

### Concurrent chemoradiotherapy followed by adjuvant cisplatin-gemcitabine versus cisplatin-5-fluorouracil chemotherapy for N2-3 nasopharyngeal carcinoma: A multicentre, open-label, randomised, controlled, phase 3 trial.

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**Background:** Patients with N2-3 nasopharyngeal carcinoma have a high risk of failures, despite the current practice of concurrent adjuvant cisplatin-5-fluorouracil (PF) regime. Adjuvant PF regimen may not be adequate for tumor control of high risk patients, emphasizing the need for more effective regimen of adjuvant chemotherapy in N2-3 nasopharyngeal carcinoma. **Methods:** We conducted this multicentre, open-label, phase 3, randomised, controlled trial in four centers in China. Patients aged 18–65 years with stage T1–4N2–3 nasopharyngeal carcinoma were randomly assigned (1:1) to receive concurrent cisplatin (100mg/m<sup>2</sup> intravenously) on days 1, 22, and 43 of radiotherapy followed by either gemcitabine (1 g/m<sup>2</sup> intravenously on days 1 and 8) and cisplatin (80 mg/m<sup>2</sup> intravenously on day 1) (GP) once every 3 weeks or 5-fluorouracil (4 g/m<sup>2</sup> in continuous intravenous infusion over 96 h) and cisplatin (80 mg/m<sup>2</sup> on day 1 given intravenously) once every 4 weeks for three cycles. Randomisation was by a computer-generated random number code with a block size of six, stratified by treatment centre and nodal stage (N2 or N3). The primary endpoint was 3-year progression-free survival in the intention-to-treat population. This study is registered in ClinicalTrials.gov, NCT03321539. **Results:** From October 30, 2017 to July 9, 2020, 240 were randomly assigned to PF group (n = 120) or GP group (n = 120). After a median follow-up of 40 months (IQR: 32–48), the 3-year progression-free survival was 83.9% (95% CI 75.9–89.4) in GP group and 71.5% (62.5–78.7) in PF group (stratified HR 0.54; 95% CI, 0.32 to 0.93; p = 0.023). Significantly lower cumulative incidence of locoregional relapse (2.6% vs. 12.5%; HR 0.33; 95% CI, 0.12 to 0.90; Fine-Gray p = 0.030) and distant metastasis (10.4% vs. 20.1%; HR 0.50; 95% CI, 0.26 to 0.98; Fine-Gray p = 0.042) were also observed in GP group than PF group. However, there was no effect on early 3-year overall survival (90.7% vs. 94.0%; HR 1.12; 95% CI, 0.50 to 2.55; log-rank p = 0.779). Overall incidence of treatment-related adverse events was not significant different between the two treatment groups in the concurrent phase. In the adjuvant phase, significant higher incidence of grade 3–4 leucopenia (42 [41.2%] vs. 19 [16.8%], p < 0.001), neutropenia (33 [32.0%] vs. 10 [8.9%], p = 0.001) and thrombocytopenia (9 [8.7%] vs. 2 [1.8%], p = 0.044) was observed in GP group than PF group, whereas the frequency of diarrhea (6 [5.3%] vs. 0 [0%], p = 0.030) and mucositis (21 [18.6%] vs. 7 [6.8%], p = 0.010) was higher in PF group than in GP group. **Conclusions:** Concurrent adjuvant GP regimen significantly improved progression-free survival in patients with N2-3 nasopharyngeal carcinoma with acceptable toxicity. Long term follow-up is needed to confirm the ultimate therapeutic ratio. Clinical trial information: NCT03321539. Research Sponsor: National Key Research and Development Program of China, National Natural Science Foundation of China, the Sun Yat-sen University Clinical Research 5010 Program; Guangdong Major Project of Basic and Applied Basic Research, Sci-Tech Project Foundation of Guangzhou City, Innovative Research Team of High-level Local Universities in Shanghai, Natural Science Foundation of Guangdong Province for Distinguished Young Scholar, Postdoctoral Innovative Talent Support Program, the Pearl River S&T Nova Program of Guangzhou, Planned Science and Technology Project of Guangdong Province, Key Youth Teacher Cultivating Program of Sun Yat-sen University, and Fundamental Research Funds for the Central Universities.

**Induction chemotherapy plus radiotherapy alone versus cisplatin-based concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: An open-label, non-inferiority, randomized phase 3 trial.**

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**Background:** Cisplatin-based concurrent chemoradiotherapy (CCRT) has long been regarded as standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC) due to its favorable local control. However, concurrent platinum is associated with intolerable toxicities and ineffective in preventing distant metastasis. Since IMRT enhances the local control and induction chemotherapy (IC) decreases the risk of distant failure, it is worth exploring whether IC plus IMRT alone regimen could replace CCRT for patients with LA-NPC. **Methods:** This open-label, phase 3, non-inferiority clinical trial was conducted from June 12, 2015 to April 30, 2019. Patients with stage T1-4N2-3 or T3-4N0-1 MO NPC were randomly assigned (1:1) to receive gemcitabine (1000 mg/m<sup>2</sup>) and cisplatin (80 mg/m<sup>2</sup>) IC for 2 cycles followed by IMRT alone or IMRT plus concomitant weekly cisplatin (40 mg/m<sup>2</sup>) up to 7 cycles. 2-year failure-free survival was set as primary endpoint and non-inferiority margin of 10% was established. Efficacy analysis and safety analysis were dividedly performed in the intention-to-treat and safety population. **Results:** A total of 249 patients were enrolled, including 124 patients in IC group and 125 patients in CCRT group. Median follow-up time was 60 months (IQR, 48-71). 2-year failure-free survival was 90.2% in IC group versus 86.3% in CCRT group, with an HR of 0.818 (95% CI, 0.479-1.397) and absolute difference of 3.9% (1-sided 95%CI, -4.2 to 11.9). No significant differences were observed between groups in overall survival, locoregional relapse, or distant metastasis. Compared with CCRT group, fewer grade  $\geq 3$  AEs occurred in IC group (47.5% vs 61.5%,  $p = 0.015$ ), including leucopenia, anemia, mucositis, nausea and dysphagia. The IC group had significantly better QoL during and short periods after IMRT, including domains of global health status, physical functioning, fatigue, nausea and vomiting, pain, and appetite loss. **Conclusions:** For LA-NPC, gemcitabine and cisplatin induction chemotherapy plus IMRT alone was not inferior in 2-year failure-free survival to concurrent chemoradiotherapy. Clinical trial information: NCT02460887. Research Sponsor: the Key-Area Research and Development of Guangdong Province (2020B1111190001), the National Natural Science Foundation of China (No. 82002857, 82230034, 81874134), Sun Yat-Sen University Clinical Research 5010 Program (No. 2015010 , 2018015).

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Oral Abstract Session

**PD-1 blockade with sintilimab plus induction chemotherapy and concurrent chemoradiotherapy (IC-CCRT) versus IC-CCRT in locoregionally-advanced nasopharyngeal carcinoma (LANPC): A multicenter, phase 3, randomized controlled trial (CONTINUUM).**

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**Results of the multicenter phase II FRAIL-IMMUNE trial evaluating the efficacy and safety of durvalumab combined with weekly paclitaxel carboplatin in first-line in patients (pts) with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) not eligible for cisplatin-based therapies.**

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**Background:** For pts with R/M SCCHN, new standard of care (SoC) has been recently established with pembrolizumab either alone or combined with platin-5FU (KN 048 – median Overall Survival (OS): 13 months when combined). For pts who need chemotherapy, platinum-5FU-pembrolizumab as first-line treatment appears associated with substantial toxicity that precludes its use in fragile patients. In this context, we investigated the efficacy and tolerance of PDL-1 inhibition with durvalumab combined with weekly carboplatin-paclitaxel as first-line treatment in frail R/M SCCHN pts. **Methods:** This single-arm phase II study enrolled pts in first-line of their R/M SCCHN and not eligible to standard cisplatin-based CT with an ECOG PS of 0 or 1. Pts received 4 cycles of CT (carboplatin AUC2; paclitaxel 80mg/m<sup>2</sup> both at D1, D8, D15) and durvalumab (D) 1500mg repeated every 4 weeks for a maximum of 12 months. The primary endpoint was OS Rate at 12 months (m). The study used a Fleming A'Hern design (inefficacy boundary: 47% and target efficacy: 65%), requiring 38 successes among 64 pts. Secondary endpoints were Progression-Free Survival (PFS), Time to Treatment Failure (TTF), objective response rate (ORR) and tolerance. **Results:** 64 pts (median age 69.5y; 90.6% males, 62.5% PS1) were included, regardless of their PDL-L1 status. Primary tumors were mainly located in oropharynx (37.5%) and larynx (28.1%) with 37.3% PD-L1 CPS $\geq$ 20. 54.9% were metastatic. The efficacy rule for OS was met with 40 pts (62.5%, unilateral 95%CI: [51.5% - ]) alive at 12m. With a median follow-up of 27.1 m, median OS was 18.0 m (95% CI [11.9-NR]) and the 24m-OS rate was 45% [32%-57%]. Median PFS was 7.0 m (95% CI [5.4-9.9]) and median TTF was 6.0 m (95% CI [4.7-9]). 44/62 pts (71%) achieved an OR (11.3% complete response and 59.7% partial response). Median duration of response was 5.9 m (95% CI [3.4-9.6]). 20.3% of pts experienced G $\geq$ 3 adverse events related to D, Toxicity led to permanent discontinuation of D in 3.1% of pts. No D-related death was reported. **Conclusions:** This study performed in fragile patients not amenable to cisplatin-based CT met its primary endpoint on OS and showed a 18 months median OS rate. This combination of durvalumab with weekly carboplatin/paclitaxel was associated with a favorable toxicity profile. Clinical trial information: NCT0372967. Research Sponsor: AstraZeneca.

**Phase 3 randomized study for evaluation of physician choice Rx and triple metronomic as second-line therapy in head and neck cancer (CRSF 2021-HN-001).**

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# **Dose expansion results of the bifunctional EGFR/TGF $\beta$ inhibitor BCA101 with pembrolizumab in patients with recurrent, metastatic head and neck squamous cell carcinoma.**

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**Background:** Pembrolizumab (P) is approved to treat patients (pts) with recurrent, metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). BCA101 is a first-in-class bifunctional EGFR antibody fused to a TGF $\beta$  immune modulating payload which is well tolerated and has clinical activity as monotherapy and in combination with pembrolizumab in advanced solid tumors (ESMO 2022 731MO). Here we report the results from the interim analysis of an expansion cohort combining BCA101+P as first line therapy in R/M HNSCC. **Methods:** This ongoing single-arm, open-label multicenter dose expansion cohort enrolled pts with R/M HNSCC with a tumor PD-L1 CPS $\geq$ 1 with no prior systemic therapy for R/M disease, ECOG 0-1, and measurable disease (RECIST v1.1). Pts received BCA101 (1500 mg IV on days 1, 8, 15) with P (200 mg IV on day 1) every 21-days. Primary endpoint: safety; secondary endpoints: overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS). Exploratory: molecular and immunologic predictors of response. A Simon optimal two-stage design was employed: among 18 evaluable pts in stage 1,  $>3$  pts in response triggered continuation to stage 2 enrolling 21 additional pts targeting an ORR $>35\%$ . **Results:** From 2/2022 to 1/2023, 20 pts enrolled while 18 were evaluable (had first restaging scans) in stage 1. Pts were more often men (n=13, 65%) with a median age of 66 (range: 31-77). Oropharynx (10, 50%) [7/10 (70%) were HPV/p16-pos] and oral cavity (7, 35%) were the most common primary subsites (larynx/hypopharynx: 3). Fifteen (75%) had distant metastatic disease. The ORR in stage 1 was 44% (8 PRs, 4 SD) with a clinical benefit rate (CBR=PR+SD) of 67%; 7/12 (58%) HPV-neg pts achieved a response. Median DOR not reached, but median time on-treatment was 6.7 months (range: 2.7-11.0+) among responders. Ten pts discontinued therapy; all but 1 for PD (n=1 for toxicity). Grade 3+ treatment-related adverse events (TRAEs) were observed in 4 pts (20%, most common: anemia). No treatment-related deaths were observed. Acneiform rash was the most common TRAE of any grade (15, 75%). PFS and OS estimates are forthcoming. Eight (44%) had baseline PD-L1 CPS scores of 0-19, while ten (56%) were  $\geq$ 20. Stage 2 is actively enrolling with completion of accrual expected by the meeting. **Conclusions:** Stage 1 of this dose expansion cohort of BCA101+P shows encouraging anti-tumor activity with additive potential, particularly among HPV-neg pts; and the combination is well tolerated among this R/M HNSCC population. Further investigation is warranted. Study funded by Bicara Therapeutics and conducted in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. USA (NCT04429542). Clinical trial information: NCT04429542. Research Sponsor: Bicara Therapeutics; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc. USA.

Efficacy evaluable	PR	SD	PD	ORR	CBR (PR+SD)
HPV-neg (n=12)	7	3	2	7/12 (58%)	10/12 (83%)
HPV-pos (n=6)	1	1	4	1/6 (17%)	2/6 (33%)
Total (n=18)	8	4	6	8/18 (44%)	12/18 (67%)

# Randomised phase III trial of the hypoxia modifier nimorazole added to radiotherapy with benefit assessed in hypoxic head and neck cancers determined using a gene signature (NIMRAD).

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**Background:** Tumour hypoxia is an adverse prognostic factor in head and neck squamous cell carcinoma (HNSCC). We assessed whether patients with hypoxic HNSCC benefited from the addition of nimorazole to definitive radiotherapy (RT). **Methods:** NIMRAD was a phase III, multi-centre, placebo-controlled, double-blind trial in patients with HNSCC unsuitable for concurrent platinum chemotherapy or cetuximab with definitive RT (NCT01950689). Patients were randomized 1:1 to receive nimorazole (1.2 g/m<sup>2</sup> daily, prior to RT) + RT (65 Gy in 30 fractions over 6 weeks) or placebo (taken via the same schedule) + RT. The primary endpoint was loco-regional control (freedom from loco-regional progression, FFLRP) in patients with hypoxic tumours, defined as greater than or equal to the median hypoxia score of the first 50 patients analysed ( $\geq 0.079$ ), using a validated 26-gene signature. The planned sample size was 340 patients allowing for signature generation in 85%, assumed HR 0.50 for nimorazole effectiveness in the hypoxic group, and requiring 66 loco-regional failures to have 80% power in a two-tail log-rank test at the 5% significance level. **Results:** 338 patients were randomised by 19 UK centres from May 2014 to May 2019, with a median follow-up of 3.1 years (95%CI 2.9-3.4). Hypoxia scores were available for 286 (85%). The median patient age was 73 years (range 44-88); and clinical factors were balanced between the arms, both for the whole population and hypoxic group (Table). There were 36 (25.9%) loco-regional failures in the hypoxic group, where nimorazole + RT did not improve FFLRP (adjusted HR 0.72; 95% CI 0.36-1.44; p=0.35), or overall survival (adjusted HR 0.96; 0.53-1.72; p=0.88) compared with placebo + RT. Similarly, nimorazole + RT did not improve FFLRP or OS in the whole population. In total (n=338), 73% of patients allocated nimorazole adhered to the drug for  $\geq 50\%$  of RT fractions. Nimorazole + RT caused more acute nausea compared with placebo + RT (CTCAE v4.0 G1+2: 56.6% vs 42.4%, G3: 10.1% vs 5.3%, respectively; p=0.003), with no differences in other early or late toxicities. **Conclusions:** Addition of the hypoxia modifier nimorazole to RT for locally advanced HNSCC in older and less fit patients did not improve loco-regional control or survival. Clinical trial information: NCT01950689. Research Sponsor: Cancer Research UK.

