{log-rank}$=0.011). The 3-year OS was 89.2% vs. 85.3% (HR, 0.595; 95% CI, 0.361-0.982; $P_{log-rank}$=0.039). The 3-year DMFS was 89.7% vs. 80.5% (HR, 0.468; 95% CI, 0.266-0.821; $P_{log-rank}$=0.007). The 3-year LRRFS was 91.5% vs. 90.8% (HR, 0.808; 95% CI, 0.407-1.604; $P_{log-rank}$=0.541). Patients in the CCRT+E group and in the CCRT group had similar Grade 3-4 acute and late toxicity profile (61.7% vs. 65.3%, p=0.519 and 8.0% vs.7.3%, p=0.815). **Conclusions:** The addition of Endostar to standard CCRT significantly improved the 3-year PFS of LA-NPC patients with good safety profile. Clinical trial information: NCT02907710. Research Sponsor: National Natural Science Foundation of China (82272736); National Natural Science Foundation of China (82160467); the Research Foundation of the Science and Technology Department of Guangxi Province, China (No. 2023GXNSFDA026009).

6003 Oral Abstract Session

Results of a randomized, double-blind, placebo-controlled, phase 2 study (Opce-mISA) of the combination of ISA101b and cemiplimab versus cemiplimab for recurrent/metastatic (R/M) HPV16-positive oropharyngeal cancer (OPC).

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Background: ISA101b (peltopepimut-S) is a therapeutic vaccine targeting the HPV16 E6/E7 oncoproteins. The synthetic long peptides of ISA101b induce specific expansion of both $CD4^+$ T-helper cells and CD8+ cytotoxic T-cells against E6/7 oncogenes[1]. Combination of cemiplimab, an anti-PD-1 antibody with ISA101b elicits a synergistic anti-tumor effect[2]. **Methods:** First and second line anti-PD-1 naïve patients with confirmed HPV16+ R/M OPC were randomized to treatment with either ISA101b (subcutaneously 100μg/peptide on days 1, 29, and 50) or placebo, with cemiplimab (intravenously 350mg q/21 days) for up to 24 months or until disease progression or treatment withdrawal. The primary efficacy endpoint was ORR after ≥6 months of follow-up by independent review as per RECIST1.1. Data cut-off for this analysis was 5 July 2023. The primary safety endpoint was frequency and severity of AEs. Secondary endpoints included PFS and OS. For the latter 12-month survival data are shown. Combined Positive Score (CPS) analyses were planned subgroup analyses. A p-value <0.1 was defined as statistically significant. Predefined analysis sets are the full analysis set (FAS), i.e. all patients who received ≥1 dose of study drug, and the per protocol set (PPS) which includes patients with centrally confirmed HPV16-positivity who received all 3 doses of ISA101b/placebo, had at least 1 post-baseline tumor assessment and no major protocol deviations. **Results:** A total of 198 patients (mean age 62.8 ±9.6 years) received ≥1 dose of study drug: 173 (87.4%) male, and 25 (12.6%) female; 110 (55.6%) were treated in first, and 74 (37.4%) in second line. Baseline characteristics were well balanced. In the ISA101b arm, ORR was 25.3% compared to 22.9% in the control arm (NS, Table). SAEs occurred in 33.0% of patients in the ISA101b arm vs 31.6% in the control arm. Patients with a CPS ≥20 treated with cemiplimab and 3 doses of ISA101b had a significantly better ORR and OS compared to patients in the control arm (Table; mOS (95% CI) not reached (28.1, -) vs 23.3 (11.9, 30.1) months, P = 0.0232 (PPS)). Patients with CPS <20 had on average a shorter OS in the ISA101b arm. **Conclusions:** Whereas there was no advantage of the addition of ISA101b to cemiplimab regarding ORR on the overall population, in patients with CPS ≥20 ISA101b significantly improved the ORR. Median OS was better in patients with CPS ≥20 who completed a full course of ISA101b. In contrast, patients with lower CPS did not benefit. Toxicity was comparable between the 2 arms. Clinical trial information: NCT03669718. Research Sponsor: ISA Pharmaceuticals B.V.; Regeneron Pharmaceuticals, Inc.

Analysis Set/group	Arm	No. of Patients	ORR (%)	P value
FAS	ISA101b	91	25.3	0.590
	Control	96	22.9	
PPS	ISA101b	61	38.9	0.064*
	Control	79	27.3	
FAS CPS ≥20	ISA101b	27	51.9	0.078*
	Control	30	26.7	
PPS CPS ≥20	ISA101b	21	61.9	0.026*
	Control	25	28.0	

*Statistically significant.

[1]Welters *PNAS* 2010.
[2]de Sousa *JITC* 2022.

6004 Oral Abstract Session

A phase 1 dose-escalation and expansion study of CUE-101, given as monotherapy and in combination with pembrolizumab, in patients with recurrent/metastatic HPV16+ head and neck squamous cell cancer (R/M HNSCC).

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Background: Immuno-STATs are modular T cell engagers engineered to selectively activate tumor-antigen specific CD8+ T cells via targeted delivery of cytokines. CUE-101, the first Immuno-STAT in clinical trials, is composed of a human leukocyte antigen (HLA) complex, HLA-A*0201, a peptide epitope derived from the HPV16 E7 protein and 4 molecules of attenuated human interleukin-2 (IL-2), to bind, expand, and activate HPV16-specific CD8+ T cells for the treatment of HPV16+ HNSCC. **Methods:** CUE-101-01 is an ongoing first-in-human study in HLA-A*0201 patients with HPV16+ R/M HNSCC. Escalating doses of CUE-101 monotherapy (0.06 mg/kg to 8 mg/kg) were evaluated in R/M HNSCC refractory to $\geq$ 1 platinum or checkpoint inhibitor (CPI) based therapy, alone or combined with pembrolizumab (1 mg/kg to 4 mg/kg + 200 mg pembrolizumab) in the first line treatment of PD-L1+ R/M HNSCCs. Enrollment at the recommended phase 2 dose (RP2D) was expanded. Therapy was administered every 3 weeks (Q3W) until disease progression or intolerable toxicity. Safety, PK/PD, and antitumor activity were assessed. **Results:** Enrollment in both monotherapy and combination cohorts is now completed (N=80 patients, 49 in monotherapy and 31 CUE-101 plus pembrolizumab). Following dose escalation, 4 mg/kg Q3W of CUE-101 was selected for RP2D for both monotherapy and pembrolizumab combination cohorts. At data cut-off, adverse events (AEs) have been manageable and 92% grade $\leq$2. The most frequent grade 3 AEs reported include lymphocyte count decreased (7.6%), anemia (6.3%), decreased appetite (5.1%) and infusion-related reactions (5.1%). In combination with pembrolizumab no unanticipated significant safety concerns have emerged. Exposure-dependent PD effects of CUE-101 are consistent with IL-2 pharmacology and indicate preferential expansion of CUE-101 on E7-specific T cells. Among the 19 evaluable patients treated with the RP2D of CUE-101 plus pembrolizumab, an ORR of 47% (1 CR, 8 PRs), a Disease Control Rate (ORR + durable SDs) of 74%, and mPFS of 5.8 months [95% CI 2.56; NA] were observed. A median OS has not been reached. Of the 9 patients with confirmed objective responses, all achieved >99% reduction in HPV16 cfDNA in plasma during their treatment course. Among the 19 evaluable monotherapy RP2D patients, 1 PR and 6 durable SD (SD $\geq$ 12 weeks) and mOS of 20.8 months [95% CI 11.0; NA] were observed. **Conclusions:** An ORR of 47% and a mPFS of 5.8 months were observed in R/M HNSCC patients treated with CUE-101 4 mg/kg + pembrolizumab as 1L therapy. A median OS of 20.8 was observed in patients treated with CUE-101 monotherapy as post-platinum/CPI therapy. CUE-101 continues to demonstrate safety, tolerability and meaningful clinical benefit in patients with HPV16+ R/M HNSCC. Clinical trial information: NCT03978689. Research Sponsor: CUE Biopharma.

6005 Oral Abstract Session

HB-200 arenavirus-based immunotherapy plus pembrolizumab as first-line treatment of patients with recurrent/metastatic HPV16-positive head and neck cancer: Updated results.

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Background: Treatment options are limited for patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) with no approved treatment specifically targeting human papillomavirus (HPV) 16-positive tumors. In the first-line (1L) R/M setting, only a minority of patients (~20%) respond to pembrolizumab monotherapy, including those with high programmed death ligand 1 (PD-L1) expression in the tumor. HB-200 comprises an alternating sequence of two replicating attenuated arenavirus vectors derived from LCMV (HB-201) and Pichinde virus (HB-202), respectively. HB-200 vectors express a non-oncogenic HPV16 E7E6 fusion protein and induce E6 and E7-specific CD8 T-cell responses. Previously, we reported promising preliminary clinical activity of HB-200 in combination with pembrolizumab as 1L treatment for patients with HPV16+ PD-L1+ R/M HNSCC. Here, we report updated results with a focus on PD-L1 status. **Methods:** In this non-randomized Phase 2 part of the study, participants with HPV16+ PD-L1 combined positive score (CPS) ≥1 R/M HNSCC were treated with HB-200 intravenously (every 3 weeks [Q3W] then Q6W) in combination with pembrolizumab (200 mg Q3W or 400 mg Q6W). Safety, T cell response, and preliminary antitumor activity were assessed. **Results:** As of 12 January 2024, 42 patients with HPV16+ PD-L1+ R/M HNSCC (41 of oropharynx as primary cancer site) were treated with HB-200 plus pembrolizumab in the 1L setting. Median follow-up time was 5.6 months. Characteristics of this cohort included: median age 66 years (range 50-77), 41 (98%) male, 37 (88%) White, 14 (33%) with ≥ 10 pack/year smoking history, 40 (95%) check point inhibitor (CPI) naïve (2 received CPI in the adjuvant setting), and 21 (50%) with PD-L1 CPS ≥ 20. HB-200 + pembrolizumab were generally well tolerated. Grade ≥3 treatment-related adverse events (TRAEs) were reported in 6 (14%) patients, serious TRAEs in 3 (7%) patients, and TRAEs leading to treatment discontinuation in 2 (5%) patients. No treatment-related death were reported. Among 35 evaluable patients (those with ≥ 1 tumor response assessments), the overall response rate (ORR) was 43% (3 complete response [CR], 9 partial response [PR], 3 unconfirmed PR) and the disease control rate (DCR) was 71%. Notably, among patients with PD-L1 CPS ≥20 (N = 17), ORR was 59% (3 CR, 6 PR, 1 unconfirmed PR) and DCR was 88%. **Conclusions:** Updated data of HB-200 arenavirus-based immunotherapy plus pembrolizumab continued to demonstrate a favorable safety profile and promising clinical activity as 1L treatment in patients with HPV16+ PD-L1+ R/M HNSCC and confirms previously reported data. The results suggest that the subgroup of patients with PD-L1 CPS ≥20 may benefit more from this treatment, which warrants further development in a randomized pivotal study. Clinical trial# NCT04180215. Clinical trial information: NCT04180215. Research Sponsor: HOOKIPA Pharma, Inc.

6006 Oral Abstract Session

Phase III randomized trial of intensity-modulated proton therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for the treatment of head and neck oropharyngeal carcinoma (OPC).

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Background: IMPT has unique biologic and physical properties compared with IMRT, limits radiation dose beyond the targeted tumor volumes, and is a novel de-intensification strategy for the management of head and neck tumors. This study was designed to compare the outcomes for patients with OPC after chemoradiation therapy (CRT) with IMRT vs IMPT. **Methods:** This is a multi-center, randomized, phase III non-inferiority OPC trial Stage III/IV (AJCC 7^{th}) squamous cell carcinoma stratified patients by human papillomavirus status, smoking status, and receipt of induction chemotherapy (IC). The primary endpoint was the rate of progression-free survival (PFS) rate at 3 years, where progression was defined as disease recurrence or death. Under the null hypothesis, H0: $r \geq 1.535$ established the margin for non-inferiority of IMPT. Secondary endpoints include overall survival (OS), treatment-related malnutrition, and gastrostomy-tube dependence. Analyses were conducted on intent-to-treat (ITT; n=440), per-protocol (PP; n=296), and as-treated (AT; n=397) populations. **Results:** Patients (n=440) were randomized to undergo IMRT(n=219) or IMPT (n=221) at 21 institutions. The median age was 61 years and HPV/p16 was positive in 95%. IC was the initial treatment in 13% of patients. All patients were treated with CRT to 70 Gy in 33 fx with bilateral neck treatment, and post-CRT surgical lymph node dissection occurred in 8%. The median follow-up was 3.14 years. In the ITT analysis, the hazard ratio (HR) for disease progression or death at 3 y was 0.87 (95%CI 0.56,1.35); p=0.006 and the corresponding HR for death (OS) was 0.63 (95%CI 0.36-1.10) suggesting a protective affect with IMPT. In PP analysis, the PFS HR was 0.85 (95%CI 0.52,1.38); p=0.009 and HR for death (OS) was 0.60 (95%CI 0.32-1.12). In the AT analysis, PFS HR was 0.88 (95%CI 0.56,1.37); p=0.007 and the corresponding HR for death (OS) was 0.70 (95%CI 0.40-1.22). For each analysis above, the null hypothesis was rejected and IMPT was non-inferior to IMRT. PP gastrostomy-tube dependence decreased with IMPT vs. IMRT from 42% to 28% (p=0.019), and more IMPT patients sustained their nutrition with end of treatment weight loss $< 5\%$ from baseline: 24% vs 14% (p=0.037). **Conclusions:** IMPT is non-inferior to IMRT and has emerged as a standard of care CRT approach for OPC that reduces malnutrition and gastrostomy-tube dependence. Clinical trial information: NCT01893307. Research Sponsor: Hitachi.

6007 Oral Abstract Session

Intra-treatment hypoxia directed major radiation de-escalation as definitive treatment for human papillomavirus-related oropharyngeal cancer.

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Background: We previously reported that surgery to the primary site with hypoxia-directed de-escalated radiation to the neck for human papillomavirus associated oropharyngeal carcinoma (HPV+ OPC) can lead to excellent oncologic outcomes. We now report the results of a successor multi-center phase II trial of hypoxia-directed de-escalated chemoradiotherapy without surgery for HPV+OPC. **Methods:** HPV+ OPC (T0-2/N1-N2c/AJCC 7^{th}) patients were eligible for enrollment. Tumors without evidence of hypoxia on ^{18}F-FMISO (fluoromisonidazole) PET received de-escalated chemoradiation to 30Gy while those with hypoxia received chemoradiation to 70Gy. The primary objective was achieving a 2-year locoregional control (LRC) of 95% (failure was locoregional recurrence where surgical salvage was unfeasible) with a 7% non-inferiority margin. We enrolled a total of 158 subjects upfront to account for a 5% loss due to death (of reasons other than cancer) or follow-up. Secondary objectives were local failure (LF), regional failure (RF), distant metastasis (DM), overall survival (OS), toxicities, and patient-reported MD Anderson Dysphagia Inventory (MDADI) scores. LF, RF, and DM were estimated using the Cumulative Incidence Function, and OS was estimated using the Kaplan-Meier method. Results were reported up to 1/31/2024. **Results:** From 4/28/20-4/17/23, 158 HPV+ OPC patients were enrolled where150 patients were eligible for analyses. Patient characteristics: Tonsil (43%); Base of Tongue (47%); unknown primary (10%); >/=10 pack years (22%); T0 (9%), T1 (44%), T2 (47%); N1 (14%), N2a (11%), N2b (59%), N2c (16%). 111 (74%) received 30Gy; 95% cisplatin. With 24 months (8-43) of median follow-up, the 2-year LF, RF, DM rates were 4.2%, 6.9%, 2.0%, respectively. The 2-year overall survival probability was 99%. Only 2 patients could not undergo salvage surgery [one 30Gy (second recurrence); one 70Gy (M1)], both received systemic therapy with durable response. Acute grade 3-4 toxicities were 32% (67% neutropenia). Mean MDADI scores: 92.93 (baseline); 68.24 (3 weeks), 91.45 (4 months) after chemoradiation. **Conclusions:** These early data indicate that major de-escalation to 30Gy based on hypoxia status achieved significant toxicity reduction without compromise in survival for HPV+ OPC treated with chemoradiation without surgery. Clinical trial information: NCT03323463. Research Sponsor: NIH R01 CA238392-02A1; NCI Cancer Support GRANT P30 CA008; DIMON HPV Foundation, Serra Initiative on the Management of Head and Neck Cancer Side Effects, and James A. Rowen Precision Radiotherapy Fund.

6008 Oral Abstract Session

A randomized, double-blind, placebo-controlled phase II study of adjuvant pembrolizumab versus placebo in patients with head and neck squamous cell cancers at high risk for recurrence: The PATHWay study.

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Background: Anti-PD1 therapy has become an essential treatment in recurrent and metastatic head/neck squamous cell carcinoma (HNSCC). The optimal use of anti-PD1 therapy in the curative setting is not established. Understanding the benefits of adjuvant anti-PD1 treatment in high risk HNSCC patients treated with curative intent is necessary. **Methods:** The PATHWay trial (NCT02841748) is a multi-site, randomized, placebo (PL) controlled trial of pembrolizumab (IO) in patients following curative treatment of high recurrence risk HNSCC. Patients with AJCC 7^{th} edition stage IVa, IVb, and select III HNSCC or multiple primaries were eligible if their cancers had an estimated $>$ 40% chance of recurrence and were not eligible for additional therapy. Patients enrolled into six group criteria: A) high risk nodal disease or interrupted radiation treatment; B) salvage surgery including positive margin; C) Indeterminate distant lesions concerning for metastasis; D) Oligometastatic disease treated definitively; E) Microscopic residual disease after surgery; or F) Multiple prior recurrences or multiple treated primaries who have undergone surgery $\geq$ 2 times. Patients were randomized with stratification for HPV and EBV status, and received pembrolizumab 200mg IV or placebo for up to 18 cycles. The primary study endpoint was progression-free survival (PFS). The targeted sample size was N=100 patients (50 per arm), which provided $>$90% power to detect a hazard ratio (HR) of 0.45, based on a stratified logrank test at a one-sided alpha level of 0.10. **Results:** A total of n=49 IO and n=51 PL patients were enrolled between 2016 and 2023 across 10 US sites. Mean age was 62; 33% female; 45% nonsmoker; 20% HPV+, 2% EBV+. Cancers were stage III (24%), IVa (39%), IVb (8%), with prior surgery in 95% and prior RT in 78%. Median follow-up was 33 months. Compared to PL, IO treated patients had superior PFS with HR 0.61 (80% CI: 0.43-0.86, one-sided p=0.021). PFS rates for IO were 65% and 54% at 1 and 2 years, respectively compared to 48% and 33%, respectively for PL. Overall survival (OS) was not significantly different in IO vs. PL treatment (HR = 1.00, 80% CI: 0.6-1.68, p=0.45). IO improved PFS in 2 sub-groups: In post-salvage surgery patients (group B, n=37), IO had superior PFS vs. PL (HR 0.34, 80% CI: 0.18-0.67, p=0.016); In patients with multiple recurrences/primaries (group F, n=37) IO had superior PFS vs. PL (HR 0.48, 80% CI: 0.27-0.88, p=0.057). Adverse events between treatments were comparable, with 3 (6%) grade 4 adverse events in PL and 1 (2%) grade 5 (2%, unrelated) and 1 grade 4 (2%) in IO. **Conclusions:** Pembrolizumab treatment for 1 year in patients with high risk of recurrent HNSCC following curative therapy resulted in a statistically significant improvement in PFS compared to placebo, and the benefit was maintained in key subgroups. Clinical trial information: NCT02841748. Research Sponsor: None.

6009 Clinical Science Symposium

Long-term follow up of E3311, a phase II trial of transoral surgery (TOS) followed by pathology-based adjuvant treatment in HPV-associated (HPV+) oropharynx cancer (OPC): A trial of the ECOG-ACRIN Cancer Research Group.

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Background: E3311 is a phase II trial of TOS by credentialed surgeons with pathology-driven deintensified post-operative management in HPV+ OPC. Intermediate risk patients were randomized between standard and reduced dose radiation. We present mature outcome data, at median follow up of 52.4 months (m). **Methods:** Patients were eligible who had resectable cT1-2 stage III/IV AJCC7 p16+ OPC without matted neck nodes. Those with clear margins, 0-1 + nodes (LN), and no extranodal extension (ENE) were observed (Arm A, N=38); those with clear margins, 2-4 + LN, or ENE ≤1mm were randomized to 50Gy (Arm B, N=100) or 60Gy (Arm C, N=108); those with involved margins, >4 + LN, or >1mm ENE received weekly cisplatin 40 mg/m^2 and 60-66Gy (Arm D, N=113). Progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan-Meier method and compared using a log-rank test, stratified by arm for comparisons of primary site and smoking history. **Results:** Among 359 evaluable patients, 54-m PFS and OS were 90.6% (90% CI: 87.2%, 93.1%) and 95.3% (90% CI: 93.0%, 96.9%). 54-m PFS by arm was: A 93.2% (90% CI: 79.6%, 97.8%); B 94.9% (90% CI: 89.7%, 97.5%); C 90.2% (90% CI: 82.7%, 94.6%) and D 85.5% (90% CI: 77.5%, 90.8%). 54-m OS by arm was: A 97.1% (90% CI: 85.7%, 99.4%); B 97.9% (90% CI: 93.5%, 99.3%), C 95.1% (90% CI: 90.1%, 97.6%) and D 92.5% (90% CI: 86.9%, 95.7%). Among patients in Arm A, 11 had N0 and 27 N1 stage. Median Arm A lymph node yield (LNY) was 29 (11 to 91 LN) and did not differ for patients with/without recurrence (p=0.83). All Arm A recurrences were in N1 patients: 1 at 18 m and 3 at > 40 m. No significant difference in PFS or OS was observed by prescribed radiation dose for intermediate risk patients (Arm B vs. C). Outcome did not differ by primary site of tonsil vs. other OPC (oOPC): 54-m PFS Tonsil 89.3% (90% CI: 84.9%, 92.5%) vs. oOPC 92.9% (90% CI: 87.0%, 96.2%), p=0.28, and 54-m OS Tonsil 94.6% (90% CI: 91.5%, 96.6%) vs oOPC 96.6% (90% CI: 92.4%, 98.5%), p=0.35. Smoking history also did not impact outcome. 54-m PFS was 89.9% (90% CI: 85.9%, 92.9%) for those with ≤10 pack-years (PY) tobacco exposure and 91.7% (90% CI: 83.9%, 95.9%) for those with >10 PY. **Conclusions:** TOS, neck dissection with deintensified risk-based post-operative management results in outstanding 54-m PFS and OS across all subsites of T1-2 p16+ OPC, irrespective of smoking history. Late recurrence is not increased when post-operative radiation is reduced from 60 to 50Gy for intermediate risk patients. Pathologic >1mm ENE (N=87), involved margin (N=12) or >4 involved LN (N=30) accurately identify patients at increased recurrence risk and outcomes were favorable among such patients. Among patients with favorable pathologic characteristics, a subset with N1 disease are at risk for late recurrence and further characterization of these patients is warranted. Clinical trial information: NCT01898494. Research Sponsor: ECOG-ACRIN Cancer Research Group.

6010 Clinical Science Symposium

Prospective validation of ctHPVDNA for detection of minimal residual disease and prediction of recurrence in patients with HPV-associated head and neck cancer treated with surgery.

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Background: Prediction of minimal residual disease (MRD) following surgery, and thus the need for adjuvant therapy, is currently based on clinicopathologic risk factors which have poor individual prognostic capacity. We previously reported that MRD detection by ctHPVDNA droplet digital (dd)PCR as early as post-operative day (POD) 1 is predictive of recurrence in stage I-II HPV+HNSCC patients. Here, we applied a significantly more sensitive custom whole genome hybrid-capture-based next generation sequencing assay, termed HPV-DeepSeek, to validate the prognostic capacity of ctHPVDNA detection and explore the optimal timing of MRD testing in HPV+HNSCC patients. We tested the primary hypothesis that patients with MRD detection within 6 weeks of surgery would have inferior PFS at 2 years and the secondary hypothesis that patients with ctHPVDNA positivity detected at any point following treatment completion would have inferior PFS at 2 years. **Methods:** 98 patients with HPV+HNSCC were prospectively enrolled with a mean follow-up of 712 days. All patients underwent surgery as primary treatment and clinicopathologic adjusted adjuvant treatment. 10ml blood samples were collected before surgery, in the post-operative period (POD 1-42), and serially in follow-up. MRD was defined as a lack of ctHPVDNA clearance during the 6 weeks following surgery. Cell free DNA was extracted from plasma and run on HPV-DeepSeek, and on existing ddPCR assays for head to head comparisons. **Results:** 96/98 (98%) of patients had detectable ctHPVDNA pre-treatment. 30/98 patients (31%) were MRD positive. Patients who were MRD positive had significantly worse 2 years PFS compared to MRD negative patients (78% vs 98%, P=0.0009). Predictive performance improved by limiting time points to POD 7-42 (2 year PFS 60% vs 97%, $P<0.0001$) as significantly fewer patients were MRD positive >1 week after surgery, suggesting the use of an ultra-sensitive assay such as HPV-DeepSeek requires adjustment of MRD time points. Patients with detectable ctHPVDNA following completion of all treatment had significantly worse 2-year PFS compared to patients without detectable ctHPVDNA (0% vs 97%, $P<0.0001$). 7/98 patients had cancer recurrence during follow-up that was detected by ctHPVDNA with a mean lead time of 207 days (35-518) to clinical diagnosis. **Conclusions:** ctHPVDNA detection by HPV-DeepSeek is a highly specific biomarker of MRD in HPV+HNSCC, accurately predicts disease progression and detects recurrence earlier than standard care clinical. Research Sponsor: Cell free HPV DNA detection in the diagnostic and surgical settings; 5R03DE030550-02.

6011 Clinical Science Symposium

Neoadjuvant sintilimab and platinum-doublet chemotherapy followed by transoral robotic surgery for HPV-associated resectable oropharyngeal cancer: Single-arm, phase II trial.

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Background: De-escalation treatments for HPV-associated (HPV+) oropharyngeal cancer (OPC) have been well discussed. Meanwhile, the combination of anti-PD-1 therapy and chemotherapy (immunochemotherapy, ICT) and transoral robotic surgery (TORS) shows promising results in OPC, especially in HPV+ ones. This study aims to investigate the efficacy and safety of neoadjuvant ICT and sequential TORS to reduce functional impairments and omit adjuvant radiotherapy for resectable HPV+ OPC. **Methods:** In the single-arm, phase II trial, patients with resectable HPV+OPC (cT2-4N0-3M0, AJCC 8.0) were recruited and received neoadjuvant sintilimab (200mg), platinum (cisplatin 60mg/m^2, or carboplatin AUC=5), and paclitaxel (nab-paclitaxel 260mg/m^2, or docetaxel 75mg/m^2) every 3 weeks for 2 cycles, followed by radical surgery (with TORS as an option). The primary endpoint was major pathological response (MPR; defined as residual viable tumor of less than or equal to 10%) in the primary lesion. The secondary endpoints include pathologically complete response (pCR) of all resected lesions, objective response rate (ORR) according to RECIST 1.1, disease-free survival (DFS) rate and overall survival (OS) rate at 1 and 3 years, quality of life (QoL) by EORTC QLQ-H&N35 questionnaire. **Results:** From February 1, 2022 to November 30, 2023, 27 patients were enrolled and received 2 cycles of neoadjuvant ICT. After neoadjuvant therapy, all 27 cases achieved partial response (PR), the ORR was 100%. Among them, 25 patients received radical surgery (per-protocol population), including 21 with TORSs. The pathological evaluation showed 24 patients (96.0%) achieved MPR, and 13 (52.0%) achieved pCR of all samples including primary lesions and resected lymph nodes. Grade 1-2 treatment-related adverse events (TRAE) occurred in 24/27 patients (88.9%). The most common TRAEs included rash (12, 44.4%), alopecia (10, 37.0%), nausea (8, 29.6%) and weakness (8, 29.6%), while only one patient (3.7%) experienced grade 3 TRAEs, including febrile leukopenia, pneumonia and diarrhea. These adverse reactions were manageable and no surgical delay occurred. After the surgery, the majority of patients had active follow-up without any adjuvant treatment (19/25, 76%), while 4 patients received adjuvant anti-PD-1 therapy and only 2 had adjuvant radiotherapy. At an average follow-up time of 8.2 months, the 6-month DFS and OS were both 100%. Furthermore, compared to the baseline, 22 patients (88%) reported similar or improved QoL scores at 3 months after surgeries. **Conclusions:** Neoadjuvant sintilimab plus platinum-doublet chemotherapy and sequential TORS achieved satisfactory pathological response, favorable functional preservation and tolerable toxicity in patients with resectable HPV+OPC. Further follow-up is warrant to confirm long-term survival benefits. Clinical trial information: ChiCTR2200058650. Research Sponsor: None.

6012 Rapid Oral Abstract Session

Tisotumab vedotin in head and neck squamous cell carcinoma: Updated analysis from innovaTV 207 Part C.

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Background: Recurrent or metastatic (r/m) head and neck squamous cell carcinoma (HNSCC) is treated in the first-line with an immunotherapy-based approach, including in combination with platinum-based chemotherapy or as monotherapy, or platinum-based combination plus targeted therapy. Still, most pts experience disease progression, and the efficacy of subsequent line treatment options is limited. Tisotumab vedotin (TV) is an investigational antibody-drug conjugate directed to tissue factor. TV at 1.7 mg/kg IV Q2W has demonstrated encouraging antitumor activity in 2L-4L r/m HNSCC from the innovaTV 207 (NCT03485209) study. Here, we present data from the full cohort, Part C. **Methods:** innovaTV 207 is an open-label, global, phase 2, multicohort, multicenter study evaluating TV monotherapy or in combination for advanced solid tumors. In Part C, pts with r/m HNSCC received TV monotherapy (1.7 mg/kg IV Q2W). All pts were required to have received a platinum-based regimen, either in the r/m setting, or have persistent disease following platinum-based chemoradiation and a checkpoint inhibitor (CPI), if eligible. Primary endpoint was confirmed objective response rate (cORR) per investigator. Secondary endpoints included duration of response (DOR), time-to-response (TTR), and safety. **Results:** As of 6 Sept 2023, 40 pts with HNSCC were treated. 39 (97.5%) pts received prior platinum-based therapy. In the r/m setting, 25 (62.5%) pts received ≤2 prior lines of systemic therapy (median: 2; range: 1-3), 40 (100%) pts received prior CPI, 23 (57.5%) pts received prior taxane, and 27 (67.5%) pts received prior cetuximab. The most common subsites at diagnosis were oropharynx (n=16, of which 12 were p16 positive), larynx (n=10), and oral cavity (n=9). In the full cohort, cORR was 32.5% (95% CI, 18.6-49.1), with 1 complete response and 12 partial responses. Median DOR was 5.6 mo (95% CI, 3.0-NR) and median TTR was 1.4 mo. Among pts with ≤2 prior lines (n=25), cORR was 40.0% (95% CI, 21.1-61.3). In this subgroup, DOR is not yet mature (range: 1.2+ to 7.9+ mo), and among the 10 responders, 6 pts remain in response; median TTR was 1.5 mo. In the full cohort, 85.0% of pts had at least 1 treatment-related adverse event (TRAE). Grade ≥3 TRAEs occurred in 25.0% of pts, of which the most common were peripheral neuropathy events (12.5%). Adverse events of special interest were prespecified for ocular, peripheral neuropathy, and bleeding events, and occurred in 21 (52.5%), 19 (47.5%), and 15 (37.5%) pts, respectively. Updated efficacy and safety data are planned. **Conclusions:** TV demonstrated encouraging antitumor activity in a heavily pretreated r/m HNSCC population with a manageable safety profile consistent with previous TV monotherapy data. The study is ongoing; TV represents a promising treatment option for pts with r/m HNSCC who have progressed after prior platinum-based therapy and immunotherapy. Clinical trial information: NCT03485209. Research Sponsor: This study was funded by Genmab (Copenhagen, Denmark), Seagen Inc., which was acquired by Pfizer in Dec 2023.

6013 Rapid Oral Abstract Session

Preliminary results of phase I/II study to evaluate safety and efficacy of combination pucotenlimab with epidermal growth factor receptor-ADC (EGFR-ADC) MRG003 in patients with EGFR positive solid tumors.

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Background: Pucotenlimab (HX008) is a recombinant humanized PD-1 inhibitor approved for marketing in China, and MRG003 is an EGFR-ADC which has shown promising anti-tumor activity in squamous cell carcinoma of the head and neck (SCCHN) and nasopharyngeal carcinoma (NPC) in multiple clinical studies. In the preclinical studies, the combination of them has demonstrated a synergistic antitumor effect. This study was aimed to assess the safety and efficacy of the combination therapy in patients (pts) with locally advanced or metastatic solid tumors known to express EGFR. **Methods:** In this Phase I/II dose escalation and expansion study, eligible pts were treated with 3.0 mg/kg HX008 combined with MRG003 every 3 weeks, with an escalated dosing ranging from 1.5 mg/kg to 2.3 mg/kg. The primary endpoints were maximum tolerated dose (MTD), recommended Phase II dose (RP2D) of combination and objective response rate (ORR). Secondary endpoints included duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS). **Results:** As of 30 January 2024 (cut-off date), 33 pts (9 NPC, 1 SCCHN and 3 other solid tumors pts in Phase I, 14 NPC and 6 SCCHN pts in Phase II) were enrolled in this study with a median age of 52 (31,65), and 25 pts (76%) were male. 11 (33%) pts were ECOG PS 0. The most commonly reported treatment-related adverse events (TRAEs) included pruritus (46%), rash (33%), AST increased (30%), anemia (30%). Grade 3-4 TRAEs occurred in 4 pts (12%), and mainly was white blood cell count decreased (9%) and hypokalemia (6%). The only DLT event occurred in the 2.3mg/kg dose group, and the RP2D of MRG003 determined was 2.0mg/kg by SMC. Out of the 27 evaluable pts, 17 pts achieved PR and 7 pts achieved SD, thus the ORR and DCR were 63.0% (95%CI: 42.4, 80.6) and 88.9% (95%CI: 70.8, 97.7), respectively. In the Phase II, among 9 evaluable EGFR-positive NPC pts progression after first-line treatment of PD-1 plus platinum-based chemotherapy, 2 CR, 5 PR and 2 SD were observed, ORR and DCR were 77.8% (95%CI:40.0, 97.2) and 100% (95%CI:66.4, 100), respectively. Five evaluable systemic treatment naïve SCCHN pts with EGFR-positive, 3 PR and 1 SD were observed, ORR and DCR were 60% (95%CI:14.7, 94.7) and 80% (95%CI:28.4, 99.5), respectively. The DOR and PFS in the study were immature. The longest patient treated has had a DOR for more than 17 months and still ongoing. **Conclusions:** The Phase I/II study pts treated with HX008 in combination with MRG003 demonstrated good tolerability and encouraging antitumor activity in NPC and SCCHN, especially in PD-1 treatment failed NPC pts. The Phase II study is currently ongoing. Research Sponsor: Shanghai Miracogen Inc. Clinical trial information: NCT05688605. Research Sponsor: None.

6014 Rapid Oral Abstract Session

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

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Background: EGFR is a known oncogenic driver in HNSCC, and the leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5) is a receptor expressed on cancer stem cells, including in HNSCC. Petosemtamab is a human, common light chain, IgG1 bispecific antibody with ADCC-enhanced activity, targeting EGFR and LGR5. In the dose escalation part of a phase 1/2 study, the recommended phase 2 dose (RP2D) was determined to be 1500 mg every 2 weeks (Q2W). Interim data of petosemtamab monotherapy at the RP2D in 2L/3L HNSCC led to a 37.2% overall response rate (ORR; per investigator) with 6.0 months (mo) median duration of response (DOR) [Cohen, Cancer Research 2023]. Petosemtamab (RP2D) with pembrolizumab (400 mg Q6W) is being investigated in an expansion cohort of the ongoing phase 2 study (NCT03526835) in 1L HNSCC. **Methods:** Primary endpoints are safety and investigator-assessed ORR (RECIST v1.1). Secondary endpoints include DOR, progression-free survival (per investigator), and overall survival. Key eligibility criteria were r/m HNSCC with no prior systemic therapy, PD-L1 combined positive score ≥1, ECOG PS 0–1, measurable disease, and primary tumor location in oropharynx (regardless of p16 status), oral cavity, hypopharynx, or larynx. **Results:** No dose-limiting toxicities were observed in the safety run-in. As of a November 6, 2023 data cutoff, 26 pts were treated (24 continuing therapy at the data cutoff) and median follow-up was 1.35 mo. Median age was 62.5 years (range 23–80), ECOG PS 0/1 in 10/16 pts, and 65.4% were male. The most frequent primary tumor locations were oropharynx (34.6%), oral cavity (19.2%), and hypopharynx (19.2%). A median of 2 cycles (range 1–8) were administered. The combination was well tolerated and no significant overlapping toxicities were observed. Treatment-emergent adverse events (AEs) were reported in 26 pts, and most were Grade (G) 1 or 2 in severity (no G4–5 were observed). The most frequent AEs (all Gs/G3) were acneiform dermatitis (30.8%/0%), asthenia (26.9%/0%), and rash (26.9%/0%). Infusion-related reactions (composite term) were reported in 26.9% (all Gs) and 3.8% (G3) of pts, all occurred during the first infusion and resolved. Among 10 pts evaluable for efficacy (≥2 cycles and ≥1 post-baseline scan, or early progressive disease), there were 1 confirmed complete response, 2 confirmed and 3 unconfirmed partial responses (2 confirmed after data cutoff), 3 stable disease, and 1 progressive disease; with all 6 responders on treatment at data cutoff. Enrollment has been completed and updated data will be presented. **Conclusions:** Petosemtamab, a first-in-class EGFR x LGR5 bispecific antibody, in combination with pembrolizumab demonstrates a well-tolerated safety profile and promising preliminary clinical efficacy as 1L treatment for pts with r/m HNSCC. Clinical trial information: NCT03526835. Research Sponsor: Merus N.V.

LBA6015 **Rapid Oral Abstract Session**

PRGN-2012, a novel gorilla adenovirus-based immunotherapy, provides the first treatment that leads to complete and durable responses in recurrent respiratory papillomatosis patients.

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6016 Rapid Oral Abstract Session

Intralesional nivolumab in oral potentially malignant disorders: A phase 1 pilot study on safety, tolerability, and preliminary efficacy.

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Background: Oral Potentially Malignant Disorders (OPMD) encompass a diverse group of oral mucosal diseases, including the prevalent oral leukoplakia (OL), serving as precursors to invasive oral squamous cell carcinoma. OPMD exhibits an annual malignant transformation rate up to 36%. Despite the breadth of research on OPMD the standard-of-care remains surgery or observation. We aim to evaluate the safety and tolerability of intralesional injections of Nivolumab in patients with OPMD. Secondary objectives include assessing objective response rate and pathologic complete response rate. We describe the results of an immune prevention trial designed to avoid systemic toxicities of immunotherapy in patient with pre-malignancy by administrating aPD1 intralesionaly. **Methods:** Phase 1, single-arm, open-label, dose-escalation pilot study that involves intralesional injections of Nivolumab (index lesion) in patients with high-risk OPMD lesions every 3 weeks (total of 4 doses, 12 weeks). Non-index, non-injected, oral lesion(s) were also documented and monitored. The study includes two dose cohorts (10 mg and 20 mg) to assess maximally tolerated dose with a 3 + 6 dose-escalation design. Adverse events were reported according to NCI CTCAE Version 5.0. Serial biopsies at baseline and up to 8 weeks after treatment were taken to assess efficacy using a composite score (i.e., size and degree of dysplasia) in index lesion. Major response was defined as >80% decrease in score; partial response as 40%-80% decrease. Freshly frozen tumors were subjected to RNA sequencing and gene pathway analysis to identify biomarkers of response or progression. **Results:** At the time of data analysis, 13 patients have completed treatment (61.5% males), both dose levels were well tolerated. The adverse event grades ranged from grade 1 (i.e. diarrhea, elevated LFT and skin rash) constituting the majority at 80.5% of reported adverse events, grade 2 (i.e. skin rash, cellulitis) at 13.9%, and grade 3 (i.e. hypertension) at 5.6%. Ten patients had multifocal disease. Major response was observed in 22.5% and partial response in 50% of the patients. One patient progressed to invasive SCC in a non-index lesion. RNA sequencing based immune phenotyping revealed increased infiltration of CD8 cytotoxic T cells in index lesions after treatment. Pathway analysis revealed significant alterations in immune pathways including Th1 and Th2 pathways, Natural killer and immunoregulatory pathways. Spatial transcriptome analysis and pharmacokinetics data are pending. **Conclusions:** Intralesional nivolumab is well tolerated in OPMD with suggested potential biological and clinical activity. A randomized phase II trial to assess cancer free survival is recommended to determine the efficacy in preventing cancer progression. We recommend dose of 20mg for phase II as it was well tolerated. Clinical trial information: NCT05327270. Research Sponsor: None.

6017 Rapid Oral Abstract Session

Neoadjuvant HPV16-specific arenavirus-based immunotherapy HB-200 plus chemotherapy followed by response-stratified de-intensification in HPV16+ oropharyngeal cancer: TARGET-HPV.

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Background: The role of immunotherapy in curative viral-mediated oropharyngeal cancer (OPC) remains undefined. Human papillomavirus (HPV) 16 positive (+) OPC constitutively expresses viral epitopes that drive antigen-specific anti-tumor immunity, supporting rationale for evaluating neoadjuvant HPV16 directed therapeutics in non-metastatic OPC. HB-200 is an arenavirus-based vector therapy derived from LCMV (HB-201) and Pichinde virus (HB-202) each expressing a non-oncogenic HPV16 E7E6 fusion protein to induce HPV16 specific CD8+ T-cell responses. Building on our OPTIMA II results demonstrating that neoadjuvant chemotherapy/nivolumab led to deep responses in 71% of patients who went on to receive reduced radiation (RT), we hypothesized that adding HB-200 to chemotherapy to drive HPV16-specific anti-tumor immunity would be safe and effective to further deepen responses and facilitate more de-escalation. **Methods:** In this Phase 1 dose escalation investigator-initiated study, patients with non-metastatic HPV16+ OPC were treated with escalating doses of HB-201 single vector (Arm A) or HB-202/201 alternating vector (Arm B) x3 with neoadjuvant carboplatin AUC5 on day 1 and paclitaxel 100mg/m2 on days 1/8/15 of a 21-day cycle for 3 cycles. Deep responders ($\geq$50% tumor shrinkage) received transoral robotic surgery (TORS) alone or RT to 50Gy +/- cisplatin, while non-responders ($<$50% shrinkage) received 50 or 70Gy of RT with cisplatin. Primary objective was safety/tolerability and recommended phase 2 dose of HB-200 with chemotherapy. Additional objectives included deep response rate, circulating tumor (ct) HPV-DNA dynamics, and HPV16-specific T-cell response. **Results:** Twenty-one patients with HPV16+ OPC were enrolled and treated (Arm A, n=9, 43%; Arm B, n=12, 57%). Median age 57, 91% male, 75% base of tongue, 52% non-smokers, and 33% stage II/III (AJCC 8th edition). $\geq$Grade 3 treatment-emergent adverse events (AEs) occurred in 13 (62%) of patients overall and 3 (14%) non-hematologic during neoadjuvant. There were no Grade 4 AEs reported. All patients completed neoadjuvant HB-200/chemotherapy and response-stratified locoregional treatment. Deep responses following HB-200/chemotherapy were observed in 17/21 (81%) of patients, and in 14/15 (93%) treated on higher dose levels 1 or 2 (p=0.05). All three patients who underwent TORS had no viable tumor at time of surgery. Two patients (9%) had persistent disease following CRT and underwent salvage surgery with no evidence of disease at last follow-up. ctHPV-DNA and HPV16-specific T-cell response data will be presented at the meeting. **Conclusions:** Neoadjuvant HB-200/chemotherapy is safe and feasible with early efficacy signal in this setting warranting further study. Enrollment to the subsequent randomized phase II part is ongoing (NCT05108870). Clinical trial information: NCT05108870. Research Sponsor: HOOKIPA Pharma, Inc.; Grant Achatz and Nick Kokonas; University of Chicago Comprehensive Cancer Center; P30 CA014599.