		Whole population (N=338)	Nimorazole (n=168)	Placebo (n=170)	Hypoxic Group (N=139)	Nimorazole (n=70)	Placebo (n=69)
Site (%)	Oropharynx	207 (61.2)	110 (65.5)	97 (57.1)	71 (51.1)	40 (57.1)	31 (44.9)
	Hypopharynx	51 (15.1)	25 (14.9)	26 (15.3)	29 (20.9)	14 (20.0)	15 (21.7)
	Larynx	80 (23.7)	33 (19.6)	47 (27.6)	39 (28.1)	16 (22.9)	23 (33.3)
HPV positive (%)		142 (42.0)	75 (44.6)	67 (39.4)	42 (30.2)	24 (34.3)	18 (26.1)
Stage AJCC 7 <sup>th</sup>	II	15 (4.4)	7 (4.2)	8 (4.7)	5 (3.6)	3 (4.3)	2 (2.9)
Edition (%)	III	103 (30.5)	52 (31.0)	51 (30.0)	56 (40.3)	29 (41.4)	27 (39.1)
	IVab	220 (65.1)	109 (64.9)	111 (65.3)	78 (56.1)	38 (54.3)	40 (58.0)

**Neoadjuvant nivolumab, paclitaxel, and carboplatin followed by response-stratified chemoradiation in locoregionally advanced HPV negative head and neck squamous cell carcinoma (HNSCC): The DEPEND trial.**

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**Background:** The role of neoadjuvant immunotherapy in curative-intent head and neck squamous cell carcinoma (HNSCC) remains poorly defined. Survival for locoregionally advanced (LA) HPV negative (-) HNSCC remains poor with two-year survival of ~50%, and substantial treatment-related toxicity with standard chemoradiation (CRT). Given the activity of anti-PD1 in recurrent/metastatic HNSCC, we studied neoadjuvant nivolumab with chemotherapy and the feasibility of subsequent response-stratified CRT in HPV(-) LA HNSCC. **Methods:** The DEPEND trial (NCT03944915) is a phase II trial of nivolumab, paclitaxel, and carboplatin followed by response-stratified CRT for previously untreated stage IVA-B (AJCC-8th edition) HPV(-) HNSCC. The ultimate goal is to evaluate radiation volume and/or dose reduction to decrease long-term toxicities. Eligible patients received three 21-day cycles of nivolumab 360mg day 1, paclitaxel 100mg/m<sup>2</sup> on days 1/8/15, and carboplatin AUC5 day 1. Patients with ≥50% reduction by RECIST 1.1 received response-adapted CRT to 66Gy with elimination of elective nodal volumes; < 50% reduction received standard-dose CRT to 70-75Gy. Post-CRT nivolumab 480mg every 4 weeks for 9 months was administered. The primary endpoint was deep response rate (DRR) defined as the proportion of patients with ≥50% reduction. Tumor PD-L1 immunohistochemistry was reported as combined positive score (CPS). **Results:** Thirty-six eligible patients started treatment between September 2019 and June 2022. Median age 59 (range 27-77), 22% female, 80% 20PYH smoking, 39% oral cavity, 19% oropharynx, 25% larynx/hypopharynx, 78% T3/4 and 78% N2/3. PD-L1 CPS ≥1 in 58%. The DRR with nivolumab/chemotherapy was 54% (95% CI 0.37-0.72), which met our statistical endpoint. The ORR was 89%. CRT stratification was as follows: Response-adapted CRT (n = 19) and standard-dose CRT (n = 16). At a median follow-up of 14 months, 2-year PFS and OS were 64% (95%CI 0.41-0.80) and 76% (95%CI 0.53-0.89), respectively. By CRT stratification, 2-year PFS was 79% and 46% in response-adapted and standard-dose CRT, and 2-year OS was 86% and 67% in response-adapted and standard-dose CRT, respectively. One patient died from disease progression during neoadjuvant therapy. 2-year distant control in response-adapted and standard-dose CRT arms was 100% and 63%, and 2-year locoregional control was 85% and 92%, respectively. PD-L1 CPS ≥1 and < 1 demonstrated DRR of 75% and 27%, respectively (p= 0.01). **Conclusions:** Nivolumab-based neoadjuvant chemo-immunotherapy led to deep responses, and response-adapted CRT was associated with favorable survival and locoregional control. PD-L1 expression was predictive of deep response to nivolumab-based neoadjuvant therapy. Late toxicity analysis between treatment arms is planned. Clinical trial information: NCT03944915. Research Sponsor: BMS.



**Immuno-chemotherapy as single treatment modality for larynx preservation (ICoLP): Co-primary endpoints and safety results.**

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**Background:** Optimal treatment of larynx squamous cell carcinoma (LC) maximizes functional outcomes and survival. Surgery and radiotherapy (RT) may lead to significant morbidity, notably dysphonia and dysphagia. Our group published durable pathologic complete response (pCR) with normal function in 33% of patients (pts) with stage II-IV LC treated with single modality chemotherapy. We hypothesized that pembrolizumab (P), cisplatin (C), and docetaxel (D) will cure a subset of LC pts and preserve larynx function. **Methods:** Eligible pts had stage II-III LC measurable per RECIST 1.1. Treatment consisted of P 200 mg, C 75 mg/m<sup>2</sup> or carboplatin AUC 6, and D 75 mg/m<sup>2</sup> IV Q3W. After 2 PCD cycles, pts with radiological response (complete [CR], partial [PR], or stable disease [SD]) received 2 additional PCD cycles. After 4 cycles, pts underwent larynx biopsy. Those with pCR received 4 doses of consolidation P; those without pCR received local therapy (LT; RT or surgery). Co-primary endpoints are disease control rate (DCR; CR+PR+SD) after 2 PCD cycles and pCR rate after 4 cycles. Secondary endpoints include safety, laryngeal preservation rate, relapse-free survival, and swallow function. Per Bayesian design ( $H_0$ : 65% DCR, 15% pCR;  $H_1$ : 85% DCR, 30% pCR), we reject  $H_0$  if of 25 pts, 19 have DCR or > 7 achieve pCR (10% alpha, 88% power). **Results:** 24 pts enrolled from 8/9/19-12/15/22, 62.5% were stage III (54.2% were T3 and 16.7% were N1); 23 were evaluable for the efficacy endpoints. DCR was 100% with 74% (17/23) being objective responses and 52% CR; pCR rate to date is 77.3% (17/22; 1 pt is on-treatment). 6 of 17 (35%) pts with pCR developed recurrence, mostly (4/6) within 4 months of pCR, and were salvaged with LT. 5 pCR lasted  $\geq 1$  y; 2 additional pCR pts unable to perform serial laryngoscopy or imaging due to loss of insurance ( $n = 1$ ) or moving to another state ( $n = 1$ ) have not had clinical recurrence for  $\geq 2$  ys. The median follow-up is 17.2 mos (range: 1.4 – 39.4 mos). One patient who refused LT at early recurrence was lost to follow-up and eventually underwent a total laryngectomy and RT then recurred locally and died of disease. An additional patient who had pCR with early recurrence received definitive RT with CR, but subsequently developed a solitary lung metastasis treated with RT; 2 pts remain on trial treatment. The most common treatment-related adverse events (TRAE) were fatigue (91.6%), anemia (79%), diarrhea (45.8%), and nausea (41.6%). 10 grade 3-4 TRAE were reported in 5 (20.8%) pts with the most common being neutropenia (3/24, 12.5%) and anemia (2/24; 8.3%). 2 pts discontinued PCD treatment due to toxicity. **Conclusions:** The study reached its primary endpoint with a DCR of 100% (23/23) and a pCR in 77.3% (17/22) of evaluable patients; 5 pCR last  $\geq 1$  y. Recurrences after pCR occurred stressing the importance of close follow-up. Updated efficacy and swallow function results will be presented at the meeting. Clinical trial information: NCT04030455. Research Sponsor: Merck.

### Final overall survival analysis of JUPITER-02: A phase 3 study of toripalimab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC).

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**Background:** There are currently no FDA-approved IO therapies for NPC. Toripalimab in combination with Gemcitabine-Cisplatin (GP) chemotherapy had shown significant improvement over chemotherapy alone in progression-free survival (PFS) as first-line treatment for recurrent or metastatic (r/m) NPC at the interim PFS analysis of JUPITER-02 (NCT03581786) study. The final overall survival (OS) analysis results are summarized here. **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 Q3W 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) at enrollment. The primary endpoint was PFS by an independent review committee. Secondary endpoints included OS and safety. **Results:** By the cutoff date of Nov 18, 2022, when 133 events were reached for the final OS analysis, the median survival follow up was 30.1 months. A significant improvement in OS was observed for the toripalimab arm over the placebo arm: HR = 0.63 (95% CI: 0.45-0.89), two-sided p = 0.0083. The median OS was not reached in the toripalimab arm and was 33.7 months in the placebo arm. The 2-year and 3-year OS rates were 78.0% vs. 65.1%, and 64.5% vs. 49.2% respectively. A consistent effect on OS, favoring the toripalimab arm, was observed in nearly all subgroups, including PD-L1 high and PD-L1 low expression subgroups. No new safety signals were identified in the toripalimab arm since the interim report. The incidence of Grade  $\geq 3$  adverse events (AEs) (89.7% vs 90.2%) and fatal AEs (3.4% vs 2.8%) were similar between two arms. However, AEs leading to discontinuation of toripalimab/placebo (11.6% vs 4.9%), immune-related (irAEs) (54.1% vs. 21.7%) and Grade  $\geq 3$  irAEs (9.6% vs. 1.4%) were more frequent in the toripalimab arm. **Conclusions:** The addition of toripalimab to GP chemotherapy as 1<sup>st</sup>-line treatment for r/m NPC provided clinically important and highly significant OS advantage over GP alone with a manageable safety profile. These results support the use of toripalimab with GP chemotherapy as the new standard care for this population. Clinical trial information: NCT03581786. Research Sponsor: Shanghai Junshi Biosciences.

# NEOSPACE trial: Neoadjuvant pembrolizumab-gemcitabine-cisplatin followed by concurrent pembrolizumab-chemoradiation and maintenance pembrolizumab for stage IVA nasopharyngeal cancer (NPC).

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**Background:** Stage IVA NPC had the worst prognosis despite the current standard of neoadjuvant chemotherapy and concurrent chemoradiation (CRT). There is no safety and efficacy data combining immune checkpoint inhibitor (ICI) and CRT in NPC. **Methods:** We conducted an open label, single arm, multi-site, phase 2 clinical trial in AJCC 8th Edition Stage IVA (T4 and/or N3, M0) WHO type 2/3 Epstein Barr virus (EBV) +ve NPC (Clinical trial register NCT03734809). The experimental treatment consisted of neoadjuvant pembrolizumab (200 mg D1), gemcitabine (1000 mg/m<sup>2</sup> D1+8) and cisplatin (80 mg/m<sup>2</sup> D1) q3w x2 followed by concurrent pembrolizumab (200 mg x3 week 1, 4 and 7) and cisplatin (40 mg/m<sup>2</sup> weekly x7) during intensity-modulated radiation (IMRT), and maintenance pembrolizumab 200 mg q3w x12 from 4 weeks post-RT. By Fleming one-stage design (type I error 0.05, power 0.80, 10% drop out), planned sample size is 46. Primary endpoint is 2-year (yr) progression free survival (PFS). Secondary endpoints include safety and tolerability. Plasma EBV DNA (pEBV DNA) was monitored. **Results:** Accrual was completed with 46 subjects recruited at two study sites from May 2019 to June 2022 in Hong Kong (n=31) and Singapore (n=15). This protocol specified analysis included 37 subjects with >12 months post-treatment follow up (median 26.8 months, 95% CI 21.3-32.9). Patient demographics: mean age 52 (range 27 - 84); M:F 31:6; ECOG 0=23, 1=14; stages: T4N1-2 (16), T1-3N3 (18), T4N3 (3). Overall compliance rate: neoadjuvant cisplatin 98.6%, gemcitabine 97.7%, concurrent cisplatin 73.7%, pembrolizumab 100% (neoadjuvant), 77.5% (concurrent), 77% (maintenance), IMRT 99.7% (69.96 Gy). Treatment related adverse events (≥ grade 3, >10%): dysphagia (32.4%), mucositis (29.7%), neutropenia (29.7%), radiation dermatitis (24.3%), anemia (18.9%), hyponatremia (13.5%), thrombocytopenia (10.8%). No ≥ grade 4 mucositis/dermatitis. The 2-yr PFS was 69.6% (95% CI 53.8 - 88.5%). At the end of neoadjuvant, CRT and maintenance phases, molecular remission (pEBV DNA = 0) was achieved in 24.3%, 70.3% and 70.3% of patients respectively, which strongly correlated with PFS (p=0.0253, 0.0007 and <0.0001 respectively, Table). **Conclusions:** Pembrolizumab incorporated into neoadjuvant, CRT and maintenance protocol is safe with promising results. This strategy of combining ICI with neoadjuvant chemotherapy and CRT is being tested in several ongoing phase 3 trials in advanced NPC. Clinical trial information: NCT03734809. Research Sponsor: Funding for this Investigator-initiated Research was provided by MSD.

Primary endpoint	1-yr rate (%)	2-yr rate (%)
PFS	88.9	69.6
Secondary endpoints		
Overall survival	97.2	88.1
Distant metastasis free survival	94.4	80.8
Locoregional PFS	94.5	87.8
PFS by molecular remission		
pEBV DNA at the end of maintenance		
0	100	91.1
> 0	63.6	21.2
	p<0.0001	
Events	No of patients	
Progression	12	
Death	5	
Second primary cancer (without NPC progression)	2 (lung, cholangiocarcinoma)	

### Dual PD1 and CTLA4 immune checkpoint blockade and hypofractionated radiation in patients with salivary gland cancers.

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**Background:** No systemic therapy standard of care exists for recurrent/metastatic malignancies of the salivary glands (SGC) and immune checkpoint inhibitors (ICIs) have low response rates. Preclinical data in solid tumors suggest synergistic antitumor effects of ICIs with hypofractionated radiation (XRT). This study explored the safety and activity of nivolumab (N) and ipilimumab (I) with palliative XRT. **Methods:** This phase I/II open label single arm trial enrolled patients (pts) with incurable SGCs (WHO 2017) with evidence of progression, ECOG 0-1, no prior antiPD1 or CTLA4 directed therapy, RECIST 1.1 measurable disease excluding the XRT site. Pts received N 3mg/kg IV Q 2 weeks x 12 doses followed by 480 mg IV Q4 weeks x 8 doses and I 1 mg/kg IV Q6 weeks x 4 doses. XRT was given to a total dose of 24Gy in 3 fractions every other day over 1 week (wk) and initiated 2 wks after the first dose of N and I. Research blood collection was obtained prior to wks 1, 8 and 16. The primary endpoint was safety and tolerability using CTCAE v. 4, secondary endpoints were objective response rates (ORR) by RECIST 1.1 criteria in non-radiated sites of measurable disease, overall survival (OS) and progression free survival (PFS). The study was approved by the FHCC IRB and registered on clinicaltrials.gov (NCT03749460). **Results:** Between 4/2019 and 5/2022, 20 pts were enrolled, the median age was 58 (range 27-77) years, 10 (50%) were male, 12 (60%) had ECOG 0, and 7 (35%) were Asian. Most common histologies were adenoid cystic 9 (45%) and salivary duct 4 (20%), 15 (75%) had no prior systemic therapy. Ten (50%) had both local and distant disease, 14 (70%) had commercial NGS testing, all had TMB < 10mut/Mb, MSI-stable tumors. All patients completed XRT with the most common XRT site being the lung 13(65%) and bone 7(35%). The median number of N doses received was 12 (range 3-20) and I doses 4 (range 1-4). Enrollment was halted until first 6 pts were assessed for dose limiting toxicities during initial 12 wks of treatment, none were observed. Among all pts enrolled, 5 (20%) Grade 3 AEs were observed: adrenal insufficiency, hypokalemia, lung infection, hypotension, and mania. No grade 4/5 toxicities were observed. One pt was not evaluable for RECIST 1.1 due to rapid disease progression: partial responses were observed in 4 (20%: 2 pts with salivary duct, 1 acinic cell and 1 adenoid cystic) with a median duration of 15.5 months (mos) (range 6-16 mos), stable disease in 6 (30%) all lasting 6 mos or greater, and progressive disease in 9 (45%). With a median follow-up of 16 mos, median OS was 25 mos (95% CI: [1.56, 2.59]) and median PFS was 7.2 mos (95% CI: [0.21, 1.56]). Exploratory correlative peripheral blood analysis is ongoing and will be reported. **Conclusions:** Nivolumab/ipilimumab and palliative XRT results in low rates of severe toxicities, modest ORR but durable ORR/SD. Further work is necessary to explore predictors for response. Clinical trial information: NCT03749460. Research Sponsor: Bristol Myers Squibb.

**Safety and efficacy of immune checkpoint inhibitor (ICI) naïve cohort from study of PDS0101 and pembrolizumab in HPV16-positive head and neck squamous cell carcinoma (HNSCC).**

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**Background:** Up to 70% of oropharyngeal cancers in the US are reported to be HPV-mediated with most caused by HPV16 infection. First line treatment for patients with unresectable, recurrent or metastatic (R/M) disease is pembrolizumab with or without chemotherapy, but most patients eventually experience disease progression. PDS0101 is a novel, investigational HPV16-targeted immunotherapy that stimulates a potent, targeted T cell attack against HPV16-positive cancers. **Methods:** VERSATILE-002 (NCT04260126) is an open-label, non-randomized, Simon 2-stage study evaluating the combination of PDS0101 and pembrolizumab in subjects with HPV16-positive R/M HNSCC in 2 cohorts: ICI-naïve and ICI-refractory. All subjects receive pembrolizumab IV Q3W with PDS0101 SC administered concurrently during Cycles 1, 2, 3, 4, and 12 (max 5 doses). The primary endpoint of the study is confirmed Best Overall Response per RECIST 1.1. Herein we update the safety, PFS, and OS data for the ICI-naïve subjects. **Results:** Forty-eight subjects who received at least one cycle of combination therapy (safety population) had a median age of 62.5 (range 45 – 83), were 93.8% male, 93.8% White, and 62.5% ECOG 0. Among this population, the median overall treatment duration in months was 3.5 (range 0.0 – 19.5). The median number of PDS0101 doses was 4 (range 1 – 5); 56.3% received 4 doses and 22.9% received 5 doses. The median number of pembrolizumab doses was 5 (range 1 – 29); 27.1% received  $\geq 10$  doses. Efficacy was evaluated in 34 subjects (47.1% with CPS  $\geq 20$ ) who had assessment of tumor response following treatment (efficacy population). Tumor reduction (maximum percent change from baseline) was seen in 23 (67.6%) subjects. Nine subjects (26.5%) had confirmed response including 1 CR and 8 PR, 15 subjects had SD (44.1%), and 9 subjects had PD (26.5%). One subject was not evaluable (2.9%). The median PFS was 10.4 months (95% CI 4.2, 15.3). Among the safety population, median overall survival was non-estimable due to the ongoing survival status of study subjects. The estimated 12-month OS rate was 87.1%. Thirty-three (68.5%) subjects had mild or moderate (Grade 1 or 2) PDS0101-related TEAE (TRAE); the most common were fatigue and injection site reactions (ISRs). Only 3 subjects (6.3%) had Grade 3 TRAEs: fatigue, ISR, blood alkaline phosphatase increased, and hyperglycemia. No subjects had Grade 4 or 5 TRAE. No subject came off study due to toxicity. **Conclusions:** PDS0101 with pembrolizumab is well tolerated in this ICI naïve R/M HPV-associated HNSCC population. Median PFS was 10.4 months which compares favorably to published median PFS of 2-3 months for approved ICIs when used as monotherapy in patients with similar PD-L1 levels. The estimated 12-month OS of 87.1% is promising compared to published results of about 36-50%. These results justify a confirmatory randomized, controlled study. Clinical trial information: NCT04260126. Research Sponsor: PDS Biotechnology.