LBA6018 **Rapid Oral Abstract Session**

Covalent FAPI PET enables accurate management of medullary thyroid carcinoma: A prospective single-arm comparative clinical trial.

Ziren Kong, Zhu Li, Xi-Yang Cui, Wang Jian, Mengxin Xu, Yang Liu, Junyi Chen, Song Ni, Xiaowei Fan, Jiazhao Huang, Yansong Lin, Xinfeng Lin, Tianyu Men, Changming An, Nan Li, Chen Liu, Yi-Ming Zhu, Zhi Yang, Zhibo Liu, Shaoyan Liu; Department of Head and Neck Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Department of Nuclear Medicine, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; Changping Laboratory, Beijing, China, Beijing, China; Beijing National Laboratory for Molecular Sciences, Radiochemistry and Radiation Chemistry Key Laboratory of Fundamental Science, NMPA Key Laboratory for Research and Evaluation of Radiopharmaceuticals, Key Laboratory of Bioorganic Chemistry and Molecular, Beijing, China; Department of Nuclear Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

LBA6019 **Rapid Oral Abstract Session**

Phase 3 randomized study for evaluation of physician choice Rx versus best supportive care as second-line or beyond therapy in head and neck cancer with poor performance status.

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6020 Rapid Oral Abstract Session

A phase II trial of neoadjuvant docetaxel/5-FU/cisplatin in combination with prophylactic pegteograstim in unresectable, locally advanced nasal cavity/paranasal squamous cell carcinoma: KCSG HN18-07.

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Background: Squamous cell carcinoma (SCC) arising from paranasal sinus and nasal cavity (PNSNC) is often diagnosed at locally advanced stage. Neoadjuvant strategies have been explored to improve prognosis and facilitate organ preservation. The efficacy of triplet neoadjuvant chemotherapy (NAC) has not been established prospectively. We conducted a phase II trial of neoadjuvant docetaxel/5-FU/cisplatin (DFP) combined with prophylactic pegteograstim in unresectable, locally advanced PNSNC (KCT0003377). **Methods:** Eligible patients had unresectable SCC of PNSNC, were aged 19-75, had an ECOG performance status of 0/1, and demonstrated adequate organ function. Patients with distant metastasis were excluded. Criteria for unresectability included tumor or lymph node fixation, clinical T3/4 stage, or potential compromise of critical organ function (e.g., necessitating eyeball exenteration). NAC comprised three cycles of docetaxel (75mg/m2 on Day 1), cisplatin (75mg/m2 on Day 1, 60mg/m2 for those aged ≥65), and 5-FU (1,000mg/m2 on Days 1-4) administered every 3 weeks. Prophylactic pegteograstim (6mg) was administered on Day 6 or 7. The primary outcome was the overall response rate (ORR), with secondary outcomes including progression-free survival (PFS), the eyeball preservation rate at 24 months, and safety. The study required 28 patients to achieve a power of 80% (P0=0.45, P1=0.70, α-error=0.05, 10% dropout rate). **Results:** Between 2019 and 2023, 28 patients were screened, and 27 received at least one cycle of NAC. The median age was 58 years (range: 41-71), with 24 males. Seventeen had maxillary sinus origin, and ten had nasal cavity origin. Twenty-two patients had T4 disease, and six had N2 disease. The ORR was 64.3% (5 complete responses, 13 partial responses). Post-NAC treatments included surgery alone (n=2), concurrent chemoradiotherapy (CCRT) (n=15), surgery followed by CCRT (n=2), or radiotherapy (RT) (n=5). Procedures performed were total maxillectomy (n=4), partial maxillectomy (n=3), and endoscopic sinus surgery (n=2). With a median follow-up of 21.5 months (range: 0.1-53.0), the 2-year PFS and eyeball preservation rate were 64% and 100%, respectively. Fourteen patients experienced Grade ≥3 adverse events (AEs): hematologic (46.4%), non-hematologic (14.3%), with Grade 3/4 neutropenia (32.1%) and febrile neutropenia (14.3%). Dose reduction or delay occurred in 9 patients (33.3%). One patient died on Day 6 of cycle 1. **Conclusions:** DFP NAC demonstrated promising efficacy and an excellent eyeball preservation rate with manageable toxicity. DFP NAC with prophylactic pegteograstim, could be a reasonable option for patients with locally advanced SCC of the PNSNC. Follow-up is ongoing. Clinical trial information: KCT0003377. Research Sponsor: None.

6021 Poster Session

BMI correlation with outcomes in patients with head and neck cancer undergoing immunotherapy: A comprehensive review and meta-analysis.

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Background: Currently, the landscape of treating advanced malignancies has undergone a transformative shift with the advent of immunotherapy employing immune checkpoint inhibitors (ICIs). Notably, several ICIs have emerged as promising therapeutic modalities for individuals with head and neck cancer (HNC). An emerging body of evidence implies a plausible link between body mass index (BMI) and the effectiveness of ICIs in the broader context of cancer patients. Nevertheless, the specific correlation within the subset of head and neck cancer patients undergoing immunotherapeutic interventions remains unclear and warrants meticulous investigation. **Methods:** PubMed, Web of Science, and Google Scholar databases were searched extensively for records published until January 2024. Full-text articles aligned with the research objective were included, while records published in English, case reports, reviews, editorials, and studies reporting immunotherapy combined with other cancer therapies were excluded. The data required for review and analysis was abstracted in Excel files by two independent reviewers. Additionally, statistical analyses were performed using the Review Manager software, and methodological quality was assessed using the Newcastle Ottawa scale. **Results:** Only six studies were eligible for review and analysis. A subgroup analysis of data from these studies showed that obese HNC patients on immunotherapy had significantly better overall survival (OS) rates than non-obese patients (HR: 0.51; 95% CI: 0.29 – 0.93; p=0.03). However, the progression-free survival (PFS) was statistically similar between obese and non-obese patients (HR: 0.72; 95% CI: 0.39 – 1.33; p=0.30). In addition, when BMI was stratified as either low or high, no significant difference was observed in the OS and PFS of HNC patients (HR: 0.99; 95% CI: 0.59 – 1.66; p=0.97 and HR: 0.93; 95% CI: 0.61 – 1.41; p=0.42, respectively). Similarly, the statistical analyses showed that overweight patients have similar OS and PFS as patients with normal BMI (HR: 0.53; 95% CI: 0.15 – 1.92; p=0.33 and HR: 0.55; 95% CI: 0.20 – 1.52; p = 0.25, respectively). In contrast, underweight patients demonstrated poor OS and PFS (HR: 2.56; 95% CI: 1.29 – 5.12; p=0.008 and HR: 2.76; 95% CI: 1.17 – 6.52; p=0.02, respectively). **Conclusions:** Obese HNC patients on immunotherapy tend to have improved OS than non-obese patients, while underweight patients have worse clinical prognoses than those with normal or above BMI. Research Sponsor: None.

Comparative analysis of pembrolizumab and cetuximab-based therapy in patients with recurrent/metastatic head and neck squamous cell carcinoma: Real-world data.

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Background: The preferred treatment for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) not amenable to localized/curative treatment is pembrolizumab, either monotherapy or in combination with chemotherapy based on the results of KEYNOTE-048. Since the FDA's approval of pembrolizumab in 2019, real-world data has been scarce. Using the TriNetX platform, we retrospectively compared survival outcomes between patients treated with pembrolizumab vs. cetuximab-based treatment. **Methods:** Cohorts were identified on TriNetX platform using the US Collaborative Network, which includes anonymous clinical information of patients between 2007-2023. Three cohorts were selected: patients treated with pembrolizumab monotherapy (P), patients treated with pembrolizumab and platinum+5-FU chemotherapy (P+CT), and patients treated with cetuximab and platinum+5-FU chemotherapy (C+CT). All patients had non-nasopharyngeal R/M HNSCC with no prior systemic therapy. The study objective was to compare overall survival (OS) between these three cohorts using the Kaplan-Meier method. **Results:** Our analysis identified 409 patients in cohort P, 161 patients in cohort P+CT, and 176 patients in cohort C+CT. Median age at initiation of treatment was 69.8, 62.2, and 57.7 years in cohort P, P+CT, and C+CT, respectively. Male percentage was 61%, 75%, and 77%, respectively. The most common primary tumor sites for cohorts P, P+CT, and C+CT were as follows: oropharynx 28%, 37%, and 48%, hypopharynx 10%, 19%, and 11%, larynx 31%, 29%, and 40%, and oral cavity 4%, 6% and 9% respectively. Information on PD-L1 and HPV (Human Papillomavirus) status was not available. Median OS was 13.7, 15, and11.4 months in cohorts P, P+CT, and C+CT, respectively. Survival probability at 5 years was 25.7% in cohort P, 32.2% in cohort P+CT, and 9.9% in cohort C+CT. Based on our analysis, patients treated with pembrolizumab (P or P+CT) demonstrated superior OS compared to those who received cetuximab-based therapy (P-Value <0.05). There was no statistically difference in median OS between P and P+CT group. (P-Value 0.6). **Conclusions:** Our retrospective analysis of real-world data from a large national database shows superior OS with pembrolizumab- based treatment compared to cetuximab-based treatment in the first line setting for patients with R/M HNSCC. This analysis is consistent with KEYNOTE-048 outcomes. we found no difference in OS between Pembrolizumab alone or in combination with chemotherapy. Limitations include unknown PD-L1 and HPV status. Further long-term and prospective analysis is imperative to enhance the care and outcomes of patients with metastatic HNSCC. Research Sponsor: None.

Cohorts	Number of Patients in the Cohort	Number of Patients with Outcome (Death)	Median OS (months)	5-Year Survival Probability (%)
P	409	203	13.7	25.7
P+CT	161	82	15	32.2
C+CT	176	130	11.4	9.9

6023 Poster Session

Pembrolizumab plus nab-paclitaxel and platinum as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): A prospective, single-arm, open-label, phase 2 study.

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Background: Based on KN-048, pembrolizumab combined with PF regimen has become the first-line standard treatment for R/M HNSCC. KN-B10 confirmed pembrolizumab combined with carboplatin and paclitaxel has a promising effect with manageable safety. This study aims to supplement the efficacy and safety data of pembrolizumab combined with nab-paclitaxel and platinum in the Chinese population. **Methods:** Untreated R/M HNSCC patients were treated with pembrolizumab 200mg, nab-paclitaxel 260mg/m^2 , plus cisplatin 75 mg/m^2 or carboplatin AUC 5 (only if patients have cisplatin contraindications) on day 1 every 21 days for up to six cycles, followed by pembrolizumab maintenance therapy until progression or intolerable toxicity or completion of 35 cycles. Efficacy was evaluated according to RECIST 1.1, and survival analysis was performed using the Kaplan-Meier method. Adverse events were assessed using the CTCAE 5.0. The primary endpoint was ORR. Secondary endpoints include safety, DCR, OS, and PFS. High-resolution sequencing based on probe capture was performed on eligible patients. **Results:** Between Sep 15, 2020, and Nov 8, 2023, 67 R/M HNSCC patients were enrolled. Baseline characteristics are shown in the table. The median follow-up time was 12.7 months at the data cut-off date of January 8th, 2023, the ORR was 62.7%, and the DCR was 88.1%. The median PFS and OS were 11.6 months and 18.7 months, respectively. The median DOR was 14.7 months. The most common TRAEs of grade ≥3 were leukopenia (22.4%) and neutropenia (28.4%). Grade≥3 immune-related AEs were pneumonitis (1.5%), hepatitis (1.5%), and enteritis (1.5%). Of the 35 patients with sequencing results, the most common alterations were the TP53 mutation (86%), CDKN2A mutation (22%), FGF19 (26%), FGF4 (20%), FGF3 (20%), and CCND1 (20%) amplification. FGF19, FGF4, FGF3, and CCND1 amplification were associated with poor ORR, and CDKN2A mutation was associated with poor OS. **Conclusions:** Pembrolizumab combined with nab-paclitaxel and platinum shows encouraging antitumor activity accompanied by a manageable safety profile in untreated R/M HNSCC patients in China. CDKN2A mutation was a potential independent prognostic factors for this patient population. Clinical trial information: NCT04857164. Research Sponsor: None.

Characteristics		n(%)	Characteristics		n(%)	Characteristics		n(%)
Sex	Male	61 (91.0)	ECOG	0	8 (11.9)	Stage	IVA	18 (26.9)
	Female	6 (9.0)		1	48 (71.6)		IVB	15 (22.4)
Age		57 (34-73)		2	11 (16.4)		IVC	34 (50.7)
	≥65	13 (19.4)	Disease status	Distant metastatic	9 (13.4)	PD-L1 CPS	< 1	8 (11.9)
Primary tumor sites	Hypopharynx	20 (29.9)		Local recurrence	32 (47.8)		1-19	25 (37.3)
	Larynx	15 (22.4)		Distant metastatic and local recurrence	26 (38.8)		≥20	30 (44.8)
	Oral cavity	27 (40.3)	p16	positive	11 (16.4)		unknown	4 (6.0)
	Oropharynx	5 (7.5)		negative	48 (71.6)	Platinum	Cisplatin	62 (92.5)
				unknown	8 (11.9)		Carboplatin	5 (7.5)

6024 Poster Session

Efficacy of nimotuzumab added to concurrent chemoradiotherapy after induction chemotherapy for patients with locally advanced nasopharyngeal carcinoma.

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Background: To investigate the efficacy and toxicities associated with adding nimotuzumab to concurrent chemoradiotherapy (CCRT) in locally advanced nasopharyngeal carcinoma (LANPC) patients who received induction chemotherapy (IC). **Methods:** Patients with stage III-IVA nasopharyngeal carcinoma who received IC (TPF/TP/GP) and platinum-based CCRT between January 2017 and October 2021 were retrospectively included. We performed propensity score matching (PSM) to balance and control confounding factors, and the matching variables included gender, age, T stage, N stage, and Epstein-Barr virus (EBV) status. Patients were divided into two treatment groups: CCRT+nimotuzumab (200mg iv, weekly for 7 courses) and CCRT alone. Primary endpoints were overall survival (OS) and disease-free survival (DFS), the secondary endpoints were locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS). **Results:** We screened 242 patients in the analysis. After PSM, 121 (50.0%) and 121 (50.0%) had CCRT+nimotuzumab and CCRT alone, respectively. The 3-year OS was 95.4% and 88.0% in those with and without nimotuzumab treatment (P=0.041), and the 3-year DFS of the CCRT+nimotuzumab group was significantly better than that in the CCRT alone group (90.3% vs. 77.5%, P=0.003). Similar LRFS was found between those with and without nimotuzumab treatment (96.5% vs. 93.7%, P=0.297). The 3-year DMFS for CCRT+nimotuzumab versus CCRT alone was 92.9% versus 82.5% (P=0.008). No significant differences in major toxicities were found between the two treatment arms including hematologic toxicities, hepatoxicity, nephrotoxicity, gastrointestinal reactions, and mucositis (P>0.05). **Conclusions:** The addition of nimotuzumab to CCRT after IC in LANPC has shown promising results in treatment outcomes and acceptable toxicities. Research Sponsor: None.

Off-label use of checkpoint inhibitor (CPI) monotherapy in PD-L1–negative or unknown recurrent/metastatic head and neck cancer (R/M HNSCC).

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Background: The KN-048 study established that the CPI pembrolizumab with chemotherapy should be used for PD-L1 negative R/M HNSCC, while CPI monotherapy has limited efficacy (ORR 4%) in PD-L1 negative disease and should be reserved for PD-L1 positive disease. National patterns of PD-L1 testing and PD-L1 guided treatment selection are unknown. We examined PD-L1 testing rates, the use of CPI overall, and the use of CPI monotherapy in PD-L1 negative or unknown R/M HNSCC ("off-label"), and associated factors. **Methods:** This retrospective analysis included adult patients starting treatment for R/M HNSCC from 2019-2023 in the Flatiron Health electronic health record (EHR)-derived de-identified national database. Demographics, treatment type, and PD-L1 test results were summarized using descriptive statistics. Specifically, first-line therapy was categorized as CPI monotherapy, CPI with chemotherapy, or chemotherapy and/or cetuximab without CPI. "Off-label" use of CPI was defined as single-agent use without concurrent chemotherapy in patients with negative or unknown PD-L1. Factors associated with "off-label" use were identified using multivariable logistic regression analysis. **Results:** Our cohort included 3,395 patients with median age 66 (IQR 59-73), 65% White, 77% treated in a community setting, 76% with smoking history, 37% HPV positive, and 72% ECOG PS 0-1. Almost half of patients (44%) did not have a recorded PD-L1 test result; of those with known PD-L1 status (n=1886), distribution of combined positive score (CPS) 0, 1-19, and 20 was 19%, 41%, and 40%, respectively. The most common frontline treatment was CPI monotherapy (43%), followed by chemotherapy/cetuximab (33%) and CPI with chemotherapy (25%). CPI monotherapy use was highly prevalent in patients aged ≥75 (54%) and with ECOG PS ≥ 2 (52%). Among the subgroup of PD-L1 negative or unknown patients (n=1831), 37% (678) received CPI monotherapy ("off-label"). Factors associated with "off-label" CPI monotherapy use included ECOG PS ≥ 2 (OR 1.3), age ≥ 75 (OR 1.3), community practice (OR 1.7), and earlier year (HR 1.2) (all $p<0.05$). **Conclusions:** Most US patients with R/M HNSCC are now receiving CPI-based therapy in the frontline setting, but PD-L1 testing rates remain suboptimal. Use of CPI monotherapy in PD-L1 negative or unknown HNSCC is common, particularly in elderly patients and those with poor performance status. Research Sponsor: None.

Treatment for frontline R/M HNSCC by PD-L1 levels, 2019-2023.

PD-L1/Treatment	PD-L1 CPS ≥ 20	PD-L1 CPS 1-19	PD-L1 CPS <1	PD-L1 unknown
CPI monotherapy	398 (53%)	371 (47%)	116 (33%)	562 (38%)
CPI + chemotherapy	181 (24%)	232 (30%)	121 (34%)	289 (20%)
Chemotherapy +/- cetuximab	173 (23%)	179 (23%)	115 (33%)	628 (42%)
Total	752	782	352	1479

6026 Poster Session

Safety and efficacy of iparomlimab and tuvonralimab in combination with gemcitabine and cisplatin as first-line treatment for patients with recurrent or metastatic nasopharyngeal carcinoma: A multicenter, single-arm, phase 2 trial (DUBHE-N-302).

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Background: Programmed cell death 1 (PD-1) inhibitor plus chemotherapy has been the standard first-line (1L) treatment for patients with recurrent or metastatic (R/M) nasopharyngeal carcinoma (NPC). Iparomlimab and tuvoralimab (QL1706), a novel bispecific antibody targeting PD-1 and cytotoxic T-lymphocyte antigen 4, indicated promising anti-tumor activity for advanced solid tumors including NPC in phase 1/1b trial. This study aimed to evaluate the safety and efficacy of QL1706 combined with chemotherapy as 1L treatment in R/M NPC. **Methods:** This multicenter, single-arm, phase 2 study (NCT05576272) recruited patients with NPC who had no prior systemic therapy in the R/M setting. Intravenous injection of QL1706 5 mg/kg (day 1) combined with gemcitabine 1000 mg/m^2 (days 1 and 8) and cisplatin 80 mg/m^2 (day 1) was administered for four to six cycles (21 days per cycle), followed by maintenance treatment of QL1706. The primary endpoint was safety and tolerability. Key secondary endpoints were objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DoR), and overall survival (OS). **Results:** From May 19 2022 to Dec 9 2022, 29 patients were included. The median age was 50 years (range, 25-65), with 24 (83%) being male. Seven patients (24%) had an Eastern Cooperative Oncology Group Performance Status of 1. Nineteen (66%) had recurrent disease. As of the data cut-off on Dec 31 2023, the median follow-up was 15.5 months. Treatment-related adverse events (TRAEs) occurred in 29 patients (100%). TRAEs of grade 3 or 4 occurred in 18 patients (62%), with the most common being decreased neutrophil count (41%), decreased white blood cell count (35%), anemia (21%), and decreased platelet count (21%). Twenty patients (69%) experienced immune-related adverse events, with the most common being grade 1-2 hypothyroidism (38%). Serious TRAEs occurred in five patients (17%). Three patients (10%) discontinued treatment due to adverse events. No treatment-related deaths occurred. Among the 28 evaluable patients, the ORR was 82.1% (95% confidence interval [CI], 63.1% to 93.9%), including one achieving complete response. The DCR was 96.4% (95% CI, 81.7% to 99.9%). The median PFS was 12.5 months (95% CI, 5.7 to not evaluable [NE]), and the median DoR was 14.1 months (95% CI, 7.6 to NE). In 14 patients with high expression level of programmed cell death ligand 1 (combined positive score≥50), the median PFS was 16.2 months (95% CI, 9.9 to NE). The median OS was not reached. **Conclusions:** Iparomlimab and tuvoralimab combined with chemotherapy showed tolerable safety and promising efficacy as 1L treatment for patients with R/M NPC. Clinical trial information: NCT05576272. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

6027 Poster Session

The role and mechanism of circadian clock gene BMAL1 in the proliferation and metastasis of nasopharyngeal carcinoma by inhibition TGF-β1/Smads pathway.

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Background: To explore the molecular mechanism of biological clock gene BMAL1 inhibiting the proliferation and metastasis of nasopharyngeal carcinoma(NPC). **Methods:** 1. IHC detected the expression of BMAL1 in 41 cases of nasopharyngeal chronic inflammatory tissue and 71 cases of NPCtissue. PCR and Western blot measured the expression levels of BMAL1 in NP69 in NPC cells and human immortalized nasopharyngeal epithelial cells, respectively. 2. To detect the effect of BMAL1 on the proliferation capacity of NPCcells in vitro and in vivo; Scratch healing and Transwell invasion migration experiments detected the effect of BMAL1 on the invasion and migration ability of NPCcells in vitro. Fluorescence in vivo imaging and HE staining to determine the transfer of nude mouse tail intravenous injection model. PCR and Western blot detect the effect of BMAL1 on the expression of EMT-related markers at the transcriptional and protein levels in NPC cells. 3. A series of molecular biological means such as bioinformatics technology, ChIP experiment, double luciferase reporter gene experiment, immunofluorescence colocalization experiment and Co-IP were used to verify its mechanism. **Results:** 1. The expression of BMAL1 in NPCtissues and cells is reduced. The expression of BMAL1 in NPC tissues was associated with the M stage of nasopharyngeal carcinoma patients (p=0.006). 2. Overexpression of BMAL1 can inhibit the proliferation, invasion and migration ability of nasopharyngeal cancer cells, while knocking down BMAL1 is the opposite. Overexpression of BMAL1 inhibits EMT of NPCcells. 3. There are 5 BMAL1 binding sites in the TGF-β1promoter region, and BMAL1 can directly bind to the TGF-β1promoter region, which can inhibit the transcriptional activity of TGF-β1. Overexpression of BMAL1 inhibits TGF-β1/Smads pathway activity. Under the induction of recombinant human TGF-β1, the proliferation ability of NPC cells was enhanced, the activity of TGF-β1/Smads signaling pathway was enhanced, and nasopharyngeal cancer cells underwent EMT, and cell invasion and migration capacity increased. After overexpression of BMAL1, TGF-β1 no longer promotes TGF-β1/Smads signaling pathway activity, EMT is inhibited, and cell invasion and migration ability is weakened. BMAL1 combined with TGF-β1 has certain diagnostic value in predicting whether nasopharyngeal carcinoma metastasis. **Conclusions:** BMAL1 expression is downregulated in nasopharyngeal carcinoma, and its expression level is related to the development and metastasis of nasopharyngeal carcinoma. BMAL1 can inhibit the proliferation, epithelial-mesenchymal transformation and invasion and metastasis ability of NPC cells, and its mechanism is related to the inhibition of TGF-β1/Smads signaling pathway activity. It is speculated that it may become a new prognostic marker and therapeutic target for nasopharyngeal carcinoma. Research Sponsor: National Natural Science Foundation of China; The Technology Achievements Application and Industry Plan Clinical Special; The Guizhou Medical University Affiliated Hospital Doctoral Research Initiation Fund Project; The Guizhou Medical University Affiliated Hospital 2023 National Natural Science Foundation Cultivation Project.

6028 Poster Session

Impact of immune-related adverse events (irAE) onset on disease response and survival in patients (pts) with head-neck cancer treated with immune check point inhibitors (ICI).

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Background: ICI or combination chemo-immunotherapy are the mainstay of therapy for metastatic head-neck squamous cell carcinoma (mHNSCC) due to durable responses in certain pts. irAEs have emerged as a new challenge in the management of these pts. Some studies suggest a positive correlation between irAE onset and ICI efficacy in other cancers, however, whether such an association exists in HNSCC remains incompletely explored. **Methods:** We performed a retrospective, single-center cohort study of pts ≥ 18 years of age, with histologically confirmed mHNSCC who received ≥ 1 dose of ICIs at the University of Virginia Comprehensive Cancer Center, VA, USA between 2013-2022. Demographics, disease and treatment characteristics, and clinical outcomes related to irAEs and ICI re-challenge were analyzed. IrAEs were graded using CTCAE v4.0 criteria by chart review. Independent sample t-tests and chi-square analyses were used for univariate comparisons. Median PFS and OS from ICI therapy initiation were estimated using Kaplan-Meier methodology and censored at date of last follow up. P-values <0.05 were considered statistically significant. **Results:** Of 1979 pts who received ICI, 110 had mHNSCC (72.7% male; 84.5% White) with a median age of 62.4 years. ICI type included pembrolizumab or nivolumab in 109 pts, and nivolumab/ipilimumab in one pt. 53 (48%) pts experienced any grade irAE and 12 pts (11%) experienced >1 irAE. The most common irAEs were hypothyroidism (30.4%), dermatitis (14.3%), and hepatitis (10.7%). CTCAE ≥G3 irAEs were seen in 22.6% pts (n=12). These included hepatitis (n=3), colitis (n=3), hypothyroidism (n=1), arthritis (n=1), pneumonitis (n=1), adrenal insufficiency (n=1), vasculitis (n=1), and cardiomyopathy (n=1). Men (62% vs 37%, p= 0.015) and pts with prior radiation therapy (83% vs 17%, p=0.047) were more likely to experience irAEs. Treatment interruption/discontinuation occurred in 43% pts with irAEs. Topical/supportive therapy was required in 52.8%, and 35.8% required systemic corticosteroids, with more than half experiencing complete irAE resolution. A statistically significant association was observed between irAE onset and objective response rate (68% vs 39%, p= 0.009). 12 pts underwent ICI re-challenge, resulting in partial response in 3 (25%), stable disease in 4 (33.3%) and progressive disease in 3 (25%) pts. There was no statistically significant difference in PFS (4.9 vs 9.7 months, p = 0.731) or OS (30.5 vs 21 months, p = 0.159) in irAE vs non-irAE groups, respectively. **Conclusions:** irAEs onset was associated with improved best response to ICI therapy in mHNSCC. Although OS was numerically superior in the irAE group, it did not meet statistical significance. ICI re-challenge is feasible in select pts, however further studies are needed to evaluate long term benefit of ICI re-challenge. Research Sponsor: None.

6029 Poster Session

Correlation between irAEs and treatment efficacy of anti-PD-1 single agent in patients with recurrent/metastatic head and neck squamous cell carcinoma: A monocentric real-world observational study.

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Background: Immune-related adverse events (irAEs) are associated with efficacy of ICIs-based treatment in various cancer types. The aim of this retrospective study was to assess the relationship between irAEs and outcomes in patients with recurrent/metastatic Head and Neck squamous cell carcinoma (R/M-HNSCC) treated with immune checkpoint inhibitors (ICIs) monotherapy. **Methods:** We retrospectively reviewed data from patients with R/M HNSCC treated with ICIs single-agent between January 2018 and June 2023 at the Istituto Oncologico Veneto of Padua. Common Terminology Criteria for Adverse Events v.5.0 was used to assess irAEs evaluation. Patients were stratified into irAEs (any grade) and non-irAEs groups. Overall survival (OS) and progression free survival (PFS) were assessed using the Kaplan-Meier method. Univariate and multivariate Cox-regression were used to compare survival outcomes. The chi-square test was used to assess the association between irAEs and objective responses (ORR). **Results:** A total of 89 patients were eligible for the analysis. Patients with platinum-refractory disease received nivolumab (64 patients, 72%). All the 25 patients (28%) with platinum-sensitive disease were PD-L1 positive (CPS≥1) and received pembrolizumab as first line treatment for R/M disease. Median follow-up was 8.7 months. IrAEs (any grade) were observed in 60 patients (67%), including 9 patients (10%) with grade ≥3 AEs. The most common irAEs were endocrinopathies (35%), skin events (15%), hepatic events (13%), diarrhea/colitis (10%) and lipase/amylase elevation (10%). The ORR was higher in the irAEs group than in the non-irAEs group (19.5% vs 2%, p=0.017). PFS and OS were also significantly longer in the irAEs group: median PFS was 3.9 months vs 2.1 months (HR 0.48 95% CI 0.30-0.77; p=0.003) and median OS was 12.5 months vs 4.3 months (HR 0.36 95% CI 0.21-0.60; p=0.000). The statistically significant benefit for both PFS and OS was confirmed at the multivariate analysis (Table1). Patients who experienced endocrine-related irAEs (p=0.004), diarrhea/colitis (p=0.040) and lipase/amylase increase (p=0.005) had significantly longer OS than those without the corresponding toxicity. A positive trend was observed for skin toxicity (p=0.051). **Conclusions:** The occurrence of irAEs was a predictor of response and survival outcomes in patients with R/M HNSCC treated with ICIs single-agent. Research Sponsor: None.

Multivariate analysis.

OS	HR	95%CI	p-value
ECOG 0 vs ≥1	0.40	0.15 - 1.05	0.063
Platinum-sensitive yes vs no	0.37	0.19 - 0.72	0.003
Metastatic only vs Locoregional ± metastatic	0.75	0.43 - 1.33	0.327
irAEs yes vs no	0.33	0.18 - 0.60	0.000
PFS			
ECOG 0 vs ≥1	0.42	0.19 - 0.93	0.032
Platinum-sensitive yes vs no	0.57	0.33 - 0.97	0.039
Metastatic only vs Locoregional ± metastatic	0.75	0.46 - 1.21	0.238
irAEs yes vs no	0.50	0.30 - 0.83	0.007

6030 Poster Session

Identifying patients at high risk of recurrence by rebound of plasma Epstein-Barr virus DNA in nasopharyngeal carcinoma.

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Background: About 10-30% of patients with nasopharyngeal carcinoma (NPC) would develop disease recurrence following treatment. The optimal method to screen patients needing early medical intervention remains to be studied. We investigated the potential cut-off values of plasma EBV DNA in identifying patients at high risk of recurrence. **Methods:** From 2012 to 2020, 950 patients with detectable pre-treatment plasma EBV DNA and undetectable EBV DNA within 3 months after treatment were retrospectively reviewed. Survival outcomes of patients with different plasma EBV DNA rebound patterns were analyzed. The diagnostic performance of different cut-off values was evaluated in patients with ≥ 2 positive tests. **Results:** The number of patients with continuous negative plasma EBV DNA, only 1 positive test, and ≥ 2 positive tests during post-treatment surveillance were 747, 89, and 114, respectively. Patients with ≥ 2 positive plasma EBV DNA tests had worse PFS, LRRFS, and DMFS when compared with the ones with negative tests ($P < 0.001$, $P < 0.001$, and $P < 0.001$) and only 1 positive test ($P < 0.001$, $P < 0.001$, and $P < 0.001$). Superior PFS was observed for patients with negative tests compared to patients with only 1 positive test ($P = 0.006$). Of 56 patients with more than 50 copies/ml plasma EBV DNA in both tests, 48 developed recurrences within 4 years. The sensitivity, specificity, PPV, and NPV of this cut-off for recurrence prediction were 35.8%, 99.0%, 85.7%, and 90.4, respectively. Then, the whole population was divided into the low-risk group (≤ 1 positive test), the intermediate-risk group (≥ 2 positive tests and at least one test had < 50 copies/ml) and the high-risk group (≥ 2 positive tests and both tests had ≥ 50 copies/ml). The PFS of the high-risk group was worse than that of the low-risk group ($P < 0.001$) and the intermediate-risk group ($P < 0.001$). The PFS of the high-risk patients with and without capecitabine or tegafur/gimeracil/oteracil before clinical confirmed relapse were 59.3% and 15.0% ($P = 0.004$). **Conclusions:** NPC patients with ≥ 2 positive tests and ≥ 50 copies/ml in both tests during follow-up were at high risk of relapse. Early medical intervention could bring survival benefits to this cohort. Research Sponsor: None.

6031 Poster Session

Duvelisib with docetaxel for patients with anti-PD-1 refractory, recurrent, or metastatic head and neck squamous cell carcinoma.

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Background: Anti-PD-1 therapy alone or in combination with chemotherapy has improved outcomes as first line treatment for patients with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), but therapy options are limited in the second line and beyond. The phosphatidylinositol 3-kinase (PI3K) signaling cascade is frequently dysregulated in HNSCC, and blocking this pathway may lead to modifications in the tumor immune microenvironment and enhanced taxane microtubule inhibitor sensitivity. BERIL-1 investigated buparlisib with paclitaxel in platinum-pretreated R/M HNSCC, but here we conducted a phase 2 trial (NCT05057247) evaluating the dual PI3K (δ/γ isoforms) inhibitor duvelisib in combination with docetaxel in patients with R/M HNSCC who previously received anti-PD-1 therapy. **Methods:** Patients (pts) with R/M HNSCC who had received anti-PD-1 blockade as part of 1-2 prior lines of R/M therapy were eligible regardless of HPV or PI3K tumor mutational status. Pts received duvelisib (25 mg orally twice daily) with docetaxel (75 mg/m^2 IV) every 21-days until progression. The primary endpoint was overall response rate (ORR) (RECIST v1.1), employing a Simon two-stage design (stage 1: enroll 13, <2 in response yields futility; stage 2: enroll 13, $>4/26$ in response rules out 10% ORR [89% power, $\alpha=0.09$] warranting further investigation). Secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), and correlating pre-treatment PD-L1 status and genomics with outcomes. **Results:** Twenty-six pts enrolled from 11/1/21 to 10/10/23. Median age of the cohort was 64 (34-74), comprised of 96% (25/26) men, 69% (18/26) former/current smokers, and 50% (13/26) with HPV+ disease (primary site: 12 oropharynx, 11 oral cavity, 3 larynx/hypopharynx). Best ORR was 19% (5/26) (95%CI: 6.8-40.7%), all 5 were partial responses (median duration: 6.9 months [0.7-15.5]); with 46% (12/26) exhibiting stable disease and 32% (8/26) progression (1 unevaluable). Two pts remain on-treatment at data cutoff; 25% (6/24) came off for toxicity. Grade 3+ treatment-related adverse events were observed in 13/26 (50%), most often elevated liver function tests (6, 23%). No deaths were treatment related. At median follow-up of 7.1 months (0.7-22+), median PFS was 2.8 months (95%CI: 1.9-7.0); 10/26 pts had died. Median OS was 10.2 months (95%CI: 6.7-NA) and 1-year OS was 48%. Median baseline tumor PD-L1 score was 18 (0-100), which did not differ statistically by response (p=1.00; Wilcoxon rank-sum test). Disease in response was observed in 3/8 pts with somatic alterations in *PIK3CA*. **Conclusions:** We report a favorable response rate when combining a PI3K pathway inhibitor with taxane chemotherapy in patients with anti-PD-1 refractory HNSCC. Further evaluation of this strategy is ongoing in the phase 3 BURAN trial which is investigating buparlisib with paclitaxel. Clinical trial information: NCT05057247. Research Sponsor: Secura Bio.

6032 Poster Session

A phase 2 study of trifluridine/tipiracil (FTD/TPI) in recurrent/metastatic nasopharyngeal (r/m NPC) carcinomas with or without prior exposure to fluoropyrimidines.

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Background: Despite effective local treatment, up to 30% of patients with nasopharyngeal carcinoma (NPC) relapse and require systemic treatment. There are limited therapeutic options beyond cisplatin, gemcitabine and immunotherapy and the median survival of r/m disease is about 20 months. Capecitabine, a fluoropyrimidine, has shown some efficacy with a median time to progression of 4.9 months in heavily pretreated r/m NPC but there is a need for alternative treatments. FTD/TPI is an oral drug combination of trifluridine and tipiracil, a thymidine phosphorylase inhibitor preventing rapid degradation of trifluridine, thus increasing its exposure. It has shown activity in colorectal, gastric and breast cancers despite prior fluoropyrimidines. This study explores the efficacy and safety of FTD/TPI in r/m NPC, with or without prior exposure to fluoropyrimidines. **Methods:** In this single-arm phase II trial, patients were administered oral FTD/TPI twice daily at 35mg/m^2 on days 1-5 and 8-12 of a 28-day cycle. The primary endpoint was disease control rate (DCR) at 12 weeks, with secondary endpoints including progression-free survival (PFS), overall response rate (ORR), safety, and tolerability. **Results:** A total of 33 patients were recruited. Median age was 56 years (range: 34-82), most were males (n=27, 82%), with median of 3 (range: 1-12) prior lines of treatment in the metastatic setting. Approximately half (48.5%) received prior fluoropyrimidines. DCR at 12 weeks was 63.6%, with an ORR of 18.2%. DCR was 68.8% and 58.8% in patients with and without prior fluoropyrimidine exposure respectively. Median PFS was 6.5 months (95% CI 2.8-10.2) and overall survival was 13.1 months (95% CI 7.1-19.2). FTD/TPI demonstrated a manageable safety profile, with most common treatment-related adverse events of neutropenia, anaemia, fatigue, nausea and anorexia. 60% of patients required dose modifications, most commonly due to neutropenia, that could be overcome by dose reduction or prolongation to 5-weekly cycles. 1 patient required discontinuation due to anaemia resulting in syncope. **Conclusions:** FTD/TPI is well tolerated, compares favorably to Capecitabine and showed promising anti-tumor activity with meaningful clinical benefit regardless of prior exposure to fluoropyrimidines. This oral chemotherapy offers an attractive choice for patients valuing quality of life, minimizing hospital visits and resource utilization such as chemotherapy infusions. Further investigations in randomized studies are warranted. Clinical trial information: NCT04627961. Research Sponsor: Tai Ho.

6033 Poster Session

Anti-LAG-3 antibody LBL-007 in combination with anti-PD-1 antibody tislelizumab with or without chemotherapy in patients with advanced nasopharyngeal cancer and other malignant tumors: A phase Ib/II dose escalation/expansion study.

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Background: Dual inhibition of PD-1 and LAG-3 is expected to synergistically increase immune response against tumor growth while chemotherapy can enhance the efficacy of immunotherapy through various mechanisms. Here we report the safety and efficacy of LBL-007 (anti-LAG-3) in combination with tislelizumab (anti-PD1) with or without chemotherapy in advanced solid tumors (Phase Ib) and previously untreated patients with advanced nasopharyngeal carcinoma (NPC) (Phase II). **Methods:** In phase Ib, patients with relapsed and refractory advanced solid tumor received LBL-007 (300 or 600 mg) plus tislelizumab (200 mg) (both i.v. Q3W), and in phase II, patients with previously untreated recurrent or metastatic NPC patients received LBL-007 (600 mg) plus tislelizumab (200 mg) in combination with GC chemotherapy [gemcitabine (1000 mg/m^2) and cisplatin (80mg/m^2)] (i.v. Q3W). The primary endpoints were tolerability, safety, and efficacy. **Results:** Updated data with more follow up including duration of response and progression free survival will be available to report at the meeting. As of January 10, 2024, 21 patients (4 NPC, 7 NSCLC, 7 melanoma and 3 others) and 42 NPC patients were enrolled in in phase Ib and phase II respectively. The median follow-up was 13.1 months. During the study, no Dose limiting Toxicity (DLT) was observed, and Recommended Phase 2 Dose (RP2D) was determined to be 600mg Q3W for both chemo and chemo free regimens. In phase II, all grades TRAEs occurred in 39 patients (92.9%), with grade ≥3 TRAE in 24/42 patients (57.1%). The most common TRAEs (≥20%) included white blood cell count decreased, neutrophil count decreased, anaemia, ALT increased, AST increased, platelet count decreased, nausea, hyponatraemia, hypochloraemia, blood creatinine increased, vomiting, and hypothyroidism. Treatment interruption due to TEAEs occurred in 31 (73.8%) patients. 13 patients (31%) experienced SAEs. 1 patient experienced Grade 5 AE due to exacerbation of cachexia unrelated to LBL-007/tislelizumab. The clinical efficacy is shown in the table. **Conclusions:** LBL-007/tislelizumab combination is well-tolerated in patients with advanced malignant tumors. LBL-007/tislelizumab/GC combination showed manageable, no new safety concerns and encouraging antitumor activity in previously untreated and advanced NPC patients. The encouraging efficacy and safety profile may support a pivotal study with LBL-007 in combination with tislelizumab and GC chemotherapy for NPC development in 1L setting. Clinical trial information: NCT05516914. Research Sponsor: None.

Clinical benefit of evaluable patients in phase Ib and phase II.

	Phase Ib (n=20)	Phase II (1st line NPC, n=41)
ORR (CR+PR), %	5(25.0)	37(90.2)
DCR (CR+PR+SD), %	13(65.0)	41(100.0)
3-month PFS rate	-	97.6%

Significance of imaging-detected extranodal extension (iENE) in locally advanced head and neck squamous cell carcinoma (LASCCHN) treated with induction chemotherapy followed by chemoradiotherapy.