**A phase 1 dose-escalation and expansion study of CUE-101, a novel HPV16 E7-pHLA-IL2-Fc fusion protein, given as monotherapy and in combination with pembrolizumab in patients with recurrent/metastatic HPV16+ head and neck cancer.**

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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) designed to bind, expand, and activate HPV16-specific CD8+ T cells for the treatment of HPV16+ cancers. **Methods:** CUE-101-01 is an ongoing first-in-human study in HLA-A\*0201 patients with HPV16+ recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Escalating doses of CUE-101 monotherapy (0.06 mg/kg to 8 mg/kg) and in combination with pembrolizumab (1 mg/kg to 4 mg/kg + 200 mg pembrolizumab) were evaluated, followed by expanded enrollment at the recommended phase 2 dose (RP2D). Patients with R/M HNSCC refractory to  $\geq 1$  platinum-based or checkpoint inhibitor therapy received CUE-101 monotherapy. Patients with previously untreated PD-L1+ R/M HNSCC received CUE-101 + pembrolizumab as first-line treatment. Therapy was administered every 3 weeks until disease progression or intolerable toxicity. Safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity were assessed. **Results:** As of January 12, 2023, 67 patients were enrolled. A MTD was not established in monotherapy or combination-treated patients; 4 mg/kg of CUE-101, alone or in combination with pembrolizumab, was chosen as the RP2D dose in both cohorts. Monotherapy RP2D enrollment is complete and combination RP2D enrollment is ongoing. Frequent adverse events include fatigue (45%), anemia (34%), chills (27%), infusion related reactions (25%), constipation (22%), lymphopenia (22%) and nausea (22%). CUE-101 PK data demonstrate dose-dependent increases in drug exposure sustained with repeat dosing. PD data demonstrate selective expansion of HPV-16 E7<sub>11-20</sub>-specific CD8+ T cells, sustained increase in NK cells and transient increase in Treg cells. Among 19 evaluable monotherapy RP2D patients, 1 PR and 6 durable SD (SD  $\geq 12$  weeks) were observed, with mOS of 24.4 months (9.1, NA). Among 12 evaluable RP2D combination patients to date, 5 PRs, and 2 durable SDs have been observed, with 71% (5/7) of patients expressing PD-L1 CPS  $\leq 20$ . **Conclusions:** CUE-101 facilitates the targeted delivery of high concentrations of IL-2 to relevant tumor-specific CD8+ T cells. We demonstrate safety and tolerability with encouraging PD signals and antitumor activity with monotherapy and in combination with pembrolizumab in HPV+ R/M HNSCC patients. Enrollment continues in the CUE-101 and pembrolizumab combination cohort. Clinical trial information: NCT03978689. Research Sponsor: CUE Biopharma Inc.

**Phase II trial of adjuvant de-escalated radiation + adjuvant nivolumab for intermediate-high risk P16+ oropharynx cancer.**

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**Background:** Treatment de-intensification for resected, human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) is an area of active investigation, with a goal of providing a less toxic adjuvant regimen compared to the current standard of care 66 Gy of radiation (RT) combined with concurrent cisplatin defined in recently reported as Arm D of the ECOG3311 trial. Here, the programmed death 1 (PD-1) antibody nivolumab was added to de-intensified RT in high risk, resected HPV+ OPC. **Methods:** Eligible patients included transorally resected pathologic stage III or IVA HPV+ OPSCC using p16 immunohistochemistry, featuring high-risk neck disease factors (gross extracapsular extension >1mm or  $\geq 5$  positive lymph nodes) to mirror ECOG3311 Arm D patients accrued. Positive margin status was excluded except by PI approval. Postoperative treatment consisted of accelerated fractionation RT (50 Gy over 4 weeks) concurrent with nivolumab at 240 mg every 2 weeks, followed by 6 months of adjuvant nivolumab biweekly or monthly. The primary endpoint was progression-free survival (PFS). Swallowing and quality of life patient reported outcome (PRO) measures were collected at baseline and defined intervals after treatment. **Results:** Forty-one patients (n=41) were accrued and were analyzed. Forty of 41 patients remain alive with a median follow-up of 30 months (range 1 – 49 months). The probability of 3-year overall survival is 97% (95% CI = 90% - 100%) and the probability of 3-year PFS is 86% (95% CI = 68% - 100%). Two patients developed recurrent disease, one of whom died. One patient developed isolated metastasis while a second developed local, regional, and distant metastasis. The most common adverse grade  $\geq 3$  adverse events were lymphocytopenia (n=24), dysphagia (n=2) and oral mucositis (n=2). One grade 4 sepsis/multi-organ failure was reported. Comparison of PRO results with those observed in ECOG3311 trial are underway and will be reported. **Conclusions:** De-intensification of adjuvant treatment adding nivolumab to RT is tolerable and demonstrates favorable clinical outcome for high-risk, resected, HPV+ HNSCC patients. Further targeted immunotherapy combinations are warranted. Clinical trial information: NCT03715946. Research Sponsor: U.S. National Institutes of Health.

**Correlation of *CDKN2A* genomic alterations with tumor response to palbociclib given before chemoradiation therapy (CRT) to patients with human papillomavirus (HPV)-negative, locally advanced head and neck squamous-cell carcinoma (LA-HNSCC): A single-arm, phase 2 trial.**

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**Background:** Cell cycle deregulation is ubiquitous in HNSCC. In HPV-negative disease, the most common genomic alteration of cell-cycling included *CDKN2A* deletions (57%), mutations (27%) or hypermethylation (12%). Selective CDK4/6 inhibition arrested cell cycling and inhibited tumor growth in cell-line and xenograft models of HPV-negative HNSCC, and *CDKN2A* alterations were predictive of response. An exploratory analysis of a double-blind, randomized, phase 2 trial of patients with HPV-negative recurrent/metastatic HNSCC showed that *CDKN2A* alterations were associated with better overall survival (OS) with palbociclib and cetuximab vs placebo and cetuximab (median 9.7 vs 4.6 months, HR 0.38). OS was similar between the two arms in patients without *CDKN2A* alterations. A phase 2 basket trial of patients with *CDKN2A*-altered head and neck cancers observed that palbociclib resulted in a target lesion decrease in 25% of patients. Collectively, these data warrant further studies to delineate predictive biomarkers of response to selective CDK4/6 inhibitors in HPV-negative HNSCC. **Methods:** The primary aims of this single-arm, phase 2 trial were to determine the objective response rate (ORR) of HPV-negative, LA-HNSCC to palbociclib, and to correlate responses to somatic *CDKN2A* alterations. HPV-negative disease was defined as SCC of the larynx, hypopharynx or oral cavity, or SCC of the oropharynx if negative for p16 by IHC and/or high-risk HPV-RNA by ISH. Genome sequencing (FoundationOne CDx/Tempus xT) was performed on tumor tissue obtained before treatment. Patients received palbociclib 125 mg/d orally on days 1-21 of each 28-day cycle. Tumor response was assessed using RECIST 1.1 with CT scans performed pre and post two cycles of palbociclib. Patients then received CRT. A sample size of 24 patients yielded an 80% power if the ORR was  $\geq 38\%$ , using an exact binomial test of one sample proportion comparison with an upper one-sided nominal significance level of 0.05 and null ORR of  $\leq 17\%$ . **Results:** 24 patients enrolled and completed two cycles of palbociclib: primary site (larynx-15; hypopharynx-4; oropharynx-4, oral cavity-1), clinical stage (III-7; IV-17), and smoking history (yes-23; no-1). The ORR with palbociclib was 41.7%. Best tumor response included: CR (1), PR (9), SD (13), and PD (1). *CDKN2A* altered disease was identified in 15 patients (62.5%) [mutation: 8, deletion: 7]. Tumor response to palbociclib occurred in 10 of 15 patients (66.7%) with *CDKN2A* altered disease versus 0 of 9 patients (0%) without *CDKN2A* altered disease ( $p=0.002$ , Fisher's Exact Test). **Conclusions:** The primary hypothesis was met: the ORR with palbociclib in HPV-negative, LA-HNSCC was 41.7%. The ORR with palbociclib was significantly higher in *CDKN2A* altered disease. Clinical trial information: NCT03389477. Research Sponsor: Pfizer.



**Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, in combination with pembrolizumab and carboplatin as first-line treatment of recurrent or metastatic head and neck squamous-cell carcinoma (RM-HNSCC): A single-arm, phase 2 trial.**

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**Background:** The homologous recombination deficiency (HRD) phenotype is common in HNSCC and is due to mutation and promoter hypermethylation of DNA repair genes (*BRCA1*, *BRCA2*, *ATR*, *ATM*, and *FANCD1*) and *PTEN*. In pre-clinical models of HNSCC, HRD sensitizes tumor to PARP inhibition and to additive antitumor activity of PARP inhibition in combination with platinum agents. PARP inhibitors also activate the STING pathway and upregulate PD-L1 expression, resulting in synergistic antitumor activity when given with PD-1 inhibitors. Olaparib is a highly selective PARP inhibitor that has been safely combined with pembrolizumab and carboplatin. **Methods:** In this single-arm phase 2 trial, patients with RM-HNSCC, no prior therapy for RM disease, and adequate performance status and organ function received up to six 21-day cycles of olaparib (200 mg bid orally days 1-10), pembrolizumab (200 mg IV day 1), and carboplatin (AUC 5 IV day 1), followed by up to twenty-nine 21-day cycles of olaparib (oral 300 mg bid days 1-21) and pembrolizumab (200 mg day 1). Treatment continued until discontinuation criteria were met. The primary endpoint was objective response, assessed by an independent radiologist using iRECIST. The primary hypothesis was that this regimen would result in a higher objective response rate (ORR) than historically reported with 5-FU, pembrolizumab and a platinum agent in similar patients. A Simon optimal two-stage design tested the null hypothesis ( $H_0$ : ORR $\leq$ 36%) versus the alternative hypothesis ( $H_1$ : ORR=62%) at a type I error rate of 10% and 90% power. In the first stage, up to 13 patients could be accrued. If  $\geq 6$  responses occur, 16 additional patients will be accrued. The null hypothesis will be rejected if  $\geq 14$  responses are observed in these 29 patients. At the end of the first stage, an interim analysis was performed to assess olaparib delivery during cycles 1 and 2 with the goal of 100% delivery in  $\geq 80\%$  of patients. We report the results of the primary endpoint and olaparib delivery for the first stage of the trial. **Results:** Twelve patients enrolled into the first stage of the trial. Key characteristics included median age 62 years (range 59-74), tobacco history (Y-5; N-7), primary site (oropharynx-7; oral cavity-4; larynx-1), HPV status (positive: 6; negative: 6) and PD-L1 status (CPS 0: 1; 1-19: 4;  $\geq 20$ : 7). Tumor response occurred in 8 patients (ORR 67%). The best tumor response to date was CR (1), PR (7), SD (3) and PD (1). Olaparib delivery during cycles 1 and 2 was 100% for all patients. **Conclusions:** Among patients with RM-HNSCC, first-line treatment with olaparib, pembrolizumab and carboplatin resulted in an ORR of 67% during the first stage of the trial. Olaparib delivery was 100%. Enrollment into the second stage is ongoing. Clinical trial information: NCT04643379. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ; Joseph Sanchez Foundation.

**Enfortumab vedotin in the previously treated advanced head and neck cancer (HNC) cohort of EV-202.**

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**Background:** Globally, HNCs accounted for an estimated 932,000 new cases and 467,000 deaths in 2020. Nectin-4 is expressed in a majority of HNCs. Given the poor prognosis (median survival < 1 y) of recurrent/metastatic disease in patients (pts) with head and neck squamous cell carcinoma, effective treatments are needed. Targeting Nectin-4 with an antibody–drug conjugate (ADC) may be a novel strategy. Enfortumab vedotin (EV) is a Nectin-4 directed ADC approved for treatment of adults with locally advanced or metastatic (la/m) urothelial carcinoma previously treated with platinum-containing chemotherapy and PD-1/L1 inhibitor based on survival benefit shown in the phase 3 EV-301 trial. Use of EV for HNC is investigated in EV-202 (NCT04225117). **Methods:** In this multicohort, open-label phase 2 study, pts with previously treated la/m solid tumors not amenable to curative-intent treatment and Eastern Cooperative Oncology Group performance status 0–1 were enrolled into tumor-specific cohorts. For the HNC cohort, pts must have progressed/relapsed/discontinued treatment for toxicity after 1 platinum-based therapy for la/m disease and no more than 2 lines of cytotoxic therapy in the la/m setting. Unless contraindicated, pts must have received a programmed cell death protein 1/ligand 1 (PD-1/L1) inhibitor (based on PD-1/L1 expression). Pts received EV 1.25 mg/kg intravenously on days 1, 8, and 15 of a 28-d cycle until disease progression/discontinuation criteria were met. Primary endpoint was confirmed objective response rate (ORR; per RECIST v1.1) per investigator assessment. Secondary endpoints were duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety/tolerability. **Results:** As of April 11, 2022, a total of 46 pts were in the HNC cohort; median follow-up was 9.33 mo. Median age was 65 y, 87% of pts were men, and most had received ≥2 lines of systemic therapy in the metastatic setting. Histology at diagnosis was squamous cell carcinoma for 45 (97.8%) pts and “other” for 1 pt. ORR was 23.9% (n = 11). Median DOR was not reached. DCR was 56.5% (n = 26). Median time to response was 1.74 mo. Median PFS and OS were 3.94 and 5.98 mo, respectively. Common adverse events (AEs) were fatigue, alopecia, and peripheral sensory neuropathy (28.3% for each; n = 13). Grade ≥3 AEs occurring in > 1 pt were anemia (n = 3), decreased neutrophil count (n = 2), and malignant neoplasm progression (disease progression of HNC; n = 2). Of treatment-related AEs of special interest for EV, skin reactions occurred in 45.7% of pts, peripheral neuropathy in 32.6%, and hyperglycemia in 4.3%. **Conclusions:** In pts with heavily pretreated HNC, antitumor activity of EV monotherapy and tolerability, with manageable adverse events, was observed, consistent with that in previously studied populations with advanced urothelial carcinoma. Further investigation of EV activity in HNC is warranted. Clinical trial information: NCT04225117. Research Sponsor: Astellas Pharma, Inc. and Seagen Inc.

# Neoadjuvant nivolumab alone or in combination with relatlimab or ipilimumab in resectable head and neck squamous cell carcinoma (HNSCC).

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**Background:** PD-1 inhibition using nivolumab (nivo) monotherapy is modestly effective in metastatic HNSCC. Neoadjuvant trials using nivo may permit development of more effective combinations in surgically resectable HNSCC. We evaluated combinations with nivo plus additional immune check-points, CTLA-4 (ipilimumab, ipi) and LAG-3 (relatlimab, rela). **Methods:** Phase II randomized trial of neoadjuvant nivo alone (240 mg q2 weeks), or with ipi (1 mg/kg q3 weeks) or rela (160 mg q4 weeks) for 4 weeks prior to surgery. Response was scored using RECIST and standard pathologic response criteria. Patients were stratified by p16, PD-L1, and LAG-3, with staining assessed by immunohistochemistry. Freshly digested tumors were subjected to single cell RNA sequencing (scRNAseq) for T cell receptors and gene pathways to identify biomarkers of response or progression. The Cochran-Armitage trend test was used to explore associations with increasing pathological response efficacy. **Results:** 41 patients (pts) have been enrolled, with 33 evaluable for this analysis. Of these 33, median age is 63 (32-81), primary site oral cavity (n=25), oropharynx (n=5, 3 HPV), larynx (n=3), clinical T2 (n=5), T3 (n=12), T4 (n=13), and cNO/1 (n=22), cN2 (n=9), and PD-L1 CPS > 1 (n=25). There were no serious study drug-related AEs or unexpected surgical delays/complications. Pathologic response (Table) was more frequent with nivo/rela (11/13) vs. nivo/ipi (6/10) or nivo (4/10). Partial (>50%) or major (>90%) pathologic responses were more frequent and deeper in the combination arms. Minor (<50%) pathologic responses were more frequent with nivo/rela, and similar between nivo/ipi and nivo. There was no association between RECIST response, PD-L1, or LAG3 and pathologic response. Combined PD-L1 and LAG3 expression was not associated with pathologic response in the nivo/rela arm, however more patients with combined positivity had a >50% response (4 vs. 0). Expansion of CD8<sup>+</sup> T cells, as well as expanded proportion of CD8<sup>+</sup> CXCL13<sup>+</sup> T cells in responder tumors were identified in post-treatment specimens using scRNAseq. **Conclusions:** Neoadjuvant nivo/ipi or nivo/rela combinations were safe and associated with promising pathologic responses compared to nivo monotherapy. Anti-tumor CD8<sup>+</sup> T cell populations and targetable pathways are emerging in responder patients. The trial continues to enroll and further evaluation of this strategy is warranted. Clinical trial information: NCT04080804. Research Sponsor: U.S. National Institutes of Health.

RECIST and pathologic response.

	RECIST				Pathologic Response			
	PR	SD	PD	None	pmPR (10-49%)	pPR (50-90%)	pMPR (>90)	pCR (100%)
Nivo (10)	8	2	6	4	0	0	0	0
Nivo/Ipi (10)	5	5	4	3	2	1	0	0
Nivo/Rela (13)	1	10	2	2	7	2	1	1

**Neoadjuvant cemiplimab with platinum-doublet chemotherapy and cetuximab to de-escalate surgery and omit adjuvant radiation in locoregionally advanced head & neck squamous cell carcinoma (HNSCC).**

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**Background:** Locoregionally advanced (LA) HNSCC treated with surgery can carry significant functional morbidity, further intensified by adjuvant (adj) radiation (RT) often with concurrent chemotherapy. Although the pathologic response rate of anti-PD1 therapy is modest, combination approaches may provide enhanced clinical benefit. This pilot study evaluates whether the combination of neoadjuvant cemiplimab + platinum-doublet chemotherapy + cetuximab is safe, feasible, and effective in pathologic down-staging to reduce the extent of surgery and justify omission of adj RT. **Methods:** 10 patients (pts) with resectable LA HNSCC who would warrant adj RT per clinical stage were enrolled. Neoadjuvant treatment consisted of cetuximab loading dose with cemiplimab followed by 3 cycles of chemotherapy (cisplatin or carboplatin + docetaxel) with cetuximab and cemiplimab prior to definitive surgical resection. Standard of care adj RT+/- chemotherapy was administered based on pathologic staging. Pts with ypT0-2N0 tumors without adverse features or ypT0-1N1 tumors with minimal residual disease (< 10% viable tumor) were offered 6 months of adj cemiplimab in lieu of RT. Primary endpoint was safety (defined by dose limiting toxicity (DLT) related to the addition of cemiplimab to this combination regimen). Secondary endpoints included feasibility (defined as no surgical delay > 20 weeks from start of neoadjuvant therapy due to treatment toxicity) and pathologic down-staging allowing for omission of adj RT. **Results:** 10 pts completed treatment with no DLTs and surgical delays. 8/10 (80%) pts were clinically staged as T3/T4 and 5/10 (50%) were N2b/c (AJCC 7<sup>th</sup> Ed). Pathologic down-staging was observed in 9/10 (90%) pts after neoadjuvant therapy. 60% had a major pathologic response and 40% had a complete pathologic response. 6/8 pts and 7/10 pts who would have required a mandibulectomy and free flap, respectively, did not require it following neoadjuvant treatment. Of the 5/10 (50%) pts who were eligible for omission of adj RT, 4 did not undergo RT and 3 received adj cemiplimab. All pts remain disease-free at a median follow-up of 16 months. The most common adverse events (AEs) of any grade (G) were rash (80%), nausea (70%), fatigue (50%), and diarrhea (50%). 2/10 (20%) pts experienced a G3 or G4 immune-related AE attributed to the addition of cemiplimab. One pt developed G3 transaminase elevation prior to surgery and 1 pt experienced G3 myasthenia gravis and G4 myocarditis (resolved) outside the DLT window. **Conclusions:** Neoadjuvant cemiplimab with platinum-doublet chemotherapy and cetuximab has an acceptable toxicity profile, is feasible in pts with LA HNSCC, and led to notable pathologic down-staging allowing for reduction in extent of surgery and omission of adj RT. Further evaluation of this regimen is clearly warranted. Clinical trial information: NCT04722523. Research Sponsor: Regeneron Pharmaceuticals; The Sierra Initiative on the Management of Head and Neck Cancer Side Effects; Investigator Initiated Trial RFA, Department of Medicine, Memorial Sloan Kettering Cancer Center.

**The Quarterback trials: A phase 2 series of sequential studies of induction chemotherapy followed by reduced dose chemoradiation for human papillomavirus positive oropharynx cancer.**

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**Background:** Human Papilloma Virus (HPV) oropharynx cancer (HPVOPC) is highly curative. Current standard of care treatment recommendations result in over treatment with chemoradiotherapy (CRT) across all stages of the disease and lead to significant long-term morbidity. The Quarterback (QB) trials (NCT01706939, QB1; NCT02945631, QB2a/2b) applied induction chemotherapy (IC) with modified Taxotere, cis-platinum and 5-fluorouracil (TPF) and reduced dose chemoradiotherapy (rdCRT) in very advanced HPVOPC. The primary endpoints were local regional control (LRC) and progression-free survival (PFS) at 3 years. **Methods:** Patients with locally advanced HPVOPC and High Risk (HR) features (radiographic ECE, T4 primary,  $\geq$ N2c disease or non-HPV16 HR genotype) or who were candidates for organ preservation were entered on sequential trials of 3 cycles of TPF IC followed by rdCRT to 5600 cGy with weekly carboplatin. The only variable in IC treatment were 3 sequential reductions of 5-fluorouracil from 800 to 500 mg/M<sup>2</sup>/day across the trials (QB1, QB2a/2b). Major inclusion criteria were: molecularly documented high risk HPV and  $\leq$ 20 pack year smoking history. Patients were eligible for rdCRT if they had a significant clinical response to IC. The hypothesis for non-inferiority was that LRC and PFS at 3 years would be at least 85% and 80%, respectively, based on results from RTOG 1029. Analysis was limited to those patients who received or were randomized (QB1) to rdCRT. **Results:** Of 45 subjects treated with rdCRT, 35 (78%) had HR features. Overall survival (OAS) is 39 (87%), LRC 39 (87%), PFS 35 (78%) with a median follow up of 57m (range: 12-120). Kaplan Meyer 3 year LRC is 88% (95% CI: 79-99), PFS 86% (95 CI 76-97) and OS 93% (95% CI 86-100). 2 subjects (4%) developed an in-field non-HPV, p53 positive squamous cancer and 1 (2%) died. 1 subject (2%) died of non-HPV related disease (SLE); 2 (4%) developed distant metastases; 4 (9%) subjects are alive after recurrence. Disease specific survival is 40/43 (93%). 19 patients signed consent and did not receive rdCRT: 8 were randomized to standard dose (QB1), 2 withdrew consent, 5 had an inadequate response to IC and 4 were screen failures. All 15 treated with IC are alive and disease free. There are no treatment related deaths. **Conclusions:** TPF IC in HPVOPC with HR features, followed by rdCRT met its predetermined statistical goals for LRC, PFS and OAS. Treatment was tolerable and toxicity was manageable. Compared to other Phase 2 and 3 de-escalation trials this approach is reasonable, effective and feasible. QB1 demonstrated improved quality of life in rdCRT with 5600 cGy compared to standard chemoradiotherapy. Randomized trials to establish de-escalation as a standard of care are warranted. Further de-escalation of treatment to further reduce acute and long-term radiation toxicity in HR populations appears feasible. Clinical trial information: NCT01706939; NCT02945631. Research Sponsor: Philanthropy.

**Association of neutrophil-lymphocyte ratio (NLR) with clinical outcomes in patients (pts) with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with combination of cetuximab and nivolumab (C+N).**

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**Background:** Combination of anti-epidermal growth factor receptor (EGFR) and anti-programmed cell death-1 (PD-1) inhibitors such as C+N is highly efficacious in R/M HNSCC. While PD-1 ligand 1 (PD-L1) combined positive score (CPS) is predictive of anti-PD-1 inhibitor response, there is no predictive biomarker for the combination. NLR is a known prognostic biomarker in HNSCC pts treated with chemotherapy with/without radiation. We evaluated NLR as a potential predictive biomarker in R/M HNSCC pts treated with C+N. **Methods:** The clinical data were obtained from R/M HNSCC pts treated with C+N from a completed clinical trial (NCT03370276) and pts treated with nivolumab or pembrolizumab (N/P) as a standard of care in a retrospective chart review study. NLR were collected at baseline (NLR1) and on-treatment (1-month from the treatment initiation; NLR2). The median NLR was applied as a cut-point. Pts were stratified into NLR-high (H;  $\geq$  median) or -low (L;  $<$  median). Time-to-event endpoints were evaluated to assess survival and response at the initiation treatments using the Kaplan Meier and Cox Proportional Hazards Models. Selected variables included in the multivariate (MV) analyses were  $\log_2(\text{NLR1} + 2)$ , PD-L1 CPS, p16 and smoking status, and prior exposure to anti-PD-1 inhibitors. **Results:** Total 83 C+N and 40 N/P pts were included. In C+N, the median NLR cut-points were NLR1 6.27 and NLR2 5.98 while they were NLR1 5.87 and NLR2 8.21 in N/P. NLR1-H vs. -L in C+N showed no difference in OS ( $p = 0.26$ ) and progression-free survival (PFS;  $p = 0.95$ ), but NLR2-H had worse OS ( $P < 0.001$ ) and PFS ( $P < 0.001$ ) compared to NLR2-L. Similarly, in N/P, NLR1-H vs. -L did not show difference in OS ( $p = 0.23$ ), but NLR2-H had worse OS ( $P < 0.046$ ) compared to NLR2-L. In C+N, NLR2 ( $\log_2(\text{NLR2})$ ) consistently correlated with worse OS [univariate (UV), HR 1.69, CI 1.36-2.12; MV, HR 1.63, CI 1.26-2.11] and PFS (UV, HR 1.63, CI 1.22-2.19; MV, HR 1.70, CI 1.21-2.42). In N/P, PFS and MV analyses were not feasible due to lack of reliable data in the retrospective study. In C+N, NLR2 ( $p < 0.001$ ), but not NLR1 ( $p = 0.93$ ), was correlated with lower best overall response (BOR). Similarly, in N/P, NLR2 ( $p = 0.004$ ), but not NLR1 ( $p = 0.12$ ), was associated with lower BOR. In addition, a significantly larger reduction in NLR on-treatment from baseline ( $\log_2(\text{NLR2}) - \log_2(\text{NLR1})$ ) was observed in C+N compared to N/P ( $P = 0.005$ , Student t-test). **Conclusions:** On-treatment NLR2-H is associated with worse response and survival in pts with R/M HNSCC treated with C+N and N/P. C+N is associated with a greater reduction in NLR compared to N/P, suggesting that the combination enhances a favorable peripheral immunologic response. Further evaluation is warranted to determine the role of NLR as a biomarker of immunotherapy response. Research Sponsor: Lilley Oncology, Bristol Myers Squibb; James and Esther King Biomedical Research Grant (grant no. 7JK02); Junior Scientist Research Program (Moffitt Cancer Center).

**Tazemetostat, a selective EZH2 inhibitor, with pembrolizumab as treatment of anti-PD-1 resistant head and neck squamous-cell carcinoma (HNSCC): A phase 1-2 trial.**

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**Background:** EZH2 is the catalytic subunit of PRC2, which catalyzes H3K27me3 of target gene promoters and silences transcription of several cancer-related genes. EZH2 overexpression is common in HNSCC and correlated with methylation of several tumor suppressor genes. EZH2 siRNA down-regulated EZH2 mRNA and protein and reduced colony formation in an EZH2-expressing HNSCC cell line. EZH2 inhibitors decreased H3K27me3 in HPV + and - cell lines. Tazemetostat, an EZH2 inhibitor, upregulated expression of HLA class I molecules in anti-PD-1-resistant HNSCC cell lines and mouse models, and increased antigen-specific CD8+ T cell proliferation, IFN- $\gamma$  production, CXCL10 expression, and tumor cytotoxicity. In an anti-PD-1-resistant HNSCC model, tazemetostat and an anti-PD-1 suppressed tumor growth. The primary aims of this phase 1-2 trial were to establish 1) the recommended phase 2 dose (RP2D) of tazemetostat given with pembrolizumab and 2) the objective response rate of this regimen among patients (pts) with anti-PD-1 resistant, PD-L1 positive HNSCC. We report the results of Phase 1. **Methods:** In phase 1, eligible pts had recurrent/metastatic (RM) HNSCC, adequate performance status and organ function, and ability to swallow study drug. A 3+3 dose-escalation phase 1 design was used to assess 3 dose-levels of tazemetostat (400, 600, and 800 mg orally twice daily) with pembrolizumab (200 mg IV). Cycle 1 was 35 days, with tazemetostat given on days 1-35 and pembrolizumab on day 15. Subsequent cycles were 21 days, with tazemetostat given on days 1-21 and pembrolizumab on day 1. Dose-limiting toxicity (DLT), assessed during cycle 1, was defined as grade 4 neutropenia/thrombocytopenia, grade 3 febrile neutropenia, or study drug-related grades 3-4 non-hematologic adverse events (AEs). Pts must have completed cycle 1 to be evaluable for DLT assessment; otherwise, an equal number of additional pts were enrolled. The RP2D was defined as the highest dose level in which 0 of the first 3 or <1 of 6 pts experienced a DLT. **Results:** 12 pts enrolled to phase 1: 3 each on the 400 and 600 mg dose-levels of tazemetostat and 6 on the 800 mg dose-level. Key tumor characteristics included primary site (larynx: 4, oral cavity: 3, oropharynx: 3, nasopharynx: 1, cutaneous: 1), HPV status (+: 1, -: 11), and number of lines of prior systemic treatment for RM disease (1-2: 6, >3: 6). Nine pts were evaluable for DLT; 3 pts on the 800 mg dose-level did not complete cycle 1 and were not evaluable for DLT. DLT events and grade 4-5 AEs did not occur. Grade 3 AEs that occurred after cycle 1 included anemia (2 pts, both at 800 mg dose) and fatigue (1, at 400 mg dose). Across all cycles, the most common AEs included anemia (10 pts), fatigue (9), rash (7), and myalgia (4). **Conclusions:** Among pts with RM-HNSCC, the RP2D of tazemetostat was 800 mg twice daily when given with pembrolizumab. Enrollment to phase 2 is ongoing. Clinical trial information: NCT04624113. Research Sponsor: Epizyme, an Ipsen Company.

**Nanoparticle albumin-bound (nab) paclitaxel in combination with nivolumab as treatment of recurrent or metastatic head and neck squamous-cell carcinoma (RM-HNSCC) that progressed on a PD-1 inhibitor: A single-arm, phase 2 trial.**

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**Background:** Drugs bound to albumin selectively target cancer cells with upregulated macropinocytosis, an endocytic nutrient-scavenging process driven by constitutive hyper-activation of the EGFR, RAS, PIK3CA and Syndecan1 signaling pathways that frequently occur in HNSCC. *nab*-paclitaxel is an active drug in HNSCC and has immunologic effects that can prime an immune response to PD-1 inhibitors, potentially reversing resistance to these agents. These effects include decreased TREGs, increased pro-inflammatory macrophages and differentiation of MDSC to dendritic cells, increased HLA class I expression and antigen presentation, and recruitment of CD8+ CTLs into tumor. **Methods:** In a single-arm phase 2 trial, patients with RM-HNSCC that progressed on a PD-1 inhibitor received 28-day cycles of *nab*-paclitaxel (125 mg/m<sup>2</sup> IV days 1, 8, and 15) and nivolumab (480 mg IV day 1). Treatment continued until discontinuation criteria were met. The primary endpoint was objective response, assessed with RECIST1.1 by an independent radiologist. The primary hypothesis was that this regimen would result in a higher objective response rate (ORR) than historically reported with standard chemotherapy or cetuximab in similar patients. A Simon optimal two-stage design tested the null hypothesis ( $H_0$ : ORR  $\leq$  30%) versus the alternative hypothesis ( $H_1$ : ORR = 50%) at the type I error rate of 5% and power 0.80. In the first stage, 15 patients were to be accrued. If  $\geq 6$  responses occurred, 31 additional patients were to be accrued. The null hypothesis will be rejected if  $\geq 19$  responses are observed in these 46 patients. We report the results of the primary endpoint for the first stage of the trial. **Results:** 15 evaluable patients enrolled into the first stage of the trial. Key tumor characteristics and prior treatment history included HPV status (positive: 8; negative: 7), PD-L1 status (CPS 1-19: 7;  $\geq 20$ : 8), # of lines of prior systemic treatment for RM disease (1-2: 12;  $\geq 3$ : 3), interval (months) from prior PD-1 inhibitor ( $< 6$ : 11;  $\geq 6$ : 4), duration (months) on prior PD-1 inhibitor (median: 6, range: 1-16), and best response to prior PD-1 inhibitor (PR: 4; SD: 6; PD: 5). Tumor response to *nab*-paclitaxel and nivolumab occurred in 7 of 15 patients (ORR 47%). The best tumor response was PR (7), SD (5) and PD (3). **Conclusions:** Among patients with RM-HNSCC that progressed on a PD-1 inhibitor, the ORR with *nab*-paclitaxel and nivolumab was 47% during the first stage of the phase 2 trial. Enrollment to the second stage is ongoing. Clinical trial information: NCT04831320. Research Sponsor: Bristol-Meyers Squibb; Generous support from Gregory Stubblefield and Nancy Apel.