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Background: Extranodal extension (ENE) of nodal metastasis is a significant prognostic factor in p16-negative SCCHN and is classified as N3b by the AJCC 8th edition. Therefore, pretreatment determination of ENE has significant clinical implications in SCCHN, and iENE has just recently been proposed. We previously discussed association with pathological ENE and iENE (Jpn J Radiol. 2020;38(6):489-506.). However, the role of iENE in non-surgical sequential therapy remains unclear. **Methods:** We retrospectively reviewed patients with LASCCHN originating from the oropharynx, hypopharynx, and larynx who received enhanced computed tomography (CT), then treated with induction chemotherapy (IC) with paclitaxel, carboplatin, and cetuximab followed by chemoradiotherapy (CRT) from 2013 to 2022 in our hospital. Two radiologists specializing in head and neck cancer blindly annotated the status of iENE in baseline CT images by the previously reported criteria (Oral Oncol. 2022;125:105716.). Multivariate analysis variables for event-free survival (EFS) and overall survival (OS) included the presence or absence of iENE, a response to IC, clinical T-category, performance status, smoking status, etc. **Results:** In the 88 patients, 67 (76.1%) had iENE and 21 (23.9%) did not at baseline. In the former and latter group, stage II/III/IV were 10.4%/26.9%/62.7% and 0%/28.6%/71.4%, HPV-positive were 37.3% and 28.6%, respectively. With the median follow-up of 37.4 months (range: 6.7-108.8), the former had significantly shorter EFS (3-y EFS: 41.9% vs. 75.6%, hazard ratio [HR]; 2.9 (1.2-7.4), *p*-value; 0.02) and OS (3-y OS: 72.8% vs. 100%, HR; Inf (0.01-Inf), *p*-value=0.003). Multivariate analysis identified the presence of iENE (HR for EFS: 2.80, 95%CI: 0.97-8.05, HR for OS: 2.93, 95%CI: 1.01-8.44) and unresponsiveness to IC (HR for EFS: 2.47, 95%CI: 1.31-4.68, HR for OS: 2.87, 95%CI: 1.13-7.26) as mutually independent unfavorable prognostic factors for both EFS and OS. Furthermore, classification based on the two factors could identify the population with a worse prognosis (Table). **Conclusions:** In the sequential therapy of IC followed by CRT, the current study revealed for the first time that subjects with an iENE at baseline, together with an unsatisfactory response to IC would require special attention, such as more intensified post-treatment follow-up as well as additional therapeutic interventions to improve their prognosis. Research Sponsor: None.

Prognosis by the status of imaging-detected extranodal extension (iENE) and response to induction chemotherapy (IC).

iENE at Baseline	Response to IC	n	3-y EFS	p-Value	3-y OS	p-Value
Negative	Positive (CR/PR)	9	89%	0.08	100%	0.01
Negative	Negative (SD/PD)	5	27%		100%	
Positive	Positive (PR/CR)	42	49%		89%	
Positive	Negative (SD/PD)	22	35%		51%	

6035 Poster Session

Early signs of efficacy in patients with anti-PD-1 naïve and anti-PD-1 resistant HNSCC treated with NBTXR3/SBRT in combination with nivolumab or pembrolizumab in the phase I trial Study 1100.

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Background: Overcoming resistance to immune checkpoint inhibitors (ICIs) is a major clinical challenge. NBTXR3, a novel radioenhancer composed of functionalized hafnium oxide nanoparticles administered by a single intratumoral injection, locally amplifies radiotherapy (RT) dose without adding toxicity to surrounding healthy tissue. NBTXR3/RT enhances tumor cell death, tumor antigen release, and effectively expands T-cell repertoire in preclinical models, thus potentially triggering local and systemic immune responses to help improve ICI treatment. NBTXR3 has demonstrated favorable local control in pts with LA-HNSCC. Here we report early outcomes from the ongoing Study 1100 trial in pts with locoregionally recurrent (LRR) or metastatic (M+) head & neck squamous cell carcinoma (HNSCC) who were either naïve to or who continued anti-PD-1 therapy combined with NBTRX3/RT after primary or secondary resistance to anti-PD-1 alone. **Methods:** A phase I dose escalation/expansion trial [NCT03589339] evaluating NBTXR3/Stereotactic Body RT (SBRT) followed by nivolumab or pembrolizumab in 3 cohorts of pts with advanced solid tumors. Pts have H&N lesions either resistant to prior ICI or naïve, or lung, liver, or soft tissue metastases from ICI-resistant advanced solid tumors. SBRT doses were: HN 35 Gy/ 5 fxns; lung 45 Gy/ 5 fxns; liver 45 Gy/ 3 fxns; soft tissue as per investigator. Primary objective is safety of NBTXR3/RT/anti-PD-1 combination and its RP2D. Secondary objectives include efficacy. **Results:** The RP2D was 33%. There were 55 pts with HNSCC treated in the dose escalation/expansion parts. NBTXR3 injection was feasible and safe. There were 11pts (20%) who experienced G≥3 treatment related AEs, of which 3 pts experienced G≥3 AEs (5.5%) related to NBTXR3. Preliminary results of 33 pts, who were evaluable for efficacy: are reported. 6 pts with LRR disease: (2 ICI resistant, 4 naïve);. 27 pts with M+ disease (18 ICI resistant, 9 naïve). In ICI-resistant pts, objective tumor responses were observed in 25% (5/20), and the disease control rate (DCR) was 75% (15/20). In the ICI-naïve population, objective tumor responses were observed in 54% (7/13) of pts and DCR was 77% (10/13). There were observed improvements in injected lesions as well as in some noninjected target lesions. Updated efficacy data including OS in resistant and naïve pts will be presented. **Conclusions:** NBTXR3/RT/anti-PD-1 combination was feasible and well tolerated. Early data suggest the addition of NBTXR3/RT to ICI showed evidence of efficacy, including in patients who failed prior ICI, opening up an opportunity to further explore the ability of NBTXR3/RT to mitigate primary or secondary resistance to ICI. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix.

Clinical, molecular, and immunologic profiling of brain metastases (BM) in head and neck squamous cell carcinoma (HNSCC).

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Background: BM is a rare complication of HNSCC that carries a high rate of morbidity and poor prognosis. Clinical risk factors, molecular characteristics, and the immunogenicity of HNSCC BM are not well defined, leaving a critical knowledge gap in this field. We performed one of the largest multi-institutional analyses summarizing the clinical, molecular, and immunologic profile of 61 cases of BM-HNSCC. **Methods:** We conducted a pooled analysis of the clinical characteristics pertaining to BM-HNSCC from 3 academic institutions (n=24). Next-generation sequencing (NGS) and immune profiling (IP) of primary and BM specimens was conducted on a subset of cases (n=19 and n=16, respectively); there were 3 paired samples for NGS and 0 for IP. Four samples (2 BM and 2 non-BM) were submitted to Phase Genomics, Inc for evaluation of structural variants in BM genomes by proximity ligation sequencing (PLS). These results were complimented by a comparative analysis of genomic alterations in an additional cohort of BM (n=37) and local samples (n=4082) submitted for NGS at Foundation Medicine, Inc (FMI). Statistical comparisons were done using Fisher's exact testing of 2x2 contingency tables with p-values controlled for FDR by the Benjamini-Hochberg procedure. **Results:** Clinical features were as follows: median age at diagnosis 59 years, 75% male, 55% current/former smokers, 75% oropharyngeal primary, and 84% HPV+ or p16+. The most frequently altered genes in BM specimens (62% HPV/p16+) were *ATM* (54%), *KMT2A* (54%), *PTEN* (46%), *RB1* (46%), and *TP53* (46%). BM and non-BM samples demonstrated significant levels of structural rearrangement ranging from 9 to 90 variants by PLS. IP identified lower densities of CD8+, PD1+, PDL1+, and FOXP3+ cells in BMs compared to primary tumors. PDL1 combined positive scores were <1% in 12/13 unpaired samples (92%; 10 BM and 2 primary). The FMI BM-HNSCC cohort (51% HPV+) identified *CDKN2A* (40.5%), *TP53* (37.8%), and *PIK3CA* (27.0%) as the most frequently altered genes. Enrichment analysis of the FMI cohort showed MAP2K2 alterations significantly enriched in BM (11.8% vs 6.4%, P=0.005) and TSC1 alterations significantly enriched in the local site (67.3% vs 37.8%, P=0.008). HPV+ was also significantly enriched in the BM cohort (51.25% vs 26.11%, P=0.001). Overall survival from BM diagnosis was 6m (range 0-27m). **Conclusions:** HNSCC patients with BM have higher-than-expected proportions of oropharyngeal primary site and HPV/p16-positivity. The most frequent molecular alterations in BM samples are also commonly found in non-BM HNSCC, including targetable *PIK3CA* alterations. *MAP2K2* alterations were significantly enriched in BM compared to non-BM samples, which warrants further investigation. BM samples also tended to have lower markers of immunogenicity. This latter finding could have important clinical implications when considering immunotherapy or immune-modulating drugs. Research Sponsor: None.

6037 Poster Session

Trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing head and neck tumors: Outcomes from DESTINY-PanTumor02 (DP-02).

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Background: In DP-02, T-DXd demonstrated an objective response rate (ORR) by investigator (INV) of 37.1% (95% CI 31.3, 43.2) and clinically meaningful survival outcomes in 267 pretreated pts with HER2-expressing tumors. In this post-hoc analysis, we report outcomes and characterize those with an objective response (OR) in a subset of pts with head and neck cancers (previously included in the 'other tumor' cohort), most of which were salivary gland tumors. **Methods:** This open-label, Phase 2 study (NCT04482309) evaluated T-DXd (5.4 mg/kg Q3W) in pts with HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing) locally advanced/metastatic disease after ≥1 systemic treatment or without treatment options. The primary endpoint was confirmed ORR by INV. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and safety. Exploratory endpoints included efficacy outcomes by HER2 expression. **Results:** At data cutoff (June 2023), 24 pts with head and neck tumors (n=19 salivary gland, n=3 squamous cell carcinoma [SCC], n=1 adenoid cystic carcinoma, n=1 lacrimal gland) had received treatment (median [m] follow up: 20.8 months [range: 4.7–31.6]). Of these pts, 15 (62.5%) had received ≥2 prior treatment regimens. 10/24 pts (41.7%; 95% CI 22.1, 63.4; n=8 salivary gland, n=1 SCC, n=1 lacrimal gland) had a confirmed OR by INV; 9 responders had received prior radiation therapy, and 4 had known PD-L1 immune cell status ≥1%. The Table shows efficacy outcomes in all pts and by HER2 expression (central testing). Grade (G) ≥3 drug-related adverse events occurred in 10/24 (41.7%) pts. Adjudicated drug-related interstitial lung disease / pneumonitis occurred in 3/24 (12.5%) pts (n=1 G1; n=1 G2; n=1 G5). **Conclusions:** T-DXd showed clinically meaningful benefit in pretreated pts with head and neck tumors. Responses were observed across HER2 expression levels. Safety was consistent with the known profile. These data support T-DXd as a potential treatment for pretreated pts with HER2-expressing head and neck tumors. Clinical trial information: NCT04482309. Research Sponsor: This study is sponsored by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

	All pts	HER2 IHC 3+	HER2 IHC 2+	HER2 IHC 0	HER2 unknown
n	24	7	6	4	7
Pts with OR, n	10	4	1	1	4
ORR, % (95% CI)	41.7 (22.1, 63.4)	57.1 (18.4, 90.1)	16.7 (0.4, 64.1)	25.0 (0.6, 80.6)	57.1 (18.4, 90.1)
mDOR, months (95% CI)*	22.1 (2.8, NE)	22.1 (4.1, NE)	2.8	NR	NR (10.9, NE)
mPFS, months (95% CI)	12.4 (8.7, 23.4)	23.4 (9.7, NE)	7.1 (2.9, NE)	6.5 (4.2, NE)	12.5 (8.8, NE)
DCR at 12 weeks, % (95% CI)	87.5 (67.6, 97.3)	100 (59.0, 100)	66.7 (22.3, 95.7)	75.0 (19.4, 99.4)	100 (59.0, 100)

By INV. Local HER2 status confirmed by central testing; upon reanalysis, some pts were IHC 0/unknown.
*Responders only; CIs omitted where n=1. NE, not evaluable; NR, not reached.

6038 Poster Session

A phase 1 study of fianlimab (anti–LAG-3) in combination with cemiplimab (anti–PD-1) in patients with advanced HNSCC.

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Background: Concurrent blockade of LAG-3 may enhance efficacy of anti–PD-1 therapies. We present safety and clinical activity data from a Phase 1 study in patients (pts) with head and neck squamous cell carcinomas (HNSCC) treated with anti–LAG-3 (fianlimab) + anti–PD-1 (cemiplimab). **Methods:** Two expansion cohorts of adult pts with recurrent and/or metastatic HNSCC with no curative options who were anti–PD-1/PD-L1-naïve (cohort 11) or anti–PD-1/L1-experienced with most recent dose within 3 months (mos) prior to screening (cohort 12) were enrolled. All pts received fianlimab 1600 mg + cemiplimab 350 mg intravenously every 3 weeks (wks) for up to 24 mos. Tumor measurements were performed every 6 wks for 24 wks, then every 9 wks. **Results:** 15 pts each in cohort 11 and 12 (total N=30; median age: 69 years) were enrolled and treated with fianlimab + cemiplimab as of 04 Oct 2023 data cutoff.For cohorts 11 and 12 respectively, 80% and 87% of pts were male, and 53% and 80% were White. All pts had prior cancer-related systemic therapy. 33% (5/15) and 87% (13/15) of pts in cohorts 11 and 12 had ≥2 lines of prior therapies, respectively. For cohorts 11 and 12, median treatment duration was 12 wks (mean: 41 wks) and 13 wks (mean: 24 wks), and median follow-up was 12 mos and 10 mos, respectively. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 47% of pts each in cohorts 11 and 12. Serious TEAEs occurred in 13% and 20% of pts in cohorts 11 and 12, respectively. Treatment-related TEAEs (TRAEs) were reported in 67% of pts in cohorts 11 and 53% of pts in cohort 12. The most common TRAEs (any grade) were hypothyroidism (33%) in cohort 11; and fatigue (20%) and pneumonitis (20%) in cohort 12. Grade ≥3 TRAEs occurred in 7% of pts in cohorts 11 and 13% of pts in cohorts 12. Treatment-related immune-related AEs were reported in 47% and 40% of pts in cohorts 11 and 12, respectively. Treatment was discontinued due to any TEAE in 2 pts in cohort 12. In cohort 12, there was one death due to grade 5 respiratory failure attributable to aspiration pneumonia. RECIST 1.1-based investigator-assessed objective response rate (ORR) was 33% (5 partial responses [PRs]) in cohort 11 and 7% (1 PR) in cohort 12. The disease control rate (DCR) was 47% and 67% in cohorts 11 and 12, respectively. Kaplan–Meier estimation of median progression-free survival was 2 mos (95% CI, 1–14) in cohort 11 and 4 mos (95% CI, 1–7) in cohort 12 pts. Duration of responses were 17, 10, 20, 22, and 20 mos in 5 responders in cohort 11; and 32 mos in 1 responder in cohort 12. Estimated event-free probability at 12 month was 33% (95% CI, 12–56) in cohort 11 and 16% (95% CI, 3–40) in cohort 12 pts. **Conclusions:** Fianlimab + cemiplimab in pts with HNSCC showed signs of clinical activity with durable responses among pts with anti–PD-1/PD-L1-naïve (cohort 11) and anti–PD-1/L1-experienced (cohort 12), with an acceptable safety profile which warrants further investigation. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

6039 Poster Session

Four-year overall survival follow-up and dynamic EBV titer analysis of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (r/m NPC).

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Background: In October 2023, the US FDA approved toripalimab in combination with Gemcitabine-Cisplatin (GP) as first-line treatment for recurrent or metastatic (r/m) NPC based on the results of JUPITER-02 study (NCT03581786). Here we report the results of four-year overall survival (OS) follow-up and dynamic EBV DNA copy number and its correlation with clinical outcome. **Methods:** Patients with r/m NPC (n=289) were randomized (1:1) to receive toripalimab 240 mg (n=146) or placebo (n=143) in combination with GP once every 3 weeks (Q3W) for up to 6 cycles, followed by monotherapy with toripalimab or placebo until disease progression, intolerable toxicity, or completion of 2 years of treatment. Stratification factors were ECOG performance score (0 *vs.* 1) and extent of disease (recurrent *vs.*primary metastatic). The primary endpoint was progression free survival by an independent review committee. Secondary endpoints included OS and safety. Exploratory endpoints included dynamic blood EBV DNA copy number and its correlation with clinical efficacy. **Results:** By the cutoff date of January 9, 2024, 50 months after the last patient was enrolled, 150 deaths were recorded. Compared with the results from the final OS analysis, consistent survival improvement was observed for toripalimab over placebo: HR=0.61 (95% CI: 0.44-0.85), nominal p=0.0027. The median OS was not yet reached in the toripalimab arm and was 33.7 months in the placebo arm. The 5-year OS rates were 52.0% in the toripalimab arm, and 33.9% in the placebo arm. Among patients with detectable baseline EBV DNA copy number and at least one EBV result after study treatment, significantly more patients from the toripalimab arm had EBV DNA copy number decreased to undetectable level than those in the placebo arm, 96.3% vs. 84.5%, p= 0.004. In addition, significantly less patients experienced EBV DNA copy number rebound in the toripalimab arm than in the placebo arm after the initial reduction, 36.5% vs, 57.4%, p=0.002. The median time from the lowest EBV DNA copy number to the rebound was 20.5 vs. 6.0 months in the toripalimab and placebo arms respectively. The rebound also preceded investigator-assessed disease progression by a median of 1.9 months in the toripalimab arm. **Conclusions:** The combination of toripalimab and chemotherapy showed long term survival benefit than chemotherapy alone with a 5-year OS rate at 52%. EBV DNA copy number might be used to monitor clinical response and predict disease progression. Clinical trial information: NCT03581786. Research Sponsor: None.

Long-term outcomes of anlotinib and penpulimab combined with chemotherapy in the treatment of patients with metastatic nasopharyngeal carcinoma that failed definitive platinum-based chemoradiotherapy.

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Background: The median progression-free survival (mPFS) of anti-PD-1 monoclonal antibody (mAb) plus gemcitabine (G) and cisplatin (C) in the first-line treatment of metastatic nasopharyngeal carcinoma (M NPC) is still limited in about 10 ~12 months. The tolerance is also unfavorable, especially for patients (pts) who had undergone platinum-based chemoradiotherapy (CRT) previously. We performed a phase 2 study to explore the potency of replacing cisplatin with anloinib (A), a multi-kinase inhibitor in combined with penpulimab (P), a novel anti-PD-1 mAb as the first-line treatment of M NPC for pts with prior explosure of platinum-based CRT. Here we report the updated long term outcomes of this study. **Methods:** This is a prospective, three cohorts, single-arm study. Eligible pts were aged 18 ~ 75 years old, diagnosed with NPC and developed metastasis after platinum-based CRT. Pts who were diagnosed as having M NPC at the first visit or experienced treatment failure within 6 months after definitive CRT or adjuvant therapy were excluded. Pts were randomized to receive G + A + P (cohort GAP), G + C + A + P (cohort GCAP) or G+C+P (cohort GCP). Gemcitabine (1000mg/m^2, d1, d8) and cisplatin (80mg/m^2, d1) were given intravenously for 4 to 6 cycles, 3 weeks per cycle. Penpulimab (200mg, d1) and anlotinib (10mg, qd, d1-14) were given intravenously and orally respectively until disease progression, or unacceptable toxicities. The primary endpoint was objective response rate (ORR). **Results:** 21 pts were randomized to three cohorts in lead-in phase while only cohort GAP was selected into expansion phase to enrolled another 7 pts. Finally, totally 28 pts were enrolled and received study treatment. The data cutoff date was December 1, 2023. The median follow-up was 20.2 month (95% CI: 17.0, 23.4). The results were summered in the table below. In cohort GAP, the confirmed ORR was 92.3% (95% CI: 64.0%, 99.8%) and the mPFS was still not reached (95% CI: NE, NE). The most common Grade 3 treatment-related adverse event (TRAE) was neutrophil count decreased (3 pts). Only one patient occurred Grade 4 TRAE (neutrophil count decreased) and no treatment-related death was observed. **Conclusions:** The long term outcomes of this phase 2 study preliminarily disclosed the advantage of the treatment regimen including gemcitabine, anlotinib and penpulimab as the first-line treatment of M NPC, especially for pts who had exposed to platinum-based chemotherapy. The further study with more sample size is warranted. Clinical trial information: NCT04736810. Research Sponsor: None.

Cohort	GAP	GCAP	GCP
No. of Pts enrolled	14	8	6
No. of pts received efficacy evaluation	13	7	6
mPFS, month (95% CI)	NR (NE, NE)	4.17 (0.0, 22.4)	18.6 (NE, NE)
CR, n (%)	1 (7.7)	1 (14.3)	2 (33.3)
Confirmed ORR, % (95% CI)	92.3 (64.0, 99.8)	71.4 (29.0, 96.3)	83.3 (35.9, 99.6)
≥ G3 TRAE, n (%)	11 (78.6)	7 (87.5)	6 (100)
G4 TRAE, n (%)	1 (7.1)	2 (25.0)	2 (33.3)

6041 Poster Session

A phase II study of nivolumab in patients with recurrent or metastatic carcinosarcomas.

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Background: We aimed to determine the activity of anti-PD-1 inhibitor, nivolumab in metastatic and/or recurrent carcinosarcoma. **Methods:** In this phase 2 trial, eligible patients had histologically confirmed metastatic and/or recurrent carcinosarcoma, measurable disease, 1-3 prior chemotherapy, and adequate renal/hepatic/hematologic function. In this single arm phase 2 trial, treatment consisted of nivolumab 3 mg/kg every 2 weeks. Primary outcome was progression free rate (PFR) at 6 months and secondary outcomes included overall response rate, progression-free survival (PFS), overall survival, and safety. **Results:** Between July 2020 and Nov 2023, 28 patients enrolled and received trial treatment. As of the time of data cut-off (Feb 1, 2024), 4 remains on treatment. Of the 28 patients evaluable, 4 (14.3%) achieved confirmed partial response, and 9 (32.1%) had stable disease, yielding and disease control rate of 46.4%. The median PFS was 2.6 months. The pre-specified primary endpoint was met with 6-months PFR of 30.8%. The common-treatment related adverse events included urticaria (5 [17.9%]), dyspepsia (4 [14.3%]), elevated aspartate aminotransferase (3 [10.7%]), and anemia (3 [10.7%]). The genomic analysis will be available at the meeting. **Conclusions:** Nivolumab demonstrated promising efficacy with favourable toxicity profile in metastatic/recurrent carcinosarcoma. Clinical trial information: NCT05224999. Research Sponsor: None.

6042 Poster Session

Efficacy from the phase 1 study of FID-007, a novel nanoparticle paclitaxel formulation, in patients with head and neck squamous cell carcinoma.

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Background: Patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (HNSCC) have limited treatment options after progression on first-line immunotherapy with or without platinum-based chemotherapy. Taxanes in this setting have historically demonstrated response rates around 14-27%. FID-007 (FID) consists of paclitaxel encapsulated in a polyethyloxazoline (PEOX) polymer excipient designed to enhance PK, biodistribution, and tolerability. This allows the drug to remain in solution until it can enter a cancer cell and preferentially delivers paclitaxel to the tumor through the leaky hyperpermeable vasculature. Preclinically, FID was more effective at lower or comparable taxane doses, including nab-paclitaxel. In the phase I study of FID, we determined 125 mg/m2 as the recommended phase 2 dose. Here we present updated safety and efficacy data with emphasis on pts with HNSCC. **Methods:** The study evaluated the safety, PK, and preliminary efficacy of FID in pts with advanced solid tumors. The primary objective is to determine the MTD and RP2D. Pts received FID in doses between 15mg/m^2 and 160mg/m^2 using a 3+3 dose escalation. FID was given IV on Days 1, 8, and 15 of a 28-day cycle. Eligibility included ECOG 0-2, adequate organ function, and $<$ 3 prior lines of cytotoxic therapy. **Results:** 46 patients were enrolled, of which 9 had HNSCC (2 nasopharynx, 2 sinonasal, 3 oropharynx, 1 oral cavity, and 1 occult primary). Median age (range) was 60 (53-75). ECOG PS was 1 in all HNSCC pts. Median number of prior therapies was 3 (1-5) and all had received prior immune checkpoint inhibitor. All grade treatment related adverse events (TRAEs) in $\geq$ 25% of pts included rash (72%), alopecia (52%), leukopenia (46%), pruritus (43%), neutropenia (41%), anemia (37%), fatigue (37%), nausea (28%), and anorexia (28%). Grade 3/4 TRAEs occurring in $>$1 pt were maculopapular rash (35%), neutropenia (20%), leukopenia (20%), anemia (17%), lymphopenia (7%), and febrile neutropenia (4%). No pts experienced $>$ grade 2 peripheral sensory neuropathy; 20% experienced grade 1-2. Across all solid tumors, the overall response rate (ORR) was 17%. In patients with HNSCC, 5 (56%) had a partial response, 2 (22%) had stable disease, and 2 (22%) had PD. Three out of 5 HNSCC patients previously treated with a taxane achieved a partial response. Median duration of treatment was 4 months (1-15). **Conclusions:** FID demonstrates preliminary evidence of anti-tumor activity in heavily pre-treated HNSCC pts across different primary tumor sites, with an ORR 56%, including those with prior taxane exposure. A phase 2 study of FID with cetuximab in pts with HNSCC is planned to begin enrollment in 2024. Clinical trial information: NCT03537690. Research Sponsor: Fulgent Pharma.

Associations of ctDNA clearance and pathological response after neoadjuvant treatment in patients with locally advanced oral cancer.

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Background: Neoadjuvant treatment (NAT) has improved clinical outcomes in some patients with locally advanced oral squamous cell carcinoma (LAOSCC). Effective biomarkers assessing the treatment response is still lacking. Previous studies have posed the potential of circulating tumor DNA (ctDNA) in monitoring treatment response, but the underlying mechanisms behind non-shedding in tumors remain unclear. **Methods:** 29 LAOSCC patients received NAT followed by surgery were enrolled. Seven (24.1%), 9 (31%), and 13 (44.8%) patients received NAT of apatinib+camrelizumab, TPF chemoagents, and toripalimab+paclitaxel+cisplatin, respectively. Tumor tissues before NAT underwent whole exome sequencing and whole transcriptome resequencing. Blood samples at pre-NAT (T0), mid-NAT (T1), before surgery (T2) and after surgery (T3) were analyzed using a tumor-informed, personalized NGS assay. Multi-omics analysis, including ctDNA status, was performed with patients' clinical features and outcomes. **Results:** Among the 29 patients received NAT, the MPR rate was 55.2% (16/29), and the pCR rate was 27.6% (8/29). At baseline(T0), ctDNA was detectable in 25/29 (86.2%) patients, which decreased over time (T1: 77.8%; T2: 51.7%; T3: 6.9%). Persistent ctDNA at T2 indicates a higher rate of residual disease after NAT (100% non-pCR) compared to ctDNA-negative patients (42.8% non-pCR; p = 0.0047). All patients achieving pCR at T2 were ctDNA-negative (n=8, 100%) including 2 non-shedders. The PPV and NPV for predicting pCR by ctDNA clearance at T2 were 57.1% (8/14) and 100% (15/15), respectively. ARSF, CFAP47, or HAUS8 mutations at baseline were associated with significantly higher pCR rates ($p < 0.05$). Four non-shedders with undetectable ctDNA at T0 were significantly enriched in patients with negative lymph nodes, lower clinical T stage, and high CPS score. The non-shedders had significantly lower tumor mutational burden (TMB), higher stromal score and cancer-associated fibroblast (CAF) ($p < 0.05$). Spatial transcriptome analysis further supports that MHC-II pathway-related genes were significantly up-regulated in the non-shedders. The enhancing communication intensity between CAFs, endothelial cells and T cells might provide an anti-cancer immune microenvironment for non-shedders. **Conclusions:** Our results indicate that the clearance of ctDNA clearance at T2 was associated with an improved pCR rate. Furthermore, our findings shed light on the factors that prevent ctDNA release from oral squamous cell carcinoma. Research Sponsor: None.

Baseline patient demographic and clinical characteristics.

Time point	ctDNA positive rate	Median ctDNA fraction	pCR		Non-pCR	
			PPV	NPV	PPV	NPV
T0	**86.2%**	**6.2E-04**	**50.0%** (**2/4**)	**76.0%** (**19/25**)	**76%** (**19/25**)	**50%** (**2/4**)
T1	77.8%	7.8E-05	50.0% (3/6)	76.2% (16/21)	76.2% (16/21)	50% (3/6)
T2	51.7%	1.5E-05	**57.1%** (**8/14**)	**100%** (**15/15**)	**100%** (**15/15**)	**57.1%** (**8/14**)

6044 Poster Session

An open-label, single-center phase II trial of cadonilimab (an anti-PD-1/CTLA-4 bispecific antibody) in combination with platinum-based dual-drug neoadjuvant chemotherapy for locally advanced, resectable head and neck squamous cell carcinoma.

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Background: Consensus on neoadjuvant treatment strategies for resectable head and neck squamous cell carcinoma (HNSCC) is not proposed currently. Preclinical and clinical findings suggested that PD-1/CTLA-4 bispecific antibodies may have synergistic anti-tumor activity. This study aimed to explore the safety and activity of cadonilimab in combination with platinum-based dual-drug neoadjuvant chemotherapy in locally advanced, resectable HNSCC. **Methods:** In this open-label phase II trial, eligible patients with untreated locally advanced, resectable HNSCC (T2N2-3M0、T3-4N0-3M0; stage III-IV, AJCC 8th Edition) were enrolled to receive cadonilimab (10 mg/kg) and platinum-based dual-drug [docetaxel (75 mg/m2) plus cisplatin (60 mg/m2)] on day 1 of each 21-day cycle for three cycles, followed by surgery and postoperative adjuvant therapy. The primary endpoint was objective response rate (ORR) per RECIST1.1. Secondary endpoints included pathologic complete response (pCR), safety, disease-free survival (DFS), and overall survival (OS). **Results:** Between July 2023 and December 2023, 24 patients were enrolled (median age, 55 years [range 34–69]; 21 men [87.5%]), tumors were located in the oral cavity (10/24, 41.7%), hypopharynx (8/24, 33.3%) and larynx (6/24, 25.0%), 20 (83.3%) patients were clinical T3/4 while 10 patients (41.7%) ≥N2 . After completion of neoadjuvant therapy, the ORR was 87.5% (21/24). Of the 24 patients, 12 (50.0%) patients reached pCR. Treatment-related adverse events (TRAEs) occurred in 14 (58.3%) patients. Grade 3-4 TRAEs were reported in 4 (16.7%) patients, including rash (12.5%), pruritus (12.5%) and Guillain-Barre syndrome (4.2%). DFS and OS data were not yet mature as of the cutoff date (January 1,2024). **Conclusions:** Cadonilimab plus platinum-based dual-drug neoadjuvant chemotherapy achieved favorable ORR and pCR with manageable toxicities in patients with HNSCC. Follow-up is still underway to obtain long-term survival data. Clinical trial information: NCT06023875. Research Sponsor: None.

6045 Poster Session

Tislelizumab plus neoadjuvant chemotherapy and concurrent chemoradiotherapy versus neoadjuvant chemotherapy and concurrent chemoradiotherapy in local advanced nasopharyngeal carcinoma.

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Background: Given the recent successes of immunotherapy in local advanced nasopharyngeal carcinoma (LA-NPC), maybe it is promising to achieve better response and improve the survival of LA-NPC if immunotherapy plus neoadjuvant and concurrent chemoradiotherapy (CCRT). Therefore, we retrospectively analysed the safety and efficacy of tislelizumab plus neoadjuvant chemotherapy and CCRT and neoadjuvant chemotherapy followed CCRT in the treatment of LA-NPC. **Methods:** A total of 90 patients with stage III-IVa NPC were enrolled between January 2020 and March 2021 at Affiliate Hospital of Guangdong Medical University. 43 patients were treated with tislelizumab plus TP (nab-paclitaxel 260mg/m^2, cisplatin 80mg/m^2, Q3W, 3 cycles) regimen followed tislelizumab plus CCRT as the combination therapy group (CG) and 47 patients were treated with TP regimen followed CCRT as the observation group (OG). **Results:** As of January 30th, 2024, the median follow-up time is 37.5 months. The median age was 42 years (range: 16–75 years). A total of 37 patients had stage III cancer and 53 had stage IVa, with 43 and 47 patients in OG and CG, respectively. The male–female ratio in the entire cohort was approximately 2.15:1. All reported parameters were balanced between the two groups with no statistical differences. The complete response rate (CRR) in CG after neoadjuvant therapy improved significantly (37.2% in CG vs 12.8% in OG). The ORR was 88.4% in CG and 70.2% in OG, respectively. The 3-year PFS was 93.75% in CG and 80% in OG. The incidence of acute treatment related adverse events in grades 3 or 4 was 70.2% and 65.6%, respectively. The most common grade 3-4 immune-related adverse events were hypothyroidism (7.0%) and hepatotoxicity (4.7%). No patients in CG had disease progression during treatment. **Conclusions:** Compared with regular treatment, tislelizumab plus neoadjuvant chemotherapy and concurrent chemoradiotherapy was feasible and well tolerated in LA-NPC patients. This trial is supportive of further prospective trials in LA-NPC. Research Sponsor: Zhanjiang Science and Technology Development; 2020A01023, 2021A05084; Affiliated Hospital of Guangdong Medical University; LCYJ2019A001, LCYJ2021A002.

6046 Poster Session

Characterizing the impact of sarcopenia on treatment response and survival in previously treated recurrent or metastatic nasopharyngeal carcinoma: Insights from a secondary analysis of the KL-A167 randomized trial.

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Background: The relationship between sarcopenia and adverse outcomes among patients with recurrent and metastatic nasopharyngeal carcinoma (R/M NPC) undergoing immunotherapy remains underexplored. This secondary analysis of the KL-A167 clinical trial data aims to elucidate the impact of sarcopenia on treatment efficacy and prognosis in this cohort, while also identifying potential mediating hematological biomarkers. **Methods:** A cohort of 148 patients enrolled in the KL-A167 clinical trial was analyzed. Logistic and Cox regression models were applied to assess the association between sarcopenia and treatment response, overall survival (OS), and progression-free survival (PFS), with adjustment for clinical prognostic factors. Counterfactual causal mediation analysis was conducted to identify hematological biomarkers potentially mediating the relationship between sarcopenia and prognosis in R/M NPC patients. **Results:** The presence of sarcopenia was significantly associated with reduced objective response rate (ORR: OR = 0.25, 95% CI = 0.08–0.81, p = 0.020) and disease control rate (DCR: OR = 0.23, 95% CI = 0.07–0.70, p = 0.010). Furthermore, sarcopenia was linked to inferior OS (HR = 2.07, 95% CI = 1.12–3.81, p = 0.020) and PFS (HR = 2.59, 95% CI = 1.48–4.54, p = 0.001). Notably, sarcopenia was characterized by elevated levels of neutrophil count, fibrinogen, and white blood cell count, alongside decreased creatine kinase levels. Fibrinogen emerged as the sole elevated biomarker significantly associated with both OS and PFS. Causal mediation analysis indicated that fibrinogen accounted for 23.5% of the association between sarcopenia and OS and 15.7% of PFS. **Conclusions:** Sarcopenia significantly correlates with poor treatment response and survival outcomes in patients with R/M NPC receiving immunotherapy. Targeting fibrinogen may offer a novel strategy to mitigate the negative impact of sarcopenia on patient survival. Research Sponsor: None.

6047 Poster Session

Validation of HLA presented tumor-exclusive peptides in an independent cohort of head and neck squamous cell carcinoma.

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Background: Response rates to anti-PD1 antibodies in head and neck squamous cell carcinoma (HNSCC) range from 13-20% in recurrent / metastatic disease and up to 50% in locoregionally advanced disease. Vaccines composed of tumor-exclusive antigens may increase response rates to immunotherapy. We have previously identified HLA-presented tumor-exclusive peptides (TEP) in a cohort of 40 oropharyngeal HNSCC (UL dataset) and defined a warehouse of HLA allotype specific TEP (EP2023/071063, patent pending) for semipersonalized vaccine composition for 15 HLA allotypes. **Methods:** The HLA-bound immunopeptidome of a validation cohort of 40 HNSCC from Tübingen University was analyzed by tandem mass spectrometry (TÜ dataset). Data were processed as previously described to identify TEP. The TÜ dataset was queried for TEP from the previously defined warehouse containing 48 TEP for the respective 15 HLA allotypes in a cohort of 40 oropharyngeal HNSCC (UL dataset) patient samles. Coverage was defined as the fraction of patients presenting at least one of the TEP for a certain HLA allotype. **Results:** Among all 80 patients, 75 had at least one of the 15 HLA allotypes (36 in the TÜ cohort and 39 in the UL cohort). Of the 48 TEP, 28 TEP for 11/15 HLA allotypes were found in the TÜ validation cohort. The best coverages with the warehouse TEP were found for the following four HLA allotypes: HLA-A*01:01 (TÜ: 91%; UL: 79%), A*02:01 (TÜ: 81%; UL: 52%), B*40:01 (TÜ: 63%; UL: 100%) and A*24:02 (TÜ: 60%; 44%.). Based on a semipersonalized TEP selection by HLA allotype, 27/40 patients in the TÜ cohort presented at least one of the TEP selected (range: 0-10), whereas 28/40 patients in the UL cohort presented at least one of the TEP (range: 0-7). Thus, the total cohort coverage based on a semipersonalized peptide selection was 55/80 patients (68.8%). **Conclusions:** We validated previously identified TEP from oropharyngeal HNSCC for frequently occurring HLA allotypes in an independent, equally sized cohort of HNSCC patients. A semipersonalized vaccine composition strategy using a warehouse / off-the-shelve approach for immunotherapy trials seems feasible. Research Sponsor: Deutsche Forschungsgemeinschaft; 288342734; Deutsche Forschungsgemeinschaft; 451445144; Ulm University.

Interrogating the tumor microenvironment (TME) in patients (pts) with head and neck mucosal squamous cell carcinoma (HNmSCC) treated with programmed death-1 (PD-1) inhibitors.

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Background: Survival in recurrent/metastatic HNmSCC remain poor. PD-1 inhibitors have become standard of care, demonstrating improved overall survival and toxicity when compared to chemotherapy and targeted therapy. Biomarkers such as PD-Ligand(L)1 combined proportion score (CPS) remain rudimentary, with CPS >20 showing a response rate of only 23% to pembrolizumab (KEYNOTE-048). We used high-dimensional imaging mass cytometry (IMC) to explore predictive biomarkers in HNmSCC pts receiving PD-1 inhibitor-based therapy. **Methods:** We retrospectively analysed 27 formalin-fixed paraffin embedded tissue samples from 24 pts prior to receiving PD-1 inhibitor-based therapy between May 2016 – April 2021. Clinicopathological characteristics including PD-L1, p16 status, prior treatment and survival data were collected. Pts were classified into responders (RES, Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 complete response (CR) or partial response (PR), stable disease (SD) >6 months (mths)) and non-responders (non-RES, RECIST SD <6 mths or disease progression (PD)). An antibody panel (n = 40) was created to interrogate specific components of interest within the TME and was analysed by IMC using the Hyperion$_{TM}$ Imaging System. **Results:** Of the 24 patients, 16/24 were male and median age 57.6 year. 8 pts were RES (RECIST CR, n = 1; PR, n = 3; SD > 6 mths, n = 4) and 14 pts were non-RES (RECIST SD < 6 mths, n = 1; PD, n = 11; clinical PD, n = 4). Four patients underwent rapid clinical disease progression prior to progress imaging and were categorised as non-RES. At time of data cut off on January 2024, and 23/24 pts had progressed on treatment. The cellular landscape within the TME was similar, irrespective of the location of the primary and p16 status. However, distinct immune profiles were observed between RES vs non-RES: RES showed higher infiltrates of CD4+ T cells, B cells, PD-1+ CD8+ T cells ($P < 0.05$) and both central memory and effector memory T cell subsets ($p < 0.01$). In contrast, non-RES showed high frequencies of CD44+ NK cells. Key cell interactions within the TME identified proliferating malignant squamous cells closely interacting with CD8+ T cells, CD4+ Tregs and endothelial cell in RES but not interacting in non-RES. Further spatial regional analysis identified a distinct tissue architecture with hallmarks of Tertiary Lymphoid-like Structures (TLS), present in higher proportions in RES. RES pts with TLS proportions >20% (n = 3) had a progression free survival of 80.3 mths, 26.8 mths and NE (unrelated death at 15.6 mths). **Conclusions:** The findings of this study identify mechanisms of PD-1 inhibitor response and resistance in HNmSCC pts, providing a unique opportunity to guide combination strategies and improve outcome. Research Sponsor: Cancer Institute NSW Translational Program Grant; NHMRC.

6049 Poster Session

A phase II trial of reirradiation combined with pembrolizumab in patients with locoregional inoperable recurrence or second primary squamous cell carcinoma of the head and neck (HNSCC).

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Background: Better outcomes are needed for patients (pts) with locoregional inoperable recurrence or second primary HNSCC after prior radiation therapy. **Methods:** We conducted a phase II single arm trial of hyperfractionated reirradiation (ReRT, 1.2 Gy BID for total 60Gy to gross disease + margin without elective nodal radiation) plus pembrolizumab (P) (200mg q3 weeks starting day 1 of ReRT). P was continued until confirmed CR or if no CR, until disease progression or up to 24 months. All pts underwent a 3 month post ReRT PET/CT and subsequently CT neck/chest after every 3rd cycle of P. Pts included had: Locoregional recurrence or second primary HNSCC (excluding skin or salivary), were unresectable or not willing to undergo resection, one RT course completed at least 6 months prior, with >50% tumor volume treated at doses >45Gy, ECOG PS 0-1, a target lesion by RECIST, no distant metastasis, and no prior anti-PD-1/PD-L1. Primary endpoint was PFS, and the hypothesis was that the median PFS would increase from the historical control of 8 months (mo) to 12 mo, α=0.05, power 78%, n=48. Secondary endpoints: ORR by RECIST, OS, toxicity, QOL (EORTC). The Kaplan-Meier method was used to estimate PFS and OS. **Results:** In the 48 evaluable pts, median age was 65.5 (range 44-79), 62.5% male. Primary site: hypopharynx (8.3%), larynx (6.3%), nasopharynx (10.4%), oral cavity (43.7%), oropharynx (31.3%, one HPV+ pt). Median doses of P was 8, median RT dose was 60 Gy and 20.8% received proton RT, remainder IMRT. Median follow up was 49.1 months. The median PFS was 8.3 mo (95%CI 5.5-10.3), and median OS was 13.8 mo (95% CI 9.5-21.8). 1 and 3-year PFS were 28.9% and 22.3% respectively, and for OS 54.2% and 25.7%, respectively. 42 pts were evaluable for response and the ORR was 54.8% (33.3% CR, 21.4%PR), 21.4% SD, 23.8% PD. In an exploratory analysis, the median PFS was 13.8 mo (95% CI 9.1-NR) and the median OS was 57.8 mo (19.6-NR) in patients that had a response (CR/PR, n=23), with a 1 and 3-year PFS of 51.8% and 42.4%, respectively, and for OS 78.3% and 51.7%, respectively. All patients had at least one treatment related AE (TRAE), defined as possibly, probable, or definitely related to treatment. 39% of pts had a G3 TRAE and the most common ones were: aspiration, dehydration, anemia, dysphagia, dyspnea. 4 patients had a G5 TRAE (found down deceased, epistaxis, aspiration pneumonia, iRAE pneumonitis). **Conclusions:** Our prospective trial uniquely evaluated ReRT plus pembrolizumab in patients with locoregional recurrence/second primary HNSCC that did not undergo salvage surgery. The primary endpoint of PFS was not improved compared to historical control. PD-L1 biomarker analysis is ongoing and will be reported subsequently. Clinical trial information: NCT02289209. Research Sponsor: Merck.

6050 Poster Session

Real world effectiveness and safety of low dose nivolumab with metronomic chemotherapy in patients with advanced platinum-resistant head and neck cancer: An Indian institutional experience.

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Background: Triple Metronomic chemotherapy (TMC) regimen of low-dose methotrexate, erlotinib, and celecoxib has been proven to improve overall survival (OS) of advanced platinum-resistant head and neck cancer (HNC) patients. The addition of low-dose nivolumab to metronomic chemotherapy is an alternative standard of care for those patients, who cannot access full-dose checkpoint inhibitors. In the present study, we aimed to assess the real world effectiveness and safety of low-dose nivolumab along with TMC. **Methods:** We performed a prospective analysis of advanced platinum-resistant HNC patients treated at our institute from June 2021 to June 2023 with TMC and low-dose immunotherapy consisting of capsule celecoxib (200 mg twice daily), tablet methotrexate (9 mg/m^2/week), and erlotinib (150 mg once daily), along with intravenous nivolumab 20 mg (once every 2 weeks). Data was analysed descriptively and the Kaplan-Meier method was used to estimate OS, progression-free survival (PFS), and duration of response (DOR). **Results:** Overall, 85 patients of advanced platinum-resistant HNC were enrolled in this study. The median age of the patients was 54 years with male predominance. The most common primary sites were buccal mucosa (54%) and tongue (32%). The median follow-up was 6.5 months with 5 months of DOR to therapy. Median number of nivolumab doses received were 8 (IQR 2–48). The termination of therapy in the majority of patients was due to disease progression (55%). Most common adverse events reported were acneiform rash (62%), mucositis (52%), and fatigue (34%). Dose reduction for triple metronomic chemotherapy was required in 42% of patients for grade 3 and above adverse events. No grade 3/4 immune-related adverse events were reported throughout the study period. The median PFS and OS of the study population were observed to be 4.3 months and 8.8 months, respectively. Overall, 8 of 85 patients survived for ≥30 months and 20 (24%) patients were on treatment at the time of data analysis. **Conclusions:** Low-dose immunotherapy along with triple metronomic chemotherapy is a safe treatment option in real world advanced platinum-resistant HNC patients with acceptable outcomes. Research Sponsor: None.

6051 Poster Session

Predicting response to immune checkpoint blockade in recurrent/metastatic head and neck squamous cell carcinoma using personalized circulating tumor DNA.

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Background: Immune checkpoint blockade (ICB) is the standard of care for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) yet, response rates are poor. Currently there are no real-time, non-invasive biomarkers of treatment response. Circulating tumor DNA (ctDNA) has shown promising results as a non-invasive response prediction tool in several solid malignancies. In this retrospective study we applied a tumor-informed next-generation sequencing liquid biopsy assay (RaDaR, NeoGenomics Laboratories, Inc.) to track the dynamics of ctDNA in HNSCC patients treated with ICB to test the primary hypothesis that ctDNA detection across treatment predicts disease progression and the secondary hypothesis that ctDNA clearance during treatment positively impacts clinical outcomes in HNSCC. **Methods:** Whole exome sequencing was performed on pre-ICB archival tumor sections from 16 R/M HNSCC patients. A median sequencing coverage of 306x was obtained. Personalized assays targeting a median of 48 tumor-derived somatic variants were used in serial plasma samples for the detection and monitoring of ctDNA during ICB. Response was assessed using RECIST 1.1 or clinical assessment when imaging was unavailable. Multivariable logistic regression was performed to measure the effect of clinicopathologic features on achieving ctDNA-clearance. Multivariate Cox regression was performed to measure the effect of achieving ctDNA-clearance on survival. **Results:** 137 plasma samples were collected from 16 patients with a median of 6.5 samples per patient. 14/16 patients had a pre-ICB plasma sample available and ctDNA was detected in 12 (85.7%) (median estimated variant allele frequency: 0.28%, range: 0.004%-1.8%). In the cohort there were 2 patients with complete response (CR), 4 patients with partial response (PR), 2 patients with stable disease (SD), 7 patents with progressive disease (PD), and 1 patient whose response could not be assessed. In patients who cleared ctDNA (n=9) during ICB, there were 2 CR, 4 PR, 1 SD, and 1 PD. In patients who did not clear ctDNA (n =7) there was 1 SD and 6 PDs. ctDNA-clearance at any point after ICB start, including beyond PD on ICB, was associated with 33-fold increased odds of achieving CR, PR, or SD (OR 33.6, 95% CI 2.4-1400.6, p=0.022) independent of PD-L1 status, ICB regimen, and if ICB was administered as first or later line. Achieving ctDNA-clearance was associated with improved overall survival (OS) (HR 0.052, 95% CI 0.005-0.493, p=0.0101) after controlling for ICB regimen, virus status, and PD-L1 status. Median OS from start of ICB was 7.1 months in patients who remained ctDNA-positive and 28.5 months in those who became ctDNA-negative at any point after starting ICB. **Conclusions:** Undetectable levels of ctDNA at any point during ICB treatment were strongly predictive of achieving CR, PR, or SD in patients with R/M HNSCC. Research Sponsor: NeoGenomics Laboratories.

6052 Poster Session

The potential prognostic value of the head and neck advanced lung inflammation index (HN-ALI) for patients treated with immunotherapy.

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Background: The ALI is recognized as a potential prognostic and predictive biomarker for patients (pts) treated with immune checkpoint inhibitors (ICIs) in non-small-cell lung cancer. In head and neck squamous cell carcinoma (HNSCC) its prognostic role has been acknowledged in locally advanced setting. We evaluated whether HN-ALI could provide similar value in pts with recurrent/metastatic (R/M) HNSCC undergoing treatment with ICIs. **Methods:** We conducted a multicentric observational retrospective study including R/M HNSCC pts treated with ICIs alone or in combination with chemotherapy from April 2016 to November 2023. The ALI was calculated as follows: BMI (kg/m^2) $\times$ serum albumin (g/dL)/neutrophil-to-lymphocyte ratio (NLR). Using the bibliographic cut off value of 18, pts were divided into two groups: ALI < 18 (high inflammation) and ALI > 18 (low inflammation). The primary outcomes were overall survival (OS) and progression free survival (PFS), evaluated with the Kaplan-Meier estimator. Cox proportional hazard regression models were employed to perform multivariate analysis. **Results:** A total of 145 pts [105 males, median (m) age 66 years, 128 with ECOG PS < 1] were treated with ICIs (35% nivolumab, 64% pembrolizumab) across two Italian centers. Primary tumor sites were: oral cavity (35%), oropharynx (33%), larynx (14%), hypopharynx (7%), other (9%). ICIs were administered as single agents in 86 pts and in combination with chemotherapy in 59 pts. The HN-ALI was collected for 92 pts. The mPFS was 6 months (95%CI, 2.16-9.83) within the ALI group > 18 versus 1 month for the ALI group < 18 (95%CI, 0.26-1.73) ($p< .001$); analogously, the mOS was 17 months (95%CI, 11.63-22.36) versus 2 months (95%CI, 0.68-3.32) for the ALI group > 18 and < 18, respectively ($p< .001$). At the multivariate analysis, high ALI score represented an independent risk factor for better OS, also including ECOG PS and PD-L1 expression [HR 0.38; (95% CI,0.15 – 0.96), p= .042], while showing a trend towards longer disease progression [HR 0.52; (95% CI, 0.26 - 1.02), p= .058]. **Conclusions:** In our experience, ALI value >18 is associated with better prognosis in pts treated with ICIs alone and in combination with chemotherapy. Further analyses are warranted to validate the prognostic relevance of the ALI value in pts with HNSCC undergoing ICIs. Research Sponsor: None.

LBA6053 **Poster Session**

A phase III randomized, open-label study to establish the superiority of triple oral metronomic therapy (OMCT) used in addition to chemotherapy regimen (paclitaxel + carboplatin) over chemotherapy alone for the treatment of advanced unresectable head and neck cancer squamous cell cancer (HNSCC).

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LBA6054 **Poster Session**

Long term results of phase 3 randomized study evaluating the addition of low dose nivolumab to palliative chemotherapy in head and neck cancer.

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6055 Poster Session

Features of HPV+ OPSCC predictive of recurrence identified by transcriptional profiling of a case-control cohort.

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Background: De-escalating therapy for HPV+ oropharyngeal cancers (OPSCCs) is hampered by poor ability to predict recurrence, and limited insight into the biologic traits predisposing to recurrence impedes personalizing therapy. We aimed to (1) define biologic features underlying therapy resistance by transcriptional profiling and (2) evaluate the features for prognostic utility. **Methods:** A single institution cohort of 851 HPV+ OPSCC patients undergoing transoral robotic surgery during 2007-2020 was used to identify 50 cases that recurred locoregionally in the adjuvant RT field (n=14) and/or at distant sites (n=43). As controls, we used 49 recurrence-free patients with long-term follow up and similar stage, smoking history, and adjuvant therapy. RNAseq of pretreatment tumors was used to compare individual gene expression and Hallmark/Kegg pathway activity between cases and controls using unpaired t-test ($p<.05$) and Gene Set Enrichment Analysis (p-adj$<.05$), respectively. Activity of the significant pathways was quantified in individual tumors using Gene Set Variation Analysis (GSVA), and a regression-based composite of GSVA scores was developed to distinguish cases from controls by ROC analysis. The composite score was used to test for stratification of recurrence free survival (RFS) in external cohorts using Youden Index and logrank test. **Results:** The21 Hallmark/Kegg pathways downregulated in cases indicated suppression of anti-tumor immunity, and the 20 upregulated ones revealed increased biosynthetic function and tumor cell proliferation. The 1472 upregulated mRNAs contained several components of the ATR-chk1 DNA repair pathway and trans-lesion synthesis polymerases, suggesting that mitigation of DNA replication stress enhanced tumor growth. The 958 downregulated mRNAs suggested reductions in the cytoplasmic dsDNA sensing and downstream NF-kB signals that lead to replication stress-driven anti-tumor immunity. Two GSVA scores were created to quantify the key tumor-intrinsic and immune suppressive features separately in each tumor. The scores correlated with each other ($R=0.6$, $p<.001$), and a regression-based combination of them distinguished cases from controls ($AUC=.76$, $p<.001$). This composite score also stratified RFS in three external cohorts: TCGA (n=52, $p<0.001$) and two single institution cohorts containing both surgical and nonsurgical cases (n=46, $p=.002$; n=81, $p<0.001$). **Conclusions:** HPV+ OPSCCs failing primary surgical therapy show evidence of reduced replication stress mediating tumor progression and low anti-tumor immunity. These features appear generalizable to heterogeneously treated external cohorts, where they predicted recurrence. Our results provide a new basis for creating transcriptomic predictors of treatment response and suggest targetable molecular mechanisms to overcome therapy resistance. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; UH2CA267502.

Personalized circulating tumor (ct)DNA for monitoring disease status in HPV-negative head and neck squamous cell carcinoma.

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Background: Highly sensitive minimal residual disease (MRD) assays using circulating tumor (ct)DNA have broad clinical potential and are impacting cancer care. Circulating human papillomavirus (HPV) DNA has emerged as a biomarker of occult MRD among patients (pts) with HPV+ oropharyngeal cancers, but most head and neck squamous cell carcinomas (HNSCC) are not virally driven. Despite multimodality therapy, nearly half of pts with locoregionally advanced HPV-negative HNSCC relapse. As ctDNA has the potential to identify MRD, predict outcomes, and guide treatment for these pts, we performed a retrospective cohort study to evaluate the performance of a custom-built, clinically and commercially available ctDNA assay for this population. **Methods:** Pts with newly diagnosed HPV-negative HNSCC (all mucosal sites) treated at a single academic institution with pre-treatment ctDNA testing (Signatera, Natera) performed during clinical care were identified. Signatera utilizes up to 16-plex PCR from matched tumor and blood to develop a personalized ctDNA assay. A subset of patients had additional ctDNA testing during follow-up. Study objectives were to understand baseline ctDNA detection in relation to disease characteristics, and to correlate ctDNA changes on- and post-treatment with disease status and survival. **Results:** Testing was performed in 92 of 115 (80%) pts with HPV-negative HNSCC (median age: 66, 69% male, 64% smokers); ctDNA testing could not be performed in 23 (20%) pts due to insufficient tumor tissue. Oral cavity (43%) and larynx (22%) were the most common subsites; with most having clinical T2-3 (54%) and N1-2 (51%) disease (AJCC 2017 8^{th} edition) treated with definitive surgery (46, 40%) and/or chemoradiation (59, 51%). Pre-treatment, 69/92 (75%) pts had detectable ctDNA (range: 0.03-4049.69 mean tumor molecules/mL). No baseline independent clinical features predicted pre-treatment ctDNA detectability or levels (multiple logistic/linear regression modeling), but levels varied by T and N stage in univariate analysis (both $p<0.05$; Kruskal-Wallis test). At a median follow-up of 5.2 months (range: 0.2-15.1), 47 pts (51%) had >1 test result (range: 1-7; 170 total samples). Of 47 pts, 17 (36%) had ctDNA detected after treatment. Disease-free survival was significantly worse for pts who were ctDNA positive vs. negative after treatment (HR 4.35, 95% CI: 1.68-11.21, $p<0.01$); 1-year overall survival was 83.7% vs. 100% for pts who were ctDNA positive vs. negative. **Conclusions:** Tumor-informed, personalized ctDNA testing is feasible among pts with non-virally mediated HNSCC. ctDNA positivity as an early indicator of MRD positivity post-treatment was associated with inferior survival, identifying a high-risk subgroup. Further research is warranted to understand whether ctDNA may be leveraged to guide therapy and improve outcomes for HNSCC. Research Sponsor: None.

6057 Poster Session

Saliva-based detection of oral HPV and oral cancer.

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Background: Head and neck cancers (HNC) consist of a group of biologically and clinically diverse malignancies. Oral cavity squamous cell carcinoma (OCSCC) and oropharyngeal squamous cell carcinoma (OPSCC) are the most common subtypes, together comprising the majority of HNC cases. While these cancers are associated with tobacco use and alcohol consumption, infection with human papilloma virus (HPV) is also etiologic to HNC, with OPSCC known to harbor higher HPV positivity (HPV+) rates relative to OCSCC, which is largely HPV-negative (HPV-). This distinction is clinically relevant as HPV+ tumors are more responsive to therapy and associated with better prognosis. While early-stage OCSCC/OPSCC has 5-year survival rates of >80%, diagnosis typically occurs at advanced stages, where the survival rate drops to 20-40%. Compounding this grim outlook is the growing incidence in patients that do not smoke or drink alcohol, as well as the startling rise in HPV+ OPSCC cases, thus increasing the affected population and burden on the healthcare system. Currently, painful incisional biopsies are the standard method to diagnose HNC, and there are no accepted non-invasive screening options for early disease detection or serial assessment of treatment efficacy. There is an urgent need for non-invasive diagnostic solutions that accurately identify disease at an early stage and quickly discern HPV status to inform effective treatment decisions and improve patient outcomes. **Methods:** We have recently developed a novel salivary liquid biopsy screening method for early detection of OCSCC, which relies on targeted NGS of 7 commonly mutated genes associated with OCSCC tumorigenesis, and shown that it is able to accurately and reproducibly identify ~93% of patients with OCSCC, including early stage cases. To enhance the capabilities of this screening platform we have incorporated probes targeting high-risk HPV strains (hrHPV16/18) into the sequencing panel. **Results:** Applying this multi-functional assay to a cohort of 20 primary OCSCC tumors, driving somatic mutations were detected in all cases. Furthermore, using the 5% alignment cutoff, all OCSCC specimens were HPV-. We next sequenced HPV+ OPSCCs using the same criteria, detecting 93% of the cases as HPV positive by our combined assay. We next applied this updated assay to saliva specimens collected from 30 OCSCC patients and 10 healthy individuals. Somatic mutations were detected in all OCSCC saliva specimens, while no actionable aberrations were found in healthy controls. As expected, 27 of 30 OCSCC saliva samples were HPV-, with the remaining 3 samples being inconclusive. **Conclusions:** While additional validation is needed to accurately assess the performance of this dual panel in saliva specimens, such multi-functional (mutational drivers/HPV) detection assay may facilitate personalized treatment decisions based on tumor biology (mutations) in addition to clinical risk factors (presence of hrHPV). Research Sponsor: V Foundation; U.S. Department of Defense.

6058 Poster Session

The combination of patient-specific tumor and HPV sequencing to enable high-sensitivity detection of ctDNA in patients with HPV-associated oropharyngeal carcinoma.

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Background: Detection of Human papillomavirus (HPV) in plasma has been used to monitor treatment response in HPV-associated oropharyngeal carcinoma (OPC) but was found to have limited sensitivity in patients with low disease burden. We hypothesized that the combined detection of personalized tumor-specific alterations and HPV could provide a more sensitive approach for detecting circulating tumor DNA (ctDNA) and for disease monitoring in early-stage HPV-associated OPC patients. **Methods:** Patients with HPV-associated OPC (T0-2/N1-N2c) enrolled in a phase II chemoradiation (CRT) de-escalation trial (NCT03323563) were chosen for this study. The patients underwent resection of the primary tumor prior to CRT and a baseline plasma was drawn at this time. Additional plasma samples were collected weekly throughout CRT. Whole-exome and targeted HPV sequencing was performed on the primary resection to build a dictionary of somatic variants and for HPV typing, respectively. A dual PCM-HPV assay was developed based on the Invitae Personalized Cancer MonitoringTM (PCM) platform and used to evaluate the plasma samples. Tumor volume was measured by T2 MRI using a region of interest outlining the largest lymph node in the undissected neck. **Results:** 158 patients with T0-2/N1-N2c HPV-OPC were enrolled on the trial and the dual PCM-HPV assay was successfully designed for 111 patients targeting a median of 50 patient-specific mutations (range: 26-50). Preliminary analyses were performed on 71/111 patients (64.0%) with HPV16-associated tumors and available baseline plasma. 64/71 (90.1%) and 61/71 (85.9%) were ctDNA positive by PCM testing and HPV testing alone, respectively. Combining HPV plasma testing with PCM (PCM-HPV) improved the sensitivity to 68/71 (95.7%). This increased sensitivity was maintained when analyzing plasma samples collected weekly following CRT. The 3 patients with double negative HPV and PCM results at baseline had a lower tumor volume (p=0.05) and lower levels of genome instability (p=0.02) than those with ctDNA or PCM positive baseline plasma. HPV cfDNA levels are weakly correlated with tumor HPV genome copy number (r=0.16; p=0.001). **Conclusions:** The combined detection of personalized tumor-specific alterations and HPV provides a highly sensitive approach for detecting low disease burden in early stage HPV-associated OPC patients before and during treatment. Research Sponsor: None.

ctDNA positivity by timepoint.

	Pre-CRT	Week 1	Week 2	Week 3	Week 5
N	71	68	69	63	17
PCM	90.1%	75%	70%	50.8%	5.9%
HPV	85.9%	79.4%	72.5%	50.8%	5.9%
PCM-HPV combined	95.7%	86.8%	82.6%	65.1%	5.9%

6059 Poster Session

Neoadjuvant immunotherapy for oropharynx cancer: Correlative studies and long-term outcomes from the CIAO trial.

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Background: CIAO (Checkpoint Inhibitors Assessment in Oropharynx cancer) was a window of opportunity trial evaluating the anti-PD-L1 durvalumab (durva) with or without the anti-CTLA-4 tremelimumab (treme) prior to surgery in 28 oropharynx squamous cell carcinoma (OPC) patients (pts). Here we report correlative analyses and long-term survival outcomes. **Methods:** A total of 28 OPC pts were randomized to receive durva (n=14) or durva plus treme (n=14) for 2 cycles prior to surgery. Adjuvant radiotherapy with or without concomitant chemotherapy was recommended based on pathology findings, per standard of care. Efficacy and safety results have been previously reported. Whole exome sequencing (WES), RNA sequencing (seq), and TCR-seq were performed on available pre- and post-treatment primary tumor specimens. Circulating HPV was quantified pre-treatment and longitudinally. Associations with objective response (OR) to therapy per RECIST were determined using either Fisher's exact test (binary variables) or rank-sum test (continuous variables). Multiple comparisons were corrected for by the Benjamini and Hochberg method. Disease-free survival (DFS) was defined as the time from surgery to recurrence or death. **Results:** Of the 28 enrolled pts, 20 were newly diagnosed and 8 had locoregional recurrent disease; 25 were HPV-positive. The OR rate per RECIST was 43%. Efficacy was equivalent in both arms. Responders tended to be of younger age (p=0.02). At the DNA level, baseline tumor mutation burden was not associated with response, but mutational contraction post-treatment was more often observed among responders (p=0.02). There were no statistically significant differentially expressed genes between responders and non-responders, however, immune deconvolution revealed that a low inferred tumor neutrophil-to-leukocyte ratio was associated with response (p=0.01). TCR-seq revealed 8 TCR motifs enriched in responders at 25% false discovery rate. Serum HPV levels significantly decreased in responders after treatment (p=0.02). With a median follow-up from surgery of 59.6 months (range 14.9-71.5 months; data cut-off 1/19/24), none of the 20 patients with newly diagnosed OPC had recurrence and all remain alive at the last contact date (DFS=100%). Of the 9 patients with recurrent OPC, 3 had subsequent distant recurrence and died of disease (median DFS=5.7 years, overall DFS=66.7%). **Conclusions:** Responses to neo-adjuvant checkpoint inhibitors was associated with tumor mutational contraction and a low baseline neutrophil-to-leukocyte ratio in OPC. Eight TCR motifs were enriched in responders. Serum HPV level dynamics was associated with tumor burden and may be useful in response monitoring. DFS outcomes were favorable in both newly diagnosed and recurrent cohorts. Research Sponsor: Stiefel grant.

Effect of CBD on anti-tumor immune response and interaction with GPR55 on MAPK signaling in head and neck squamous cell carcinoma.

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Background: Head and neck squamous cell carcinoma (HNSCC) is a lethal malignancy and comprises two distinct etiology: human papillomavirus (HPV)+ve and -ve. Marijuana use is associated with HPV+ oropharyngeal infection and conflicting data show positive and negative associations of daily marijuana use with HPV+ and tobacco-associated HPV- HNSCC. However, cannabinoid use continues to increase in the US general population for recreational purposes as well as in cancer patients for palliative care. G-protein coupled receptors (GPCRs), including cannabinoid GPCRs, stimulated by specific ligands interact with multiple G proteins creating diversity and complexity of signaling. In this study, we aimed to investigate the CBD-induced GPCR coupling and its effect on anti-tumor activity by modulating immune response in HNSCC by using pre-clinical models. **Methods:** The anti-cancer effect of CBD was measured by cell proliferation, apoptosis and migration analysis. Next, TGF-α shedding assay was performed to identify the CBD-induced GPCR coupling with different cannabinoid receptors. The cannabinoid receptor GPR55 was subjected to silencing by siRNA and western blot analysis was performed to evaluate its role in activation of p38 MPAK pathway. Next, the anti-tumor immune response of CBD was evaluated by using an immunocompetent syngeneic C57BL/6 mEER RasG12D+/- HPV E6/E7 transformed tongue epithelial cell model that serves as a model for HPV+ HNSCC and the 4MOSC1 orthotopic, syngeneic, 4NQO (4-nitroquinoline-1 oxide)-induced murine oral tongue squamous cell carcinoma C57BL/6 mouse model that serve as HPV- HNSCC model as well as in immune-deficient Rag1 -/- and athymic nude mouse followed by measurement of immune cell infiltration by IHC analysis. **Results:** We found that 10μM of CBD treatment inhibited cell proliferation and migration in HNSCC cells by promoting apoptosis. Interestingly, we observed that CBD resulted in GPCR coupling for Gαi with GPR55 and Gαq/o and Gαq/s for CNR1, CNR2 and GPR55. Furthermore, we silenced GPR55 and observed that 10μM of CBD treatment inhibits the activation of p38 MAPK pathway whereas it promotes activation in non-silenced HNSCC cells. Next, we observed that treatment with 10μM of CBD significantly inhibited tumor growth compared to control in both HPV- and HPV+ models in immune-intact animals whereas, no significant difference in the tumor growth was observed in immune-deficient (Rag1 -/- and athymic nude) mouse, indicating role of CBD in modulating tumor immune microenvironment. We also observed CBD treatment enhanced CD4+ and CD8+ T cell infiltration into the primary tumors of HPV+ and HPV- mice models, implicating a downstream cytotoxic T cell response. **Conclusions:** Our study suggests that CBD promotes anti-tumor activity by modulating the immune microenvironment and interacts with GPR55 to activate intrinsic MAPK signaling pathway. Research Sponsor: None.

6061 Poster Session

Association of artificial intelligence–derived collagen disorder architecture (CoDA) features with survival outcome and objective response to immune checkpoint inhibitors in patients with head and neck squamous cell carcinoma.

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Background: In several cancers, including head and neck squamous cell carcinoma (HNSCC), the immunosuppressive components of the tumor microenvironment (TME) can impact the effectiveness of immune checkpoint inhibitors (ICI). One significant component of the TME is the extracellular matrix, which is rich in collagen fibers. In this work we used machine learning and image analysis approaches on whole slide images (WSIs) to characterize collagen disorder architecture (CoDA) features and evaluated their association with outcomes in HNSCC patients receiving ICI. **Methods:** WSIs of HNSCC patients treated with ICI were obtained from University Hospitals (S1, n=43) and Emory University (S2, n=31). Tiles from the tumor annotated regions of the WSIs were extracted, and a derivative-of-Gaussian model was used to identify collagen fibers in the stroma of these tiles. Various CoDA features were then calculated as follows: (1) collagen fiber fragmentation measure, (2) collagen fiber bundling percentage, (3) collagen fiber rigidity measure, (4) collagen fiber anisotropy index and (5) collagen fiber density index. CoDA features of S1and S2 were combined and split into 50:50 for training and validation. For survival analysis using overall survival (OS) as endpoint, the median risk score in the training set was applied for risk stratification in the validation set by means of a Least Absolute Shrinkage and Selection Operator (LASSO) and Cox regression model. For predictive analysis, CoDA features from patients with objective response (OR) to ICI were identified (S1, non-responder=23, responder=20), (S2, non-responder=23, responder=8). The top features were then selected using the LASSO and combined with a Generalized Linear Model classifier. A 5-fold cross-validation assessed Area Under the Receiver Operating Characteristics Curve (AUC) for predicting OR, with average AUC as the final performance metric in the validation set. **Results:** For survival analysis, high risk patients in the validation set had worse survival than low risk patients (HR=2.7 (95% CI=1.1-6.6, p=0.02)). For predicting OR, the selected top CoDA features were collagen fiber fragmentation measure, collagen fiber bundling percentage, collagen fiber rigidity measure and collagen fiber density index and the average AUC was 0.64 ± 0.16. More fragmentation of the collagen fibers along with dense thick bundles and straightened fibers were observed in the WSIs of non-responder patients to ICI. **Conclusions:** High risk CoDA features correlated with worse survival in patients with HNSCC receiving ICI. Also, we established a correlation of specific CoDA features with OR to ICI. The prognostic and predictive value of CoDA deserves additional exploration with confirmatory data from larger, independent multi-site validation. Research Sponsor: National Cancer Institute; National Heart, Lung and Blood Institute; National Institute of Biomedical Imaging and Bioengineering; VA Merit Review Award; Bristol Myers-Squibb; Boehringer-Ingelheim; Eli-Lilly; Astrazeneca.

6062 Poster Session

Genomic characteristics of exceptional responders to treatment with PD-1 inhibitors in refractory/metastatic head and neck squamous cell carcinoma.

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Background: With the emergence of immune checkpoint inhibitors (ICIs), there are patients with advanced cancers experiencing exceptional treatment response with overall low treatment-associated toxicities. Despite success in refractory/metastatic head and neck squamous cell carcinoma (HNSCC), only a portion of patients experience benefit from the treatment with ICIs. Critical information on predictors of patient's response to treatment is limited. At our institution we analyzed the genomic profiles of 36 patients with advanced HNSCC who demonstrated an exceptional response to treatment with PD-1 inhibitors. **Methods:** We reviewed patients with histologically confirmed HNSCC that had been treated with PD-1 inhibitors at Atrium Health Wake Forest Baptist Health. Treatment regimen included pembrolizumab 200mg every 3 weeks or nivolumab 240mg every 2 weeks. Response to therapy and duration of remission were monitored via CT scans and/or MRI scans at 3-month intervals, using RECIST 1.1 criteria. Exceptional responders were defined as achieving complete response (CR) or partial response (PR) for greater than six months, or stable disease (SD) for greater than one year. Progression free survival (PFS) and overall survival (OS) were measured from the date of PD-1 inhibitor initiation. PD-L1 level was measured via FoundationOne immunohistochemistry staining and reported as combined positive score (CPS). Additionally, next generation sequencing was performed on tumor (30/36 patients) and blood (33/36 patients) specimens via FoundationOne and Guardant360 testing platforms. **Results:** Out of 155 HNSCC patients treated with a PD-1 inhibitor, 36 patients demonstrated an exceptional response as defined above. 20 with CR, 9 with PR and 7 with SD. With an average follow up of 32 mo (95% CI, 26 mo-ongoing), the average OS was 33 mo (95% CI, 28 mo–ongoing) and the average PFS was 25 mo (95% CI, 20 mo-ongoing). These patients underwent an average of 27 treatments (range, 10-64 treatments to date). PD-L1 average score at 36 (95% CI, 22-49) and average TMB at 19 mut/mb (range, 0-90 mut/mb). Of 290 detected gene mutations, the most frequently mutated genes were TP53 (75%), PIK3CA (42%), CDKN2A (36%), EGFR (33%), TERT (25%), BRCA2 (22%), ERBB2 (22%), HNF1A (22%), MLL2 (22%), NOTCH1 (22%), and RAD21 (22%). **Conclusions:** There is limited data reporting the genomic profile of exceptional responders to PD-1 inhibitors in refractory/metastatic HNSCC. Higher TMB and single gene mutations such as TP53, PIK3CA, CDKN2A, EGFR, and TERT are frequently detected in exceptional responders and may provide future direction into the investigation of predictors of response to ICIs. Research Sponsor: None.

6063 Poster Session

Molecular analysis of surgical margins with NGS to assess microscopic residual disease in early oral squamous cell carcinomas.

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Background: The prognosis of early oral squamous cell carcinomas (OSCC) is strongly correlated with local disease control. However, patients with T1-T2 OSCC operated with clear margins have a 5-year local relapse rate of 10 to 15%. An accurate evaluation of the microscopic residual disease (MRD) is therefore essential. Interestingly, innovative techniques have recently been developed to detect circulating tumor DNA. **Methods:** A prospective multicenter trial based on patients with T1-T2 OSCC treated surgically with clear margins, was designed to assess the feasibility of a molecular analysis (tetranucleotide instability) of these margins to evaluate a potential MRD while adapting the postoperative strategy (NCT00232960). We, then, evaluate the feasibility of detecting MRD in the margins by identifying specific molecular abnormalities in the primary tumor with Whole Exome Sequencing (WES) and explore them in margins with deep target NGS panel (TGS) and digital PCR (dPCR) for hotspot mutations. **Results:** 310 patients were included initially with 216 tumor/margins samples available for molecular analysis. After a standard pathologic analysis, all surgical margins were negative.-Median follow-up was 58 months [30;83].Tumor was informative for tetranucleotide instability analysis in 63% of cases. Positive molecular margins were observed in 17.3% of cases, leading to a postoperative treatment (surgery or radiotherapy). In informative tumors, molecularly driven treatment seemed to lower the 5-year local recurrence rate from 14.1% to 6.4% (p=0.15). Among this initial cohort, 108 primary tumors were secondarily screened by WES to find mutations of interest, with an informativity rate of 75%. Positive molecular results (TGS or dPCR), with at least one positive margin, were observed in 19.4% of patients. Then, analyzing retrospectively the oncologic outcomes, we observed a significant benefit for local control at 5 years for patients with TGS-dPCR negative results in all margins compared to pathologic negative margins (91.7% versus 64.1%, p=0.02). **Conclusions:** To our knowledge, this is the first report of local MRD assessment after surgery using NGS.Molecular analysis of resection margins for early OSCC lead to a better evaluation of MRD and personalized postoperative decision making to improve local control. Clinical trial information: NCT00232960. Research Sponsor: PRISM program (Gustave Roussy).

6064 Poster Session

Multi-feature next-generation liquid biopsy for diagnosis and prognosis in HPV-associated head and neck cancer.

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Background: Human papillomavirus-associated head and neck squamous cell carcinoma (HPV+HNSCC) releases circulating tumor HPV DNA (ctHPVDNA) into the blood which is a highly accurate biomarker of disease status. Existing approaches based on droplet digital PCR (ddPCR) have limitations in sensitivity, genotype coverage, and do not annotate additional prognostic genomic features. In this study, we tested the diagnostic and prognostic performance of a custom HPV whole-genome next-generation sequencing (NGS) liquid biopsy, termed HPV-DeepSeek, at the time of diagnosis with HPV+HNSCC, compared to ctHPVDNA ddPCR, HPV serology, and clinical work-up. **Methods:** 304 participants (152 untreated HPV+HNSCC patients, 152 population-level controls) were prospectively enrolled in this single-center prospective cohort study. Plasma samples were analyzed using HPV-DeepSeek, a multiplexed serology assay, single-plex ddPCR, and a 5-genotype multiplexed ddPCR assay. We tested the hypothesis that HPV-DeepSeek would have the highest diagnostic accuracy. We secondarily examined the accuracy of HPV-DeepSeek for prognostic feature annotation including high-risk HPV16 single nucleotide polymorphisms (SNPs), integration events, and PIK3CA mutations. **Results:** Of 152 cases, 114 (75%) were AJCC stage 1 and 138/152 (91%) were oropharynx primary site cancers. The sensitivity (98.7%), specificity (98.7%), and diagnostic accuracy (0.974) of HPV-DeepSeek was superior ($P<0.001$) to singleplex ddPCR (94.2%, 98.6%, 0.928), multiplex ddPCR (90.6%, 96.3%, 0.869), HPV serology (86.4%, 96.3%, 0.827), and first attempt clinical diagnostic biopsy (78% sensitive). Utilizing HPV-DeepSeek, 8 different genotypes were detected. 4 patients were found to have multi-genotype infections. 137/152 cases were classified as HPV16, with A1 the most common sub-lineage (90/137). 21 of 137 HPV+HNSCC HPV16 cases (15%) displayed high risk SNPs. Head-to-head comparison of HPV SNP genotyping by HPV-DeepSeek, with the gold-standard tissue-based HPV whole genome sequencing assay, demonstrated 89% concordance in tissue and 85% in blood. The internal concordance rate for HPV-DeepSeek between tissue and blood was 91%. 48 of 152 cases (32%) had at least one viral integration event detected and 36 of 152 cases (24%) had a PIK3CA mutation detected by HPV-DeepSeek. Fragmentomic analysis demonstrated a mean ctHPVDNA fragment size of 148bp for ctHPVDNA versus 167bp for human cell free (cf)DNA from HPV+HNSCC patients and 168bp for control patient cfDNA. Baseline ctHPVDNA quantity was strongly correlated with viral integration status, T stage and N stage ($P<0.001$). **Conclusions:** HPV-DeepSeek has improved diagnostic accuracy relative to ddPCR, HPV serology and clinical work-up at the time of diagnosis and demonstrates detection of prognostic features including high-risk HPV16 SNPs, viral integration events, and PIK3CA mutations. Research Sponsor: U.S. National Institutes of Health; 5R03DE030550-02.

Development and validation of an assay to quantify plasma cell-free human papillomavirus DNA for 13 high-risk types that cause 98% of HPV-positive cancers.

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Background: Plasma cell-free HPV DNA (cfHPV) may be a valuable tool for identification of patients with local-regionally advanced HPV-positive cancers at risk for recurrence after chemoradiation. Technical validation is required for use as an integral biomarker in a prospective clinical trial. **Methods:** Cell-Free 13 (i.e., CF13) is a digital-droplet PCR assay for quantification of 13 high-risk HPV types and control ERV3 in plasma that considered both variant sequences into primer/probe design and a distance matrix in phylogenetic analysis in multiplex combinations. Oligonucleotides/plasmids encoding type-specific E6/E7 regions were used as positive controls. Limit of blank, detection, quantification (LoB, LoD, LoQ), linear range, inter- and intra-assay coefficients of variation (CoV), and type-specific cross-reactivity were determined as were sensitivity and specificity for an HPV-positive diagnosis in a cohort of 278 oropharyngeal/unknown primary/oral cavity cancers tested for HPV by E6/E7 mRNA qRT-PCR or p16 IHC and HPV in situ hybridization. **Results:** Under identical assay conditions, the LoB, LoD and linear range were <1, 5 and 5 to 200,000 virus copies without HPV type-specific cross-reactivity. Multiplexing had no effect on LoD or linearity. LoQ was 16 copies/ml plasma for all 13 HPV types. For 80 and 10,000 copies per ml, inter-assay CoV ranged from ~15-28% and ~3.2-4.6% and intra-assay CoV ranged from ~16-38% and 0.2-3.3%, respectively. cfDNA purification method (manual *v* automated; extraction efficiency 142% and 91% for 16 and 10,000 HPV16 copies/ml), input plasma volume (1, 2, or 4 ml), total background cfDNA (<1800ng) or genomic DNA (<700ng) did not affect quantification. For a diagnosis of HPV-positive cancer, sensitivity and specificity were 91.1% (214/235) and 97.7% (42/43), respectively. cfHPV was associated with gender, race, T stage, N stage, and primary treatment modality. When compared to below the median (≤230 copies/ml), cfHPV above the median was associated with worse progression-free survival (HR=2.26, 95% CI 1.23-4.17, p=0.009) in univariate analysis. However, this was no longer significant after adjustment for age, T stage, and M stage (HR_{adj}=1.78, 95% CI 0.95-3.35, p=0.07). **Conclusions:** CF13 has high sensitivity, accuracy, precision, linearity, HPV type-specificity, and robustness, offering a rigorously validated assay applicable to ~98% of patients with HPV-positive cancer. CF13 had excellent clinical sensitivity and specificity for a diagnosis of HPV-positive OPC. Research Sponsor: Cancer Prevention and Research Institute of Texas.

Can TTMV clearance predict recurrence in HPV HNSCC?

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Background: Patients with locally advanced (LA) HPV HNSCC are treated with various types of induction chemotherapy (IC) followed by standard (sd) or reduced (rd) chemoradiation (CRT). Tumor tissue-modified viral HPV DNA (TTMV) pairs with PET-CT in predicting an early detection of treatment failure in HPV-related HNSCC. Mid-treatment TTMV assessment in HPV-related HNSCC can help identify patients who are eligible to receive a lower dose of IC and/or CRT or those who may require close follow-up. **Methods:** Patients with LA HPV+ HNSCC with high-risk features (radiographic ECE, T4 primary, >N2c) and <20 pack-year (py) smoking history were treated with IC followed by rdCRT (56 Gy); sdCRT (70 Gy) was used in non-responders. 16/23 received IC with TPF, 1/23 TP, and 6/23 TP-PD1, and all patients received carboplatin weekly with their CRT. Regeneron trial patients who received TP-Cemiplimab (PD1) IC followed by sdCRT are also continuing adjuvant Cemiplimab alone for 6 months (NCT05376553). PET-CT-confirmed residual, recurrent, or metastatic diseases were defined as treatment failures; TTMV + patients only if PET-CT confirmed. **Results:** 23 subjects treated with IC followed by CRT between 2/4/21-1/26/24, who had pre- and post-treatment TTMV were included in our analysis. The median pre-IC TTMV was 8082 (27 – 90770). The median follow-up time from treatment start was 21 months. 9/23 patients had full clearance TTMV after 1 cycle of IC defined as rapid responders (RR). 11/23 patients still had positive TTMV after 1st cycle of IC were defined as slow responders (SR). 1 patient had no TTMV done after 1 cycle of IC but was elevated after 2nd IC; he was defined as SR. 2 patients had a positive pre-IC TTMV, but no TTMV was drawn during IC to see if RR. 1 of 2 patients was TTMV negative prior to CRT, and 2/2 had a 1st post IC negative TTMV done 1 week after CRT started. They were both included in the analysis but defined as unknown response status. TTMV testing was done for all 23 subjects after CRT; all were negative. All subjects have TTMV testing done during their surveillance visits. Among 9/23 RR, none developed a failure. Among 12/23 SR, 3 patients developed a failure: 1/3 was TTMV+ but PET-, being followed with TTMV and PET-CT; and 2/3 were confirmed failures, TTMV+ and PET+; 1 locoregional, 1 metastatic. 2 patients were not known to be a SR or RR and had no recurrence. Among 23 patients, NPV of TTMV to detect failure was 100%, but PPV was 96% (1/23). **Conclusions:** IC followed in rapid clearance of TTMV in 39% of patients, and all remained disease-free. 3/11 (27%) with persistently elevated TTMV after cycle 1 relapsed as of this time point. This small study was not large enough to be practice-changing. However, this is significantly hypothesis-generating and should be tested in a larger trial to help identify patients for de-escalation (RR) or closer surveillance (SR). Research Sponsor: None.

6067 Poster Session

TTMV and association with relapse in patients with HPV related SCCHN undergoing CRT.

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Background: Circulating Tumor tissue-modified viral HPV DNA (TTMV) is a highly specific and predictive plasma test for active HPV SCCHN. The clearance kinetics of TTMV during chemo-radiotherapy (CRT) has been associated with disease control and monitoring. TTMV can guide therapy, enable earlier identification of recurrence compared to PET, and guide modification of curative therapy, including CRT. **Methods:** Patients with local or locally advanced HPV+ SCCHN were treated with adjuvant post-surgical CRT at 66Gy or 56Gy or definitive CRT at 70Gy between 7/1/21-10/17/23. All patients received cisplatin with CRT. All patients had a PET at baseline and 12 weeks after the CRT to assess their response to treatment. All patients had pre and post TTMV done and then as a part of surveillance. PET confirmed residual, recurrent, or metastatic diseases were defined as treatment failures in TTMV + patients only if PET was confirmed. **Results:** 21 patients were treated with either adjuvant post-surgical CRT at 66Gy (2/21) and 1 at 56Gy, or definitive CRT at 70Gy (18/21). 8/21 were treated with protons, and 13/21 were treated with standard IMRT photons. All patients who had pre- and post-treatment TTMV data were included in our analysis. The median pre-treatment TTMV was 9682 (5 – 166667), and the median follow-up time from treatment start was 15 months (3-40). 19/21 patients had negative TTMV after completion of CRT. 1/21 had elevated TTMV at the CRT completion and developed lung metastases PET+; biopsy confirmed. 2nd patient underwent resection of the right (R) tonsil and bilateral LND followed by adjuvant CRT at 56Gy with protons to R tonsil and R neck. PreCRT/post-op negative TTMV changed to positive and rose at weeks 1 and 3 of CRT. After completing CRT, underwent contralateral additional L LND with post-op continuously negative TTMV and no recurrence on PET. 14/21 patients undergoing CRT had TTMV testing done during CRT, and 7/21 had only pre and post-CRT and not during CRT. 7/14 had elevated TTMV and 7/14 had negative TTMV during CRT. Among 19/21 patients with post-CRT negative TTMV, only 2 recurrences were reported. Both patients developed distant metastases in their lungs and both were TTMV positive confirmed with PET and biopsy. The first patient had negative TTMV (1/7), and 2nd patient with TTMV was not done in the middle of CRT treatment. No recurrences were reported in any 7/21 patients with persistently elevated TTMV in the middle of CRT. 1/21 patients treated was altered based on the TTMV change from negative to positive. **Conclusions:** Unlike PET, TTMV lacks the capability to localize recurrences and cannot replace PET. Nevertheless, TTMV can identify recurrence or persistence and can synergize with PET to guide therapy, as evidenced in our study, where all 3 post-CRT recurrences were detected using TTMV and confirmed with PET and biopsy. Validation in a larger cohort is necessary to confirm the efficacy of combining TTMV with PET for response assessment. Research Sponsor: None.