**Prognostic value of circulating Epstein-Barr virus DNA level post-induction chemotherapy for patients with nasopharyngeal carcinoma: A recursive partitioning risk stratification analysis.**

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**Background:** To evaluate the prognostic value of plasma Epstein-Barr virus (EBV) DNA level post-induction chemotherapy (IC) for patients with nasopharyngeal carcinoma (NPC). **Methods:** A total of 893 newly diagnosed NPC patients treated with IC were retrospectively reviewed. The recursive partitioning analysis (RPA) was performed to construct a risk stratification model. The receiver operating characteristic (ROC) analysis was applied to determine the optimal cut-off value of EBV DNA and compare the predictive validity. **Results:** Post-IC EBV DNA levels and overall stage were independent predictors for distant metastasis-free survival (DMFS), overall survival (OS), and progression-free survival (PFS). The RPA model base on post-IC EBV DNA and overall stage categorized the patients into three distinct risk groups: RPA I (low-risk: stage II-III and post-IC EBV DNA < 200 copies/mL), RPA II (median-risk: stage II-III and post-IC EBV DNA  $\geq$  200 copies/mL, or stage IVa and post-IC EBV DNA < 200 copies/mL), and RPA III (high-risk: stage IVa and post-IC EBV DNA  $\geq$  200 copies/mL), with 3-year PFS of 91.1%, 82.6%, and 60.2%, respectively ( $p < 0.001$ ). The DMFS and OS rates in different RPA groups were also distinct. ROC analysis showed that the RPA model had superior predictive efficacy than the overall stage. **Conclusions:** Plasma EBV DNA level post-IC was a robust prognostic biomarker for NPC. We developed a risk stratification model that provides improved DMFS, OS, and PFS prediction over the 8th edition of the TNM staging system by integrating the post-IC EBV DNA level and the overall stage. Research Sponsor: None.

**A phase 1 study of concurrent cabozantinib and cetuximab in recurrent or metastatic head and neck squamous cell cancer.**

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**Background:** Epidermal growth factor receptor (EGFR) targeting with cetuximab (CTX) is a standard therapy for head and neck squamous cell carcinoma (HNSCC). Resistance to CTX can be mediated by activation of the receptor tyrosine kinase AXL. Cabozantinib (cabo) is a tyrosine kinase inhibitor (TKI) of AXL/c-MET/VEGFR which demonstrated antitumor activity in HNSCC preclinical models. We conducted a phase I trial to assess the safety and efficacy of the cabo-CTX combination in recurrent or metastatic (R/M) HNSCC. **Methods:** Eligibility criteria included RECIST v1.1 measurable disease and incurable R/M HNSCC. Prior treatment with CTX was allowed. Patients received an initial CTX loading dose of 400 mg/m<sup>2</sup> followed by 250 mg/m<sup>2</sup> weekly. CTX maintenance dose was later amended to 500 mg/m<sup>2</sup> biweekly. Cabo was given concurrently on days 1-28 of each 28-day cycle. Primary endpoint was maximally tolerated dose (MTD) of cabo, as identified using a 3+3 dose-escalation design. Tumor responses were assessed every 2 cycles. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). **Results:** Of 22 patients enrolled between 2018 and 2022, 2 did not start therapy. Among treated patients, median age was 59 (range 33-71) and 90% (n = 18) of patients were male. Primary tumor sites included the oropharynx (n = 13), oral cavity (n = 3), larynx (n = 2), hypopharynx (n = 1) and unknown primary (n = 1). p16 antigenic testing for HPV status was positive in 11 oropharyngeal cancers (85%). Most patients were previously treated with immune checkpoint inhibitors (n = 19), chemotherapy (n = 19), CTX (n = 16), or other TKI (n = 2). 12 patients received biweekly CTX dosing at 500 mg/m<sup>2</sup>. Initial cabo dose was 40 mg for the first 11 patients, and 60 mg afterwards (MTD). No dose-limiting toxicity (DLT) was recorded. Common adverse events (AEs) included fatigue (80%), acneiform rash (75%), increased aspartate aminotransferase (AST) (70%), anemia (70%) and hypothyroidism (70%). Grade ≥3 AEs occurred in 65% (n = 13), including increased AST (45%), increased alkaline phosphatase (15%), increased bilirubin (10%) and erythrodysesthesia (10%). AEs led to dose reductions in 20% (n = 4) and treatment discontinuation in 15% (n = 3). In the preliminary efficacy analysis, 4 patients had partial responses (PRs) with an ORR of 20%, including 2 PRs in patients with prior CTX resistance. Disease control rate (DCR) was 75% in the overall population and 75% in those with previous CTX treatment. Median PFS was 3.4 mo and median OS was 8.1 mo. PFS differed according to HPV status, with median PFS 7.1 mo versus 3.1 mo in HPV-positive and -negative patients respectively (p = 0.03). **Conclusions:** The cabo and CTX combination showed an acceptable toxicity profile with liver toxicity as a common AE. The regimen showed preliminary efficacy data in patients with R/M HNSCC, including those with prior CTX resistance. Clinical trial information: NCT03667482. Research Sponsor: None.

**A phase Ib/II study of GFH018 in combination with toripalimab in recurrent/metastatic nasopharyngeal carcinoma (R/M NPC).**

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**Background:** The transformed growth factor beta (TGF- $\beta$ ) signaling pathway is dysregulated in carcinogenesis. In NPC patients, upregulation of TGF- $\beta$  pathway is correlated with disease stage or phenotype due to Epstein-Barr virus (EBV) infection. GFH018, a novel TGF- $\beta$ RI inhibitor, can inhibit tumor growth through inhibiting the activity of TGF- $\beta$ RI kinase to block the signal transduction of TGF- $\beta$  and modulate the tumor immune microenvironment. Preclinical studies showed that GFH018 in combination with PD-1/PD-L1 monoclonal antibody can significantly inhibit tumor growth synergistically. Here we report the preliminary results of combining GFH018 and Toripalimab treating R/M NPC patients (pts). **Methods:** This is a phase Ib/II study to evaluate the safety and efficacy of the combination of GFH018 and Toripalimab in pts with advanced solid tumors. Patients with RM NPC were enrolled to receive GFH018 80mg twice a day (BID) 14-day-on/14-day-off in combination with Toripalimab 3mg/kg every two weeks. Tumor assessment was performed every 8 weeks per Response Evaluation Criteria in Solid Tumor (RECIST) 1.1. **Results:** As of 31 Dec 2022, 32 pts with R/M NPC who had progressed on at least one prior line therapy were enrolled. Sixteen (50%) had received  $\geq 3$  lines of prior therapies, and 19 (59.4%) had previously received immune checkpoint inhibitors (ICIs) and platinum-based chemotherapies. The median duration of study drug exposure was 7 weeks. Twenty-five pts (78.1%) experienced treatment-related adverse events (TRAEs) of any grades, and 11 pts (34.4%) had  $\geq$  Grade 3. The most common TRAEs (occurring in  $\geq 3$  pts) were anaemia (n = 6, 18.8%), hyponatraemia (n = 6, 18.8%), rash (n = 6, 18.8%), fatigue (n = 4, 12.5%), white blood cell count decreased (n = 4, 12.5%), aspartate aminotransferase increased (n = 3, 9.4%), back pain (n = 3, 9.4%), decreased appetite (n = 3, 9.4%), hypokalaemia (n = 3, 9.4%), and hypothyroidism (n = 3, 9.4%). As of 18 Jan 2023, among the 27 pts with post-baseline tumor assessments, 8 achieved partial response (PR), and 5 stable disease (SD); the overall response rate (ORR) was 29.6%, and disease control rate (DCR) was 48.1%. Six PR and 2 SD were observed among the 12 pts without prior treatment of ICIs; the ORR was 50%, and DCR was 66.7%. Four pts discontinued treatment without any post-baseline tumor assessments due to AEs or withdrawal of consent, and 1 patient is premature for tumor assessment. **Conclusions:** GFH018 combined Toripalimab was well tolerated and demonstrated preliminary efficacy in pts with R/M NPC. Specifically, in pts who had not previously received ICIs, promising antitumor activity was observed supporting further investigation to this group of pts. Clinical trial information: NCT04914286. Research Sponsor: Zhejiang Genfleet Therapeutics Co., Ltd.

**Effect of extended treatment with IAP inhibitor xevinapant post radiotherapy (RT) on efficacy and the tumor microenvironment (TME) in preclinical models.**

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**Background:** Xevinapant is a first-in-class, oral IAP (inhibitor of apoptosis protein) inhibitor designed to restore cancer cell sensitivity to apoptosis, induced by RT and chemotherapy, and enhance antitumor immunity. In a randomized phase 2 study of patients with unresected locally advanced squamous cell carcinoma of the head and neck, xevinapant + chemoradiotherapy (CRT) significantly improved 18-month locoregional control and improved 3-year progression-free survival and 5-year overall survival vs placebo + CRT. A phase 3 confirmatory study (TrilynX NCT04459715) and a phase 3 study to evaluate xevinapant + RT in post-operative, high-risk, cisplatin-ineligible patients (XRay Vision NCT05386550) are ongoing. In these studies, we investigate 3 additional cycles of xevinapant or placebo monotherapy after completing combination treatment. Based on the role of IAPs in apoptosis, immunity, and stromal activation, continual dosing of xevinapant post RT may have additional therapeutic benefits. **Methods:** MC38 syngeneic tumor-bearing mice were treated with vehicle control, RT alone (3.6Gy once daily [QD], 5 days), or RT + xevinapant (100 mg/kg QD, 1, 2, or 4 weeks). To assess treatment-mediated TME modulation, immune cells in tumors were evaluated by fluorescence-activated cell sorting (FACS)-based immunophenotyping, and tumor-specific T cell responses were investigated by enzyme-linked immunosorbent spot (ELISpot) assays. To understand the effect of xevinapant on RT-induced cancer associated fibroblast (CAF) activation, CAF gene expression was profiled on cell lines and patient-derived primary cultures. **Results:** Xevinapant + RT increased antitumor efficacy compared with vehicle control or RT alone. Moreover, RT in combination with extended dosing of xevinapant for 4 weeks significantly improved therapeutic efficacy and prolonged survival compared with RT + shorter xevinapant dosing durations. FACS analysis demonstrated trends of increased numbers of CD8<sup>+</sup> T cells, natural killer cells, and dendritic cells and decreased numbers of regulatory T cells in mice treated with xevinapant + RT. FACS and ELISpot further suggested an increase in antigen-specific T cell counts from baseline with combination therapy arm vs vehicle control or RT alone. Xevinapant may also suppress RT-mediated CAF activation, as indicated by downregulation of activation markers and CAF-derived secretory proteins. **Conclusions:** In preclinical models, extended dosing of xevinapant for 4 weeks post RT improved antitumor efficacy. Our data suggest that the effect may be, in part, modulated by TME responses, including enhanced antitumor immunity and suppressed protumorigenic phenotype of CAFs. Based on these results, further evaluation is warranted to determine the mechanisms that underscore the therapeutic benefit offered by extended dosing of xevinapant. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany.

### Phase 2 study of ISA101b (peltopimut-S) and cemiplimab in patients with advanced HPV16+ oropharyngeal cancer who failed anti-PD1 therapy.

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**Background:** ISA101b (peltopimut-S), a therapeutic vaccine against the HPV-specific E6/E7 oncoproteins, induces specific expansion of HPV16 targeted T-cells when given together with cemiplimab, an anti-PD-1 agent. Previously we showed that ISA101 with nivolumab achieved a higher response rate compared to immune checkpoint inhibitor (ICI) alone in trials for patients with recurrent/metastatic (R/M) HPV16+ oropharyngeal cancer (OPC)<sup>1,2</sup>. **Methods:** In this single arm phase 2 study, patients with R/M HPV16+ OPC with progressive disease (PD) within 6 months after prior 1<sup>st</sup> or 2<sup>nd</sup> line anti-PD-1 ICI were treated with ISA101b (subcutaneously 100µg/peptide on days 1, 29, and 50) with cemiplimab (intravenously 350mg as a 3-weekly regimen) until PD. Patients without PD at 6 months were offered a booster ISA101b injection. HPV16 positive tumor status was confirmed by a central reference laboratory with an established PCR assay. The primary efficacy endpoint was defined as overall response rate (ORR) as per RECIST1.1. An analysis was planned at the end of Stage 1, when 26 patients who had received at least one dose of ISA101b had been followed for 6 months. The cut-off date for this analysis, approved by the DSMB, was 31 January 2023. **Results:** Twenty-six patients (mean age 60.7 ± 12.9 years; 22 (84.6%) male and 4 (15.4%) female) enrolled in Stage 1. Median follow-up was 16.2 weeks (range 1.6-78.8). Three patients were confirmed with partial response (PR) (11.5%); two of the 3 patients with PR never responded to previous ICI treatment. In 13 patients (50.0%) best overall response (BOR) was stable disease (SD); in 8 patients (30.8%) BOR was PD. Two (7.7%) patients did not have a tumor assessment after baseline: one patient died on day 8 due to OPC and one patient withdrew consent shortly after enrolment. The clinical benefit ratio (CBR) was 61.5%. Nine (34.6%) patients received a booster injection. At the time of the booster, 2 patients had PR and 5 patients had meaningful (≥6 months) SD. Time to response ranged between 127 and 307 days. Median duration of study treatment was 13.1 weeks (range 1.1-75.9), with 4 patients still on treatment. There were two grade 3 adverse events (AEs) related to ISA101b: erythema at the injection site and diarrhea. Two patients (7.7%) had grade 3 ICI-related auto-immune events. Grade 4-5 AEs related to study treatment did not occur. Median overall survival was 8.1 months (range 0.3-17.5). **Conclusions:** This treatment appears promising for HPV16+ OPC patients who failed prior anti-PD-1 ICI therapy, with an ORR of 11.5% and a CBR of 61.5%. In this small, ongoing study the combination of cemiplimab and ISA101b was well tolerated with a safety profile resembling anti-PD-1 monotherapy. This is the first study of the combination of ISA101b and cemiplimab in 2<sup>nd</sup>/3<sup>rd</sup> line R/M anti-PD-1 refractory OPC patients. <sup>1</sup>Massarelli E. *JAMA Oncol* 2019 <sup>2</sup>de Sousa LG. *J Immunother Cancer* 2022. Clinical trial information: NCT04398524. Research Sponsor: ISA Pharmaceuticals; Regeneron Pharmaceuticals.

# Final results from TACTI-002 Part C: A phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with metastatic 2nd line head and neck squamous cell carcinoma unselected for PD-L1.

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**Background:** Eftilagimod alpha (E), a soluble LAG-3 protein, acts as an MHC class II agonist triggering activation of antigen-presenting cells (APC) and CD8 T-cells. Using efti to enhance patients' immunity may lead to stronger anti-tumor responses than observed with pembrolizumab (P) alone. We report final results from Part C of the TACTI-002 trial (NCT03625323) where 2<sup>nd</sup> line metastatic head and neck squamous cell carcinoma (HNSCC) patients (pts) unselected for PD-L1 were treated with E + P. **Methods:** Pts with metastatic HNSCC, unselected for PD-L1 expression with disease progression on or after 1<sup>st</sup> line platinum-based therapy ( $\pm$  cetuximab) were enrolled. Primary endpoint (EP) was objective response rate (ORR) by iRECIST. Other EPs included tolerability, progression free survival (PFS), duration of response (DoR), and overall survival (OS). Pts received E (30 mg SC Q2W for eight 3-week cycles and then Q3W up to 1 yr) with P (200 mg IV Q3W up to 2 yrs). Imaging was performed Q9W. PD-L1 was retrospectively assessed using the IHC 22C3 kit. The study was approved by ethic committees and institutional review boards. **Results:** 39 pts were enrolled between Mar 2019-Jan 2021 (cut-off Jul 2022) with HNSCC of oropharynx (38%), oral cavity (32%), hypopharynx (19%) and larynx (16%). Median age was 63 yrs (48-84 yrs) and 90% were male. ECOG PS was 0 and 1 in 35% and 65% of pts. Two pts were excluded from efficacy results due to fatal COVID-19 prior to their first post-baseline scan. The primary EP, ORR by iRECIST, was 30% with 14% complete responders (see table). ORR by RECIST 1.1 was comparable (24%). Median PFS by iRECIST was 2.1 mo with 32% of pts progression-free at 6 mo. Median OS was 8.7 mo with 46% alive at 12 mo. Median DoR by iRECIST was not reached with 17 mo min FU. Responses were seen in all PD-L1 subgroups (see table). ORR, 6-mo PFS, 12-mo OS rates for PD-L1 CPS  $\geq$ 20 were 60%, 53%, 73% with a median OS of 15.5 months. Two pts (5%) discontinued due to adverse events (AE) (fatigue and arthralgia [each grade 2]; pneumonitis [grade 3]) that were related to study treatment (efti and/or pembro). The most common ( $\geq$ 15%) AEs were hypothyroidism (21%), asthenia (21%), cough (18%), anemia (18%), weight decrease (18%), and fatigue (15%). **Conclusions:** Efti + pembrolizumab is safe, showing encouraging antitumor activity in platinum and partially cetuximab pre-treated, 2nd line HNSCC patients. TACTI-003 (NCT04811027) a randomized study in 1st line HNSCC is currently recruiting. Response by iRECIST: Clinical trial information: NCT03625323. Research Sponsor: Immute S.A.

	Overall (ITT) N=37	PD-L1 CPS $\geq$ 20 N=15	PD-L1 CPS <20 N=17
CR, n (%)	5 (14)	4 (27)	1 (5.9)
PR, n (%)	6 (16)	5 (33)	1 (5.9)
ORR, n (%)	11 (30)	9 (60)	2 (11.8)
DCR, n (%)	14 (38)	9 (60)	4 (23.5)
mPFS, mo	2.1	13.6	2.0
6-mo PFS rate, (%)	32.4	53.3	17.7
mOS, mo	8.7	15.5	7.5
12-mo OS rate, (%)	46.0	66.7	35.3
mDoR, mo	NR	NR	12.0
12-mo DoR rate, (%)	80.0	87.5	50.0

NR: not reached.

**Influence of widely targeted quantitative lipidomics on plasma lipid predictors and pathway dysregulation for nasopharyngeal carcinoma.**

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**Background:** Dysregulation of lipid metabolism is closely associated with cancer progression. We aimed to establish a prognostic model to predict distant metastasis-free survival (DMFS) in patients with locoregionally advanced nasopharyngeal carcinoma (NPC), based on widely targeted quantitative lipidomics. **Methods:** We measured and quantified the plasma lipid profiles of 179 patients with NPC using widely targeted quantitative lipidomics. Then, patients were randomly split into the training (125 patients, 69.8%) and validation (54 patients, 30.2%) sets. To identify distant metastasis-associated lipids, univariate Cox regression was applied to the training set ( $p < 0.05$ ). We employed a deep survival method called DeepSurv to develop our proposed model based on significant lipid species ( $p < 0.01$ ) and clinical biomarkers to predict DMFS. Concordance index and receiver operating curve analyses were performed to assess model effectiveness. We also explored the potential role of lipid alterations in the prognosis of NPC. **Results:** A total of 665 plasma endogenous lipid species consisting of 27 lipid classes and subclasses from 179 patients with NPC were annotated in lipidomics analysis. Forty lipids were recognized as distant metastasis-associated ( $p < 0.05$ ) by univariate Cox regression. The concordance indices of our proposed model were 0.764 (95% confidence interval (CI), 0.682–0.846) and 0.760 (95% CI, 0.649–0.871) in the training and validation sets, respectively. We also calculated the C-index values of the baseline survival model based only on clinical biomarkers, with 0.718 (95% CI, 0.591–0.845) and 0.672 (95% CI, 0.511–0.833) being detected in the training and validation sets, respectively, indicating the outstanding predictive performance of lipid biomarkers. High-risk patients had poorer 5-year DMFS compared with low-risk patients (Hazard ratio, 26.18; 95% CI, 3.52–194.80;  $p < 0.0001$ ). Moreover, the six lipids were significantly correlated with immunity- and inflammation-associated biomarkers and were mainly enriched in metabolic pathways. **Conclusions:** Widely targeted quantitative lipidomics reveals plasma lipid predictors and pathway dysregulation for locoregionally advanced NPC, the prognostic model based on that demonstrated superior performance in predicting metastasis in NPC patients. Research Sponsor: The National Natural Science Foundation of China; the Natural Science Foundation of Guangdong Province, China.

**Efficacy and safety of sintilimab plus bevacizumab in metastatic nasopharyngeal carcinoma after failure of platinum-based chemotherapy: An open-label phase II study.**

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**Background:** There are limited treatment options for patients with metastatic nasopharyngeal carcinoma (mNPC) after failure of platinum-based chemotherapy. In this trial, we assessed the efficacy and safety of sintilimab plus bevacizumab in mNPC patients where platinum-based chemotherapy has failed. **Methods:** This was a single-center, open-label, single-arm, phase II trial for mNPC patients progressed after at least one line of systemic therapy. Patients were enrolled and received sintilimab (200 mg) plus bevacizumab (7.5mg/kg) intravenously every 3 weeks. The primary end point was objective response rate (ORR) assessed by investigators following the guidelines of RECIST 1.1. Key secondary end points were progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety. This trial is registered with ClinicalTrials.gov (NCT04872582). **Results:** Thirty-three patients were enrolled. Median age was 46 years (range, 18-64 years), and 63.6% of patients had previously received two or more lines of chemotherapy for metastatic disease. Median follow-up was 7.6 months (range, 4.1-17.5 months). ORR was 54.5% (95% CI, 36.4- 71.9%) with 3 complete responses (9.1%) and 15 partial responses (45.5%). Median PFS was 6.8 months (95% CI, 5.2 months to not estimable). Median DOR was 7.2 months (95% CI, 4.4 months to not estimable). Median OS was not reached. The most common potential immune-related AE was grade 1-2 hypothyroidism (42.4%). Treatment-related grade 3 or 4 adverse events (AEs) occurred in 7 patients (21.2%), including nasal necrosis (9%), hypertension (3%), pruritus (3%), total bilirubin increased (3%) and anaphylactic shock (3%). No treatment-related deaths and severe epistaxis occurred. **Conclusions:** This phase II trial showed that sintilimab plus bevacizumab demonstrated promising antitumor activity and manageable toxicities in mNPC patients after failure of platinum-based chemotherapy. Clinical trial information: NCT04872582. Research Sponsor: National Natural Science Foundation of China (KY013113).



**A phase II trial of paclitaxel plus biweekly cetuximab for patients with recurrent or metastatic head and neck cancer previously treated with both platinum-based chemotherapy and anti-PD-1 antibody.**

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**Background:** An important unmet need in treatment options remains for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) previously treated with both platinum-based chemotherapy and anti-PD-1 antibody (PD-1 Ab). Recent retrospective studies suggest that previous treatment with Immune checkpoint inhibitor might augment the efficacy of subsequent chemotherapy. This phase II trial aimed to evaluate the efficacy and safety of paclitaxel plus biweekly cetuximab (PTX+bwCmab) for patients with R/M-HNSCC previously treated with both platinum and PD-1 Ab. **Methods:** This is a single-arm, multicenter phase II trial. Key eligibility criteria were R/M-HNSCC; previous treatment with both platinum-based chemotherapy and PD-1 Ab; ECOG performance status 0 or 1; measurable disease per RECIST v1.1; and adequate organ function. PTX+bwCmab consisted of weekly paclitaxel 100 mg/m<sup>2</sup> (days 1, 8, 15) and biweekly cetuximab 500 mg/m<sup>2</sup> (days 1, 15) with a cycle of 28 days. Primary endpoint was objective response rate (ORR). We set a null hypothesis of 10% and alternative of 30% with a one-sided alpha of 0.05 and power of 90%. Secondary endpoints were progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and adverse events (AEs) (CTCAE v5.0). Binominal confidence intervals (CIs) for ORR and DCR were estimated by the exact method. Time-to-event analyses were calculated by the Kaplan-Meier method with 95% CIs. **Results:** Between August 2020 and August 2022, 35 patients were enrolled, of whom 32 were evaluable for response. ORR was 68.7% (95% CI: 49.9-83.8), which met the prespecified criteria for the primary endpoint of ORR. With a median follow-up period for survivors of 16.6 months, median PFS and OS were 5.7 and 13.4 months, respectively. DCR was 93.7% (95% CI: 79.1-99.2). The most common AEs of any grade were skin rash (65%), peripheral nerve neuropathy (45%), neutropenia (40%), fatigue (40%) and paronychia (37%). Grade 3 and 4 adverse events included neutropenia (34%), mucositis (8%), pneumonitis (8%) and febrile neutropenia (5%). These AEs were manageable and no treatment-related death within 30 days was observed. **Conclusions:** PTX+bwCmab showed highly encouraging efficacy and tolerability in RM-HNSCC patients previously treated with both platinum and PD-1 Ab. Although preliminary, these results suggest that this is a promising treatment option for this hitherto untreatable patient group. Further evaluation is warranted. Clinical trial information: jRCTs051200040. Research Sponsor: None.

# **To test, or not to test, that is the question: A real-world analysis of PD-L1 expression testing patterns in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC).**

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**Background:** PD-L1 expression testing plays an important role in identifying patients who benefit from immunotherapy when treating R/M HNSCC. We aimed to understand how PD-L1 expression testing evaluated by Combined Positive Score (CPS) is used in clinical practice and how testing results impact treatment decision-making. **Methods:** A retrospective cohort study was conducted using the Flatiron Health Advanced Head and Neck database. We included adult R/M HNSCC patients who initiated first-line (1L) treatment between 07/01/19 and 12/31/21 with follow-up until 06/30/22. Patients were excluded if they received platinum therapy within 6 months prior to 1L treatment, had other primary cancers before advanced diagnosis, were treated on protocol, or were tested but did not have any record of date of specimen collected, received, or results returned. Multivariable logistic regression was conducted to assess factors associated with PD-L1 testing decisions before 1L therapy start and the association between testing results and choice of 1L treatment. **Results:** A total of 1,762 patients with R/M HNSCC were included, with 32.0% tested for PD-L1 prior to 1L therapy start, 25.6% tested after, and 42.4% never tested. Most patients were tested using the IHC 22C3 pharmDx assay, an FDA-approved companion diagnostic. Among patients tested before 1L treatment initiation, the most prescribed regimens were pembrolizumab or pembrolizumab + platinum + 5-FU for patients with PD-L1(+) (55.9%, 14.2%) and PD-L1(-) tumors (25.3%, 32.0%), respectively. Patients tested after 1L treatment initiation regardless of CPS and patients never tested were most often prescribed platinum monotherapy for 1L. In a multivariable model, patients who were older, treated in academic settings, HPV(+), or had an ECOG $\geq$ 2 were more likely to get PD-L1 testing before 1L treatment initiation. Compared to CPS<1, CPS $\geq$ 20 and 1 $\leq$ CPS<20 were associated with a higher likelihood of receiving immunotherapy (OR=3.36, 95% CI, 1.69-6.75,  $p$ <0.001; OR=3.11, 95% CI, 1.59-6.14,  $p$ <0.001, respectively). **Conclusions:** As an important part of treatment decision-making, PD-L1 testing by CPS should guide 1L single-agent immunotherapy use, but there are many patients not tested before initiating 1L therapy. Age and fitness, clinical practice setting, and HPV status appear to impact testing patterns. Research Sponsor: Merck & Co., Inc., Rahway, NJ, USA.

Patient characteristics by PD-L1 testing patterns.

	Tested before 1L therapy start (N=564)	Tested after 1L therapy start (N=451)	Never Tested (N=747)
Age, median (range)	65 (29 - 85)	64 (20 - 85)	64 (27 - 85)
Community setting	467 (82.8%)	400 (88.7%)	707 (94.6%)
ECOG PS*			
0-1	404 (71.6%)	363 (80.5%)	567 (75.9%)
$\geq$ 2	101 (17.9%)	47 (10.4%)	99 (13.3%)
CPS*			
<1	78 (13.8%)	62 (13.7%)	—
1-19	162 (28.7%)	147 (32.6%)	—
$\geq$ 20	156 (27.7%)	142 (31.5%)	—

\* Unknown category was omitted from the table.

### Afatinib in patients with recurrent/metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN) harboring alterations in the HER pathway: Results of the B1 cohort of the EORTC-HNCG-1559 trial (UPSTREAM).

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**Background:** Afatinib (A) is an irreversible pan-HER inhibitor that improved PFS in second line RM SCCHN after platinum (LUX-H&N1 trial). In a retrospective biomarker analysis, subgroups of pts with p16 negative, PTEN high or *EGFR* amplification SCCHN seem to benefit the most. Other studies suggest that A has activity in tumors with *HER2* gene activation. **Methods:** The UPSTREAM trial is a biomarker-driven umbrella trial of targeted therapies and immunotherapy for RM SCCHN (post-platinum, ECOG 0-1, measurable disease). The B1 cohort was a phase II, randomized, open-label substudy evaluating the efficacy of afatinib (orally, 40mg/day) vs physician's choice (ctrl) (2:1 ratio) in pts with p16 negative RM SCCHN harboring one of the following biomarkers (fresh biopsy): *EGFR* mutation(mut)/amplification(amp) or *HER2* mut/amp or PTEN high by immunohistochemistry (IHC, H-score > 150). Only *KRAS/HRAS/NRAS* wild type tumors were included. The primary endpoint was progression-free survival rate (PFSR) at 16 weeks after randomization. A 2-stage Simon optimal design was applied to arm A (H1 40%, H0 20%, 1-sided  $\alpha$  10%, power 90%) with 17 and 20 pts enrolled in the first and second stage respectively. Secondary endpoints included ORR, toxicity, PFS, and OS. **Results:** 59 RM SCCHN pts were included in the B1 cohort (A: n = 40, ctrl: n = 19). Out of the 59 patients, *EGFR* amp, *HER2* amp and *HER2* mut were found in 6 pts (10%), 1 pt (2%) and 1 pt (2%), respectively. PTEN (IHC) was high in 97%. 55 pts were evaluable (A: n = 38, ctrl: n = 17) (median age: 62, oral cavity: 29%, oropharynx: 36%, hypopharynx: 24%, larynx: 11%). 69% of pts had received  $\geq$  2 lines of systemic treatment for RM disease. 80% were pretreated with cetuximab. In arm A, 13/38 patients were alive and free of objective progression at 16 weeks (34.2%, 1-sided 90%CI, 23.9 $\pm$ inf), meeting the predefined criteria of success. The PFSR at 16W in ctrl arm was 29.4% (5/17). 4 objective responses were observed in arm A (3 PR and 1 CR) (ORR 11%, 95%CI 2.9-24.8%) and 1 PR in ctrl arm (6%). The median duration of response under A was 5.7 mo (range: 3.7-25.9 mo). All responding patients had previously been treated with cetuximab, were PTEN high but none had *EGFR* or *HER2* alterations. The median PFS and OS were 2.2/2.4 mo and 7.2/5.0 mo in the A/ctrl arms, respectively. Grade  $\geq$ 3 drug-related AEs were reported in 31% in arm A and 12% in ctrl arm. The most frequent drug-related AE with A were diarrhea (67%, G3:8%), rash (41%, G3: 3%), fatigue (31%, no G3) and mucositis (23%, G3: 3%). **Conclusions:** The B1 substudy met its primary endpoint of PFSR at 16 weeks. Responses were seen in cetuximab pre-treated pts. However, the clinical activity of A in this biomarker-selected population remains limited. Translational research is ongoing to better define potential biomarkers. Clinical trial information: NCT03088059. Research Sponsor: Boehringer Ingelheim.

**Phase I/IIa clinical trial of a small molecule EBNA1 inhibitor, VK-2019, in patients with Epstein Barr virus–positive nasopharyngeal cancer with pharmacokinetic and pharmacodynamic correlative studies.**

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**Background:** Epstein-Barr Virus (EBV) is associated with a diverse collection of malignancies, including nasopharyngeal carcinoma (NPC). One viral-encoded protein, EBNA1, is consistently expressed in all known EBV-associated malignancies and is critical for the replication and maintenance of the EBV genome in latently infected cells. VK-2019 is a first-in-class, orally bioavailable EBNA1 inhibitor that blocks latent replication and proliferation in preclinical studies. **Methods:** We conducted a Phase I/IIa clinical trial of VK-2019 as a single therapeutic agent in patients with advanced (recurrent or metastatic) NPC. An accelerated titration design allowed dose escalation to proceed rapidly from 60 mg/day to 1800 mg/day. Blood samples for detailed pharmacokinetic analyses were collected after the first and multiple doses. In addition, tumor biopsies were collected from 2 patients at the 1800 mg/day dose level at baseline and during treatment and analyzed for EBV copy number and viral and cellular gene expression. **Results:** A total of 22 advanced NPC patients were enrolled. VK-2019 was well tolerated with mostly grade 1-3 adverse events being reported. VK-2019 is rapidly absorbed with a biphasic distribution and a terminal  $T_{1/2}$  of ~12h after single or multiple doses.  $C_{max}$  and AUC increases with dose escalation through 920 mg with large variability at 1800mg. Accumulation has been observed with multiple doses up to 460mg. Based on preclinical efficacy models, target exposures are at or above expected activity levels for patients at least on the 920 mg daily dose and above. A partial response (> 30% decrease in tumor size) was observed for one patient. Preliminary results from biopsies from 2 patients show decreases in EBV copy number and viral gene expression (LMP2 and gp150). We also observed decreases in EBER-positive cells in one patient. **Conclusions:** In this study, VK-2019 was well tolerated, exhibiting an excellent safety profile and exposure above in vitro efficacy. An MTD has not been yet established. Preliminary results indicate a decrease in EBV copy number and viral gene expression in latently infected tumor cells in some patients. Alternate dose schedules are justified to determine the clinical efficacy of an EBNA1 inhibitor in patients with advanced NPC. Funded by NCI, R01-CA235633 and Cullinan Oncology. Clinical trial information: NCT04925544. Research Sponsor: U.S. National Institutes of Health; Cullinan Oncology.