6068 Poster Session

Photoimmunotherapy in nasopharyngeal carcinoma recurrence.

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Background: Photoimmunotherapy is a novel anticancer treatment developed by the NCI and has been covered by insurance in Japan since January 2021 for patients with unresectable, locally advanced or locally recurrent head and neck cancers. Over 400 patients have been treated with photoimmunotherapy in Japan, including 19 cases with recurrent nasopharyngeal carcinoma. Photoimmunotherapy uses an antibody-drug conjugate, cetuximab sarotalocan sodium, comprising cetuximab, a chimeric monoclonal antibody (IgG1) that targets human EGFR, and a light-sensitive dye, IRDye 700DX (IR700). The conjugate exhibits a strong affinity for cells expressing EGFR, which is enhanced in HNSCC. When exposed to a 690 nm (red) laser beam from the BioBlade laser system, the dye is activated, resulting in selective and rapid death of cells to which the conjugate is bound. The mechanism involves: (i) activation of the antibody conjugate by laser illumination, (ii) damage to the cell membrane, (iii) increased transmembrane water flux, and (iv) cell rupture and necrosis. The entire process occurs rapidly following laser illumination. Nasopharyngeal carcinoma is primarily treated with radiation therapy; however, if it persists, therapy becomes challenging. Surgical intervention for local recurrence or residual disease can be difficult due to the anatomical characteristics of the disease. Drugs and re-irradiation have limited effectiveness and significant adverse events have been reported. Photoimmunotherapy is considered more effective for nasopharyngeal carcinoma than other treatment sites. **Methods:** Nineteen patients with recurrent residual nasopharyngeal carcinoma following irradiation, who were treated with photoimmunotherapy at 15 centers across Japan, were reviewed. The study analyzed patients' previous treatment regimens, laser irradiation methods employed in photoimmunotherapy, and pathological characteristics before and after treatment. **Results:** The mean observation duration was 368 days (median 302 days). A total of 10 patients received photoimmunotherapy once, 5 received it twice, 2 received it three times, and 2 received it four times. Final local control was achieved in 14 patients with CR, 3 with PR and 1 with SD. Regrettably, 3 patients developed distant metastases after the start of photoimmunotherapy. At the end of the observation period, 11 patients were disease-free, 6 were alive with cancer, and 2 died of carotid artery rupture despite achieving local tumor control. The overall survival rate at 1 year was 88.2 %. **Conclusions:** The outcomes of the photoimmunotherapy demonstrated successful local control of recurrent nasopharyngeal carcinoma. This innovative therapeutic approach holds significant potential for addressing nasopharyngeal cancer recurrence. However, it is crucial to carefully evaluate patients who can safely be treated using this method. Research Sponsor: None.

6069 Poster Session

Perimarginal lymph node metastasis in gingivo-buccal complex carcinoma: Is it time to push the limits of neck dissection?.

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Background: Perimarginal nodes (PMN) are a group of perifacial lymph nodes that lie in close relationship with marginal mandibular nerve (MMN). They lie in the lymphatic drainage pathway of gingivo-buccal cancers (GBC), above the lower border of mandible which forms the superior limit of conventional neck dissection and thus remain unaddressed. With reported incidence of metastasis as high as 20.5%, we aimed to explore incidence of PMN metastasis in GBC, its correlation with histopathological tumor and nodal characteristics. **Methods:** A prospective study was conducted on 112 consecutive treatment naïve patients of GB squamous cell carcinoma. Patients with unresectable nodal disease, distant metastasis and prior radiotherapy or surgery to neck were excluded. PMN dissection was performed in the quadrangle bounded superiorly by the mandibular alveolar ridge, inferiorly by lower border of mandible, anteriorly by mental foramen and posteriorly by anterior border of masseter. On histopathological analysis, serial step sectioning and cytokeratin immunohistochemistry were performed. Prospective clinical characteristics analyzed were subsite, clinical tumor, nodal stage, location of primary and clinical skin involvement. PMN positivity was correlated with demographic, clinical, nodal status. Histopathological characteristics analyzed included tumor grade, pathological tumor, nodal stage, tumor size, skin and/or bone involvement, depth of invasion, Brandwein Gensler histological risk score and lympho-vascular emboli. MMN functional outcome was graded according to House-Brackman (HB) grading recorded at 3 and 6 months postoperatively. **Results:** Baseline characteristics are summarized in the table. The PMN were identified histologically in 75.89% (85/112) patients. Metastasis in these nodes were identified in 15.2% (17/112) patients. Our study revealed an occult PMN metastasis of 16.67% (13/78). None of the pre-operative clinical factors was found to be significant in predicting incidence of metastasis. Higher nodal burden (p=0.01) and pathological skin involvement (p=0.03) had statistically significant odds of having PMN metastasis on multivariable analysis. At 6 months follow-up, none of the patients had any MMN functional deformity at rest. **Conclusions:** There is a high incidence of occult PMN metastasis from gingivo-buccal complex cancer. High nodal stage and pathological skin involvement are independent adverse prognostic factors for PMN metastasis. The limits of conventional neck dissection should be expanded to include clearance of PMN in all cases of gingivo-buccal cancers. Research Sponsor: None.

Age (Years) (Mean ± SD)	49.53 ± 10.99
Sex	
Male	100 (89.3%)
Female	12 (10.7%)
Subsite	
BM	72 (64.3%)
Lower Alveolus	22 (19.6%)
GBS	8 (7.1%)
FOM	5 (4.5%)
RMT	5 (4.5%)
cT	
T1	4 (3.6%)
T2	17 (15.2%)
T3	24 (21.4%)
T4a	45 (40.2%)
T4b	22 (19.6%)
cN	
N0	78 (69.6%)
N1	17 (15.2%)
N2b	7 (6.2%)
N2c	1 (0.9%)
N3b	9 (8.0%)

Neoadjuvant tislelizumab plus chemotherapy followed by salvage surgery and adjuvant tislelizumab for recurrent head and neck squamous cell carcinoma after radiotherapy: A single-arm, phase II trial.

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Background: Locoregional recurrence remains a significant challenge in head and neck squamous cell carcinoma (HNSCC) after surgery and radiotherapy. Salvage surgery is the best option if negative margins can be achieved, and this can be strengthened in the era of immunotherapy. However, some relevant questions remain unanswered. The objectives of this prospective study were to evaluate the efficacy and safety of neoadjuvant tislelizumab plus chemotherapy followed by salvage surgery and adjuvant tislelizumab for recurrent HNSCC after radiotherapy. **Methods:** In this phase II, single-arm study, eligible pts 18 years of age or older with locoregional recurrent HNSCC after radiotherapy received neoadjuvant therapy with tislelizumab (200 mg), albumin-bound paclitaxel (260 mg/m^2), and cisplatin (60-75 mg/m^2) Q3W for 2 cycles, followed by salvage surgery and adjuvant tislelizumab (200 mg) Q3W for 6 cycles. The primary endpoint was major pathologic response (MPR) rate. Secondary endpoints included pathological complete response (pCR) rate, objective response rate (ORR), event-free survival (EFS), overall survival (OS) and safety. **Results:** Between March 2022 and September 2023, 34 pts were enrolled. Median age was 56 (30-75) yrs, 20.6% smoking history, 20.6% alcohol history and 61.8% male. All pts completed neoadjuvant therapy with an ORR of 35.3% (12/34) and DCR of 94.1% (32/34). Twenty-six pts (23 OSCC, 3 OPSCC) successfully underwent surgery with MPR rate 19.2% (5/26), of which the pCR rate was 15.4% (4/26). At median follow-up of 15.1 months, 1-year EFS was 63.4% and 1-year OS was 82.5% for per-protocol population. Twenty-five pts complained symptoms included pain, trismus, dysphagic, and speech disorders at baseline visit, and 84% (21/25) achieved remission after 2 cycles of neoadjuvant therapy. Grade 1-2 adverse events (AEs) with an incidence greater than 10% include 94.1% alopecia, 38.2% fatigue, 35.3% anorexia, 17.6% hypothyroidism and 14.7% anemia. Grade 3-4 adverse events (AEs) occurred in 1 pts (2.9%) with G3 hyperglycemia. **Conclusions:** Neoadjuvant and adjuvant tislelizumab with salvage surgery is well tolerated. The 1-year EFS and OS compared favorably with historical data. These encouraging results warrant further investigations. Clinical trial information: ChiCTR2100054296. Research Sponsor: None.

6071 Poster Session

A prospective multicenter trial of dose escalation for weekly gemcitabine concurrent with intensity-modulated radiotherapy following cisplatin and gemcitabine induction chemotherapy in patients with locally advanced nasopharyngeal carcinoma.

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Background: Gemcitabine and cisplatin induction chemotherapy, followed by cisplatin-based concurrent chemoradiotherapy, constitutes the standard treatment for locally advanced nasopharyngeal carcinoma (LANPC). However, the substantial cumulative dosage of cisplatin used in this approach renders it intolerable for many patients due to advanced age or compromised renal function. Therefore, identifying alternative chemotherapeutic agents is crucial. Gemcitabine is a potent radiosensitizer with an overall favorable safety profile. Despite extensive research on the maximum tolerated dose (MTD) of concurrent gemcitabine chemotherapy in head and neck cancer, its MTD as a single-agent chemotherapy concurrently administered with intensity-modulated radiotherapy (IMRT) in LANPC remains uncertain. **Methods:** Patients diagnosed with stage III-IVa nasopharyngeal carcinoma were prospectively enrolled in three hospitals located within the largest NPC endemic area in southern China. After two cycles of cisplatin plus gemcitabine induction chemotherapy, patients underwent combined concurrent radiochemotherapy (70 Gy/6-7 weeks) with weekly gemcitabine. The initial dose level was set at 25mg/m^2 and subsequently escalated in a sequential manner to higher doses of 50mg/m^2, 100mg/m^2, 200mg/m^2, and 300mg/m^2 etc. Our study employed a dose escalation strategy in which the dosage was incremented to the next group only if no more than one out of six patients experienced Dose-Limiting Toxicity (DLT), until DLT occurred in at least two patients. Patients underwent follow-up evaluations every three months. This study is registered with ClinicalTrials.gov under NCT04522050. **Results:** Between October 2018 and December 2023, a total of 39 Chinese patients were enrolled, 36 (27 males, 9 females) patients were considered evaluable. The incidence of DLT was observed in two out of six patients receiving a dosage level of 300 mg/m^2, with both cases presenting Grade 3 oral mucositis. Subsequently, the study was replicated using the same dosage level, resulting again in two instances of DLT: one case with Grade 3 radiation dermatitis and another case with oral mucositis. Consequently, a reduced dosage level of 200mg/m^2 was determined as MTD. No significant hematological toxicity or serious gastrointestinal adverse events were observed. Tumor response evaluation by MRI after twelve weeks of IMRT showed a complete response rate of 100%. To date, only two cases (5.56%) have been reported exhibiting tumor recurrence. **Conclusions:** The MTD for weekly gemcitabine with IMRT following induction chemotherapy in LANPC is determined to be 200 mg/m^2. The DLT associated with this treatment regimen primarily consists of radiation dermatitis and/or oral mucositis. Clinical trial information: NCT04522050. Research Sponsor: None.

Induction-concurrent versus concurrent-adjuvant chemoradiotherapy in patients with high-risk N2–3 nasopharyngeal carcinoma: An open-label, randomised, controlled, phase 3 trial.

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Background: It remains uncertain which chemotherapy sequence is more effective for locoregionally advanced nasopharyngeal carcinoma (NPC). We aimed to compare the efficacy and safety of induction-concurrent with concurrent-adjuvant chemotherapy in high-risk N2–3 NPC. **Methods:** We conducted an open-label, phase 3, single-centre, randomised controlled trial. Patients aged 18–65 years with stage T1-4N2-3M0 (AJCC 7th staging system) and pretreatment Epstein–Barr virus DNA level ≥1500 copies/ml were enrolled. Eligible patients were randomly assigned (1:1) to receive paclitaxel liposome (135 mg/m^2 intravenously on day 1), cisplatin (25 mg/m^2 intravenously on days 1-3), and fluorouracil (3.75g/m^2 continuous intravenous infusion for 120 h) induction chemotherapy once every 3 weeks, for 3 cycles, followed by concurrent cisplatin (100 mg/m^2 intravenously) on days 1, 22, and 43 of intensity-modulated radiotherapy or concurrent chemoradiotherapy followed by fluorouracil (4 g/m^2 in continuous intravenous infusion for 96 h) and cisplatin (80 mg/m^2 intravenously on day 1) once every 4 weeks, for 3 cycles. Randomisation was performed using computer-generated random number code with a block size of 6, stratified by nodal category (N2 or N3). The primary endpoint was 3-year progression-free survival (PFS) in the intention-to-treat population. This trial was registered with ClinicalTrials.gov (number NCT03306121). **Results:** Between 20 November 2017 and 19 March 2021, 162 patients were assigned to the induction-concurrent group and 162 to the concurrent-adjuvant group. Regarding the data cutoff (20 January 2024), the median follow-up period was 51.7 months. The 3-year PFS rates were 73.4% (95%CI 65.9%-79.5%) in the induction-concurrent group and 69.8% (95%CI 62.0%-76.2%) in the concurrent-adjuvant group (HR 0.85, [95%CI 0.58-1.26], P=0.43). Patients in the induction-concurrent group had significantly better 3-year distant metastasis-free survival rate at 81.4% (95% CI, 74.5%–86.6%) compared with those in the concurrent-adjuvant group at 71.0% (95% CI, 63.3%–77.3%) (HR, 0.64; 95% CI, 0.42–0.98; p=0.04). There were no differences on overall survival and locoregional failure-free survival between the two groups. The most common acute grade 3 + adverse events were leukopenia (53 [33.1%] of 160 in the induction-concurrent group vs. 47 [33.1%] of 142 in the concurrent-adjuvant group), neutropenia (51 [31.9%] vs. 32 [22.5%]), and mucositis (47 [29.4%] vs. 42 [29.6%]). The most common grade 3 + late adverse event was auditory or hearing loss (10 [6.3%] vs. 12 [8.5%]). **Conclusions:** Induction-concurrent chemotherapy does not significantly improve PFS compared with concurrent-adjuvant chemotherapy in high-risk N2–3 NPC. Long-term follow-up is required to determine long-term efficacy and toxicities. Clinical trial information: NCT03306121. Research Sponsor: None.

6073 Poster Session

Neoadjuvant tislelizumab with afatinib for locally advanced head and neck squamous cell carcinoma (neoCHANCE-1): An open-label, single-arm, phase 2 study.

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Background: For patients with locally advanced head and neck squamous cell carcinoma (HNSCC), even receiving surgery with adjuvant radiotherapy or chemoradiotherapy, those remain at high risk of recurrence or metastasis. Neoadjuvant immunotherapy has been used in HNSCC, but provides only modest pathological response. Given single agent activity and unique mechanism of action of immune checkpoint inhibitors and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), we aimed to evaluate the antitumour activity and safety of neoadjuvant PD-1 blockade with EGFR inhibition in locally advanced HNSCC. **Methods:** This open-label, single-arm, phase 2 trial was done at a a tertiary hospital in China. Eligible patients were aged 18 years or older and had resectable HNSCC disease, had an Eastern Cooperative Oncology Group performance status of 0–1, had at least one measurable target lesion according to the RECIST 1.1, had no prior antitumor therapy for HNSCC. Patients received neoadjuvant treatment with intravenous tislelizumab (200 mg) on the first day of each 3 week, with totally two cycles and orally afatinib (30 mg) starting on the first treatment day and ending on the day before surgery, with totally six weeks, and then patients proceeded to receive surgical resection. The primary endpoint was major pathological response, defined as the presence of 10% or less residual viable tumour at the time of surgery. **Results:** A total of 25 patients were enrolled completed the neoadjuvant therapy. Eight of 23 evaluable patients exhibited a major pathological response (MPR) (35%; 95% confidence interval [CI], 16% - 57%), of which four had a complete pathological response of primary tumor (17%, 95%CI, 5% - 39%). The overall response rate was 48% (12/25, 95%CI: 28% - 69%) and disease control rate was 100% (25/25, 95%CI: 86% - 100%). Common grade 3 - 4 adverse events included diarrhea (5/25 [20%]), hypokalemia (4/25 [16%]) and rash (3/25 [12%]). No treatment related fatalities were observed. Immunologically, post-neoadjuvant treatment demonstrated increased CD3, CD8, and CD56 expression within the tumor microenvironment. The increase of CD8 and CD56 expression level was significant higher in patients achieving MPR, along with elevated circulatory NK cells at baseline, compared to those in patients achieving non-MPR. **Conclusions:** This study underscores encouraging antitumor activity, manageable toxicity profile and promising immune activation elicited by neoadjuvant tislelizumab plus afatinib for HNSCC, which deserves further assessment. Clinical trial information: NCT05517330. Research Sponsor: None.

Analysis of PD-L1 expression in locally advanced head and neck squamous cell carcinoma and its correlation with the efficacy of neoadjuvant immunotherapy + chemotherapy: A retrospective real-world study.

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Background: The incidence rate of HNSCC in Hunan China are notably higher than in other regions, likely due to the high prevalence of betel nut chewing. Therefore, we conducted a study to examine the PD-L1 expression in newly diagnosed locally advanced (stage III-IVB) HNSCC patients. **Methods:** 1. We conducted a retrospective analysis of the PD-L1 expression (represented as CPS) in pre-treatment biopsy tissues from locally advanced HNSCC. 2. 57 patients received neoadjuvant treatment consisting of nab-paclitaxel+ cisplatin+ pembrolizumab. The efficacy of the treatment was evaluated using pathology assessments. **Results:** 1. A total of 373 patients were included. The top five primary sites of the tumors were the tongue(32.17%), Buccal oris (20.91%), oropharynx (10.19%), hypopharynx(9.92%), and gingiva(7.77%). The proportion of patients with PD-L1 CPS≥20 (55.23%) was significantly higher than the 43.20% reported in the KEYNOTE-048 study. Furthermore, the subgroup was even higher in the buccal oris (70.51%) and gingiva (72.41%). 2. A total of 57 patients were tested for PD-L1 CPS and received neoadjuvant treatment.After surgery, 22/57 (38.60%) achieved pathological complete response (pCR) or major pathological response (MPR), 29/57 (50.88%) achieved partial pathological response (pPR), resulting in an overall response rate (ORR) of 89.47%. In the PD-L1 CPS ≥20 group, the ORR was as high as 91.89% (34/37). 3. Among the 57 patients, 36 patients had lymph node metastasis. After treatment, 15/36 patients (41.67%) achieved pCR/MPR in lymph nodes, 7/36 patients (19.44%) achieved pPR, resulting in an ORR was 61.11% (22/36). **Conclusions:** 1. The oral cavity is the most common primary in HNSCC in Hunan,China. In the locally advanced , the proportion of PD-L1 CPS ≥20 is higher than reported in other studies. 2. Regardless of PD-L1 expression, neoadjuvant treatment with nab-paclitaxel+ cisplatin+ pembrolizumab has shown a high rate of local disease control in newly diagnosed HNSCC patients. Additionally, the use of neoadjuvant therapy has improved the delineation of surgical safety margins, leading to 100% R0 resections in all 57 patients. 3. The response of the primary lesion in patients treated with neoadjuvant therapy is better than that of the lymph node. Patients with a well-responding primary lesion but multiple lymph node metastases should be closely monitored for the possibility of short-term systemic metastasis. Research Sponsor: Subprojects of major scientific and technological research projects in Hunan Province; 2023ZJ1120; Research Program Project of Hunan Provincial Health Commission; B2019095.

Disease status	Tongue	Buccal oris	Oropharynx	Hypopharynx	Gingiva	Cervical esophagus	Throat	others
Number	120	78	38	37	29	18	14	39
CPS < 1	8(6.67%)	2(2.56%)	6(15.79%)	4(10.81%)	3(10.34%)	3(16.67%)	1(7.14%)	7(17.95%)
1≤CPS < 19	41(34.17%)	21(26.92%)	15(39.47%)	20(54.05%)	5(17.24%)	11(61.11%)	8(57.14%)	12(30.77%)
CPS≥20	71(59.17%)	55(70.51%)	17(44.74%)	13(35.14%)	21(72.41%)	4(22.22%)	5(35.71%)	20(51.28%)

6075 Poster Session

Sequential chemoradiotherapy versus induction chemotherapy plus concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: A multicentre, open-label, non-inferiority, randomised, phase 3 trial.

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Background: Induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT) has been regarded as standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC) due to its favorable disease control. Now, distant metastasis was the main cause of failure. However, concurrent cisplatin is associated with intolerable toxicities and ineffective in preventing distant metastasis. Since IMRT enhances the local control and chemotherapy before or after radiotherapy decreases the risk of distant failure, it is worth exploring whether sequential chemoradiotherapy (SCRT) regimen could replace IC+CCRT for patients with LA-NPC. **Methods:** This open-label, phase 3, non-inferiority clinical trial was conducted from January 2018 to September 2021 in 6 centers in China. Patients aged 18–65 years with stage T1-4N2-3 or T3-4N0-1 M0 NPC were randomly assigned (1:1) to receive 2 cycles of IC with GP regimen (gemcitabine 1000mg/m^2 d1,8 + cisplatin 25 mg/m^2 d1-3, q21d) plus IMRT, followed by 2 cycles of adjuvant chemotherapy (AC) with the same regimen or IC with GP regimen for 2 cycles followed by IMRT plus concomitant weekly cisplatin (30 mg/m^2). The primary endpoint was 3-year failure-free survival (FFS) with non-inferiority margin of 10% (HR$<$1.6) and the incidence of grade $\geq$3 acute mucositis during radiotherapy. Efficacy analysis and safety analysis were dividedly performed in the intention-to-treat and safety population. **Results:** A total of 420 patients were randomly assigned to SCRT group (n = 210) or IC+CCRT group (n = 210). With a median follow-up of 47.0 months (IQR: 35.0-57.8), the 3-year FFS was 84.0% in SCRT group versus 79.8% in IC+CCRT group (log rank P=0.344), with an HR of 0.804 (95% CI, 0.510 to 1.266) and absolute difference of 4.2% (95% CI, -3.2 to 11.6). No significant differences were observed between groups in 3-year overall survival (97.4% vs. 94.5%; HR 0.413; 95% CI, 0.159 to 1.076; log rank P=0.061), locoregional control (91.7% vs. 88.8%; HR 0.767; 95% CI, 0.420 to 1.401; log rank P=0.386), or distant metastasis-free survival (93.6% vs. 91.5%; HR 0.756; 95% CI, 0.376 to 1.520; log rank P=0.430). Compared with IC+CCRT group, the SCRT group had significantly lower incidences of grade $\geq$3 acute nonhematological AEs due to the omission of concurrent chemotherapy (including acute mucositis 29.0% vs. 41.9%, P$<$0.001; nausea 9.5% vs. 18.1%, P=0.011; and vomiting 3.8% vs. 9.5%, P=0.019), and higher incidences of grade $\geq$3 acute hematological AEs (including thrombocytopenia and leukopenia) due to the additional AC. **Conclusions:** For LA-NPC, SCRT was not inferior in 3-year FFS to IC+CCRT. It might be an alternative treatment for LA-NPC patients with fewer sever nonhematological AEs during IMRT. Clinical trial information: NCT03366415. Research Sponsor: Shanghai Sailing Program; Scientific and Innovative Action Plan of Shanghai.

Induction chemotherapy effects on very advanced (T3/T4) human papillomavirus-related oropharyngeal cancer for participation in hypoxia-directed major de-escalation (30 Gy) definitive treatment trial.

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Background: De-escalation trials in human papillomavirus associated oropharyngeal carcinoma (HPV+ OPC) often exclude patients with very locally advanced disease. We previously demonstrated in a Phase II study that for patients with T1-T2 HPV+OPC that de-escalation to 30Gy of definitive chemoradiation based on lack of hypoxia on ^{18}F-FMISO (fluoromisonidazole) PET (ROC Study) is associated with excellent outcomes (JNCI 2021; JCO 2024). Here, we hypothesized that induction chemotherapy (ICT) could be used in locally advanced (T3-T4) HPV+OPC to down-stage patients and make them eligible for de-escalation and simultaneously improve 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 (i.e. pts ineligible for 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 (ROC), after ICT, patients needed to be down-staged (<=T2). ^{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 at any time point, no further scans 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 (description only in this pilot study). This abstract reports only on the outcomes of the ICT portion of the study. **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. Of the 17 evaluable patients post ICT, 14 (82%) had no hypoxia on post ICT scan (other 3 still receiving ICT). Of 3 patients with hypoxia after ICT, 2 had resolution 2 weeks into radiotherapy, and 1 patient is still pending intra-treatment scan. All 17 evaluable patients had a significant enough of a response anatomically to allow treatment on the ROC Study. All patients to date were able to receive 2 cycles of cisplatin (100 mg/m2) without dose or treatment adjustment. **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, but a larger study is needed to confirm these results. Further followup of outcomes (2 year local control rate) is still needed. Clinical trial information: NCT05491512. Research Sponsor: None.

6077 Poster Session

Mapping the mental health correlates of head and neck cancer: A systemic review and meta-analysis.

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Background: Patients with head and neck cancer (HNC) present particularly high levels of mental health disorders. Yet the actual rate of relevant mental health symptoms and disorders, along with its determinants, remains unclear. **Methods:** A PRISMA/MOOSE-compliant systematic review and quantitative effects meta-analysis (PROSPERO: CRD42023441432) was conducted to determine the prevalence of depression, anxiety, distress, post-traumatic stress, insomnia and suicide among patients with HNC. MEDLINE, WebofScience, Cochrane Central Register, KCI-Korean Journal, SciELO, Russian Science Citation Index and Ovid/PsycINFO databases were searched from database inception to August 1, 2023. Secondary analyses were used to assess longitudinal trajectories of the samples over time. **Results:** 208 studies (n=713,527, median age 60.7; 25.5% female) were included. 19.5% patients reported depressive symptoms (95% confidence interval [CI]=17-21%), 17.8% anxiety symptoms (95%CI=14-21%), 34.3% distress (95%CI=29-39%), 17.7% post-traumatic symptoms (95%CI=6-41%) and 43.8% insomnia symptoms (95%CI=35-52%). Diagnostic criteria assessments revealed lower prevalence of disorders: 10.3% depression (95%CI=7-13%), 5.6% anxiety (95%CI=2-10%), 9.6% insomnia (95%CI=1-40%), and 1% post-traumatic stress (95%CI=0-84.5%). Pooled suicide incidence was 161.16 per 100,000 individuals per year (95%CI=82-239). A higher prevalence of anxiety was found in patients undergoing primary chemoradiation compared to surgery, and increased distress in smokers and advanced tumor staging. European samples exhibited lower prevalence of distress. Patients were more likely to be depressed after finishing radiation treatment. **Conclusions:** Patients with HNC exhibited a notable prevalence of mental health issues across various domains, where suicide emerged as a particular concern. There is a need for improved methods of assessment and intervention for these mental health concerns. Preventive interventions should be implemented before the start of radiation treatments. Research Sponsor: None.

Prevalence of mental health symptoms across each of the domains and scales studied.

Scale	No. Studies	Sample size	Prevalence	95% CI	Heterogeneity I^2 (%)	Heterogeneity *p*value
Depressive symptoms	127	23302	0.195	0.173 – 0.218	93.3	< 0.01
Depression disorder	27	331653	0.103	0.079 – 0.133	99.5	< 0.01
Anxiety symptoms	80	10478	0.178	0.145 – 0.215	90.9	< 0.01
Anxiety disorder	15	215368	0.056	0.029 – 0.105	99.5	< 0.01
Distress symptoms	38	5057	0.343	0.298 – 0.390	88.2	< 0.01
Insomnia symptoms	3	667	0.438	0.358 – 0.522	0.00	0.63
Insomnia disorder	6	67364	0.096	0.016 – 0.406	99.4	< 0.01
PTSD symptoms	3	180	0.177	0.061 – 0.413	61.5	0.07
PTSD disorder	3	344	0.010	0.000 – 0.848	66.5	0.05

Neoadjuvant immunochemotherapy for locally advanced hypopharyngeal squamous cell carcinoma: Pooled results analysis from two prospective single-arm phase 2 trials.

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Background: Hypopharyngeal squamous cell carcinoma (HPSCC) suffered poorest prognosis among various head and neck lesions. The efficacy, safety, and biomarkers of immunochemotherapy as neoadjuvant treatment for locally advanced HPSCC deserves further investigation. **Methods:** This study enrolled untreated (AJCC^{8th}) stage III-IV HPSCC patients (pts) from two phase 2 trials (ChiCTR2200060094; ChiCTR2200055719). The treatment regimen involved PD-1 inhibitors plus taxanes and platinum-based chemotherapy for two cycles. A multidisciplined team consultation determined either surgery or chemoradiotherapy. The primary endpoint was ORR and pCR. Second endpoints included DCR, PFS, OS, and safety. Biomarker analysis mainly via plasma Olink proteomics assay. **Results:** From June 9, 2021 to December 5, 2023, 68 pts received treatment and 30 pts underwent surgery. The baseline characteristics were shown in the table. Most AEs were grade 1-2, and the incidence of grade 3 AEs was 30.9% , mainly neutropenia (20.6%). The ORR, DCR were 63.2% (43/68) and 100% (68/68). Imaging results showed that 38.2% (26/68) of patients were assessed as depth partial response (shrinkage $\geq$ 50%) after neoadjuvant treatment. Among 30 patients who underwent surgery, pCR reached 23.3% (7/30), two pts with CT/MRI assessed SD were ultimately confirmed pCR. Median follow-up was10.5 months, the median PFSand OS were not reached. The 1 year-PFS and OS rates were 74.2% and 86%. The 1 year- laryngeal function preservation rate was 93.9%. 22 pts with baseline plasma samples were included in the analysis of serum proteome biomarkers. The plasma protein expression of GZMH, GZMA, KLRD1, IL12RB1, CD244, NCR1, CXCL10, CXCL13, LAG3, IL10, MCP-3, CCL20, CD8A, TWEAK, and HGF at baseline was significantly lower in pts with tumor shrinkage$\geq$50% which suggested the potential of these biomarkers in predicting treatment response. **Conclusions:** PD-1 inhibitors combined with taxanes and platinum-based chemotherapy are well tolerated and effective in the neoadjuvant treatment of locally advanced HPSCC. The discordance between radiological and pathological assessments after neoadjuvant immunotherapy deserves further exploration, which requires a more precise method to screen the appropriate treatment population. Alterations in plasma proteins may be promising biomarkers for predicting treatment response in the future. Clinical trial information: ChiCTR2200060094; ChiCTR2200055719. Research Sponsor: None.

Baseline characteristics of pts.

	Overall (N=68)
Age	
Median [range]	58.0 [42.0, 74.0]
Stage	
III	8 (11.8%)
IV	60 (88.2%)
PD-L1 CPS	
<1	2 (2.9%)
1-19	36 (52.9%)
>=20	24 (35.3%)
unknown	6 (8.8%)
TMB	
<10	34 (50%)
>=10	5 (7.4%)
unknown	29 (42.6%)
Following therapy	
Surgery	30 (44.1%)
Not surgery	38 (55.9%)
PD-1	
Pembrolizumab	47 (69.1%)
Tislelizumab	21 (30.9%)

PD-L1: programmed death-ligand 1; CPS: combined positive score.

6079 Poster Session

Evaluating perceived barriers to optimal care in head and neck cancer: A mixed-methods study.

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Background: Head and neck cancer (HNC) is a complex disease that requires multidisciplinary care and poses significant challenges for patients and healthcare providers. Despite the availability of evidence-based guidelines, achieving optimal HNC care faces many barriers. This mixed-methods study explores the perceived barriers by patients and clinicians to optimal HNC care. **Methods:** The Association of Cancer Care Centers (ACCC) collaborated with the Head and Neck Cancer Alliance and the American Society for Radiation Oncology (ASTRO), along with an expert steering committee of multidisciplinary roles representing diverse cancer care centers, to evaluate the current landscape of HNC care delivery. Using an explanatory sequential design, ACCC conducted patient (n= 247) and provider (n=206) surveys and four focus groups which included patients with HNC and clinicians to capture barriers to optimal HNC care. **Results:** Barriers were classified as patient-related, provider-related, and system-related factors. Survey highlights include: 32% of patients received multimodal treatment including surgery, radiation, and medications; 50% of clinicians were at centers that utilized multidisciplinary clinics for HNC; 60% of patients "strongly agreed" they were satisfied with their care; 48% of patients felt members of their treatment team communicated and coordinated care "very well"; and 56% of patients "strongly agreed" clinicians explained their diagnosis comprehensibly. Clinicians and patients differed in their perspectives on how care was delivered in a few areas: 52% of clinicians vs. 40% of patients agreed that side effects of treatment were explained in ways that patients could understand; 29% of clinicians vs. 21% of patients felt that emotional concerns and mental health needs were addressed. Clinicians identified key areas that needed improvement to provide more effective care: financial resources (62%), dedicated navigation (45%), and coordination across members of the care team (45%). Qualitative analysis of focus group responses identified travel logistics to care centers, inadequate health insurance coverage, and lack of dental insurance delaying care as major systems-related barriers to optimal HNC care. **Conclusions:** This study revealed insights into the delivery of optimal care in HNC in the US, including being a high-volume center, having dedicated HNC nurse navigators, and multidisciplinary meetings for care coordination. Multifactorial barriers to optimal HNC care were also identified and will be used to inform future educational programming and the development of interventions to improve care. Research Sponsor: EMD Serono.

Nivolumab combined with radical chemoradiotherapy sparing concurrent cisplatin in high-risk locoregionally advanced nasopharyngeal carcinoma (PLATINUM): An investigator-initiated, open-label, multicenter, single-arm, phase II clinical trial.

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Background: The current standard therapy for locoregionally advanced nasopharyngeal carcinoma (LANPC) is radical chemoradiotherapy using induction chemotherapy plus concurrent chemoradiotherapy. However, concurrent cisplatin leads to severe acute (54.0–61.0%) and late (9.2–11.4%) toxicities. We hypothesized that nivolumab combined with radical chemoradiotherapy sparing concurrent cisplatin would obtain promising survival and low toxicity in high-risk LANPC. **Methods:** In this single-arm, phase II clinical trial (NCT03984357), patients with high-risk LANPC (T4N1M0 or T1–4N2–3M0) were recruited from 7 hospitals in China to receive nivolumab (360 mg once every 3 weeks for 3 cycles [Q3W x 3]) + induction chemotherapy (gemcitabine 1000 mg/m^2 + cisplatin 80 mg/m^2, Q3W x 3), followed by nivolumab (360 mg, Q3W x 3) + intensity-modulated radiotherapy (PGTVnx, 70Gy/33fx), and thereafter adjuvant nivolumab (480 mg, Q4W x 6). The primary end point was 3-year failure-free survival (FFS), defined as the time from enrollment to any disease failure or death. Secondary end points were safety and quality-of-life (QoL) assessed by cellphone-based EORTC/FACT questionnaires. **Results:** Between April 2020 and October 2020, 152 patients (median [IQR] age, 49 [39–56] years; 18.4% women) were included. After a median follow-up of 39 months (≥ 36 months, 89.5%), the 3-yr FFS was 88.8% (95% CI, 83.9–94.0%) and the 3-yr overall survival was 98.0%. Sixty (40.2%) patients had grade 3–4 acute treatment-related adverse events (trAEs) throughout treatment; 11 (7.2%) were associated with potential immunologic causes mainly involving hepatic (aspartate aminotransferase increased, 3.3%) and skin toxicities (rash/dermatitis, 2.0%). A total of 123 patients completed all required treatment, including 6 cycles of adjuvant nivolumab, with an overall compliance rate of 80.9%. The incidences of grade 3–4 acute trAEs in the induction, radiotherapy, and adjuvant phases were 30.2%, 16.7%, and 6.0%, respectively; compliance rates, 95.4%, 96.5%, and 91.8%, respectively. Eight (5.2%) patients had grade 3–4 late trAEs, e.g., hearing impaired (3.3%) and dry mouth (0.7%). No treatment-related death was observed. Patients had consistent negative changes in general QoL from baseline between the radiotherapy and induction phases, except for the domains of global health status and physical function/well-being, which were more common during the radiotherapy phase. **Conclusions:** Nivolumab incorporated into induction chemotherapy followed by radiotherapy has a promising efficacy and low toxicity for high-risk LANPC patients. A phase 3 non-inferior randomized clinical trial assessing PD-1 blockade plus this de-intensified radical chemoradiotherapy is underway (NCT04907370). Clinical trial information: NCT03984357. Research Sponsor: Bristol Myers Squibb; Chinese Society of Clinical Oncology.

Beyond the initial diagnosis: Epidemiological factors associated with second primary cancers among patients with head and neck squamous cell carcinoma (a SEER-based study).

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Background: Patients with Head and Neck cancer squamous cell carcinoma (HNSSC) have an increased risk of developing a Second Primary Cancer (SPC). We evaluated the epidemiological factors associated with SPC among patients with Stage 1-4 HNSCC using the SEER database from 2004-2020. **Methods:** Stage 1-4 HNSSC cases from 2004-2020, with a minimum of six months of follow-up, were identified using SEER.Stat 8.4.2 using ICD-10 CM codes. Adjusted odd's ratios (aOR) for developing SPC (dependent variable) and the independent variables (sex, age, race and ethnicity, site of primary cancer, and marital status) were generated using multivariate logistic regression. All the analyses were performed on SAS OnDemand. **Results:** 127,919 cases of HNSCC were identified from 2004-2020. Oral cavity cancer accounted for 41.2% of the cases. 18,192 (14.2%) patients developed SPC. Patients with primary hypopharynx, laryngeal, and oral cavity cancer had the highest odds of developing SPC ($p < 0.0001$). The most prevalent sites for developing SPC were the lung (25.0%), head and neck (24.1%), and prostate (10.6 %). Males had significantly higher odds of developing SPC than females (aOR - 1.11 (1.07, 1.5)). When compared to the NH-white population, Hispanics and NH-Asian had significantly lower odds of developing SPC (aOR - 0.72 (0.68, 0.77) and 0.72 (0.68, 0.78) respectively), while NH-Blacks had higher odds of developing SPC (aOR - 1.1(1.01,1.23)). **Conclusions:** Our study emphasizes the substantial risk of SPC in HNSCC patients, with oral cavity cancer as the predominant primary cancer subtype. Specific HNSCC sites show elevated SPC odds, mainly primary hypopharyngeal cancer, emphasizing the need for targeted surveillance. Demographic variations reveal gender and racial disparities in SPC susceptibility, advocating for tailored monitoring and preventive strategies in high-risk subpopulations to enhance overall cancer care and survivorship. Research Sponsor: None.

Characteristic	Total Cohort (N = 127,919)	Second Primary Cancer (N = 18,192)	aOR (95% CI)	Characteristic	Total Cohort (N = 127,919)	Second Primary Cancer (N = 18,192)	aOR (95% CI)
Sex, Female, N(%)	34,174 (26.7)	4,480 (24.6)	**0.90 (0.86, 0.93)**	Primary Cancer site, N(%)			
Age, median (IQR)	61 (53,69)	63 (56, 70)	1.012 (1.011, 1.013)	Oral cavity	52,639 (41.2)	7,570 (41.6)	ref
Race, N(%)				Tonsil	23,131 (18.1)	2,809 (15.4)	**0.86 (0.82, 0.90)**
NH-White	94,066 (73.5)	14,125 (77.6)	ref	Nasopharynx	6,936 (5.4)	588 (3.2)	**0.66, (0.60, 0.72)**
NH-Black	11,699 (9.2)	1,774 (9.8)	**1.1 (1.01, 1.13)**	Oropharynx	3,900 (3.0)	497 (2.7)	**0.89 (0.81, 0.98)**
Hispanic	11,467 (9.0)	1,238 (6.8)	**0.72 (0.68, 0.77)**	Hypopharynx	2,161 (1.7)	379 (2.1)	**1.30 (1.16, 1.45)**
NH-Asian	9,313 (7.3)	933 (5.1)	**0.72 (0.67, 0.78)**	Larynx	25,767 (20.1)	4,765 (26.1)	**1.28 (1.22, 1.33)**
NH- Alaska Native	830 (0.6)	105 (0.6)	0.90 (0.72, 1.10)	Other HNC	13,385 (15.4)	1,584 (8.7)	0.77 (0.72, 0.83)

6083 Poster Session

Recent safety and efficacy findings from a phase 1b/2 open-label combination study of ASP-1929 photoimmunotherapy with anti-PD-1 therapy in EGFR-expressing advanced head and neck squamous cell carcinoma (HNSCC).

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Background: In the challenging landscape of advanced HNSCC, patients (pts) have overall low survival and high locoregional (LR) recurrence rates. While LR progression is a key contributor to morbidity and mortality, LR control remains low despite aggressive therapy including surgery, radiation, chemotherapy, and immunotherapy. ASP-1929 photoimmunotherapy (PIT) combines EGFR-targeting cetuximab, with a light-activatable dye, IRDye 700DX, and a laser light for localized drug activation. This novel approach has demonstrated rapid and selective tumor necrosis in preclinical studies, and a manageable safety profile in HNSCC early clinical trials. Phase I/II and preclinical data indicate a potential synergy in anti-tumor activity of PIT when combined with anti-PD-1 therapy. Here we present updated interim evaluation findings based on a recent data cut from this study initially presented at the 2023 American Head and Neck Society meeting. **Methods:** A phase 1b/2 open-label study of pts with recurrent locally advanced (rLA) and/or metastatic (m) HNSCC evaluating the safety and efficacy of ASP-1929 PIT in combination with anti-PD-1 (pembrolizumab) therapy (NCT04305795). Pts with measurable disease by modified RECIST 1.1, at least 1 lesion accessible to light illumination, combined positive score (CPS) ≥1, and who were not candidate for LR therapy could be eligible for the study. Treatment included ASP-1929 PIT (infusion day 8, target tumors illuminated 24±4 hours later) plus anti-PD-1 (days 1&22) during a 6-week cycle for up to 24 months. Primary objectives: safety/tolerability; objective response rate (ORR). Secondary objectives: overall survival (OS); progression-free survival (PFS); duration of response (DOR). Planned sample size: 26 HNSCC pts. **Results:** Of the 19 r/m HNSCC pts enrolled, 18 pts received both study therapies (PIT-evaluable). Data cut-off was August 31, 2023 (previously reported data cut-off: October 4, 2022). Efficacy results updated for the 18 PIT-evaluable pts: ORR of 33.3% (95% CI 13.3-59.0), including 4 CRs (22.2%) and 2 PRs (11.1%). Median OS not reached; 24-month OS rate estimate was 52.4% (95%CI 25.9-73.4). No change in median PFS, 2.9 months (95%CI 1.4-14.6). Median DOR was not reached at data cut-off (range 2.8+ to 18.0+ months). Safety data remained consistent with the data previously presented. Most common serious adverse reactions were dysphagia (10.5%) and tongue edema (10.5%). There were two grade 4 events: laryngeal edema (PIT-related) and tumor hemorrhage due to advanced disease, and no fatal events. **Conclusions:** ASP-1929 PIT in combination with anti-PD-1 therapy was generally well tolerated. Initial data demonstrate promising overall survival and response rates with this combination therapy in pts with rLA and/or m HNSCC lacking LR treatment options. Clinical trial information: NCT04305795. Research Sponsor: None.