**Outcomes by time to adjuvant therapy in 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 randomized study of intermediate risk HPV+ OPC patients who underwent TOS by credentialed surgeons and were then treated by pathology-guided, deintensified post-operative treatment. Recent retrospective population data suggest that time to post-operative radiotherapy (PORT) > 6 weeks is associated with worse progression-free survival (PFS). **Methods:** We retrospectively analyzed demographics, pathologic characteristics, and oncologic outcomes in E3311 by time to initiation of PORT (short vs long, exploring both 6 and 7 weeks postop as the cutpoint). Binary and categorical variables were compared using a chi-square test (or a Fisher's exact test for small sample sizes). Ordinal variables were compared using a Wilcoxon rank sum test. PFS and overall survival (OS) were estimated using the Kaplan-Meier method and compared using a log-rank test, which was stratified by intermediate- (Arms B/C) vs high-risk (Arm D). **Results:** Among 321 evaluable patients, the median time to initiation of PORT was 5.1 weeks (range 0.7-15.7); 5.0 (0.7-15.7) for Arm B, 5.1 (2.4-7.0) for Arm C, 5.6 (3.6-7.9) for Arm D. No significant difference in PFS or OS was observed whether PORT commenced by 6 or 7 weeks postoperatively, compared with longer time to initiation of PORT ( $p = 0.62$  and  $0.65$ ,  $p = 0.30$  and  $p = 0.41$ , respectively). 3-yr PFS rates were 93.5% (95% CI: 89.4%, 96.0%) among those treated  $\leq 6$  weeks, and 91.2% (95% CI: 81.4%, 95.9%) among those treated > 6 weeks; 3-yr OS rates were 96.1% (95% CI: 92.7%, 98.0%) among those treated  $\leq 6$  weeks, and 94.1% (95% CI: 84.9%, 97.8%) among those treated > 6 weeks. No significant differences in outcomes were observed between intermediate risk treatment arms (deintensified (50Gy) or standard dose (60Gy) RT). Additional demographic and pathologic characteristics, including primary site, margin status, histologic grade, stage, and extranodal extension were not significantly different between those with short vs long time to PORT, whether 6 or 7 weeks was used as the cutpoint. There were more T2 tumors in those treated > 7 weeks postop (84% vs. 49%,  $p = 0.007$ ). PS = 1 patients were more numerous among those with shorter time to PORT (10% vs 0%, with the 7 week cutpoint). **Conclusions:** In contrast to retrospective NCDB data, intermediate- and high-risk HPV+ OPC patients enrolled on E3311 had favorable 3-yr PFS and OS rates that were not significantly worse when adjuvant therapy was started > 6 wks or > 7wks. These results argue against a survival advantage for initiation of PORT within 6 or 7 weeks for early-stage HPV+ OPC managed with high-quality transoral resection. The optimal time window to initiate PORT in HPV+ OPC patients remains to be determined. Clinical trial information: NCT01898494. Research Sponsor: U.S. National Institutes of Health.

# Results from two phase II studies of SI-B001, an EGFR×HER3 bispecific antibody, with/without chemotherapy in patients (pts) with recurrent and metastatic head and neck squamous cell carcinoma (HNSCC).

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**Background:** SI-B001 is an EGFR×HER3 bispecific antibody. We present the efficacy and safety results from two ongoing studies of SI-B001, S209 and S206, in recurrent and metastatic HNSCC. **Methods:** S209 included pts with recurrent and metastatic HNSCC progressed on prior anti-PD-1/L1 plus platinum-based chemotherapy (PBC). Pts were treated with SI-B001 16mg/kg IV QW. S206 included pts with recurrent and metastatic HNSCC progressed on prior anti-PD-1/L1 with or without PBC and received no more than two lines of treatment. Pts enrolled in S206 were divided into two groups: Group A, pts without prior exposure to paclitaxel were treated with SI-B001 (12mg/kg IV QW) plus paclitaxel (80mg/m<sup>2</sup> IV QW); Group B, pts with prior exposure to paclitaxel were treated with SI-B001 (12mg/kg IV QW) plus docetaxel (35mg/m<sup>2</sup> IV D1D8D15 Q4W). The study endpoints of the two studies were identical. The primary endpoint was objective response rate (ORR) by investigator per RECIST v1.1. Secondary endpoints were ORR by independent central review, progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), overall Survival (OS), and safety. **Results:** As of Dec 31, 2022, 11 pts in S209 received SI-B001. Pts had a median of 4 prior lines of therapy. In 9 out of 11 pts who have at least 1 post baseline tumor assessment in S209, ORR (n/N) was 22.2% (2/9), mPFS [95%CI] was 2.7 [1.8-7.9] mo. 29 pts in S206 received SI-B001 plus chemotherapy, including 19 pts in Group A and 10 pts in Group B. In 22 pts who had at least 1 post baseline tumor assessment, ORR was 45.5% (10/22), mPFS was 5.1 [3.7-5.6] mo. 1 nasal sinus cancer pt enrolled had stable disease (SD). 14 out of the 18 pts who have at least 1 post baseline tumor assessment in Group A, ORR was 64.3% (9/14) mPFS was 5.6 [5.1-6.3] mo. 8 out of 10 pts who have at least 1 post baseline tumor assessment in Group B, ORR was 12.5% (1/8), mPFS was 1.9 [1.2-3.7] mo. The most common grade 3 and above treatment-related adverse events (TRAEs) in S209 was Hypomagnesaemia (9%). The most common grade 3+ TRAEs in S206 were rash (16%), anaemia (8%) and white blood cell count decreased (8%). No SI-B001 drug-related deaths occurred in either study. **Conclusions:** SI-B001 plus paclitaxel demonstrated potential improvements in ORR and DCR compared with SI-B001 monotherapy in recurrent and metastatic HNSCC. The toxicity of SI-B001 plus chemotherapy in HNSCC is manageable and tolerable. Clinical trial information: NCT05044897; NCT05054439. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

	S209 (n=9)	S206 Group A (n=14)	S206 Group B (n=8)	S206 Total (n=22)
Best overall response, n				
cPR	2	4	0	4
PR	0	5	1	6
SD	5	4	4	8
PD	2	1	3	4
ORR, % (95% CI)	22.2% (2.8-60.0)	64.3% (35.1-87.2)	12.5% (0.3-52.7)	45.5% (24.4-67.8)
DCR, % (95% CI)	77.8% (40.0-97.2)	92.9% (66.1-99.8)	62.5% (24.5-91.5)	81.8% (59.7-94.8)

**Efficacy from the ongoing phase I trial Study 1100 with NBTXR3 activated by radiotherapy in combination with nivolumab or pembrolizumab in patients with locoregionally recurrent or metastatic HNSCC.**

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**Background:** Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment, yet most patients (pts) ultimately develop ICI resistance. Overcoming this resistance is a major clinical challenge. NBTXR3, a novel radioenhancer composed of functionalized hafnium oxide nanoparticles administered by a single intratumoral injection, locally amplifies the RT dose without adding toxicity to surrounding healthy tissue. In preclinical models, NBTXR3/RT has been shown to enhance tumor cell death and tumor antigen release and to effectively expand T-cell repertoire, thus potentially triggering both local and systemic immune responses to help improve ICI treatment. A phase I trial is ongoing to evaluate NBTXR3/RT in combination with anti-PD-1 in pts with advanced cancers. Here we report early outcomes in pts with locoregionally recurrent (LRR) or metastatic (M+) head & neck squamous cell carcinoma (HNSCC). **Methods:** Study 1100 is a phase I dose escalation/expansion trial [NCT03589339] evaluating NBTXR3 activated by stereotactic body radiotherapy (SBRT) followed by anti-PD-1 therapy (nivolumab or pembrolizumab) in 3 cohorts of pts with advanced solid tumors. Pts are either resistant to prior ICI or naïve. Escalation cohorts were defined by site of injection: H&N lesions, lung metastases, or liver metastases. SBRT was delivered as per standard practice. The primary objective of the escalation part was to determine the NBTXR3/RT/anti-PD-1 RP2D for each cohort. Secondary objectives were feasibility, safety, and anti-tumor efficacy (objective responses). **Results:** 16 pts with LRR or M+ HNSCC were treated in the escalation part. 10 pts were resistant to anti-PD-1, 6 were naïve. 8 pts were HPV+, 7 were HPV-, and 1 had HPV status unknown. 13 pts had M+ disease, of which 9 were anti-PD-1 resistant, 4 were naïve. Overall tumor responses were observed in 31.3% (5/16) with mean duration of response (DOR) for these 5 pts of 14.8 (SD  $\pm$  7.64) months, at the time of cut-off (4 pts were still responders). Disease control was observed in 75.0% (12/16). Among M+ pts, overall tumor responses were observed in 23.1% (3/13) with mean DOR for these 3 pts of 12.1 (SD  $\pm$  5.83) months (2 were still responders). Disease control was observed in 69.2% (9/13) pts with M+ disease. 25.0% (4/16) pts experienced disease progression, and all had M+ disease. All patients who progressed did so with the appearance of a new (non-treated) lesion. **Conclusions:** Promising early signs of efficacy were observed in HNSCC pts treated with NBTXR3/RT/anti-PD-1, including responses in pts resistant to anti-PD-1 and with M+ disease. Disease control was observed in M+ pts, highlighting the potential for NBTXR3 in this difficult to treat population. Overall, these results support evaluation of NBTXR3/RT/anti-PD-1 in the ongoing expansion part. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix.

**Platinum/taxane/pembrolizumab vs platinum/5FU/pembrolizumab in patients with recurrent/metastatic (r/m) head and neck squamous cell carcinoma (HNSCC).**

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**Background:** Pembrolizumab +/- chemotherapy is standard of care for patients (pts) with r/m HNSCC. Despite approval of platinum/5FU/pembrolizumab based upon the KN-048 study, a taxane is often substituted for 5FU due to ease of administration and tolerability. No studies have directly compared these approaches. We describe nationwide patterns of taxane vs 5FU chemoimmunotherapy in r/m HNSCC and compare survival and time on treatment between the two. **Methods:** This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database, and included pts treated with frontline pembrolizumab plus platinum-based chemotherapy (either taxane or 5FU) for r/m HNSCC. Demographic, cancer, and clinical outcomes were summarized. Categorical variables were compared using Pearson's chi-square test; continuous variables were compared using T-test. Overall survival (OS) was estimated using Kaplan Meier methodology, and compared using log-rank test. Multivariable Cox regression for overall survival adjusting for age, sex, race, year of diagnosis, ECOG performance status (PS), smoking history, primary tumor site, PD-L1, HPV status, cisplatin use, socioeconomic status, insurance, and practice type was performed, with multiple imputation by chained equations for missing variables. **Results:** Of 444 pts, 321 (72%) received 5FU and 123 (28%) received taxane (108 paclitaxel, 15 docetaxel). Use of cisplatin rather than carboplatin was higher in the 5FU group than the taxane group (16.8% vs 4.9%,  $p=0.001$ ). Taxane use was higher in academic vs community practices (50.7% vs 23.9%,  $p<0.001$ ); within community sites, Northeast states had highest taxane use (27.5%) and Western states had lowest taxane use (16.7%). Pts with Medicare or Medicaid were more likely to receive taxane (35.5%) vs commercial (23.6%) or other (26.7%) insurance. OS did not differ between taxane and 5FU groups (mOS 12.7 vs 13.5 months,  $p=0.743$ ). On multivariable Cox regression, HR for death associated with taxane vs 5FU was 1.01 (95% CI 0.73-1.41). HPV positive status was associated with improved survival (HR 0.58, 95%CI 0.40-0.83). PS $\geq$ 1 (HR 1.38, 95%CI 0.96-1.98) and cisplatin use (HR 1.37, 95%CI 0.95-1.98) showed non-significant trends towards worse survival. Taxane-treated pts received more treatment cycles (mean 11.3 vs 8.8 cycles,  $p=0.015$ ) and were on treatment slightly longer (mean 6.9 vs 6.0 months,  $p=0.289$ ) than 5FU-treated pts. **Conclusions:** In US pts with r/m HNSCC undergoing chemoimmunotherapy, rates of taxane vs 5FU use vary by academic setting, geographic region, and insurance status. There was no difference in survival between 5FU and taxane, and taxane-treated pts received more cycles of therapy. Platinum-taxane appears to be a non-inferior alternative to platinum-5FU with pembrolizumab for r/m HNSCC, and should be allowed in clinical trials. Research Sponsor: None.



# Updated results from a phase 2 study of the oral vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor rivoceranib for recurrent or metastatic (R/M) adenoid cystic carcinoma (ACC).

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**Background:** ACC is a rare tumor that overexpresses VEGF, primarily affecting salivary glands. Often indolent, it can progress, with metastases common in the lungs, liver, and bone. There are no FDA-approved systemic treatments (tx) for R/M ACC. Rivoceranib is an oral tyrosine kinase inhibitor (TKI) that potently and selectively inhibits VEGFR2. **Methods:** In this single-arm, open-label multicenter trial, patients (pts) with R/M ACC with evidence of  $\geq 20\%$  progression by RECIST v1.1 or new lesions within the preceding 6 months (mos) were eligible, with no limit on prior tx. Pts received rivoceranib 700 mg daily until disease progression or withdrawal with pre-planned dose reductions for toxicity. Primary endpoint was overall response rate (ORR) per RECIST v1.1 by investigator (INV) and by Independent Review Committee (IRC). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), and safety exploratory analysis included disease control rate (DCR) and ORR using Choi criteria by IRC. **Results:** As of 11/2022, 80 pts (72 evaluable) were enrolled in the US and Korea (53% male; median age, 54 yrs), and 6 pts remain on tx. Primary tumor sites: major (34%) and minor (59%) salivary glands and other (8%). 74 pts (93%) had metastatic disease. 61.3% had prior systemic tx (18% prior VEGFR TKI). INV and IRC-assessed efficacy data are listed in the table. ORR by Choi was 52.5% (53.1% VEGFR TKI-naïve and 50% VEGFR TKI treated). mOS was 25.3 mos (28.3 mos VEGFR TKI-naïve and 22.6 mos VEGFR treated). Common adverse events (AEs) were hypertension (66%), fatigue (64%), and nausea (54%). Grade  $\geq 3$  AEs that occurred in  $>5\%$  of pts were hypertension (43%), stomatitis (8%), fatigue and anemia (6% each). There were 4 Grade 5 AEs (2 epistaxis [1 related], 1 acute respiratory failure, 1 respiratory failure). **Conclusions:** Updated results with additional 9-month follow-up data continue to demonstrate that Rivoceranib has clinical efficacy and a manageable safety profile in pts with R/M ACC. Clinical trial information: NCT04119453. Research Sponsor: Elevar Therapeutics.

	Total (N=72)		VEGFR TKI-Naïve (n=59)		VEGFR TKI Prior Tx (n=13)	
	INV	IRC	INV	IRC	INV	IRC
ORR* n, (%)	11 (15.3)	7 (9.7)	11 (18.6)	5 (8.5)	0	2 (15.4)
95% CI	7.9-25.7	4.0-19.0	9.7-30.9	2.8-18.7		1.9-45.4
DOR median (mos)	14.9	7.2	13.5	8.3	17.3	6.3
DCR n, (%)	47 (65.3)	48 (66.7)	37 (62.7)	39 (66.1)	10 (76.9)	9 (69.2)
95% CI	53.1-76.1	54.6-77.3	49.1-75.0	52.6-77.9	46.2-95.0	38.6-90.9
mTTP (mos)	9.2	9.3	9.2	10.8	10.6	8.9
mPFS (mos)	9.1	9.2	9.0	9.3	10.6	8.9
6, 12 mo PFS rate (%)	77.4, 38.9	80.8, 38.6	75.8, 39.3	80.3, 40.4	84.6, 37.6	83.1, 31.2
mOS (mos)**		25.3		28.3		22.6

\*all partial responses; \*\* intention to treat population.