Neoadjuvant and adjuvant toripalimab for high-risk locoregionally advanced nasopharyngeal carcinoma: A randomized, double-blind, placebo-controlled phase 2 trial.

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Background: Patients with locoregionally advanced nasopharyngeal carcinoma with high pretreatment plasma Epstein–Barr virus (EBV) DNA levels remain at high risk for recurrence after platinum-based concurrent chemoradiotherapy. We aimed to assess whether the addition of neoadjuvant and adjuvant toripalimab (anti-PD-1) to chemoradiotherapy could improve treatment outcomes in this patient population. **Methods:** We conducted a single-center, randomized, double-blind phase 2 trial to evaluate neoadjuvant and adjuvant toripalimab treatment for high-risk locoregionally advanced nasopharyngeal carcinoma. Participants with nasopharyngeal carcinoma (stage III-IVA, AJCC 8th Staging System, pretreatment plasma EBV DNA ≥1500 copies/ml) were assigned in a 2:1 ratio to receive neoadjuvant toripalimab (240 mg) or placebo once every 2 weeks for 2 cycles, followed by concurrent chemoradiotherapy and adjuvant toripalimab (240 mg) or placebo once every 3 weeks for up to 8 cycles. The primary endpoint was progression-free survival at 2 years in the intention-to-treat population. The secondary endpoints included overall survival, locoregional relapse-free survival, distant metastasis-free survival at 2 years, a major pathological response in nasopharynx biospy, overall response, treatment adherence, quality-of-Life and safety. **Results:** From December 2019 through December 2021,100 patients were assigned to the neoadjuvant-adjuvant toripalimab group, and 50 to the placebo group. At a median follow-up of 26.9 months, progression-free survival at 2 years was 91.8% in the toripalimab group and 73.9% in the placebo group (hazard ratio for disease progression or death = 0.33; 95% confidence interval [CI], 0.15 to 0.76; P = 0.006). Overall survival was longer in the toripalimab group than in the placebo group (100% vs. 94.0% of patients alive at 2 years; hazard ratio for death, 0.10; 95% CI, 0.01 to 0.82). Distant metastasis–free survival at 2 years was 92.8% and 80.0% (hazard ratio for distant metastasis or death, 0.39; 95% CI, 0.16 to 0.96); locoregional recurrence–free survival at 2 years was 99.0% and 82.0% (hazard ratio for locoregional recurrence or death, 0.09; 95% CI, 0.02 to 0.41). Across all treatment phases, 73.7% of toripalimab group participants and 68.0% of placebo group participants had grade 3 or higher treatment-related adverse events. No deaths related to toripalimab therapy occurred. **Conclusions:** In patients with high-risk locoregionally advanced nasopharyngeal carcinoma, compared with concurrent chemoradiotherapy, neoadjuvant toripalimab combined with concurrent chemoradiotherapy and adjuvant toripalimab significantly improved progression-free survival, overall survival, locoregional recurrence–free survival, and distant metastasis–free survival. Clinical trial information: NCT03925090. Research Sponsor: None.

6085 Poster Session

MR radiomics and neoadjuvant chemo-responsiveness with insights into selective treatment de-intensification in HPV-positive oropharyngeal carcinoma.

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Background: In HPV-positive oropharyngeal squamous cell carcinoma (OPSCC), patients with good response to neoadjuvant chemotherapy (NAC) exhibit superior prognosis. Accurate prediction of NAC response allows for NAC candidate selection and personalized treatment de-intensification in HPV-positive OPSCC. In this study, we aimed to apply baseline magnetic resonance (MR) radiomic features to predict NAC response and prognosis. **Methods:** Pre-treatment MR images and clinical data of 131 patients with HPV-positive OPSCC were retrieved from Fudan University Shanghai Cancer Center. Radiomic features of both oropharyngeal lesions and metastatic nodes were extracted on T2WI and contrast-enhanced T1WI sequence. Patients were divided into training cohort (n=47), prospective validation cohort (n=49) and real-world validation cohort (n=35). Following radiomic feature selection, a linear support vector machine (SVM) model was built and validated for NAC response prediction. Nomograms that combined radiomics and clinical characteristics were then developed to predict survival outcomes. The performance of response models was assessed by the area under the curve (AUC), accuracy, sensitivity, specificity and prognostic models were measured by C-index. RNA-seq and proteomic data were further leveraged and compared to interpret the molecular features underlying radiomic signatures with differential NAC response. **Results:** For NAC response prediction, the fusion model with both oropharyngeal and nodal radiomic signatures on multi-sequence MR images achieved encouraging performance to predict good responders in the training cohort (AUC 0.89, 95% CI, 0.79-0.95) and prospective validation cohort (AUC 0.71, 95% CI, 0.59-0.83). For prognosis prediction, radiomics-based nomograms exhibited satisfactory discriminative ability between low-risk and high-risk patients in training cohort and two validation cohorts (PFS, C-index: 0.85, 0.76 and 0.83; OS, C-index: 0.79, 0.76 and 0.87). An exploratory analysis in the prospective validation cohort showed that de-intensified radiotherapy after NAC in low-risk patients yielded 100% in both PFS and OS. Furthermore, expression analysis unveiled distinct molecular phenotypes in relation to NAC response, where poor responders had predominantly enhanced keratinization while good responders were featured by stronger innate and adaptive immune response. **Conclusions:** The MR-based radiomic models and subsequent prognostic models efficiently discriminate among patients with different NAC response and survival risk. This study provides a new strategy for patient selection in HPV-positive OPSCC that are suitable for personalized de-intensification. Integration of radiomics in future trials is warranted. Research Sponsor: None.

Induction chemotherapy followed by concurrent chemoradiotherapy combined with toripalimab and Endostar in high-risk locally advanced nasopharyngeal carcinoma: A multicenter, randomized, phase 2 trial.

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Background: Even though induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) can improve the survival rate of patients with locally advanced nasopharyngeal carcinoma (LA-NPC), the recurrence and/or metastasis rates for patients with stage IV (T4 and/or N3) diseases remain high. This study investigates the efficacy and safety of adding Toripalimab (PD-1 inhibitor) and Endostar (recombinant human endostatin) to IC-CCRT in patients with high-risk LA-NPC. **Methods:** High-risk LA-NPC patients were randomly divided (1:1) into either the IC-CCRT+TE group (gemcitabine and cisplatin induction chemotherapy followed by concurrent chemoradiotherapy combined with Toripalimab and Endostar) or the IC-CCRT group (gemcitabine and cisplatin induction chemotherapy followed by concurrent chemoradiotherapy). Toripalimab (240mg, d1) was administered intravenously every 3 weeks for up to 12 cycles (3 induction, 2 concurrent, and 7 adjuvant). Endostar (7.5mg/m2, d1-10) was continuously injected intravenously every 3 weeks for a total of 5 cycles (3 induction and 2 concurrent). The primary endpoint was 3-year progression-free survival (PFS), and the secondary endpoints included 3-year overall survival (OS), 3-year locoregional relapse-free survival (LRFS), 3-year distant metastasis-free survival (DMFS), objective response rate (ORR) and safety. **Results:** From September 7, 2020, to August 23, 2022, a total of 106 eligible patients were randomly assigned to the IC-CCRT+TE group (n = 53) and IC-CCRT group (n = 53). At a median follow-up of 25 months, the PFS was significantly improved in the IC-CCRT+TE group compared to the IC-CCRT group (HR=0.36, p=0.041). 28 patients (52.8%) in the IC-CCRT+TE group and 5 patients (9.4%) in the IC-CCRT group achieved complete response (CR) after induction chemotherapy, and the difference was statistically significant ($P < 0.001$). The incidence of grade ≥3 acute adverse events in the IC-CCRT+TE group and IC-CCRT group was 66.0% and 62.3%, respectively. The incidence of grade ≥3 late adverse events in two groups was 5.8% and 5.7%, respectively. The incidence of grade ≥3 immune-related adverse events was only 4.7%. **Conclusions:** IC-CCRT combined with Toripalimab and Endostar significantly improved PFS in patients with high-risk locally advanced nasopharyngeal carcinoma, and the adverse events are manageable. Clinical trial information: NCT04447326. Research Sponsor: The National Natural Science Foundation of China (No. 82272736); The National Natural Science Foundation of China (No. 82160467); The Research Foundation of the Science and Technology Department of Guangxi Province, China (grant No. 2023GXNSFDA026009).

6087 Poster Session

Survey of long term survivors of oral cancer: Looking beyond cancer biology.

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Background: While surgery is the main stay of treatment for early stage oral cancers, advanced stages require adjuvant treatments in the form of radiotherapy or concurrent radiotherapy. Yet, the effectiveness of these interventions is not solely determined by clinical measures but also by personal factors such as individual motivation, support from loved ones, and financial security. These aspects might explain the survival rate variations among patients who, despite having similar prognostic categories and stages of disease, show differing outcomes. The role of social determinants in influencing patient survival, apart from the acknowledged impact of disease biology, is not well understood. **Methods:** All treatment-naive oral cavity cancer patients who underwent definitive treatment during 2014 to 2018 at our institute and are alive for more than five years were selected for this study. A custom investigator-administered questionnaire was developed and it had 32 questions under six domains- personal, habit history, financial, social, functional, and emotional. The study was approved by the institutional ethics committee. Of the 1787 potential participants, we found that 219 had expired, only 442 patients agreed to answer the questionnaire, while 45 refused to participate. The rest of the patients were not reachable telephonically. **Results:** This survey had 442 patients, of which 90% were males, with a mean age of 52.1 years. The most common site of the presentation was buccal mucosa (60%), and 59% presented in the locally advanced stage. Post-operatively, 71% received adjuvant therapy. All patients were motivated to undergo the radical treatments and had their family support. However, post-treatment, about 10% of individuals experienced a change in marital status. Financial constraints did affect 20% of patients during and after treatment, and more than 70% had their out-of-pocket expenditure above 50% of the total cost. While 80% did not have trouble attending social functions, 46% reported trouble eating socially. However, this was more common for patients who received adjuvant treatment ($p < 0.001$). About 21% reported shoulder dysfunction and body discomfort. However, no statistically significant associations could be drawn for any of the domains of the questionnaire when compared to patients between the early and late stages. Shoulder discomfort was experienced more by patients who were treated for tongue cancer (p-value 0.010). **Conclusions:** The results of this study shed light on the challenges faced by long-term survivors of oral cancer following radical treatment regimens. More than half of patients reported that out-of-pocket expenses constituted more than half of their total treatment costs. A notable minority of people suffer from shoulder dysfunction, suggesting there is a clear opportunity for advancements in reconstruction and rehabilitation. Research Sponsor: None.

Validation of a prognostic nomogram for locally advanced oropharyngeal carcinoma (OPC) treated with intensity modulated radiation therapy (IMRT) ± systemic therapy (ST).

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Background: The interplay among prognosticators in OPC patients (pts) may be influenced by sociodemographic, geographic, epidemiologic and genetic features. We aimed to validate an existing prognostic nomogram (PN) (Fakhry et al 2017) in a large, independent, geographically homogeneous pt cohort. **Methods:** We retrospectively collected data on consecutive OPC pts treated with definitive IMRT (66-72 Gy) ± systemic therapy (ST) in 14 South-European Centres from 2007 to 2019. We analysed the role of the nomogram prognostic factors (PF) (T and N stage, age, p16 status, smoking, performance status, weight loss, anemia, education, and marital status) with respect to overall survival (OS) and progression-free survival (PFS), and we also evaluated alcohol abuse, comorbidities according to ACE-27 and the presence of a caregiver as added PF. The PN was evaluated in terms of discrimination performance (Harrel C-index) and calibration (ratio O/E and calibration line). Model was recalibrated evaluated via optimism adjusted C-index. **Results:** We considered 786 pts, with a median follow-up of 63 months (0-189). The table reports pts characteristics. The PN showed a good discrimination for OS and PFS both at 2- and 5-years, not dissimilar from original external validation, with a C-index of 0.75 (CI 95% 0.70-0.79,) and 0.68 (0.64-0.72), respectively. Adding alcohol abuse, comorbidities and caregiver presence did not change the PN. Regarding OS, the model estimated risk was slightly higher than the observed, with an O/E ratio of 0.73 (CI 95% 0.57-0.93) and 0.60 (0.49-0.74) at 2- and 5- years and calibration slope of 1.07 (0.83-1.31). For PFS, the O/E ratio was 0.48 (0.40-0.58) at 2 years and 0.50 (0.42-0.58) at 5 years, and a calibration slope of 0.89 (0.66-1.12). Both for OS and PFS rescaling of baseline hazard and model coefficients resulted in a better calibrated model. Model was validated also after missing data imputation, via MCE (m=5) showing consistent estimates. **Conclusions:** We validated the prognostic nomogram developed by Fakhry et al. in a large independent European cohort, demonstrating its applicability. These real-life data may represent the benchmark for the design of new prospective clinical trials. Research Sponsor: None.

Pts characteristics	
Age (years)	Median age 62.1 (37.7-100)
ECOG PS	
0	508 - 64.6%
1	239 - 30.4%
2	35 - 4.5%
Missing	4 - 0.5%
Staging (AJCC 7th edition)	
I-II	15 - 1.9%
III	89 - 11.3%
IVa	576 - 73.3%
IVb	94 - 12.0%
Missing	12 – 1.5%
p16 status	
Negative	249 – 31.7%
Positive	427 - 54.3%
Missing	110 - 14.0%
Marital status	
Married	451- 57.4%
Single/Divorced	200 – 25.4%
Missing	135 – 17.2%
Education	
High school (or less)	463 - 58.9%
University	169 – 21.5%
Missing	154 – 19.6%
Smoking History	
Never	201 - 25.7%
< 10 p/y	98 - 12.5%
> 10 p/y	484 - 61.6%
Missing	3 – 0.2%
Weight loss	
< 5%	520 - 66.2%
> 5%	143 - 18.2%
Missing	123 - 15.6%
Anemia	
No	351 - 44.7%
Yes	174 – 22.1%
Missing	261 - 33.2%

6089 Poster Session

Relationship between infiltration of tissue-resident memory T cells (TRM) in head and neck squamous cell carcinoma (HNSCC) tissue and localization and age.

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Background: Elevated levels of tumor-infiltrating lymphocytes (TILs) have been correlated with improved survival rates in cancer patients. Among TIL subgroups, tissue-resident memory T cells (TRM, CD8+CD103+) are recognized as pivotal contributors to the anti-cancer immune response. In this study, we aimed to evaluate TRM presence in Head and Neck Squamous Cell Carcinoma (HNSCC) tissue utilizing a developed tissue microarray (TMA) and a multiplex immunohistochemistry (MxIHC) approach. **Methods:** HNSCC cases from Southampton Hospital spanning the years 2000 to 2016 were reviewed, resulting in the identification of approximately 300 cases with sufficient primary tumor material. A TMA was constructed by triplicate coring of marked tumor areas on all slides. Subsequently, MxIHC, incorporating markers such as CD8 and CD103, was performed using a stain-scan-strip methodology. Digital image analysis software was employed to analyze scanned slides, and a quality check (QC) was conducted. **Results:** Following QC, 193 primary tumors remained (hypopharynx and larynx: n = 28, lip and oral cavity: n = 51, oropharynx: n = 114). Significantly higher counts of CD8 T cells and TRM were observed in the combined group of oropharynx, lip and oral cavity compared to the combined group of larynx and hypopharynx. This significance persisted even after excluding HPV negative oropharynx cases. HNSCC of the lip and oral cavity itself had statistically more TRM than larynx and hypopharynx. No differences were found in the subgroups between tonsil and tongue base. Stratifying the analysis by age revealed a statistically significant increase in TRM infiltration in HNSCC among young patients (≤50 years) compared to the 51-60 years and 61-70 years age groups, a pattern not observed for CD8 alone. **Conclusions:** This study underscores the importance of HNSCC heterogeneity and highlights the impact of age on immune infiltration, emphasizing the unique contribution of TRM in the anti-cancer immune response. Research Sponsor: Deutsche Forschungs Gemeinschaft; Whittaker Funds.

Neoadjuvant immunochemotherapy and new radiomic predictor for resectable locally advanced oral squamous cell carcinoma.

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Background: The effectiveness of neoadjuvant immunochemotherapy (NAIC) in treating resectable locally advanced oral squamous cell carcinoma (LAOSCC) remains uncertain, with a notable lack of precise prognostic markers for NAIC outcomes. **Methods:** A single-arm prospective phase II trial was performed to assess the efficacy and safety of NAIC, consisting of 2 cycles of intravenous camrelizumab (200 mg), albumin paclitaxel (260 mg/m^2), and cisplatin (75 mg/m^2) administered every 3 weeks prior to radical surgery in LAOSCC patients. Adjuvant radiotherapy or chemoradiotherapy was determined by post-surgical pathology. Patients with previously untreated, stage III-IVB LAOSCC (the 8th edition of UICC/AJCC staging system), aged 18-75 years were enrolled. The primary endpoints were major pathological response (MPR, defined as ≤10% residual viable tumour (%RVT) cells) and safety, the second primary point was objective response rate (ORR) according to RECIST 1.1. To identify potential radiomic markers predictive of NAIC benefit, oscillating-gradient spin-echo (OGSE) magnetic resonance imaging sequences were obtained before and after NAIC. **Results:** From Feb 1, 2023 to Jan 1, 2024, 30 patients were enrolled, among which, 26 patients have received NAIC followed by surgery. The MPR rate was 65.4% (17/26), including a 34.6% (9/26) pathological complete response. Patients with PD-L1 (Combined Positive Score) ≥ 1 had higher MPR (80.0%, 16/20) than those with PD-L1 < 1 (16.7%, 1/6). NAIC was well-tolerated, without adverse effects on subsequent surgery, only two patients experienced grade 3 or 4 adverse events during NAIC, including one with grade 4 neutropenia (3.8%), and one with grade 3 thrombocytopenia (3.8%). The ORR was 80.8% (21/26), with 15.4% (4/26) complete response, 65.4% (17/26) partial response, and with no cases of progressive disease observed. The mean cell diameters of the whole tumor were calculated based on the OGSE sequences, twenty patients completed the OGSE scaning pre- and post-NAIC treatment. Pearson correlation analyses found that small post-NAIC mean cell diameter significantly related with fewer %RVT ($p = 0.026$), supporting its potential as new radiomic predictors of NAIC efficacy. Among patients with MPR, the cell diameters were significantly decreased after NAIC, with a mean cell diameter of 18.87 ± 2.49 μm and 14.77 ± 1.85 μm for pre- and post-NAIC tumor, respectively ($p = 0.001$). **Conclusions:** Camrelizumab combined with albumin paclitaxel/cisplatin as NAIC for LAOSCC demonstrates promising MPR and well safety. Mean cell diameter of tumor, derived from OGSE sequences, emerges as a potential new radiomic marker for predicting NAIC efficacy. Ongoing follow-ups on long-term survival and the development of a bio-radiomic prediction model integrating pathological features with OGSE data are underway. Clinical trial information: ChiCTR2200066119. Research Sponsor: Clinical Research Incubation Project, West China Hospital, Sichuan University; 2022HXFH025.

6091 Poster Session

Clinical validation of a mesenchymal gene expression signature for prognosis and treatment decision making in early-stage oral cavity squamous cell carcinoma.

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Background: Treatment for human papillomavirus (HPV)-negative oral cavity squamous cell carcinoma (OCSCC) includes surgical resection of the primary tumor, usually with elective or therapeutic neck dissection with adjuvant radiation or chemotherapy and radiation based on risk stratification. While therapeutic advances have been modest at best for over a century, the addition of chemotherapy to radiation has demonstrated benefit for the highest risk patient groups, although recurrence rates remain high for advanced-stage patients. Even more concerning, some early-stage patients demonstrate life-threatening relapses in the absence of biomarker guidance. Using retrospective analysis, our group and others have identified gene expression signatures that reveal molecular subtypes (classical, atypical, basal and mesenchymal) that could identify early-stage patients most likely to recur and are likely candidates for therapy escalation, such as chemotherapy plus radiation. We hypothesize that the mesenchymal (MS) gene expression subtype is associated with worse overall survival (OS) in early-stage, node-negative OCSCC compared to non-mesenchymal subtypes. Herein we present further clinical validation of our previously described 88-gene OCSCC classifier (Mayhew et al, 2022; PMID: 36147910). **Methods:** As part of a prospectively designed retrospective study, residual tumor samples and paired clinical data, including n-stage and survival, were collected for patients with node-negative OCSCC (IRB# 201706088 at Washington University in St. Louis). Using the NanoString nCounter platform, RNA was isolated and counts were generated according to the manufacturer's specifications. Gene expression data were used to assign molecular subtypes, and associations with overall survival (OS) were investigated using Kaplan-Meier plots and cox models in patients who were pathologically node negative. **Results:** A total of n=137 patients had node-negative OCSCC and sufficient tumor quantity to generate molecular subtype results. Consistent with our previous findings, the MS subtype was strongly associated with inferior survival in both univariate (HR = 3.24, p = 0.0019) and multivariable (HR = 3.26, p = 0.0026) analyses, confirming a potential role for gene expression-based subtyping as a biomarker for prognostication and informing clinical treatment decisions. **Conclusions:** These findings confirm that the MS subtype is associated with significantly worse survival in surgically resected, early-stage OCSCC which typically demonstrate favorable outcomes. Also, these findings strongly suggest value in gene expression subtyping for prognostication and treatment decision-making in OCSCC patients and warrant the further development of the 88-gene classifier as a diagnostic test for this clinically actionable patient population. Research Sponsor: GeneCentric.

LBA6092 **Poster Session**

Long term results of a randomized phase III study of nimotuzumab in combination with concurrent radiotherapy and cisplatin versus radiotherapy and cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck.

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6093 Poster Session

Dosimetry of lutetium-177-PSMA-I&T radioligand therapy in recurrent/metastatic adenoid cystic carcinoma.

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Background: There is a high unmet need for effective systemic therapies for recurrent and/or metastatic (R/M) adenoid cystic carcinoma (AdCC), as no standard-of-care exists. AdCC frequently expresses prostate-specific membrane antigen (PSMA), providing rationale for PSMA-targeted therapies, which have demonstrated significant efficacy in prostate cancer. In our phase 2 pilot trial (EudraCT 2019-003857-27), we assessed the safety, efficacy and feasibility of lutetium-177 (^{177}Lu)-PSMA-I&T in R/M AdCC patients. Despite well-tolerated, the efficacy was limited. To gain further insight into causes of the limited efficacy, we measured absorbed ^{177}Lu-PSMA-I&T radiation doses in tumors and organs at risk. **Methods:** Dosimetry was feasible and was performed in all 10 enrolled AdCC patients. They received ^{177}Lu-PSMA-I&T with a median activity of 7.40 (range 6.78-7.49) GBq and a median of 4 (range 1-4) cycles. For bone marrow dosimetry, blood samples were collected during cycle 1. Single-photon emission CT/CT (SPECT/CT) was performed at 1, 24, 48, 72 and 168 hours after ^{177}Lu-PSMA-I&T injection at cycle 1. Tumors >1 cm were categorized based on gallium-68 (^{68}Ga)-PSMA PET mean standardized uptake value ($SUV_{mean)}$: above, at (±10%), and below liver SUV_{mean}. Per site, up to 3 index lesions per category were selected. Volumes of interest with ~1 cm margin were drawn on SPECT/CT. Background correction was applied. Salivary gland and bone lesion volume were determined by iterative thresholding on ^{68}Ga-PSMA PET. Other tumor volumes were determined on CT. Hermes dosimetry software and Olinda 2.2 software were used to estimate doses according to the Medical Internal Radiation Dose scheme. Results were reported as the absorbed dose at cycle 1 (Gy). **Results:** In total, 66 tumor lesions were analyzed. Tumor sites included lung (n=35), pleura (n=16), liver (n=5), bone (n=4), lymph node (n=3), local recurrence (n=2) and thoracic wall (n=1). The median ^{68}Ga-PSMA PET tumor/liver SUV_{mean} ratio was 0.94 (range 0.33-2.62). The median tumor-absorbed dose was 0.47 (range, 0.01-4.66) Gy. Highest median doses by tumor site were 1.84 (range, 0.76-2.92) Gy in local recurrences and 1.35 (range, 0.33-2.62) Gy in bone lesions. Lowest median doses by tumor site were 0.18 (range, 0.14-0.27) Gy in lymph node lesions and 0.21 (range, 0.12-0.79) Gy in liver lesions. In organs at risk, the absorbed dose was highest in the kidneys, followed by the salivary glands, with mean values of 6.29 (standard deviation [SD], 2.32) Gy and 5.07 (SD, 2.47) Gy, respectively. The mean bone marrow absorbed dose was 0.53 (SD, 0.14) Gy. **Conclusions:** Tumor-absorbed radiation doses in our AdCC patient cohort receiving ^{177}Lu-PSMA-I&T were significantly lower than in prostate cancer (~10-40 Gy per cycle), likely due to lower and heterogeneous PSMA expression. This could explain the limited efficacy. Organ-absorbed doses aligned with studies in prostate cancer. Clinical trial information: NCT04291300. Research Sponsor: Dutch Cancer Society; ACC-RF.

6094 Poster Session

Clinical and genomic characterization of sporadic medullary thyroid carcinoma in Chinese patients.

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Background: Medullary thyroid carcinoma (MTC) is a C-cell-derived epithelial neuroendocrine neoplasm. MTC has a low prevalence and a relatively worse prognosis compared with differentiated thyroid carcinoma. About 75% of all MTCs are sporadic. The clinicogenomic landscape of sporadic medullary thyroid carcinoma (sMTC) in the Chinese population was rarely described. **Methods:** Formalin-fixed paraffin-embedded (FFPE) samples and/or tumor tissues from a total of 121 sMTC patients from 22 centers were retrospectively collected and tested using a targeted 28-gene next-generation sequencing (NGS) panel (May 2022 to November 2023). Clinicopathological data, including age, gender, histological diagnoses, site, tumor size, and status of the lymph nodes and distant metastasis were reviewed. Regression analyses were performed to examine the association between the clinicogenomic characterization and pathologic features. **Results:** A total of 105 out of 121 sMTC were NGS-positive. The mutant genes included RET(66.9%), RAS(20.7%), BRAF(1.6%), TSHR(0.8%). The top 5 frequent mutations were RET M918T (24.8%, 30/121), HRAS Q61R (8.3%, 10/121), RET C634R (7.4%, 9/121), RET V804M (4.1%, 5/121), HRAS Q61K (4.1%, 5/121). Of the 13 co-mutations, 12 were RET mutations or co-occurrence of RET with other genetic alterations. Besides, the higher the age, the lower the probability of lymph node metastasis (OR=0.95, p=0.005). Also, patients with common RET mutations (including M918T, C634, C630, C611, C618, C620, A883F, S891 and V804) tended to have lymph node metastases (OR=5.67, p=0.016). We observed a significant positive linear relationship (Beta=2.0) between other gene mutations (non-RET mutations and non-RAS mutations) and tumor size. However, when the tumor diameter was analyzed according to whether it was greater than 1cm, we found that clinical factors such as age, sex, and gene mutation were not related to tumor size. Moreover, we did not find any association between this cutoff value of tumor size and lymph node metastases. It indicated that sMTC clinical diagnosis and treatment may consider pathologic and genomic features, not just whether the tumor size is >1cm. **Conclusions:** Our study first provided the molecular characteristic of Chinese patients with large-scale sMTC. Analysis revealed that common RET mutations may be potential predictors of lymph node metastases. These conclusions remain to be validated in prospective large-scale cohorts. Research Sponsor: None.

Long-term efficacy and safety of larotrectinib (laro) in patients (pts) with TRK fusion thyroid carcinoma (TC).

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Background: *NTRK* gene fusions are oncogenic drivers in TC. Laro is the first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in pts with TRK fusion cancer based on overall response rate (ORR) in pts with various tumor types. Here, we report long-term efficacy and safety in a subset of pts with TRK fusion TC treated with laro. **Methods:** Pts with TRK fusion TC enrolled in 3 laro clinical trials (NCT02576431, NCT02122913, NCT02637687) were included. Laro was administered at 100 mg twice daily to most pts; 2 pediatric pts received 100 mg/m^2. Responses were assessed per independent review committee (IRC) using RECIST v1.1. **Results:** As of July 20, 2023, 31 pts were enrolled and eligible for efficacy assessment by IRC. Of the 4 pts with known CNS metastases at baseline, 3 received prior cranial radiotherapy (2, 12 and 15 months prior to laro initiation, respectively). Median age was 60 years (range 6-80) and median time since initial cancer diagnosis was 5 years (range 0-46). All *NTRK* gene fusions were identified by next-generation sequencing (NGS). 17 pts (55%) received no prior systemic therapies, 6 (19%) received 2 or more; 22 (71%) received prior radioiodine. ORR was 65% (95% CI 45-81): 3 (10%) complete responses, 17 (55%) partial responses (PR), 5 (16%) stable disease (SD) (4 for >30 months), 4 (13%) progressive disease (PD), and 2 (6%) not evaluable. For pts classified as differentiated TC (DTC; n=24 [77%]), ORR was 79% (95% CI 58-93). For pts classified as anaplastic TC (ATC; n=7 [23%]), ORR was 14% (95% CI 0-58). There were 3 pts with poorly differentiated TC, 1 (3%) classified as DTC (PR) and 2 (6%) as ATC (1 SD for >39 months and 1 PD). Median time to response was 1.9 months (range 1.6-16.2) for all pts. Median duration of response was 40.5 months (95% CI 19.4-not estimable [NE]) at a median follow-up of 39.8 months. Median progression-free survival was 44.0 months (95% CI 16.6-NE) at a median follow-up of 38.7 months. Median overall survival (OS) was not reached (NR; 95% CI 48.7-NE) at a median follow-up of 58.0 months; the 48-month OS rate was 72% (95% CI 56-89). Median OS was NR (95% CI 56.3-NE) in DTC and 8.8 months (95% CI 2.6-NE) in ATC. Treatment duration ranged from 1 to 76+ months. At data cutoff, 11 pts had progressed, with 7 continuing treatment post-progression for ≥4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 3 (10%) pts. There were no treatment discontinuations due to TRAEs. **Conclusions:** Laro continues to demonstrate rapid and durable responses, extended survival, and a favorable safety profile in pts with TRK fusion DTC. Limited single-agent activity was observed in ATC. These results support the wider adoption of NGS panels, which include *NTRK* gene fusions in pts with advanced TC, to identify those who may benefit from targeted treatment. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: These studies were funded by Bayer HealthCare Pharmaceuticals, Inc.

Safety of tabelecleucel with pembrolizumab in recurrent/metastatic Epstein–Barr virus-associated nasopharyngeal carcinoma.

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Background: Despite standard treatment with radiation and/or chemotherapy, approximately one in four patients (pts) with nasopharyngeal carcinoma (NPC) will develop recurrent/metastatic (RM) disease that is associated with poor prognosis. Programmed cell death ligand 1 (PD-L1) expression is upregulated in NPC due to Epstein–Barr virus (EBV) activation. Tabelecleucel (tab-cel), an off-the-shelf, allogeneic, EBV-specific T-cell immunotherapy, has shown promising antitumor activity in pts with RM EBV$^+$NPC (Prockop, *JCO* 2016). The anti-PD-1 antibody pembrolizumab (pembro) is also active in NPC. To characterize the safety profile and preliminary efficacy of tab-cel combined with pembro in RM EBV$^+$NPC, we initiated a phase 1b/2 study (NCT03769467). Here we report safety outcomes in 12 subjects treated in the phase 1b portion of the study. **Methods:** The multicenter, open-label, single-arm phase 1b portion of the study was designed to evaluate the safety of tab-cel in combination with pembro in pts with incurable RM EBV$^+$NPC previously treated with platinum-containing therapy. Pts were either checkpoint-inhibitor naïve (n=6) or experienced to anti-PD-1/PD-L1 therapy (n=6). Tab-cel was administered intravenously (IV) on days 1, 8, and 15 of a 21-day cycle. Initial tab-cel dose was $2x10^6$ cells/kg. Pembro was administered at 200 mg IV Q3W. Primary endpoints of phase 1b focused on assessing safety. **Results:** As of the final data cutoff, 12 subjects were treated as part of the phase 1b portion of the study. Subjects were 75% Asian and 50% male, with a median age (min, max) of 51 (20, 72) years and a median time from initial diagnosis to first dose of tab-cel (min, max) of 47.7 (8.0, 221.8) months. All subjects had received prior platinum-based chemotherapy/chemoradiation. No dose-limiting toxicities or fatal treatment-emergent adverse events (TEAEs) were identified. All 12 subjects reported ≥1 TEAE; the most common TEAEs reported by ≥4 subjects were disease progression (8 subjects, 66.7%), myalgia (5 subjects, 41.7%), pyrexia, arthralgia, and hyponatremia (4 subjects, 33.3%, each). No ≥ grade 3 TEAEs were considered related to tab-cel or pembro. No TEAEs considered related to tab-cel or pembro led to study discontinuation. No clinically significant abnormal trends were identified in laboratory parameters or vital signs. Although the phase 1b portion of the study was not designed to assess efficacy, the best response seen was stable disease in 6 of 12 pts (50%). **Conclusions:** Phase 1b data demonstrated combination therapy of tab-cel and pembro to be well tolerated and identified a recommended phase 2 dose in subjects with platinum-pretreated RM EBV$^+$NPC. The study was discontinued after the phase Ib portion due to an evolving immunotherapy treatment landscape for this disease, which would need to be considered for further clinical development. Clinical trial information: NCT03769467. Research Sponsor: Atara Biotherapeutics.

6097 Poster Session

Association of quality of life (QoL) with mortality in patients with adenoid cystic carcinoma using an internationally validated QoL questionnaire (EQ-5D-5L): A new baseline.

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Background: An evaluation of impact on quality of life (QoL) is required for regulatory approval and reimbursement of new drug therapies. Almost all studies of new therapies in adenoid cystic carcinoma (ACC) are non-randomised with no comparator QoL measure. To support Health Technology Assessments and the evaluation of the clinical utility of these therapies, we sought to determine the QoL measures in a cohort of ACC patients and to assess for change over time and associations with clinical or prognostic factors. **Methods:** An internationally validated QoL questionnaire (EQ-5D-5L) was completed by ACC patients referred to an experimental medicine centre between 2019 and 2024, who provided written informed consent to analysis. EQ-5D value scores (EQV) were calculated from each questionnaire using the EuroQol England value set. A Cox proportional hazards model was built with EQV as a time dependent variable, with a variant using penalised smoothing splines to assess linearity. A base non-linear mixed effects (nlme) model was constructed between time and EQV. The relationship between EQV and other predictors (NOTCH1 alteration status, age at diagnosis, sex, local and/or metastatic recurrence, and primary site of disease) were tested against the base model using variant models built for each predictor. Both analyses used R Statistical Software (v4.3.2) with survival and nlme packages in Rstudio (v2023.12.0.0). **Results:** Between 2019 and 2023, 563 EQ-5D-5L questionnaires were completed by 161 patients with ACC (median 2 responses/patient, range 1 to 20). NOTCH1 alteration was seen in 8% (13/161), median age at diagnosis 49 years (range 17 to 81), 40% male, 36% (58/161) had a major salivary gland as primary site, and 14% had local recurrence, 46% metastatic recurrence and 26% both for 86% total with recurrent disease (139/161). For all 161 patients, median EQV was 0.81 (range -0.22 to 1.0); an EQV of 1 is ideal QoL and 0 is QoL as bad as death. The median EQV for the clinical subgroups were 0.83 (NOTCH1, IQR 0.74-0.87), 0.84 (no recurrence, IQR 0.75-0.92), 0.80 (local recurrence only, IQR 0.70-0.86), 0.81 (distant metastasis only, IQR 0.70-0.92), 0.83 (distant and local, IQR 0.75-0.92), 0.84 (major primary site, IQR 0.75-0.92), 0.81 (other primary site, IQR 0.70-0.89), and no statistical differences were identified between these groups. However, a decrease in EQV from 1 to 0 was associated with an eightfold increase in risk of death in the total population (HR= 0.118, 95% CI 0.057 to 0.244, p= <0.001). There was a significant non-linear relationship between EQV and survival over time (p=0.011), with a greater marginal effect on survival for EQVs >0.81. **Conclusions:** For patients with ACC, a worse QoL as measured by EQ-5D-5L was associated with a significantly increased risk of death. NOTCH1 and disease recurrence were not associated with a worse QoL. Research Sponsor: The Christie Charity; The Infrastructure Industry Foundation; Syncona Foundation.

Patients with radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) with BRAF V600E and/or K601E mutation status: A real-world view of effectiveness of lenvatinib monotherapy.

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Background: Lenvatinib was approved for the treatment of patients RAI-R DTC in the United States (US) in 2015, and the treatment landscape has evolved with agents targeting specific driver mutations. We assessed real-world clinical effectiveness of first line therapy with lenvatinib in patients with BRAF-mutated tumors, wild-type (WT) tumors, and patients who have not been tested for BRAF mutations (BRAF untested tumors). **Methods:** A retrospective chart review of RAI-R DTC patients in the US who initiated first-line lenvatinib monotherapy between February 13, 2015, and September 30, 2020. Data, including a boosted cohort of patients with BRAF-mutated tumors collected in late 2023, were abstracted from patients' electronic health records and were de-identified. Descriptive analyses were conducted in patient cohorts with BRAF V600E and/or K601E mutated tumors, wild-type (WT) tumors, and BRAF untested tumors. Best response in first-line therapy was captured, real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) were assessed using Kaplan-Meier methods. **Results:** Of the 361 patients reviewed, 185 had records showing BRAF mutational status testing. 89 had BRAF V600E and/or K601E mutated tumors, 96 had WT tumors. 176 patients did not have BRAF mutational assessment. Of all subjects, 73.7% were White/Caucasian, 15.2% were African American, and 16.8% were Hispanic/Latino; 27.1% had ECOG performance status ≥2. The median follow-up times for each cohort were 30.0, 18.7 and 18.0 months, showing the longer follow up period for the BRAF-mutated cohort boost. Kaplan-Meier estimation for lenvatinib treatment discontinuation for the three cohorts at 24-months were as shown in the table below. Provider-reported overall response rate (complete or partial response) was 76.4%, 75.0% and 69.3% respectively. The estimated 24-month rwPFS rates (95% CI) were 74.1% (62.2%-82.8%), 61.7% (49.6%-71.8%), and 69.8% (60.9%-77.0%) respectively. Median rwOS was not reached for patients with BRAF-mutated and WT tumors, median OS was 54.2 months for BRAF untested tumors. Estimated rwOS rates at 12- and 48-months were 93.2% (85.4%-96.9%) and 83.9% (73.3%-90.3%) in BRAF-mutated patients, 90.6% (82.8%-95.0%) and 68.5% (53.4%-79.6%) in WT patients, and 90.2% (84.7%-93.8%) and 72.5% (61.6%-80.7%) in BRAF untested patients respectively. **Conclusions:** In this US real-world experience, the effectiveness of lenvatinib is consistent across a diverse cohort of RAI-R DTC patients with BRAF-mutated, WT, and BRAF untested tumors. This has implications for the first-line use of lenvatinib in BRAF mutated patients. Research Sponsor: Eisai Inc., Nutley, NJ, USA. Medical writing support was provided by Adelphi Real World, Bollington, Cheshire and was funded by Eisai Inc., Nutley, NJ, USA.

Kaplan Meier estimations of time to discontinuation for lenvatinib first line.

	BRAF*mut*	BRAF*wt*	BRAF untested
24-months	67.5% (55.6%-76.9%)	60.0% (48.3%-69.9%)	65.3% (56.8%-72.5%)

6099 Poster Session

Survival outcomes of concurrent radiotherapy and toripalimab versus radiotherapy alone for elderly patients with postoperative head and neck squamous cell carcinoma unfit for cisplatin.

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Background: For elderly patients with locally advanced head and neck squamous cell carcinoma (HNSCC), the role of postoperative concurrent chemotherapy was controversial since the intolerable toxicities and increased acute mortality, thus, radiotherapy alone was recommended. We aimed to assess if addition of toripalimab (anti-PD-1) to radiotherapy could improve treatment outcomes for this patient population. **Methods:** This trial was an, open-label, phase 2, randomized study.We randomly assigned (1:1) patients aged > 65 years, with ECOG Performance Status(PS) of 0–2, and with postoperative Stage III-IV (AJCC 8th Staging system) HNSCC unfit for cisplatin to concurrent radiotherapy (60-66Gy) and toripalimab (240mg on D0, D21 and D42)(RT+PD-1 group) or radiotherapy alone(RT group). The primary endpoint was 2-year disease free survival (DFS). It is hypothesized to detect a difference between arms of 45%-65% in 2-year DFS. **Results:** Between September 2020 and May 2023, 87 patients were randomly assigned (43 in RT+PD-1 group and 44 in RT group). The median age were 71.0 years (range 66-81) for the RT+PD-1 group and 72.5 years (range 67-80 years) for RT group. In the RT+PD-1 group, 35 (81.4%) patients received at least one dose of toripalimab; 38 (88.3%) patients in the RT+PD-1 group and 36 (81.8%) patients in the RT group complete the planed radiation dose. Median follow-up was 24 months in both arms. The 2-year DFS was 55.3% with RT+PD-1 and 51.2% with RT alone (p=0.866), and the 2-year OS was 63.3% with RT+PD-1 and 78.4% with RT alone(p=0.557). In RT+PD-1 group, 18(41.8%) patients were CPS≥20%; 2-year DFS was 72.2% in patients with CPS≥20%, which was 53.8% in patients with CPS < 20 (p=0.412). **Conclusions:** The primary objective of prolonging DFS with concurrent radiotherapy and toripalimab in elderly patients unfit for cisplatin with locally advanced HNSCC was not met. For patients with CPS≥20, further study still warranted to evaluate the benefit of toripalimab in this patient setting. Biomarker analysis is still ongoing. Clinical trial information: NCT04523883. Research Sponsor: Clinical Research Plan of SHDC (No. SHDC2020CR4012), WU JIEPING MEDICAL FOUNDATION (No. 320.6750.2021-01-34) and Shanghai Anti-Cancer Research Foundation (No. H8001-004).

A phase 1 clinical trial of DB-020 intratympanic injections administered prior to high-dose cisplatin chemotherapy to reduce ototoxicity.

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Background: Hearing loss (HL) as a result of cisplatin (CP) chemotherapy is common. DB-020 is a formulation of sodium thiosulfate for intratympanic (IT) injection being developed to reduce CP ototoxicity. This phase 1 study was designed to evaluate safety and tolerability of repeated IT injections of DB-020 and compare CP-induced hearing changes with DB-020 vs placebo. **Methods:** Patients scheduled for at least three cycles of CP and cumulative exposure of ≥280 mg/m^2 were randomized to blinded, bilateral, IT injection with DB-020 (12% or 25%) in one ear and placebo in the other ear, once every 3 or 4 weeks, ≤3 hours before receiving CP. Patients naïve to CP with moderate or severe HL at baseline were excluded. Ototoxicity was defined by American Speech-Language-Hearing criteria: ≥20 dB threshold increase at any one test frequency, or ≥10 dB threshold increase in any two adjacent frequencies, or loss of response at three consecutive frequencies where responses were previously obtained. Severe ototoxicity was defined as ≥20 dB threshold increase in any two adjacent frequencies. Pre-specified analyses evaluated safety, ototoxicity (with McNemar's test using the last observation carried forward), and average threshold shifts (from air conduction audiometry, analyzed with a mixed model with repeated measures). This is the final analysis of the data set following the interim analysis presented in 2023. **Results:** Twenty-two patients were randomized with a mean age of 55 years (86% male; 100% white). Pre-DB-020 treatment, mean cumulative CP dose was 255 mg/m^2, and 95% had head and neck cancers; 5% had lung cancer. Twenty patients had both baseline and follow-up audiometry, and 18/20 had baseline audiograms within 5 dB of the median threshold for age-matched controls. Free CP systemic levels (overall mean cumulative CP dose was 254.7 mg/m^2) were similar to reference values. Acute or temporary ear pain (18/22 patients, 82%), and tinnitus (11/22 patients, 50%) were common. Ear pain was more common in DB-020 treated ears, and tinnitus in placebo treated ears. No persistent tympanic perforations, no serious adverse events in the ear and labyrinth disorders category, and no deaths were reported. Ototoxicity was significantly more common and severe in placebo treated ears. **Conclusions:** In this initial clinical trial experience, there was no significant safety signal, and DB-020 IT injections showed a meaningful reduction in CP-induced ototoxicity. Clinical trial information: NCT04262336. Research Sponsor: Decibel Therapeutics, Inc., a wholly owned subsidiary of Regeneron Pharmaceuticals, Inc.

Assessment	Placebo ears (n=20)	DB-020 ears (n=20)	p-value vs placebo
Ototoxicity (250–8000 Hz), %	85	40	0.0027
Ototoxicity (9000–16000 Hz), %	90	60	0.0143
Severe ototoxicity (250–8000 Hz), %	70	15	0.0009
Severe ototoxicity (9000–16000 Hz), %	80	35	0.0027
Acoustic threshold shift (250–8000 Hz), LS mean dB	30.22	7.99	<0.0001
Acoustic threshold shift (9000–16000 Hz), LS mean dB	21.38	9.19	0.0022

LS, least squares.

6101 Poster Session

Clinical outcomes of NOTCH pathway-activated adenoid cystic carcinoma with and without co-occurrent TP53 mutation.

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Background: Adenoid cystic carcinoma (ACC) is a salivary cancer with a variable disease course. Inoperable locally advanced, recurrent or metastatic ACC (LA-R/M-ACC) are its commonest manifestations. The disease course is typically indolent with patients remaining on surveillance for many years before initiating relatively ineffective systemic therapies. A sub-group of patients experience rapid disease progression and surveillance is not indicated. NOTCH gain-of-function mutation ($NOTCH^{gof}$) is well characterised, defining a genomic sub-group with shorter survival times. However, there remains a need to identify additional prognostic biomarkers to inform the clinical management of these patients. TP53 mutation ($TP53^{mt}$) has been proposed as a prognostic biomarker warranting further evaluation. **Methods:** Clinical-genomic data from 349 ACC patients with LA-R/M-ACC were included. 198 patients provided written informed consent to an ethically approved study, and a further 151 were identified through cBioPortal (MetTropsim, Cell, 2021). ACC tumour samples were evaluated by next-generation sequencing (NGS) for the presence of $NOTCH^{gof}$ and $TP53^{mt}$. Kaplan-Meier analysis was performed, and p values calculated with the log-rank test, to calculate overall survival (OS) from inoperable LA or R/M disease for patients with either $NOTCH^{gof}$ alone, $TP53^{mt}$ alone or both $NOTCH^{gof}/TP53^{mt}$ combined. **Results:** ACC tumours harboured $NOTCH^{gof}$ in 14.0% (49/349) and $TP53^{mt}$ in 13.8% (48/349) of cases, respectively. Co-occurrence of $TP53^{mt}$ was identified in 16% of ACC tumours with $NOTCH^{gof}$ (8/49), being in 2.3 % of all LA-R/M-ACC cases. Median OS from inoperable LA-R/M disease was significantly reduced for patients with co-occurrent $NOTCH^{gof}/TP53^{mt}$ (n=8, 10.0 mo; 95% CI 8–12), followed by $NOTCH^{gof}/TP53^{wt}$ (n=41, 15.2 mo; 95% CI 8–22), $NOTCH^{wt}/TP53^{wt}$ (n=262, 58.6 mo; 95% CI 52–65) and $NOTCH^{wt}/TP53^{mt}$ (n=40, 69 mo; 95% CI 13–125) ($p=<0.001$). TP53 alterations were available for functional classification in 33 patients and were classed as loss-of-function point mutations in 81.8% or truncating frameshift mutations in 18.2%. Truncating $TP53^{mt}$ were mutually exclusive with $NOTCH^{gof}$. Although the smaller number in this group limits statistical power, patients with truncating $TP53^{mt}$ had shorter OS from recurrence (15.9 mo; 95% CI 0-39) compared with other $TP53^{mt}$ (51.0 mo; 95% CI 0-108; p=0.41). **Conclusions:** A subgroup of LA-R/M ACC patients with co-occurrent $TP53^{mt}$ and $NOTCH^{gof}$ were identified with significantly shorter OS from recurrence than either $NOTCH^{gof}$ or $TP53^{mt}$ alone. Truncating $TP53^{mt}$ may have greater prognostic value than other $TP53^{mt}$ in $NOTCH^{wt}$ ACC. This study provides further evidence of the potential prognostic utility of some TP53 mutations in ACC and highlights groups of patients with aggressive disease who are potentially suitable for inclusion in therapeutic research programmes. Research Sponsor: The Christie Charity; The Infrastructure Industry Foundation; Syncona Foundation.

Clinical outcomes in salivary adenoid cystic carcinoma.

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Background: Adenoid cystic carcinoma (ACC) is a rare salivary gland malignancy with a paucity of clinical outcome data. As such, evidence supporting and informing current guidelines remains limited. **Methods:** Inclusion criteria stipulated adults with adenoid cystic carcinoma treated at the University of Michigan between 1988 and 2019 with complete records (n=102). Clinical variables including demographics, disease stage, and treatment modality were abstracted. Pathologic variables analyzed included tumor grade, perineural invasion, lymphovascular invasion, and surgical margin status. Multivariate analyses were performed with disease recurrence calculated with Kaplan-Meier methodology as the primary outcome. **Results:** Mean age at diagnosis was 59 years; stage I and II disease accounted for 35 (38%) patients. Initial treatment was most commonly surgery with adjuvant radiation (77%). Median follow-up was 3 years. Distant metastatic disease developed in 34 (33%) patients. Most common sites included lung (68%), bone (21%), and brain (21%). Median time to distant metastases was 46 months with median overall survival of 58 months. Patients with locoregional recurrence experienced median survival of 91 months. Multivariate analysis adjusted for grade, perineural invasion, and surgical margin status (Table). Grade 3 tumors with predominantly solid histologic pattern pose higher risk of recurrence compared to grade 1 tubular histologic patterns as a reference (HR 3.69, 95% CI 1.15-11.88, p=0.028). **Conclusions:** Survival among patients with adenoid cystic carcinoma after locoregional recurrence is significantly better compared to those experiencing distant metastasis. Furthermore, tumor grade is most predictive of recurrence. Additionally, distant metastases may emerge over the course of many years. These data from one of the largest retrospective databases to date may inform the development of disease-specific surveillance guidelines and novel salvage treatment paradigms. Research Sponsor: Adenoid Cystic Carcinoma Research Foundation; University of Michigan Cancer Center Core Grant.

Variable	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age	0.98 (0.95-1.0)	0.11		
Sex (M vs F)	0.54 (0.24-1.24)	0.15		
Smoking	1.61 (0.72-3.62)	0.24		
Stage (I/II vs III/IV)	2.64 (1.02-6.80)	0.045		
Grade 2 (vs 1)	1.48 (0.49-4.53)	0.49	1.51 (0.47-4.90)	0.49
Grade 3 (vs 1)	4.81 (1.56-14.91)	0.006	3.69 (1.15-11.88)	0.028
PNI	2.05 (0.61-6.89)	0.25	1.15 (0.31-4.28)	0.84
Margins	1.80 (0.75-4.31)	0.19	1.65 (0.59-4.58)	0.34

6103 Poster Session

Efficacy and safety of anlotinib combined with sintilizumab in locally advanced or metastatic anaplastic thyroid carcinoma.

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Background: Anaplastic thyroid carcinoma (ATC) is rare aggressive and fatal malignancy with poor prognosis. Antiangiogenic and multikinase inhibitors and programmed cell death protein-1 (PD-1) antibodies have conferred benefits for ATC. We aimed to assess the efficacy and safety of anlotinib plus sintilizumab in patients with locally advanced or advanced ATC. **Methods:** In this prospective study, patients with histologically confirmed locally advanced or metastatic ATC, received a combination therapy of anlotinib and sintilizumab. Anlotinib was started at 12 mg once daily for 14 days and combined with sintilizumab at a fixed dose of 200 mg every three weeks. The primary end point was objective response rate (ORR), assessed in patients who received at least one dose of treatment. Tumor samples were characterized by next-generation sequencing in 12 patients and PD-L1 expression levels in 14 patients. **Results:** Between June 1st, 2022 and August 21st, 2023, 18 patients with locally advanced or metastatic ATC were enrolled and received combination treatment. Best overall response (BOR) within all patients was 5.6% (1/18) complete remission, 38.9% partial remission (7/18), 33.3% stable disease (6/18), and 22.2% progressive disease (4/18). ORR was 44.4% for all patients and 80.0% for 5 patients with *BRAF* V600E mutation. The only one patient with PD-L1 negative also reached PR. Median follow up time was 14.6 months for all patients and 16.1 months for patients with *BRAF* V600E mutation. The median progression-free survival was 7.5 months (0.5 to 56.3 months) for all patients and 5.7 months (1.0 to 13.1 months) for patients with *BRAF* V600E mutation. Duration of treatment was 5.9 months (0.5 to 38.2 months), and 8 of 18 ATC patients are still on therapy. Grade III/IV toxicities were observed in 4 of 18 patients, necessitating dose reduction/discontinuation of anlotinib. The 1-year overall survival (OS) rate was 61.1% and median OS was 12.9 months (0.6 to 56.3 months), with 8 ATC patients being still alive without progression. **Conclusions:** The combination of anlotinib and sintilizumab demonstrated promising activity and manageable toxicity in patients with locally advanced or metastatic ATC, suggesting its potential as a viable therapeutic option for this patient population. Clinical trial information: ChiCTR2200067045. Research Sponsor: None.

Baseline characteristics of patients.

	Overall (N=18)
Age	
Median [range]	64 [39, 80]
Gender	
Male	9 (50%)
Female	9 (50%)
Stage	
IVB	8 (44.4%)
IVC	10 (55.6%)
PD-L1 CPS	
Negative	1 (5.6%)
Positive	13 (72.2%)
Unknown	4 (22.2%)
TMB	
Median [range]	1.025 [0.42, 3.23]
Unknown	9 (50%)

PD-L1: programmed death-ligand 1; CPS: combined positive score; TMB: tumor mutation burden.

Axitinib plus avelumab for recurrent/metastatic adenoid cystic carcinoma (R/M ACC): Biomarker analysis of the phase II trial.

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Background: In the phase II axitinib (VEGFR inhibitor) plus avelumab (PD-L1 inhibitor) trial in R/M ACC, response rate was 18% with a median progression-free survival (PFS) of 7.3 months, with subsequent inclusion of the combination in NCCN guidelines as a possible treatment for ACC (category 2B). We sought to identify potential biomarkers predictive of axitinib plus avelumab benefit in R/M ACC. **Methods:** The phase II trial included 28 R/M ACC patients (pts). Pre-treatment tumors were analyzed by whole exome sequencing (n=24), using Twist Human Core Exome V2 kit, and transcriptome profiling (n=26), using HTG Transcriptome Panel (19,616 probes). For 17 pts, imaging mass cytometry (IMC) was performed with 35 metal-tagged markers and analyzed with Visiopharm software. Microbiome composition was assessed in tumor (n=20), oral rinse (n=20) and fecal (n=19) samples via 16s rRNA gene sequencing. All results were assessed for association with PFS on therapy with a Cox proportional hazards model, maintaining ACC subtype (ACC-I vs. ACC-II) as a covariate. **Results:** Only 1 (6%) of 17 assessed tumors were PD-L1 positive. By WES, tumor mutational burden (TMB) was overall low (median 1.4 mut/Mb, range 0.7 – 18.7), but higher TMB was associated with worse PFS. Four mutational signatures significantly correlated with worse PFS, including SBS86, associated with previous chemotherapy exposure. Immune deconvolution of RNA-seq data revealed that a higher neutrophil-to-lymphocyte ratio and more T follicular helper cells associated with worse PFS, while presence of cytotoxic cells, T effector memory cells, and mast cells associated with longer PFS. Notably, a 167-gene predictive signature was developed and validated in the phase II ipilimumab plus nivolumab salivary gland cancer trial. This 167-gene signature was not prognostic in ACC pts who did not receive immunotherapy. IMC single-cell immune mapping revealed that pts with longer PFS had increased presence of CD8 T cells, CD73+ macrophages in tumor, a higher stromal CD8 T cell:Regulatory T cell ratio, increased stromal SIGLEC15 positive cells, and a higher tumor-to-stroma ratio of fibroblasts. Conversely, Ki67-positive T cells, cancer stem cells, and M2 macrophages were associated with worse PFS. Through microbiome analysis, 13 bacterial genera in tumor samples, 25 in stool, and 8 in oral rinse were significantly associated with therapy outcomes. Of note, in stool microbiome, presence of *Akkermansia spp.* and *Bifidobacterium spp.* were significantly correlated with improved PFS, with the latter association also seen in oral rinse. **Conclusions:** Correlative analysis of the phase II axitinib plus avelumab trial revealed potential biomarkers predictive of combination clinical benefit in ACC, including a gene-expression signature. These findings may guide patient stratification for combinatorial therapy. Research Sponsor: U.S. National Institutes of Health; R03DE031333.

6105 Poster Session

The efficacy and safety of ulinastatin in the prevention and treatment of radiotherapy-induced oral mucositis in locoregionally advanced nasopharyngeal carcinoma (LA-NPC): A multicenter, open-label, randomized controlled clinical trial.

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Background: Severe oral mucositis is a common radiation-induced toxicity in locoregionally advanced nasopharyngeal carcinoma (LA-NPC) patients treated with concurrent chemo-radiotherapy (CCRT). Ulinastatin (UTI) can reduce the inflammatory response by inhibiting the release of inflammatory factors, but its role in radiotherapy-induced oral mucositis (RTOM) is unclear. Therefore, we conducted a multicenter, open-label, randomized controlled clinical trial to investigate the efficacy and safety of UTI in the prevention and treatment of RTOM in LA-NPC patients. **Methods:** Patients with histologically confirmed LA-NPC who met the eligibility criteria were randomly assigned to UTI group and control group. All patients received radical intensity modulated radiation therapy (IMRT) and concurrent chemotherapy (cisplatin 100 mg/m^2/3 weeks for 2 or 3 cycles). UTI of 100,000 units three times daily (5 days/week) was intravenously administrated from day 1 to the end of radiotherapy for UTI Group. The primary endpoint was the incidence of grade $\geq$ 3 acute RTOM during CCRT (Radiation Therapy Oncology Group , RTOG grading). The secondary endpoints included the cumulative incidence of RTOM, recovery rate (proportion of patients with grade $\geq$ 3 RTOM who recovered to grade $\leq$ 2 during CCRT), the onset time and duration of grade $\geq$ 3 RTOM, oral pain (Numerical rating scale, NRS), safety and survival outcomes. **Results:** From January, 2018, to December, 2021, 182 patients from 5 hospitals were enrolled. 179 patients were included for efficacy, safety and survival analysis (89 in the UTI group and 90 in the control group). All UTI group patients completed UTI treatment as planned, and both groups completed scheduled CCRT. The incidence of grade $\geq$ 3 RTOM was significantly lower in UTI group compared with control group (25.8% vs. 41.1%; P = 0.030). The recovery rate in UTI group was higher than that in control group (39.1% vs. 10.8%; P = 0.023). However, the onset time and the duration of grade $\geq$ 3 RTOM were similar between the two groups (Median [IQR] 26.00 [19.00, 33.00] days vs. 32.00 [20.50, 36.00] days; P= 0.621 and 12.00 [7.00, 18.00] days vs. 15.00 [8.00, 25.50] days; P= 0.209). The incidence of severe oral pain (NRS score$\geq$ 7) was significantly reduced in UTI group compared with the control group (22.5% vs. 36.7; P = 0.038). No UTI related adverse events were observed during treatment. With a median follow-up time of 41.6 months (IQR, 38.2 - 45.0 months), The 3-year OS, LRRFS, DMFS and PFS in UTI group and Control group were 96.5% vs. 94.3%, 91.2% vs. 87.2%, 95.2% vs. 92.1% and 89.9% vs. 85.1%, respectively (all P $>$ 0.05). **Conclusions:** Our study revealed that UTI can effectively reduce the incidence of graded $\geq$ 3 RTOM and severe oral pain without increasing adverse events and compromising survivals. Clinical trial information: NCT03387774. Research Sponsor: None.

Cobimetinib plus atezolizumab for *RAS* and *NF*1/2-mutated poorly differentiated thyroid carcinoma.

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Background: Poorly differentiated thyroid carcinomas (PDTC) are a subset of thyroid cancers characterized by high-grade pathologic features. They hold an intermediate position on the spectrum of follicular-derived thyroid cancers. Due to their more aggressive clinical behavior, PDTCs typically exhibit shorter responses to the usual kinase inhibitors (KIs) used in advanced differentiated thyroid cancers and develop resistance earlier on. In fact, median progression free survival (PFS) with single-agent lenvatinib in patients with PDTC in the SELECT trial (n=28) was 14.8 months. Although there are increasing data to support the use of immunotherapy plus KI combinations in anaplastic thyroid cancer, evidence demonstrating the efficacy of this strategy in PDTC is sparse. We aimed to study the safety and efficacy of atezolizumab combined with KIs in PDTC. **Methods:** We enrolledpatientswith PDTC in a single-center phase II prospective trial of atezolizumab plus mutation-determined targeted therapy (NCT03181100). Patients with *RAS* or *NF*- mutated tumors were treated with atezolizumab plus the MEK inhibitor (MEKi) cobimetinib. Primary outcome was median overall survival (mOS). Best response to therapy was assessed per RECIST v1.1; survival by the Kaplan-Meier method. **Results:** Eight patients with *RAS/NF*-mutated PDTC were enrolled. Median age at treatment start was 68.5 years. All patients had distant metastatic disease at time of enrollment. Prior to study entrance, 7/8 patients (88%) had surgical resection of the primary tumor, 6/8 (75%) radioactive iodine, 2/8 (25%) external beam radiation to the neck, and 3/8 (38%) bridging cytotoxic chemotherapy. All patients were naïve to KIs. Six (75%) patients had *RAS* mutations (1 *HRAS*, 3 *KRAS*, 2 *NRAS*) and 3 (38%) had *NF* mutations (2 *NF*1, 1 *NF*2). One patient's tumor harbored both *KRAS* and *NF*2 mutations at baseline. PD-L1 score was positive in 3/4 evaluable specimens. Median duration of follow-up was 65 months. Best response to therapy was stable disease in 6/8 (75%), partial response in 1/8 (12.5%) and progressive disease in 1/8 (12.5%). mOS was 23 months (95% CI, 12.8 – 33.2) and median PFS was 7 months (95% CI, 2.4 – 11.6). 4/8 patients received radioactive iodine (RAI) while on systemic therapy. Median dose of RAI was 149 millicuries (range, 108 – 153). mOS was significantly longer in patients who received RAI (32 vs 16 months; p= 0.034). The combination of cobimetinib + atezolizumab was overall well tolerated, with an expected adverse event profile. **Conclusions:** In patients with metastatic PDTC driven by *RAS* or *NF*mutations, combination of the anti-PD-L1 atezolizumab with MEKi cobimetinib showed some clinical efficacy, although PFS was shorter than with single-agent lenvatinib. However, SELECT trial did not delineate responses by driver mutations. This combination could thus be considered in selected patients at high risk of complications with antiangiogenic KIs. Clinical trial information: NCT03181100. Research Sponsor: Genentech; The Rare Tumor Initiative as a part of the STrategic Research Initiative DEvelopment (STRIDE) program at The University of Texas MD Anderson Cancer Center; National Institutes of Health through M.D. Anderson's Cancer Center Support Grant CA016672.

Effect of RGT-61159 on inhibition of oncogene c-MYB synthesis and tumor growth inhibition in a broad range of ACC PDX models, at well tolerated doses in rodents and non-human primates.

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Background: RGT-61159 is a first in-class oral inhibitor of the oncogenic transcription factor c-MYB via selective alteration of its RNA splicing machinery. RGT-61159 selectively induces the inclusion of the cryptic "poison" exon into the c-MYB RNA transcripts, resulting in the robust elimination of c-MYB canonical mRNA transcript and consequently of its protein in cells. Overactivation of the c-MYB oncogene, primarily due to chromosome rearrangements, is a hallmark of adenoid cystic carcinoma. (ACC). ACC is a rare and aggressive type of cancer for which effective treatment does not exist. By inhibiting oncogenic MYB protein production, RGT-61159 has the potential to efficiently and selectively inhibit proliferation or induce cell death of cancer cells overexpressing MYB protein. **Methods:** RGT-61159 cell killing activity was measured against a broad panel of cancer cell lines in a CellTiter-Glo assay. MYB RNA and MYB protein levels were assessed after drug treatment by RT-qPCR and JESS assay respectively. Anti-tumor activity of RGT-61159 as single agent or in combination was evaluated in a panel of ACC PDX mouse models harboring different molecular alterations in c-MYB, including ACCX6, ACCX11, ACCx5M1 and ST105B2. **Results:** Here, we showed that RGT-61159 has potent cancer cell killing activity (EC50 – 100nM -200nM) against a large panel of cancer cell lines over-expressing c-MYB, while sparing normal cells. Robust c-MYB RNA and c-MYB protein depletion (>80%) was observed in treated cells confirming RGT-61159 on-target cell killing effect. In addition, RGT-61159 single agent showed a remarkable anti-tumor activity (up to 90% TGI) at tolerated doses in the four ACC PDX models evaluated: ACCX6, ACCx11, ACCx5M1 and STB105B2. Importantly, we confirmed that RGT-61159 anti-tumor activity correlated with c-MYB target modulation. RGT-61159 efficacious doses reduced c-MYB transcript and c-MYB protein levels (by >80%) in all ACC PDx models evaluated. In addition, RNAseq analysis of ACC tumor after treatment showed that RGT-61159 drug treatment reversed the published ACC overexpression gene signature. Notably, the optimal RGT-61159 regimen was well tolerated, as assessed by changes in animal body weight and clinical signs in rodents and non-human primate. Finally, we showed that the combination of RGT-M001, an analog of RGT-61159, with the NOTCH Inhibitor AL-101 resulted in significant tumor regression at well tolerated doses. **Conclusions:** Altogether, these data demonstrated that RGT-61159 efficiently and safely targets the undruggable oncogenic transcription factor c-MYB. Down-regulation of c-MYB by the RGT-61159 RNA-targeting small molecule is a very promising therapeutic strategy to treat ACC and other cancers driven by c-MYB dysregulation. Research Sponsor: None.

6108 Poster Session

Pyrotinib in HER2-altered advanced salivary gland carcinomas: Analysis of two cohorts from an exploratory study.

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Background: The HER2 altered in a subset of salivary gland cancers (SGCs). Pyrotinib is an oral irreversible pan-HER receptor tyrosine kinase inhibitor targeting HER1, HER2, and HER4. In this study, we assessed the efficacy and safety of pyrotinib in patients with HER2-amplified/overexpressed/mutated advanced SGCs, including recurrent/metastatic(R/M) and locally advanced (LA) patients with high-risk of recurrence. **Methods:** R/M and high-risk LA SGCs with HER2-alteration were enrolled. Pyrotinib (400 mg) was given orally once daily. In LA cohort, pyrotinib were given as adjuvant therapy after standard surgery and postoperative radiation. **Results:** Between August 2019 and August 2023, 18 patients were enrolled (10 in R/M cohort and 8 in LA cohort). In R/M cohort, the median age was 58.5 years, and all patients were grade III. The ORR was 90%, including 2 CRs, 7 PRs and 1PD; median DOR was 5.7 months (range: 3.1-13.7) and median PFS was 7.6 months (range: 2.7-16.8). In LA cohort, the median age was 59.0 years, and all patients but one were grade III. All patients but one had T4 disease; 5 patients had N3 and 2 had N2b disease; 5 patients had ENE and 5 patients had positive margin. With a median follow up 21.3 months, only 3 patients experienced recurrence, and one patient died due to non-tumor reasons. The estimated 2-years PFS and 2-years OS were 75% and 100%. The most common adverse event was diarrhea, which occurred in 11/18 (61.1%) patients and 3/18 (16.7%) were grade III. **Conclusions:** Pyrotinib showed promising antitumor activity in recurrent/metastatic HER2-altered SGCs, and had a potential to prolong survival outcome as adjuvant treatment in LA patients setting, which needs further randomized studies. Clinical trial information: NCT05087706. Research Sponsor: None.

Phase II trial of regorafenib in metastatic medullary thyroid carcinoma (MTC) and radioactive iodine refractory differentiated thyroid carcinoma (RAIR DTC).

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Background: Multi-kinase inhibitors show activity in both MTC & RAIR DTC. However, therapeutic options are limited after disease becomes refractory to one or two lines of standard of care therapies. We report here results of an investigator-initiated phase II clinical trial evaluating regorafenib in this population (NCT02657551). **Methods:** Patients with MTC (disease progression within 6-12 months, mo, prior to study registration) and RAIR DTC (progression within 12 mo) were enrolled regardless of prior lines of therapy. Regorafenib (each cycle 3 weeks ON/1 week OFF) was started at 80 mg daily, with planned escalation after 1 & 2 weeks to 120 mg daily & 160 mg daily, respectively, in absence of significant treatment-related adverse events (TRAEs). The highest tolerated dose was continued from cycle 2 onwards until progression. The primary endpoints were proportion progression-free at 10 months in MTC & overall response rate (ORR) by RECIST v1.1 in RAIR DTC. Simon two-stage design was utilized; MTC: <2 in 8 progression-free in first stage stops for futility, stage 2: enroll 13, >6/21 provides 81% power for proportion >20%; DTC: <3 in 9 in response in first stage stops for futility; stage 2: enroll 11, >7/20 provides 81% power for ORR >25%. **Results:** 17 patients (8 MTC, 9 DTC) were enrolled between April 2016 and October 2022. Among MTC, median (range) age was 54.7y (48.1, 62.8), 25% female. Among DTC, median age (range) was 62.8y (44.3, 75.8), 55.6% female. In MTC group, the proportion progression-free at 10 months was 12.5% (95% CI 0.3%, 52.7%) & did not meet the criteria to continue into 2nd stage. ORR in MTC group was 12.5% (95% CI 0.3%, 52.7%). In DTC group, ORR was 11.1% (95% CI 0.3%, 48.2%), & did not meet the criteria to continue into 2nd stage. No patients were receiving treatment at cutoff. Patients with MTC and DTC with objective responses (1 each) had received one (vandetanib) & no prior systemic therapy, respectively. The most common reason for discontinuation was disease progression in MTC (4, 50%) & DTC (5, 55.6%). Grade 3-4 TRAEs were observed in 8/17 (47.1%), most frequent were diarrhea, hypophosphatemia, & hypertension (each grade 3: 2, 11.7%). There were no treatment-related deaths. Median progression-free survival (PFS) in MTC & DTC were 5.3 (95% CI 3.6, 20.1) & 11.0 (95% CI 1.2, 24.0) mo, respectively. Median overall survival (OS) in MTC & DTC were 16.1 (95% CI 5.2, NA) and 20.1 (95% CI 1.6, NA) mo, respectively. **Conclusions:** Regorafenib clinical trial did not reach its primary endpoints in MTC and DTC. Analyses are planned to investigate impact of prior VEGFR inhibitor exposure, biomarkers and resistance mechanisms. Clinical trial information: NCT02657551. Research Sponsor: Bayer.

	MTC (N=8)	RAIR DTC (N=9)
ORR, n (%)	1 (12.5%) (95% CI: 0.3, 52.7)	1 (11.1%) (95% CI: 0.3, 48.2)
PFS, mo	5.3 (95% CI: 3.6, 20.1)	11.0 (95% CI: 1.2, 24.0)
OS, mo	16.1 (95% CI: 5.2, NA)	20.1 (95% CI: 1.6, NA)
Follow up, median (range), mo	23.2 (6.7, 24.4)	23.2 (3.0, 24.0)

A non-invasive cfDNA fragmentomics assay for differentiating malignant and benign thyroid nodules.

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Background: Thyroid cancer (TC) is the most common endocrine malignancy in the world. Although it has a high survival rate, distinguishing between the common benign thyroid nodules and malignant ones remains a clinical challenge. We introduce a non-invasive assay based on cfDNA fragmentomics, aimed at accurately identifying TCs, thus reducing the discomfort and risks linked to surgical biopsies. **Methods:** We conducted a study involving 322 participants, comprising 161 early-stage thyroid cancer patients (154 stage I and 7 stage II) and 161 patients with benign thyroid nodules, of whom 68 were high-risk (Ti-Rads: 4/5) and 93 were low-risk (Ti-Rads = 2/3). The training cohort contained 94 TC and 98 BN patients, while the independent test cohort included 67 TC and 63 BN patients. Malignant and high-risk benign conditions were confirmed pathologically from surgically removed biopsy samples. Pre-operative plasma samples were collected from all patients and used for cell-free fragmentomics feature generation through low-pass WGS. A stacked machine learning model was developed using three fragmentomics features and three machine learning algorithms. **Results:** The machine learning model excelled in differentiating thyroid cancer from benign nodules, achieving area under the curve (AUC) scores of 0.973 in the training cohort and 0.965 in the independent test cohort. The model demonstrated high sensitivity (94.7% in the training cohort and 95.5% in the test cohort) and specificity (89.8% in the training cohort and 77.8% in the test cohort) after applying an optimized cutoff determined by cross-validation of the training cohort. Notably, the model was particularly effective in detecting malignant nodules smaller than 1cm, a task challenging for conventional methods, with sensitivities of 92.4% in the training cohort and 91.6% in the test cohort. For nodules larger than 1cm, the model achieved a perfect 100% sensitivity in both cohorts. Our predictive model showed universal excellent performance for accurately detecting TC patients with different histology, sex, and age in both the training cohort and the independent test cohort. Finally, the high-risk BN group showed higher risk scores compared to the low-risk BN group as expected, further validating the robustness of our model. **Conclusions:** Our study presents a non-invasive liquid biopsy assay, which utilizes fragmentomics profiling derived from low-pass WGS for differentiating between malignant and benign thyroid nodules, showcasing remarkable sensitivity and specificity. Our assay was able to accurately detect thyroid malignancies, especially in nodules smaller than 1cm, illustrating great clinical potential and therefore offers a promising alternative to surgical biopsies, potentially reducing patient discomfort and associated risks. Research Sponsor: None.

6111 Poster Session

Efficacy of cytotoxic chemotherapy in recurrent/metastatic adenoid cystic carcinoma (ACC).

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Background: Despite aggressive local therapy, many ACC patients (~50%) develop recurrent and/or metastatic (R/M) disease. However, there is no standard of care or FDA-approved systemic therapy for this population. Based on small phase II trials, mostly including multiple salivary gland histologies, cytotoxic chemotherapy is recommended for symptomatic patients with high tumor burden, but its efficacy and impact on survival in R/M ACC remain unsubstantiated. **Methods:** A retrospective cohort study was conducted at MD Anderson Cancer Center with an institutional ACC database (N=769). Patients diagnosed with R/M ACC and treated with single-agent or combination palliative-intent chemotherapy were included. The primary endpoints were overall response rate (ORR) and disease control rate (DCR) per RECIST 1.1. Secondary endpoints were median overall survival (mOS) and progression-free survival (mPFS) on chemotherapy for the entire cohort and stratified by growth pattern (solid *v* non-solid), line of therapy (1 *v* >2), chemotherapy regimen, and stage at diagnosis (M0 *v* M1). **Results:** 48 out of 115 patients who received chemotherapy were evaluated for response per RECIST.Median age at diagnosis was 43.6 years. 56% were male, 79% had M0 stage at diagnosis, 67% had minor salivary gland primary tumors, 52% had solid growth pattern, 31% had non-solid growth pattern, and 54% received first-line chemotherapy. The most common regimens were Platinum/Vinorelbine (38%), Platinum/Taxane (27%) and CAP (15%).The ORR and DCR rates were 12.5% and 56.3% respectively; 6 had partial response, 21 had stable disease, and 21 had progressive disease. The ORR and DCR rates were 20% and 52% for solid and 6.7% and 73.3% for non-solid growth pattern, respectively. The mOS from diagnosis was 7 years (95% CI, 3.5-10.7). The mOS on chemotherapy was 16 months (95% CI, 10.8-24.5). There was a significant difference in mOS between solid and non-solid growth pattern (10.8 *v* 24.1 months, p=0.015), but not by line of therapy, regimen, or stage at diagnosis. The mPFS on chemotherapy was 4.3 months (95% CI, 2.8-6.3 months). There was a significant difference in mPFS between solid and non-solid growth pattern (4.0 *v* 7.3 months, p=0.018), but not by line of therapy, regimen, or stage at diagnosis. **Conclusions:** In this largest to date real-world data on chemotherapy in ACC, response and survival outcomes were lower than historical data. The efficacy of chemotherapy may vary by growth pattern and other patient and tumor factors, which requires further investigation. Given the low ORR and overall slow-growing disease pattern, tumor volumetrics may be better than RECIST to assess treatment benefit. Research Sponsor: None.

Safety and efficacy of AIC100 chimeric antigen receptor (CAR) T-cell therapy in patients with advanced thyroid cancers: Results from the phase 1 study.

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Background: Patients with relapsed/refractory poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC) have limited treatment options and an overall poor prognosis. Several studies highlighted the role of ICAM-1, a cell surface glycoprotein that is expressed in a variety of cancers including thyroid cancers, in tumorigenesis. AIC100 is a 3rd generation anti ICAM-1 CAR T-cell product engineered with an affinity-tuned technology to selectively bind and kill tumor cells to improve safety, and co-expresses somatostatin receptor 2 (SSTR2) to allow CAR T-cell activity tracking by DOTATATE PET scan. We present here the results from the phase 1 dose-escalation clinical trial NCT04420754. **Methods:** This is a phase 1 multicenter study designed to explore 3 dose levels (DLs) of AIC100 at $1x10^7$, $1x10^8$, and $5x10^8$, respectively. Key eligibility included adult patients (≥18 years) with ICAM-1 positive relapsed/refractory PDTC or advanced ATC who had measurable disease, and with ECOG performance status 0-2. AIC100 was infused intravenously at least 48 hours after completing lymphodepletion (Fludarabine/Cyclophosphamide x 3 days). Primary objectives included safety assessment/ dose-limiting toxicities (DLTs) in the first 30 days after AIC100 infusion and to determine the recommended phase 2 dose (RP2D). **Results:** As of Feb 02, 2024, 15 patients were enrolled and 10 (5 ATC; 5 PDTC) were infused with AIC100 in 3 DLs. The treated patients had a median age of 55 (range, 47-69) years, were predominantly males (N=8), and with a median of 2 (range, 1-4) prior lines of therapies. Autologous AIC100 was successfully manufactured for all patients. No DLTs were observed across all DLs, and the maximum tolerated dose was not reached. Six (60%) patients developed grade 1/2 CRS. No ICANS or other serious adverse events related to AIC100 occurred. Nine patients (3 in each DL) were evaluable for efficacy analysis at day 42 after infusion; responses were assessed per study site investigators and not centrally. For all patients, the objective response rate (ORR) was 22% [1 ATC with partial response (PR) at DL2 and 1 PDTC with complete metabolic response (CR) at DL3] and the disease control rate (DCR, defined as ORR + stable disease) was 56%. For evaluable patients in DLs 2 and 3 (n=6), the ORR and DCR were 33% and 67%, respectively. Peripheral blood CAR T-cell expansion by PCR was observed in all patients. DOTATATE PET activity correlated with CAR T-cell activity and tumor responses. **Conclusions:** This first-in-human ICAM-1 targeted CAR T-cell study demonstrated an excellent safety profile and promising antitumor activity for AIC100 in patients with PDTC and ATC. These favorable outcomes, including a PR in DL2 and a CR in DL3, provide a proof-of-concept and support further exploration of AIC100 to optimize the RP2D and to expand for other ICAM-1-positive neoplasms. Clinical trial information: NCT04420754. Research Sponsor: AffyImmune Therapeutics.

TPS6113 Poster Session

PEMDA-HN, an open-label, phase II, randomized controlled study of danvatirsen plus pembrolizumab compared to pembrolizumab alone in first-line recurrent and/or metastatic head and neck squamous cell carcinoma (RM HNSCC).

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Background: Signal transducer and activator of transcription 3 (STAT3) plays critical roles in promotion of an immune-suppressive tumor microenvironment and survival of tumor cells. Danvatirsen (DANVA) is a 16-nucleotide, generation 2.5 antisense oligonucleotide designed to down-regulate the expression of human STAT3 mRNA. Over 500 patients with hematologic malignancies or solid tumors have been exposed to DANVA monotherapy or in combination. A tolerable safety profile has been demonstrated for DANVA and toxicities are manageable. The SCORES study in recurrent and/or metastatic (RM) HNSCC patients, naïve to programmed cell death (ligand)1 (PD-(L)1) therapy, demonstrated that DANVA in combination with the PD-L1 inhibitory antibody durvalumab administered in the second line setting appeared to result in a higher objective response rate (ORR) (22.6% [12.3-36.2]) compared with the ORRs seen with durvalumab alone in prior studies (Cohen E. et al. Ann. Oncol., 2018). Several patients had complete responses (CR, 9.4%). The ORR was higher in patients with a PD-L1 tumor proportion score (TPS) ≥1 and ≥20, with increasing benefit noted with higher PD-L1 expression compared with historic anti-PD-(L)1 monotherapy data. The current study aims at evaluating the first-line combination of DANVA with pembrolizumab, an anti-PD-1 agent approved as first-line monotherapy for RM HNSCC in patients with PD-L1 positive disease. **Methods:** PEMDA-HN is a multicenter, open-label, randomized phase 2 study utilizing a Bayesian Optimal design (BOP2). Approximatively 81 RM HNSCC patients with a PD-L1 combined positive score (CPS) score ≥1 will be randomized in a 2:1 ratio stratified based on CPS<20 and CPS≥20 to receive either DANVA (3 mg/kg IV Days 1, 3, and 5 and then weekly starting on Day 8) and pembrolizumab (200 mg IV every 3 weeks) or pembrolizumab alone as a first line therapy for recurrent or metastatic disease. Eligible patients will receive study treatment until disease progression or discontinuation. The primary endpoint of the study is ORR by response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) as assessed by the investigator. Key secondary objectives are safety, additional antitumor activity evaluation (CR rate, duration of response, disease control rate, progression-free and overall survival) and pharmacokinetics. Efficacy (e.g. ORR, CR rate) will be evaluated in all patients and in subsets of patients with CPS<20, CPS≥20 and CPS≥50. Exploratory endpoints include but are not limited to target engagement and biomarker evaluation. The study is being, or will be, conducted at US, South Korea and United-Kingdom study centers. Clinical trial information: NCT05814666. Research Sponsor: Flamingo Therapeutics.

TPS6114 Poster Session

STELLAR-305: A randomized phase 2/3 study of zanzalintinib plus pembrolizumab versus pembrolizumab alone in patients with previously untreated PD-L1 positive recurrent/metastatic head and neck squamous cell carcinoma.

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Background: VEGFR, MET, and the TAM kinase AXL are overexpressed in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC); their activation contributes to increased tumor aggressiveness and poor prognosis.The immune checkpoint inhibitor (ICI) pembrolizumab, as monotherapy or in combination with chemotherapy, is a standard of care in patients with PD-L1 expressing R/M HNSCC. However, the response rate and survival benefit with pembrolizumab monotherapy are unsatisfactory, and addition of chemotherapy results in unfavorable toxicity. Zanzalintinib is a novel, multi-targeted tyrosine kinase inhibitor (TKI) of VEGFR, MET, and the TAM kinases (TYRO3, AXL, MER). Preclinical data suggest zanzalintinib-mediated inhibition of these kinases may suppress tumor growth and angiogenesis, while simultaneously promoting an immune-permissive tumor microenvironment that may enhance response to ICIs. Zanzalintinib + ICI combination has shown promising antitumor activity and manageable safety in a phase 1 study in solid tumors. To further support the TKI-ICI combination, phase 2 clinical activity was observed in R/M HNSCC with the multi-targeted TKI cabozantinib (inhibits VEGFR, MET, and TAM kinases) in combination with pembrolizumab. The present study, STELLAR-305, will evaluate the efficacy and safety of zanzalintinib + pembrolizumab vs pembrolizumab alone in previously untreated, PD-L1-positive, R/M HNSCC. **Methods:** STELLAR-305 (NCT06082167) is a randomized, double-blind, phase 2/3 study. Eligible patients are adults (≥18 years) with histologically or cytologically confirmed R/M HNSCC that is incurable with local therapy. Patients may not have been treated with systemic therapy, unless given as part of multimodal treatment for locally advanced disease and completed >6 months before randomization. Patients must have a primary tumor location of the oropharynx (HPV testing required), oral cavity, hypopharynx, or larynx; those with nasopharynx, salivary gland, or occult primary sites are excluded. Other eligibility criteria include a PD-L1 CPS ≥1, measurable disease per RECIST v1.1, and an ECOG performance status of 0–1. Patients with prior treatment with ICIs or zanzalintinib are not eligible. Patients will be randomized 1:1 to zanzalintinib + pembrolizumab, or placebo + pembrolizumab. The dual primary endpoints are PFS per RECIST v1.1 by blinded independent radiology committee and overall survival. Secondary endpoints include safety, PFS per RECIST v1.1 by investigator, objective response rate, and duration of response. If minimum efficacy requirements are met in phase 2, the study will proceed to phase 3 with approximately 500 patients enrolled across both phases. STELLAR-305 is currently enrolling, with 200 sites estimated for global expansion. Clinical trial information: NCT06082167. Research Sponsor: Exelixis, Inc.

TPS6115 Poster Session

A phase 1b study of tbio-4101 (autologous selected and expanded tumor-infiltrating lymphocytes [TILs]) with pembrolizumab in patients with anti-PD-1–resistant, advanced head and neck squamous cell carcinoma (aHNSCC).

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Background: Despite the excitement and approval of anti-PD1 therapy in first line setting of patients with aHNSCC, prognosis remains poor, with the majority experiencing disease progression after therapy. Consequently, novel strategies to improve treatment activity represent a critical and unmet need for this patient population. Cell therapies offer the advantage of a more personalized therapy for patients over standard immune checkpoint inhibitors. Historically, cell therapies have relied on bulk products that may not effectively select a tumor-reactive T cell population. TBio-4101 is produced by an industrialized manufacturing approach leveraging single-cell sorting of patient-specific neoepitope-reactive TIL with the potential to address immunologically 'cold' tumors. The TBio-4101 process specifically enriches polyclonal, polyfunctional, tumor-reactive T cells with an endogenous neoantigen-reactive T cell receptor repertoire that can target multiple tumor antigens. Non-tumor-reactive bystander T cells, which may negatively impact treatment efficacy via product dilution, and typically account for $\geq$90% of bulk TIL, are substantially reduced by this process. Inspired by the early academic clinically efficacious NCI selection and enrichment strategies (Tran et al 2014, 2016; Zacharakis et al, 2022), TBio-4101 is refined to better identify and potentially enrich to >70% tumor-reactive CD8+ and CD4+ T cells (median < 3% in bulk TIL). **Methods:** This is a Phase 1b, open-label, single-center study of TBio-4101 and pembrolizumab. Eligible patients are 18 to 75 years of age with aHNSCC. Prior to receiving pembrolizumab with or without chemotherapy as first line standard-of-care (SOC), these patients undergo tumor harvest for TILs followed by apheresis to collect monocytes. TILs are isolated from the tumor and expanded in vitro. Patient-specific neoepitopes are defined by whole exome and RNA sequencing of tumor versus germline to manufacture a peptide pool representing potential tumor-specific mutations. Monocytes isolated from apheresis are differentiated into dendritic cells, pulsed with the neoepitope peptides, and co-cultured with the TILs. Tumor-reactive T cells are specifically activated and selected based on upregulation of activation markers prior to expansion in culture. This process results in a patient-specific T cell product enriched for tumor-reactive T cells. Enrolled patients who progress on first line SOC therapy are preconditioned with 5 days of nonmyeloablative lymphodepletion followed by TBio-4101 infusion. Thereafter, patients receive $\leq$6 doses of IL-2 (600,000 IU/kg) every 8h, and pembrolizumab (200 mg) every 3 weeks until disease progression. The trial is currently open, with a target enrollment of 15 patients (NCT06236425). Clinical trial information: NCT06236425. Research Sponsor: Turnstone Biologics.

TPS6116 Poster Session

Enfortumab vedotin and pembrolizumab as first-line treatment in recurrent or metastatic head and neck squamous cell carcinoma: A cohort of the EV-202 trial.

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Background: Novel treatment strategies are needed to treat recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) given the poor durability of response and prognosis with standard therapy. In KEYNOTE-048, among patients with R/M HNSCC and PD-L1 combined positive score (CPS) ≥1, first-line (1L) treatment with pembrolizumab demonstrated a median overall survival (OS) of 12.3 months. Nectin-4 is widely expressed in a variety of solid tumors, including bladder cancers and HNSCC. Enfortumab vedotin (EV) is a Nectin-4–directed antibody–drug conjugate approved for use in previously treated (EV monotherapy) or 1L (EV + pembrolizumab) locally advanced or metastatic urothelial carcinoma (la/mUC). EV + pembrolizumab showed superior OS and progression-free survival (PFS) vs chemotherapy in 1L la/mUC. EV-202 is a multicenter, open-label, phase 2 study (NCT04225117) evaluating the efficacy and safety of EV in multiple tumor-specific cohorts. In the previously treated R/M head and neck cancer cohort, 11 of 46 patients (23.9%) had a confirmed objective response with EV monotherapy; median PFS was 3.9 months (Swiecicki P, et al. ASCO 2023. Poster #6017). We hypothesize that EV + pembrolizumab may demonstrate benefit as a 1L therapy in patients with R/M HNSCC and CPS ≥1. **Methods:** Patients in the R/M HNSCC cohort of EV-202 have histologically or cytologically confirmed HNSCC, an ECOG performance status 0 or 1, no prior systemic therapy administered in the R/M setting (with the exception of systemic therapy completed >6 months prior if given as part of treatment for locally advanced disease), and CPS ≥1. A total of 40 patients are expected to be enrolled. An interim analysis will be conducted when 20 patients are evaluable for tumor response; 5 responders will be needed to proceed. Of 40 total patients, 14 must demonstrate response to claim promising antitumor activity. Patients will receive EV 1.25 mg/kg intravenously on days 1 and 8 and 200 mg of pembrolizumab intravenously on day 1 of each 21-day cycle until discontinuation, for reasons including disease progression or toxicity. Disease assessments will be performed 9 weeks from the first dose and every 6 weeks thereafter until disease progression, start of subsequent anticancer therapy, death, consent withdrawal, loss to follow-up, or study end, whichever occurs first. The primary endpoint is investigator-assessed, confirmed ORR per RECIST v1.1. Secondary endpoints include investigator-assessed duration of response, disease control rate, PFS, OS, and safety/tolerability. Analyses will also be evaluated per iRECIST. Exploratory analyses will include pharmacokinetics, immunogenicity, quality of life, and assessment of biomarkers that may correlate with treatment outcome, including Nectin-4 expression. Recruitment for this cohort began in November 2023 and is ongoing. Clinical trial information: NCT04225117. Research Sponsor: Astellas, Inc. and Seagen, which was acquired by Pfizer in Dec. 2023.

TPS6117 **Poster 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 an estimated ORR of 19% and median OS of 13.6 months. There are several factors which may influence which patients respond to antibodies targeting the PD-1 axis. Regulatory T cells (Tregs) play a significant role in an immunosuppressive tumor microenvironment. Anti-PD-1 antibodies induce Treg activation in part through AKT pathway activation, which may contribute to low response rates to checkpoint inhibitor therapy. AKT blockade selectively inhibits the proliferation of human Tregs. Additionally, inhibition of the PI3K-AKT-mTOR pathway limits myeloid-derived suppressor cells (MDSC) infiltration and differentiation, and boosts CD8+ T cell memory and effector function. Ipatasertib is an oral highly selective small-molecule inhibitor of all three isoforms of AKT. This phase 2 trial is designed to compare progression-free survival (PFS) in first line R/M, HNSCC patients treated with the combination ipatasertib and pembrolizumab versus pembrolizumab monotherapy treatment. **Methods:** In this open-label randomized phase 2 multicenter trial, patients with R/M HNSCC are treated with pembrolizumab 200mg on day 1 +/- ipatasertib 400mg QD days 1-14 of 21-day cycles. Patients must have PD-L1 CPS score ^{3} 1, have measurable disease per RECIST 1.1, and consent to on-treatment biopsy. Patients will be excluded if they have received prior systemic therapy for R/M HNSCC, cannot swallow a pill, or require insulin for diabetes. The primary objective is to compare the PFS between the two arms. We will estimate the relative hazard ratio associated with ipatasertib plus pembrolizumab compared to pembrolizumab alone using the Cox Model where randomized treatment assignment is the only variable in the model. Secondary objectives include ORR, safety and tolerability of the combination, and changes in tumor immune cell infiltration, AKT signaling, and changes in peripheral blood immune cells. Ultimately, a total of 48 patients will be enrolled, with 24 patients in each cohort. To date, a total of 22 patients have been enrolled from 15 sites. Accrual is ongoing (NCT05172258). Clinical trial information: NCT05172258. Research Sponsor: National Cancer Institute.

TPS6118 **Poster Session**

Phase II trial assessing safety, efficacy and immune correlates of heterologous prime-boost with pBI-11 (IM) and TA-HPV (IM) plus pembrolizumab for advanced, PD-L1 CPS≥1, hrHPV+ oropharyngeal cancer.

Michael K. Gibson, Richard Roden, TC Wu, Ellen Heimann-Nichols; Vanderbilt University Medical Center, Vanderbilt-Ingram Cancer Center, Nashville, TN; Johns Hopkins University, Baltimore, MD; Vanderbilt University Medical Center, Nashville, TN

Background: HPV-related OPSCC occurs in younger patients, has a significantly better prognosis, and is most often caused by HPV subtype 16. There is a 90% overall survival for HPV+/p16+ OPSCC (40% for HPV-/p16- OPSCC), which can be cured with multimodality care. For patients with R/M disease, treatment with pembrolizumab (P) +/- chemotherapy is palliative, with a median OS of approximately 12 months for patients with PD-L1 combined positive score (cps) >1 treated with P alone. Heterologous prime boost with DNA priming followed by vaccinia-based boosting against HPV16 viral antigens will be studied using pBI-11 [(DNA vaccine pNGVL4a-SigE7 (detox)/HSP70, HPV16 E7(detox)/ HPV18 E7(detox), HPV16 E6(detox), and HPV18 E6(detox)] followed by TA-HPV (recombinant vaccinia-human papillomavirus (denoted TA-HPV) derived from the Wyeth strain of vaccinia which carries modified E6 and E7 genes from HPV types 16 and 18). This study is approved by the Vanderbilt University IRB and is open accrual (NCT NCT05799144). **Methods:** Patients with R/M, HPV positive OPSCC without prior therapy for R/M disease, without contraindications to immunotherapy and with a PD-L1 cps > 1 will be screened. There is a 6 patient safety run-in. Treatment with pBI-11 vaccine (2 IM injections on weeks 1 and 4) plus one IM administration of TA-HPV on week 7 will be given in combination with P IV on weeks 1, 4, and 7). Following restaging, all patients will continue (including those with PD) with 3 more cycles of P followed by restaging. The primary clinical outcome is RR to addition of vaccine in the 50% of predicted P non-responders (NR) who proceed to Part II (ie conversion to responders). All responders will continue to receive P until progression. Approximately 54 patients with be enrolled. Two research tumor biopsies and blood draws will be obtained pre- and on treatment (week7-9). Tumor tissue cores will be utilized for immunohistochemical and molecular tests (e.g., expression of immune cell and viral markers, TCR sequencing and total transcripts). Blood with be tested for HPV16/18 E6, E7 antibodies and vaccinia virus neutralizing assays; proliferative responses of peripheral blood lymphocytes to stimulation by HPV16/18 E6 and E7; HPV16/18 E6- and E7-Specific T cells; and HPV DNA in plasma. Data from the 1st four patients enrolled will be presented. Clinical trial information: NCT05799144. Research Sponsor: None.

TPS6119 Poster Session

Biomarker-driven radiation therapy dose reduction after transoral robotic surgery for the treatment of HPV-positive oropharyngeal cancer.

James Edward Bates, William A. Stokes, Mark William McDonald, Soumon Rudra, Madison Miller Stallings, Natalie A Lockney, Kyle Mannion, Nabil F. Saba, Nicole C. Schmitt, Jennifer H Gross, Conor Ernst Steuer, Azeem Kaka, Michael Topf, Mihir R. Patel; Emory University, Atlanta, GA; Emory University Hospital Midtown, Atlanta, GA; Emory University Winship Cancer Institute, Atlanta, GA; Vanderbilt University Medical Center, Nashville, TN; Vanderbilt University, Nashville, TN; Vanderbilt University School of Medicine, Nashville, TN; Department of Otolaryngology Head and Neck Surgery, Winship Cancer Institute, Emory University, Atlanta, GA

Background: HPV-related oropharyngeal squamous cell carcinoma (OPSCC) is a highly curable cancer with a considerable burden of treatment-related toxicities. Transoral surgery (TOS) is a treatment option for patients with early-stage disease; however, adjuvant radiotherapy (RT) is often recommended and can add to these late toxicities. Circulating tumor HPV DNA (ctHPVDNA) is a sensitive marker of tumor recurrence, and undetectable post-operative ctHPVDNA is associated with improved recurrence-free survival. We hypothesize that patients with undetectable post-TOS ctHPVDNA without high risk pathologic factors can safely undergo de-escalation of adjuvant RT to 36 Gy, and this reduction will improve long-term swallowing function. **Methods:** We opened a multi-institutional phase II study (NCT05387915) including patients with pT1-2, N0-1, M0 HPV-related OPSCC who had TOS resection of their primary site and at least ipsilateral neck dissection. Pertinent inclusion criteria include a <10 pack-year smoking history, or a <30 pack-year smoking history if >10 years since last tobacco consumption, and pathologic findings of one or more intermediate risk factors: close margin (1 – 4 mm), perineural invasion, 2 – 4 positive lymph nodes or a single lymph node >3 cm. Patients with high risk factors (positive margin, extranodal extension, 5 or more positive lymph nodes) are excluded. Patients must have a detectable pre-operative ctHPVDNA and a post-operative ctHPVDNA drawn 7-14 days after TOS; if negative, patients receive 36 Gy of adjuvant RT in 15 fractions of 2.4 Gy delivered daily; if positive, they receive care per the discretion of the treating radiation oncologist. If the final surgical margins at the site of the primary tumor are >2mm, patients are eligible for omission of the primary tumor post-operative bed from the radiation volume. Our primary endpoint is 1-year swallowing function as measured by the composite MD Anderson Dysphagia Index (MDADI) score. Secondary endpoints include overall/progression-free survival and other quality of life metrics. The study is powered to detect an 8.5-point improvement in MDADI composite score at one year over the historical control from ECOG 3311 Arm B. With an alpha of 0.05 and a power of 0.90 we require 27 evaluable patients. Accounting for dropout and patients lost to follow-up, we aim to enroll 35 total patients.Since accrual began in June 2022, we have enrolled 18 patients as of January 2024. We recently opened the study at a second institution and are in the process of opening at a third institution. Clinical trial information: NCT05387915. Research Sponsor: Winship Cancer Institute of Emory University.

TPS6120 Poster Session

eVOLVE-HNSCC: A global phase 3 study of volrustomig as sequential therapy for unresected locally advanced head and neck squamous cell carcinoma (LA-HNSCC) following definitive concurrent chemoradiotherapy (cCRT).

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Background: Currently there are no approved maintenance therapies for patients (pts) with unresected LA-HNSCC following definitive cCRT. The PD-1 inhibitors pembrolizumab and nivolumab are licensed for treatment of pts with recurrent or metastatic HNSCC who have progressed on or after a platinum-based therapy. Dual inhibition of CTLA-4 and PD-L1 is approved in solid tumors including renal cell carcinoma (RCC), NSCLC, and melanoma, and has shown a numerical trend towards improved survival in first-line pts with recurrent/metastatic HNSCC whose tumors express PD-L1. Volrustomig (MEDI5752) is a monovalent, PD-1/CTLA-4 bispecific, humanized IgG1 monoclonal antibody engineered to specifically inhibit PD-1, with increased CTLA-4 blockade on PD-1+ activated T cells compared to PD-1– resting peripheral T cells. In a first-in-human phase 1/2 study (NCT03530397), volrustomig monotherapy showed promising efficacy with acceptable tolerability in advanced clear cell RCC and in combination with chemotherapy in advanced NSCLC. The phase 3, randomized, open-label, multicenter, eVOLVE-HNSCC study will evaluate the efficacy and safety of sequential therapy with volrustomig compared with observation in pts with unresected LA-HNSCC who have not progressed after receiving definitive cCRT (NCT06129864). **Methods:** Key eligibility criteria include histologically or cytologically confirmed, unresected LA-HNSCC with no evidence of metastatic disease, i.e. AJCC 8th edition (TNM staging system) stage IVA/B cancers of the hypopharynx, oral cavity, larynx or HPV-negative oropharynx, or stage III HPV-positive oropharynx cancer; age ≥18 years; WHO/ECOG performance score of 0 or 1; and adequate organ and bone marrow function. Key exclusion criteria include requiring further treatment with curative intent after definitive cCRT, resected LA-HNSCC, recurrent/metastatic disease, and >1 primary tumor. Following initial screening and definitive cCRT (cisplatin or carboplatin + paclitaxel or carboplatin + 5-FU, plus concomitant radiotherapy), approximately 1145 pts whose disease has not progressed within 12 weeks of the last dose of cCRT will be randomized 1:1 to Arm A or B. Arm A will receive volrustomig intravenously every 3 weeks for a maximum of 12 months or 18 cycles, or until RECIST v1.1-defined radiological progressive disease (PD) or unacceptable toxicity. Arm B will undergo observation for a maximum of 12 months or until PD. The primary endpoint is PFS in pts with PD-L1-expressing tumors. Secondary endpoints include PFS in all randomized pts, OS in pts with PD-L1-expressing tumors and in all randomized pts, PFS2, safety, patient-reported outcomes, pharmacokinetics, and immunogenicity. Exploratory biomarker analyses will also be conducted. Enrollment began in December 2023. Clinical trial information: NCT06129864. Research Sponsor: AstraZeneca.

TPS6121 Poster Session

Novel approach of prophylactic radiation to reduce toxicities comparing 2-step 40 Gy with 56 Gy simultaneous integrated boost intensity-modulated radiation therapy for locally advanced squamous cell carcinoma of the head and neck: A phase III trial (JCOG1912, NEW BRIDGE).

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Background: Chemoradiotherapy (CRT) with concurrent cisplatin is the standard of care as a nonsurgical definitive treatment for patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). However, CRT is associated with increased severe late adverse events, including swallowing dysfunction, xerostomia, ototoxicity, and hypothyroidism. Few strategies aimed at less invasive CRT without compromising treatment outcomes have been successful. The purpose of this study is to confirm the non-inferiority of reduced dose prophylactic radiation with 40 Gy compared to standard dose prophylactic radiation with 56 Gy in terms of the time to treatment failure (TTF) among patients with clinical stage III-IVB LA-SCCHN. **Methods:** This study is a multicenter, two-arm, open-label, randomized phase III trial. The main inclusion criteria are as follows: (i) Primary lesions are located in the oropharynx, hypopharynx, or larynx. (ii) Histologically proven SCC on biopsy specimens of the primary lesion. Immunohistochemistry reveals p16 negativity in patients with oropharyngeal cancer. (iii) Clinical stage of III, IVA, or IVB (excluding N3a) based on the 8th UICC-TNM classification. Patients are randomized to the standard arm or experimental arm. A total dose of 70 Gy for tumors with concurrent cisplatin at 100 mg/m^2 are administered in both arms. For prophylactic field, patients in the standard arm receive a total dose of 56 Gy in 35 fractions for 7 weeks using simultaneous integrated boost (SIB56) and those in the experimental arm receive 40 Gy in 20 fractions using two-step methods for 4 weeks (2-step40). A total of 400 patients will be enrolled from 52 Japanese institutions within 5 years. The primary endpoint is TTF, and the secondary endpoints are overall survival, complete response rate, progression-free survival, locoregional relapse-free survival, acute and late adverse events, quality of life score, and swallowing function score.Patient accrual was started in May 2021 and the study is now open for accrual. A total of 186 patients have been enrolled as of January 2024. This trial has been registered in the Japan Registry of Clinical Trials as jRCTs031210100. Clinical trial information: jRCTs031210100. Research Sponsor: The Japan Agency for Medical Research and Development; JP22ck0106751; National Cancer Center Research and Development Funds; 2020-J-3, 2023-J-03.

TPS6122 **Poster Session**

Molecular residual disease (MRD) interception in locoregionally advanced head and neck squamous cell carcinoma (LA-HNSCC): MERIDIAN study.

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Background: The detection of circulating tumor DNA (ctDNA) after definitive treatment or MRD is associated with recurrence across different tumor types. We previously showed that ctDNA detection using a bespoke tumor-informed assay (RaDaR), in LA-HNSCC patients (pts) after surgery, definitive radiation (RT) or chemoRT (CRT), is associated with recurrence within a year (Sanz-Garcia et al, ASCO 2023). To date, the impact of intercepting MRD prior to progression in HNSCC has not been explored. Anti-PD-1 blockade has shown benefit in recurrent/metastatic HNSCC but the efficacy in LA-HNSCC is still uncertain. TIGIT is overexpressed in HNSCC and could be a potential target to improve immunotherapy (IO) outcomes. Rilvegostomig (AZD2936) is a monovalent bispecific TIGIT/PD-1 antibody that has shown acceptable safety in phase I studies, currently in phase III studies. We hypothesize that IO (AZD2936) could induce ctDNA clearance post-definitive treatment and avoid, or delay recurrence. **Methods:** This study will recruit 200 pts with high-risk LA-HNSCC treated with curative intent: surgery ± adjuvant therapy, definitive RT or CRT; stage III Human Papilloma virus (HPV) positive or III-IVB HPV negative. Archival tissue must be available for whole exome sequencing (WES). Pts will be enrolled in part A (definitive therapy) and part B (follow up – FU - post-definitive therapy). Plasma samples will be collected in part A (pre-treatment and post-surgery prior to adjuvant therapy) and part B (at 4-6 weeks: FU1 and 8-12 weeks: FU2). These FU samples will be analyzed in real time for ctDNA using RaDaR, an assay that targets patient specific somatic variants identified by WES of matched tumor tissue. MRD+ pts (defined as having ctDNA detected at FU2) will be enrolled to part C (interception) and randomized 3:1 to receive AZD2936 750mg IV q3w for 6 cycles or observation. 30% of pts (N=60) will be enrolled in part C. Tumor must be positive for PD-L1 (CPS≥1) and there should not be residual primary tumor or distant metastases at FU2; residual lymph nodes are allowed if neck dissection is performed. Part D will consist of long term FU of MRD+ pts; RaDaR will be performed at week 2 (W2) and week 10 (W10), and radiological assessments will be performed at W2. MRD- pts will be enrolled in part E (long term FU). The primary endpoint of MERIDIAN is ctDNA clearance in MRD+ pts, defined as no detection of ctDNA at Part D W2 and W10. We will have 87% power to identify a significant improvement in ctDNA clearance rate from 10% (observation) to 40% (AZD2936) given a significance level of 0.1. Secondary objectives include survival and safety. Exploratory analyses include: ctDNA detection using other assays (HPV DNA, methylated ctDNA), ctDNA detection in part E and beyond W10 in part D, quality of life assessments (FACT-ICM, EORTC-HN43), health economics and radiomics. As of February 2024, 19 patients are recruited. Clinical trial information: 05414032. Research Sponsor: Astra Zeneca; Ontario Institute Cancer Research.

TPS6123 Poster Session

EFFECT-neo: A phase 3 study of pembrolizumab plus chemotherapy versus chemotherapy as neoadjuvant therapy in patients with resectable locally advanced head and neck squamous cell carcinoma.

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Background: There is still a huge need for treatment of operable locally advanced head and neck squamous cell carcinoma (LA HNSCC). Multiple phase 2 studies have shown that PD-1 combined with chemotherapy has good short-term efficacy, especially the pathological complete response (pCR) rate exceeds 30%, which is also considered to be an important factor in the survival benefit that neoadjuvant immune therapy may bring. The randomized, open-label, phase 3 EFFECT-neo study (NCT06102395) will evaluate efficacy and safety of pembrolizumab plus chemotherapy versus chemotherapy as neoadjuvant therapy in patients with resectable LA HNSCC. **Methods:** Patients with untreated LA HNSCC who met the inclusion criteria will be randomly assigned 1:1 to two treatment arms. Experimental group will be given 2 cycles of pembrolizumab (200mg d1, Q3W) + chemotherapy (perfer TPF regimens) . Control group will undergo 2 cycles of chemotherapy. Both two arms should finish imaging evaluation, and If the result is CR after neoadjuvant treatment, radiotherapy (RT) (60-70Gy) ± chemotherapy (investigator's choice) will be given as adjuvant treatment; if the result are PR or SD, surgery (within 2 weeks) will be performed, and then RT ± chemotherapy will be given. If the imaging evaluation is PD, patients will be received standard treatment. Enrolled patients must closely monitor the adverse reactions of chemotherapy and record the time, grade, treatment measures, outcomes, etc. All patients will be reviewed every 3 months for 1 year; after 1 year, they were reviewed every 6 months for 3 years; patient recurrence and survival data were recorded. Eligibility criteria will include age ≥18 years; untreated with immunotherapy, resectable, stage III/IVB HNSCC (AJCC Cancer Staging Manual, 8th edition); ECOG performance status 0-2; and the investigators believe that patients can safely receive pembrolizumab combined with chemotherapy in neoadjuvant chemotherapy. Randomization treatment will continue until disease progression, unacceptable toxicity, or decision to withdraw. Primary end points is pCR, defined as the absence of residual invasive squamous cell carcinoma within the primary tumor specimen on resection/needle biopsy (Patients with CR imaging results will undergo multipoint biopsy). Secondary end points include objective response rate, 1-year and 2-year event-free survival rates, 2-year overall survival rate, functional preservation rate, safety and Karnofsky performance status. Recruitment is ongoing and will continue until 272 patients are enrolled. Clinical trial information: NCT06102395. Research Sponsor: None.

TPS6124 Poster Session

Phase II trial of immunotherapeutic HPV vaccine PRGN-2009 with pembrolizumab before standard treatment in subjects with newly diagnosed HPV-associated oropharyngeal cancer.

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Background: A majority of oropharyngeal cancer (OPC) is caused by human papillomavirus (HPV). While highly responsive to standard of care (chemoradiotherapy or surgery) and with an overall good prognosis, both disease and treatment are highly morbid, frequently resulting in profound toxicity. Furthermore, relapsed disease is usually incurable and associated with profound morbidity. Additionally, concurrent chemoradiotherapy requires significant time and travel commitments, often resulting in major financial and caregiver burdens. Thus, treatment regimens which allow the de-escalation of therapy, radiotherapy in particular, are needed, both for improving cure rates and reducing toxicity; ideally while also improving therapeutic equity. Immunotherapy has proven, clinically significant activity in recurrent/advanced OPC (Burtness et al, Lancet 2019); recent data (Forde et al, NEJM, 2022; Patel et al, NEJM, 2023) suggest greater activity of immunotherapy in the neoadjuvant vs adjuvant setting. PRGN-2009 is a replication-deficient gorilla adenovirus vaccine targeting HPV16/18 T-cell epitopes (E6/E7) with demonstrable ability to generate T-cell responses to HPV16/18 E6/7. Pembrolizumab is an anti-PD-1 monoclonal antibody with proven activity in OPC. We hypothesize that neoadjuvant administration of immune checkpoint blockade with a therapeutic HPV vaccine will induce a significant antitumor immune response and improve outcome. **Methods:** This is a single-site, single-arm, Phase II clinical trial investigating the biological activity of neoadjuvant PRGN-2009 and Pembrolizumab in early-stage HPV-associated oropharyngeal cancer. Patients must have: newly diagnosed, biopsy-proven, HPV-associated, stage I-III OPC, RECIST 1.1 measurable disease, satisfactory organ function and functional status (ECOG $\leq$2) and be candidates for definitive therapy (either surgery or chemoradiotherapy). Exclusion criteria include: active autoimmune disease, steroid use of $\geq$10mg prednisolone-equivalent daily, pregnancy or uncontrolled medical illness which could compromise trial participation. Chronic viral infection (HIV, HBV, HCV) is permissible, if patients have a CD4+ count $\geq$200 and are on antiviral therapy with undetectable viral load. The primary objective is evaluating the antitumor immune response of PRGN-2009 in combination with Pembrolizumab (determined as a $\geq$2-fold increase in tumor infiltrating CD3+ cells); secondary endpoints include: response rate (by RECIST 1.1), relapse-free survival, safety and tolerability and if PRGN-2009/Pembrolizumab impacts time to initiation of definitive therapy. Biopsies are mandatory at baseline and at completion. This study is presently open in the NCI with 4 patients enrolled as of February 2024. Clinical trial information: NCT05996523. Research Sponsor: None.

TPS6125 Poster Session

TTCC-2022-01: Niraparib and dostarlimab in locally-advanced head and neck squamous cell carcinoma treated with (chemo) radiotherapy (RADIAN).

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Background: The prognosis of locally-advanced head and neck squamous cell carcinoma (LA-HNSCC) remains poor, with a 60% 5-year overall survival (OS) rate despite curative-intent therapies. Treatment intensification strategies with antiPD-(L)1 agents given concurrently to (chemo)radiotherapy (CRT) have failed to improve survival. New radiosensitizing agents such as PARP inhibitors have shown encouraging results in early studies, and are of special interest in cisplatin-unfit patients (pts) (Moutafi et al. 2021). Beyond radiation sensitization, PARP inhibition is predicted to trigger immune responses via STING pathway activation, and synergize with anti-PD-(L)1 agents (Sen T et al., 2019). We hypothesize that niraparib will enhance antitumor immune responses when combined with dostarlimab before and after definitive CRT and will boost RT response ultimately leading to higher disease-free survival (DFS). **Methods:** Trial design: RADIAN is an investigator-initiated, multi-center, non-randomized two-cohort phase 1b study of niraparib and dostarlimab in LA-HNSCC pts candidates for CRT (cohort A) or RT alone (cohort B – cisplatin unfit). Dostarlimab 500mg is given intravenously 3 weeks(w) before RT and then q/3w starting w4 post-RT for up to 14 cycles. Niraparib 200 or 300mg is given orally once daily 1w after dostarlimab until start of CRT (cohort A) or continuously until last dose of RT (Cohort B) and then continuously in 3w cycles from w4 post-RT for up to a year (14 cycles). Intensity-modulated RT (70 Grays:2Gray/fraction) and high-dose cisplatin are given as per standard-of-care. Study procedures include collection of baseline archival or fresh tumor sample for molecular profiling, PD-L1 expression and immunophenotyping; serial blood samples for circulating tumor (ct) DNA and clinical/endoscopic photographs of the tumor (baseline, pre-niraparib, pre-RT, 12w post-RT, end-of treatment, and at progression). Imaging and follow-up procedures are conducted as per standard-of-care. Key eligibility criteria: untreated, stage III to IVB laryngeal, hypopharyngeal, HPV-negative oropharyngeal SCC (stage III only if HPV-positive), and stage IVB oral cavity SCC as per TNM 8th edition;adequate organ function; no autoimmune disorders; no immunosuppressive therapy. Study objectives: primary objective is to evaluate 1-year disease free survival. Secondary objectives: safety/tolerability including RT delay/completion; locoregional and distant control, event-free survival, OS and ctDNA dynamics correlation with efficacy endpoints. Sample size: 32 evaluable pts for correlative studies are planned for enrollment (16/cohort). It is expected that experimental treatment will provide an increase of efficacy of 0.64 in terms of HR (1-year DFS of 75.9 % in cohort A and 68.2% in cohort B). Study activation: Nov 11th 2023, with 2 pts enrolled as of Feb 6th 2024. Clinical trial information: NCT05784012. Research Sponsor: GlaxoSmithKline Research & Development Limited; TTCC-Grupo Español de Tratamiento de Tumores de Cabeza y Cuello.

TPS6126 **Poster Session**

Xevinapant with radiation and concurrent carboplatin and paclitaxel in patients ineligible for cisplatin with locoregionally advanced squamous cell carcinoma of the head and neck (EXtRaCT study).

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Background: Locoregionally advanced (LA) head and neck cancer (HNC) patients undergoing chemoradiotherapy (CRT) who are ineligible for cisplatin have comparatively poor outcomes, with only ~40% alive at 5 years. There is an urgent unmet need to improve survival in these vulnerable patients with no standard therapeutic approach. Xevinapant, an oral inhibitor of XIAP and cIAP1/2, sensitizes cancer cells to apoptosis. Randomized phase II results in patients eligible for cisplatin combining xevinapant with CRT showed improved locoregional control, manageable toxicity, and promising survival outcomes. (Sun et al. Lancet Oncol. 2020) The current trial aims to extend these benefits to patients ineligible for cisplatin using xevinapant with carboplatin-paclitaxel-based CRT, hypothesizing safety and tolerability in this high-risk group. **Methods:** This phase I dose escalation/expansion study investigates xevinapant combined with carboplatin and paclitaxel to treat LA HNC in patients ineligible for cisplatin. Key eligibility includes previously untreated LA HNC and specific cisplatin ineligibility criteria, including >=70yo with moderate to severe comorbidity or vulnerability (Geriatric-8 score $\leq$ 14 and/or CARG score $\geq$ 30%) or <70yo with severe comorbidity and/or vulnerability, or >=18yo with an absolute contraindication to cisplatin. The treatment regimen comprises escalating doses of oral xevinapant (50-200 mg daily) on days 1-14 of a 21-day cycle for 3 cycles concurrent with CRT and 3 cycles adjuvant, weekly carboplatin AUC 1.5 IV, and paclitaxel 30 mg/m2 IV for 7 doses, and radiotherapy to 70 Gy in standard 2Gy fractions over 7 weeks with primary endpoint of tolerability and recommended phase 2 dose. A Bayesian-modified toxicity probability interval design will identify the maximum tolerated dose (MTD), targeting a 25% dose-limiting toxicity rate, with a sample size of 24 patients in dose-finding. 18 additional patients will be enrolled in the dose-expansion cohort at the MTD, totaling 42 patients. Secondary objectives include safety, response, progression-free, overall survival, and locoregional and distant control. Exploratory aims: in-clinic geriatric evaluations (Katz ADL, Lawton iADL, MMSE), QoL surveys, symptom tracking via smartphone, and wearable-derived steps and sarcopenia assessment. Recruitment began 02/2024. Clinical trial information: NCT06110195. Research Sponsor: None.

TPS6127 **Poster Session**

CTEP 10492, a phase 1/1b study of the AKT inhibitor ipatasertib with chemo-radiation for locally advanced head and neck squamous cell carcinoma.

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Background: Locally advanced head and neck squamous cell carcinoma (HNSCC) is commonly treated with definitive chemoradiation therapy (CRT). However, locoregional recurrence rates of approximately 50% may occur in high risk patients. As such, there is an unmet need for up-front treatment intensification in this patient population. Preclinical evidence suggests that both radiation therapy (RT) and cisplatin activate the PI3K/AKT pathway, leading to treatment resistance through multiple processes, including increased DNA repair, decreased apoptosis, and modulation of the tumor microenvironment by promoting angiogenesis, immune escape and hypoxia. Furthermore, AKT inhibitors have been shown to sensitize a subset of HNSCC models to RT and platinum chemotherapy *in vitro* and *in vivo*. However, radiosensitization using a specific AKT inhibitor has not yet been studied in humans. This phase I studywill bethe first to establish safety and preliminary efficacy of ipatasertib combined with standard of care definitive CRT for HNSCC. **Methods:** The primary objective of this study is to determine the maximum tolerated dose and recommended Phase 2 dose (RP2D) of ipatasertib in combination with definitive CRT in locally advanced HNSCC based on dose-limiting toxicities (DLTs). Secondary objectives include assessment of acute and late toxicities, long term swallowing function, and a preliminary assessment of efficacy. Eligible subjects must have pathologically confirmed, previously untreated, non-metastatic HNSCC that is either human papilloma virus (HPV)-negative clinical stage III-IVB, or HPV-positive clinical stage III. The study schema includes dose escalation and expansion cohorts. All subjects will receive RT for a standard 70 Gy in 7-week course, with concurrent weekly cisplatin. Two 28-day cycles of orally administered ipatasertib will be given concurrently with CRT. The four dose levels of ipatasertib range from 100-400 mg daily. Dose escalation of ipatasertib will follow a Time-to-Event Bayesian Optimal Interval (TITE-BOIN) design, with DLT window extending from the start of CRT, through 28 days after completion of RT. The expansion cohort will enroll an additional 10 subjects at the RP2D, and incorporate pharmacodynamic biopsies for each subject to evaluate whether the addition of ipatasertib to CRT will result in increased gamma-H2AX, consistent with radio-sensitization, and also decreased pS6 and pPRAS40 to evaluate AKT pathway inhibition. Additional correlative studies include assessment of the pharmacokinetic profile of ipatasertib with CRT, as well as correlation of efficacy with tumor genotype, based on whole exome sequencing of pre-treatment biopsy specimens. Enrollment is currently at dose level 2 in the escalation phase, and is expected to complete accrual in 2025. Clinical trial information: NCT05172245. Research Sponsor: National Cancer Institute.

TPS6128 **Poster Session**

HERD: A multi-centre prospective cohort study to facilitate early detection of relapse in radically treated, high risk head and neck squamous cell carcinoma.

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Background: Head and Neck Squamous Cell Carcinoma (HNSCC) is the 7th most common cancer worldwide with more than 660,000 cases diagnosed annually. Many patients present with locally advanced disease, which despite aggressive multi-modality treatment remains associated with poor survival. Approximately 50% of patients relapse within 2 years, mostly occurring in the first year after treatment. Biomarkers predicting relapse are lacking and there remains no consensus on surveillance, with strategies differing according to local guidelines and recurrence too often detected when not amenable to salvage surgery (estimated to improve survival outcomes in relapsed HNSCC by up to 73%). We hypothesize that risk of relapse relies on a dynamic interplay between the immune profile, tumor microenvironment (TME; elucidated by radiology and tissue-based laboratory imaging), genomic background and clinicopathological characteristics. Our primary objectives are to develop and validate a multi-analyte based risk prediction tool and risk-stratified follow up strategy to enhance detection of early relapse and improve survival. **Methods:** This multi-center study is prospectively collecting-samples across multiple platforms including imaging, blood, saliva, stool, urine, and tissue from patients with newly diagnosed high risk locally advanced HPV-negative HNSCC planned for radical treatment (either surgery or (chemo)radiotherapy). We aim to recruit 200 patients in 2 stages, including discovery and validation cohorts. Three mechanistic (hypothesis-driven) meta-covariates and five working platform meta-covariates will be analysed to test recurrence prediction. Each meta-covariate represents an integrated risk score from covariate subsets. The 3 hypotheses are H1) combining magnetic resonance parameters of hypoxia and stromal composition with TME changes; H2) capturing the interactions between genomic mutations, immune cells and exosomes within the TME H3) understanding the relationship between micro-organisms and TME. The technical platforms include exosomal analyses, multiparametric MRI including novel elastography (MRE) and quantitative magnetic susceptibility mapping (QSM) techniques, comprehensive circulating tumour and cell-free DNA analyses to aid detection of minimally residual disease, tissue immune profiling, somatic mutation testing and microbiome analysis. Regression Analysis will be performed by machine-learning with advanced mathematical and Bayesian statistical modelling. Accrual began in October 2023. Clinical trial information: NCT05097625. Research Sponsor: Cancer Research UK.

TPS6129 **Poster Session**

Neoadjuvant adebrelimab plus dalpiciclib in HPV-negative locally advanced head and neck squamous cell carcinoma: A phase II clinical trial.

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Background: The efficacy and safety of neoadjuvant immunotherapy (NAI) for treating resectable locally advanced head and neck squamous cell carcinoma (LAHNSCC) remain uncertain, and the comprehensive protocol of NAI needs further explored. The tumor suppressor gene CDKN2A plays a pivotal role in cell cycle regulation by modulating cyclin-dependent kinase (CDK) activity. Mutations in CDKN2A lead to continuous activation of CDK4/6, resulting in uncontrolled cell proliferation and tumor growth. Approximately 35.7% of HNSCC patients exhibit CDKN2A mutations, with the incidence rising to 58% among HPV-negative LAHNSCC patients. Studies have shown that combining immunotherapy with a CDK4/6 inhibitor produces a synergistic anti-tumor effect. This study aims to assess the efficacy and safety of combining anti-PD-L1 (adebrelimab) with a CDK4/6 inhibitor (dalpiciclib) as NAI in resectable LAHNSCC patients. **Methods:** This open-label, single-arm, prospective phase II trial will enroll LAHNSCC patients eligible for surgery. Inclusion criteria include: being 18 to 75 years old at study entry; pathologically confirmed HPV-negative HNSCC (oral, laryngeal, hypopharyngeal, and HPV-negative oropharyngeal carcinoma), determined via p16 immunohistochemistry or HPV DNA tests; with CDKN2A mutation; resectable LAHNSCC, staged III-IVB according to the UICC/AJCC 8th edition TNM system; an ECOG Performance Status score of 0 or 1; no prior relevant anti-tumor treatments; intent for curative treatment; and adequate organ function. Key exclusion criteria are active autoimmune diseases, use of immunosuppressive drugs, or systemic corticosteroids. Eligible patients receive 3 cycles of adebrelimab (1200 mg intravenously every 3 weeks, Day 1, 22 and 43) and 2 cycles of dalpiciclib (150 mg, po, every 4 weeks, day 1-21 and 29-49) before surgery. Dose adjustments are allowed based on toxicity. Surgery will follow 2-4 weeks post-NAI, with subsequent adjuvant radiotherapy or chemoradiotherapy based on risk factors after surgery. The primary endpoints are 1-year disease-free survival (defined as the time from surgical resection to local recurrence) and major pathological response (MPR, defined as ≤10% residual viable tumor cells), with secondary endpoints focusing on safety and predictive biomarkers. Clinical trial information: NCT06199271. Research Sponsor: None.

TPS6130 **Poster Session**

Sacituzumab govitecan in patients with advanced or metastatic radioactive-iodine refractory thyroid carcinoma: The phase 2 SETHY, GETNE-T2318 trial.

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Background: Current treatment options for advanced or metastatic differentiated thyroid carcinoma (DTC) with vascular endothelial growth factor inhibitors provide clinical benefit, despite the fact that most patients will acquire treatment resistance, whereas, advanced or metastatic anaplastic thyroid carcinoma (ATC) still lacks effective treatment options. Trophoblast cell surface antigen 2 (TROP-2) is highly expressed at the membrane of DTC and ATC, while it is rarely expressed in normal tissues. Moreover, TROP-2 is associated with tumor aggressiveness and poor prognosis. Targeting TROP-2 with sacituzumab govitecan, an antibody-drug conjugate with a SN-38 payload, showed efficacy in other cancer types such as triple negative or HER positive breast cancer or urothelial cancer and may be an effective treatment for thyroid carcinoma. SETHY is the first clinical trial with antibody-drug conjugates in thyroid cancer. **Methods:** The SETHY trial is a single-arm, multicohort, prospective, phase 2 trial of sacituzumab govitecan in patients with advanced or metastatic radioactive-iodine refractory thyroid cancer being recruited in 10 hospitals in Spain. Patients are $\geq$ 18 years, ECOG 0-1, should have recovered from any prior toxicity and have an adequate organ function. Patients will be included in two cohorts: DTC after progression (PD) to 1-3 prior systemic therapies (cohort 1) or ATC in 1st-line treatment or after failure of any systemic therapy (Cohort 2). Prior topoisomerase 1 inhibitors are not permitted. All patients will receive sacituzumab govitecan (10 mg/kg intravenously) on Days 1 and 8 of every 21-days cycle, until PD, death, study withdrawal, or unacceptable toxicity. Computed tomography (CT) or magnetic resonance imaging (MRI) scans and blood monitoring of tumor markers are performed every 12 weeks (Q12W) until PD. The primary endpoint is objective response rate (ORR) according to RECIST v1.1. Secondary endpoints include disease control rate, duration of response, progression-free survival, overall survival, safety, and quality of life (assessed through EORTC QLQ-C30 at baseline and Q12W until PD). Archival tumor samples will be collected at screening for retrospective central evaluation of TROP-2 expression levels and ancillary studies. The study uses a Simmon-II design considering a ORR of 5% as null hypothesis and an alternative ORR of 20% (α=0.1 one sided, β=0.2). In total, the study requires a total of 21 patients per cohort; 12 in the 1st stage and, if at least one response is reported, 9 additional in the 2nd stage. The study is approved and open to patient selection in Spain. Clinical trial identification: EU CT: 2023-504898-20-00 / NCT06235216 Clinical trial information: NCT06235216. Research Sponsor: GETNE through industry collaborator Gilead.