**Evaluation of ICI sensitivity for pembrolizumab in combination with anti-platelet therapy for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC).**

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**Background:** This study was proposed to elucidate the impact of combining anti-platelet therapy with an immune checkpoint inhibitor (ICI) in altering the CD8<sup>+</sup> T cell function in patients with head and neck squamous cell carcinoma (HNSCC). With a total enrollment of 15 of out an expected 20 patients, this report characterizes the findings thus far from the ongoing study. **Methods:** This crossover trial consisted of two different treatment regimens for two groups. Regimen A involved treatment with a PD-1 inhibitor pembrolizumab (200 mg iv over 30 min) every 3 weeks in combination of daily aspirin (81 mg orally) and clopidogrel (75 mg orally) for a total of 6 weeks. Regimen B involved pembrolizumab monotherapy (200 mg iv over 30 min) every 3 weeks for two cycles. Thus far, 15 patients with recurrent or metastatic HNSCC were randomized into the two groups, with Group 1 receiving Regimen A followed by Regimen B, while Group 2 received Regimen B followed by Regimen A. In addition to clinical endpoint, in depth analysis of the peripheral blood mononuclear cells (PBMCs) was also implemented using samples obtained prior to treatment, in between regimens, and at the end of treatment. These samples were then analyzed using a spectral flow cytometer panel specific for human CD8<sup>+</sup> T cells. Given the 75 percent accrual, we performed analysis with the obtained clinical samples and data.

**Results:** Of the 15 patients enrolled into the study, 14 remained on study and completed the trial till endpoint. All 14 patients presented with no overtly significant adverse events (AEs). In terms of clinical response, we observed in Group 1 patients (n=7) a total of 1 CR (complete response), 1 PR (partial response), 2 SD (stable disease), and 3 PD (progressive disease), while Group 2 (n=7) presented with 2 PR, 2 SD, and 3 PD. Spectral flow analysis performed on Group 1 patient samples revealed an increase in the Ki67<sup>+</sup>PD1<sup>+</sup> proliferative subset post combination treatment (p value < 0.05, paired Student's t-test). This finding indicates a potential increase in proliferation among CD8<sup>+</sup> T cells after antigen stimulation that may pertain to the combination of anti-PD-1 and anti-platelet therapy. In addition, a higher frequency of Ki67<sup>+</sup>TIGIT<sup>+</sup> CD8<sup>+</sup> population (p value < 0.05, paired Student's t-test) was also observed after combination therapy compared to pre-treatment; however, this level was not sustained after combination therapy was ceased, implying that ongoing anti-platelet therapy may be necessary for augmenting ICI. **Conclusions:** Combination of anti-PD1 and anti-platelet therapy demonstrates potential for remodeling the immune compartment pertaining to CD8<sup>+</sup> T cells without resulting in overt toxicity. Further analysis of the effects of this combination regimen will be essential to better characterize tumor specific impact. Clinical trial information: NCT03245489. Research Sponsor: U.S. National Institutes of Health.

**Evaluation of small extracellular vesicles as biomarkers of efficacy with anti-PD-1 mAb therapy in patients with recurrent/metastatic HNSCC.**

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**Background:** The development of biomarkers that reliably predict response to anti-PD-1 mAb therapy (IO) is a critical need. Small (30-150 nm) extracellular vesicles (sEV), aka exosomes, are “molecular mimics” of their parent cells. In cancer, plasma sEV are mixtures of tumor-derived exosomes (TEX) and vesicles produced by non-malignant cells. We conducted a retrospective study of R/M HNSCC patients treated with IO to evaluate sEV as predictive biomarkers. **Methods:** We evaluated sEV in plasma of R/M HNSCC patients (n = 24) obtained just prior to initiation of IO. Precleared ultrafiltered plasma was used to isolate total plasma sEV by size exclusion chromatography. Total plasma sEV were separated into two subsets, T cell-derived CD3(+) sEV and TEX-enriched CD3(-) sEV by immunocapture with anti-CD3 mAb. On-bead flow cytometry was used to estimate relative levels of proteins carried on the sEV surface. Specifically, the CD3(-) fraction was evaluated for stimulatory (stim; CD40, CD40L, OX40, OX40L, CD80) and suppressive (supp; TGF $\beta$ , CTLA4, FasL, PD-L1, PD-1) proteins. Differences between responders (CR/PR/SD) and non-responders (PD) were assessed using Wilcoxon-Mann-Whitney test. Multivariate Cox proportional hazards regression was used to evaluate the relationship between the pre-treatment sEV characteristics and outcome. **Results:** Mean age was 62, 46% had oropharynx (82% HPV+), 17% oral cavity and 29% had larynx/hypopharynx primary. Treatment indication for IO was 46% platinum failure, remainder first line. Best response: 17% PR, 29% SD, and 54% PD. Median PFS and OS were 5.3 and 16.2 months, respectively. Total sEV protein level was not associated with efficacy. Total CD3(+) sEV level was low overall and did not correlate with lymphocyte count or neutrophil/lymphocyte ratio. High CD3(+) sEV level was associated with better OS [HR: 0.16 (95% CI 0.04-0.59), P = 0.007] and PFS [HR: 0.16 (95% CI 0.04-0.58), P = 0.005] but not response. While total TEX and levels of individual stim and supp proteins carried by TEX were not predictive of response, an increased supp/stim ratio was (P = 0.02). Importantly, high TEX supp score and stim score were both associated with better OS [HR: 0.19 (95% CI 0.05-0.77), P = 0.02, and HR: 0.26 (95% CI 0.07-0.95), P = 0.04, resp.]. High PD-L1, but not PD-1 on TEX, was associated with better OS [HR: 0.15 (95% CI 0.04-0.56), P = 0.005]; and PFS: HR: 0.33 (95% CI 0.11-0.94), P = 0.04]. **Conclusions:** Evaluation of two sEV subsets, T cell-derived-CD3(+) sEV and TEX-enriched CD3(-) sEV, indicated their potential utility as predictive biomarkers with IO. High T cell-derived sEV, TEX supp/stim ratio, and TEX PD-L1 expression levels were independently associated with significantly increased efficacy with IO. Our study uniquely analyzed the predictive value of plasma sEV subsets in IO treated R/M HNSCC patients, and evaluation in a larger cohort is warranted. Research Sponsor: U.S. National Institutes of Health.

# 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 with cisplatin (CP) chemotherapy is common. DB-020 is a formulation of thiosulfate for intratympanic (IT) injection being developed to reduce CP ototoxicity. The primary objective of this Phase 1 study was to evaluate the safety and tolerability of repeated IT injections of DB-020. A secondary objective was to compare hearing changes with DB-020 vs. placebo. **Methods:** Subjects scheduled for at least 3 cycles of CP and cumulative exposure of  $\geq 280$  mg/m<sup>2</sup> were randomized to blinded, bilateral, IT injection with DB-020 (12% or 25%) in one ear and placebo in the other, once every 3 or 4 weeks, up to 3 hours before receiving CP. Subjects with moderate or severe hearing loss at baseline were excluded. Ototoxicity was defined by American Speech-Language-Hearing criteria:  $\geq 20$  dB threshold increase at any one test frequency, or  $\geq 10$  dB threshold increase in any two adjacent frequencies, or loss of response at three consecutive frequencies where responses were previously obtained. Severe ototoxicity was  $\geq 20$  dB threshold increase in any two adjacent frequencies. A pre-specified interim analysis 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). **Results:** Nineteen subjects were randomized, with mean age of 57 years (84% male and 100% white) and mean cumulative CP dose 248 mg/m<sup>2</sup>. Most (95%) had head and neck cancers (5% had lung cancer). Seventeen subjects had both baseline and follow-up audiometry, and 16/17 had baseline audiograms within 5 dB of the median threshold for age-matched controls. Free CP systemic levels were similar to reference values. Ear pain (15/19 subjects, 78.9%) and tinnitus (8/19 subjects, 42.1%) were common. Ear pain was more common in DB-020 treated ears, and tinnitus was more common in placebo treated ears. There were no tympanic perforations, no serious adverse events in the category of ear and labyrinth disorders, and no deaths. Ototoxicity was significantly more common and more severe in placebo treated ears (Table). As the overall study objectives were met at this interim analysis, no further enrollment was pursued. **Conclusions:** In this initial clinical trial experience there was no significant safety signal, and DB-020 IT injections showed a meaningful reduction in cisplatin ototoxicity. These results warrant further clinical development. Clinical trial information: NCT04262336. Research Sponsor: Decibel Therapeutics.

Assessment	Placebo ears (n=17)	DB-020 ears (n=17)	p-value vs. placebo
Ototoxicity (250 to 8000 Hz)	88.2%	41.2%	0.0047
Ototoxicity (9000 to 16000 Hz)	88.2%	52.9%	0.0143
Severe ototoxicity (250 to 8000 Hz)	64.7%	11.8%	0.0027
Severe ototoxicity (9000 to 16000 Hz)	76.5%	29.4%	0.0047
Acoustic threshold shift (LS mean dB), 250 to 8000 Hz	15.27	4.35	0.001
Acoustic threshold shift (LS mean dB), 9000 to 16000 Hz	18.23	8.45	0.010

# Abemaciclib in recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC) harboring *CDKN2A* loss, and/or *CCND1* and/or *CDK6* amplification: A phase II multicenter trial.

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**Background:** More than half of HPV negative HSNCC harbor genomic aberrations (i.e. *CDKN2A* loss, cyclin D amplification (ampl.)) that activate the cyclin-dependent kinase 4 and 6 (CDK4/6) – retinoblastoma protein (Rb) signalling pathway. Hyperactivated CDK4/6-Rb pathway leads to acceleration of G1/S transition of cell cycle and ultimately to uncontrolled cellular proliferation. We hypothesized that abemaciclib, a CDK4/6 inhibitor, could be a potent targeted strategy by inhibiting this commonly dysregulated pathway in HNSCC. **Methods:** This single arm, multicentre Phase II evaluated the efficacy of abemaciclib (200mg/d orally BID) in molecularly-selected, HPV negative (HPV<sup>-</sup>), RM-HNSCC patients (pts) progressing after at least 1 prior line of platinum and cetuximab. A molecular screening step through centralised CGH-assay was required before treatment start: only pt with tumor harboring *CDKN2A* loss and/or *CCND1* and/or *CDK6* ampl. without homozygous deletion of *RB1* were eligible to the therapeutic step. The primary endpoint was 8-week non-progression rate (PFR<sub>8w</sub>) as per central imaging review according to RECIST V.1.1. Secondary endpoints included best overall response rate (BORR), progression free survival (PFS), overall survival (OS) and adverse event (AE) according to NCI-CTCAE V5.0. The study used a Fleming A'Hern design with an inefficacy bound of 15% and a target PFR<sub>8w</sub> of 40% ( $\alpha = 5\%$  one sided,  $1-\beta = 90\%$ ). **Results:** Twenty-six HPV<sup>-</sup> RM-HNSCC pts (M: 23, F: 3, median age: 59 [range, 42-78], heavily pre-treated [84.6%  $\geq$  2 prior lines]) received at least one dose of abemaciclib. According to central CGH-assay, molecular alterations were *CDKN2A* loss + *CCND1* ampl. + *CDK6* ampl. (n = 1), *CDKN2A* loss + *CCND1* ampl. (n = 10), *CDKN2A* loss (n = 6) or *CCND1* ampl. (n = 9), all with intact Rb. Among the 24 evaluable pts, 7 pts were progression-free at 8 weeks (PFR<sub>8w</sub>: 29.2% (95% CI 14.6-)). BORR according to central imaging review was stable disease for 7 pts (31.8%) and progressive disease for 11 pts (50%); no objective response was observed. Median PFS and OS were 7.1 weeks (95% CI: 6.9-10.4) and 4.8 months (95% CI: 2.4-7.3), respectively. Most common related AEs ( $\geq 20\%$  of pts, all grade) were diarrhea/nausea/vomiting, fatigue and hematological toxicity (anemia, lymphocyte and neutrophil count decreased). Two fatal serious AE potentially related to abemaciclib according to both investigator and sponsor were reported: a case of pulmonary hemorrhage also possibly related to abemaciclib-induced tumor necrosis and a case of myocardial infarction. **Conclusions:** Abemaciclib had limited antitumor activity in RM-HNSCC harboring molecular alteration in CDK4/6 pathway. Clinical trial information: NCT03356223. Research Sponsor: Lilly.

**Personalized therapy for head and neck squamous carcinoma (HNSCC) utilizing tissue proteomics profiling.**

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**Background:** Chemotherapy is widely used in the treatment of HNSCC, yet no biomarkers for chemotherapy is used for selection of the chemo agent in the treatment of HNSCC. We examined 143 HNSCC cancer using targeted proteomics for the protein expression levels of several chemo agents. These include markers of resistance to platinum agents (ERCC1), anti-tubulin inhibitors (TUBB3) and sensitivity markers for topoisomerase inhibitors (Topo1 – irinotecan, topotecan; Topo2A – doxorubicin, etoposide). We also measured markers for several antibody-drug conjugates (EGFR, Her2, Trop2, FR-alpha, Mesothelin). **Methods:** Tumor areas from Formalin-fixed, paraffin-embedded (FFPE) tumor tissues from clinical samples of HNSCC that were received at our CLIA certified laboratory were microdissected and a selected reaction monitoring mass spectrometry (SRM-MS) quantitative proteomic analysis of 72 protein biomarkers were conducted concurrently from 2-3 sections of FFPE tissue. **Results:** Platinum agents are widely agent in HNSCC cancer. ERCC1, a resistance marker for platinum agents was expressed in 44% of HNSCC. Similarly, TUBB3, a resistance marker for Paclitaxel, docetaxel was also expressed in ~45% of HNSCC. These indicate that ~45% of HNSCC could potentially be refractory to platinum and paclitaxel-based therapy. Additionally, ALDH1A1, a marker for resistance of cyclophosphamide, was expressed in 78% of HNSCC. Temozolomide, an alkylating agent used in other cancer type could be beneficial in 14% of HNSCC because of the lack of resistance marker MGMT. On the other hand, 88% of HNSCC expressed Topo1, which is a sensitivity marker for irinotecan or topotecan based therapy. Additionally, Top1 is also the target for the payload of several ADCs (e.g. trastuzumab deruxtecan and sacituzumab govitecan). Similarly, 55% of HNSCC expressed Topo2A, a target for etoposide and doxorubicin. Additionally, 57% of HNSCC expressed hENT1, a transporter of gemcitabine. HNSCC also expressed various targets for targeted and ADC agents. These include EGFR (86% detected with 37x range of distribution), Her3 (11%), IGF1R (16%), MET (13%), Folate receptor- alpha (18%), Mesothelin (13%), and Trop2 (89% with 134x range of distribution). Her2 was overexpressed ( $> 750$  amol/ug) in 11% of HNSCC, however, it was observed in 46% of HNSCC with a 53x range (276 – 14705 amol/ug), indicating that a significant population of HNSCC might be eligible for low Her2 clinical trials. **Conclusions:** Every cancer is unique, and the ability to analyze 72 protein biomarkers from 2-3 FFPE sections simultaneously at the same time provides a wealth of actionable information for clinical treatment or patient stratification for clinical trials. Research Sponsor: mProbe.

# Phase II study evaluating the efficacy of niraparib and dostarlimab (TSR-042) in recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) patients.

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**Background:** Patients with recurrent and/or metastatic (R/M) HNSCC have poor overall survival. Immune checkpoint inhibitors (ICIs), specifically programmed death-1 (PD-1) inhibitors, result in durable responses in R/M HNSCC but <20% benefit. Tumor mutational burden (TMB) correlates with ICI response. DNA pathway repair mutations have been reported in 17% of sporadic HNSCC and are associated with higher rates of TMB. Poly (ADP-ribose) polymerase (PARP) inhibition has demonstrated efficacy as a single agent in cancers with a DNA repair defect. We tested the combination of PARP inhibitor (niraparib) with the PD-1 inhibitor (dostarlimab) in R/M HNSCC patients (NCT04313504) with funding support from Tesaro/GSK. **Methods:** Patients with R/M HNSCC who failed at least one line of prior treatment including a PD-1 inhibitor and for whom no surgical or radiation curative options existed were eligible for the study. Patients received niraparib (200 mg daily) beginning one week prior to initiation of dostarlimab (500 mg q3wks x4 followed by 1000 mg q6wks). The primary endpoint was overall response rate (ORR) including complete response (CR), partial response (PR) and stable disease (SD) using RECIST v1.1. Fourteen patients were planned for the first stage and 10 additional patients for the second stage if  $\geq 8$  patients had a confirmed response. Safety was evaluated by CTCAE v5.0. Tumor PD-L1 immunohistochemistry was performed with 22c3 antibody and reported as combined positive score (CPS). TMB was considered high if  $\geq 10$  Mut/Mb. **Results:** Ten of 24 planned patients were enrolled. Of the first 10 patients, 8 patients were evaluable by imaging and 1 patient clinically progressed on exam. Of the 9 evaluable patients, there were 0 CR, 1 PR, 1 SD, and 7 with progressive disease (PD). The trial was ended early for futility as it was not possible for at least 8 out of 14 patients to develop response. The patient with a PR remains on treatment past 24 months, was PD-L1 positive, had low TMB and no DDR deficiency. All patients had previously failed a PD-1 inhibitor. One patient had high TMB, 2 patients had a DDR, and 6 patients were PDL1 positive but 2 patients had insufficient tissue or indeterminate results for sequencing. Grade  $\geq 3$  adverse events occurred in 70% of patients with most common being hypertension (20%), hyponatremia (20%), and lung infection (20%). **Conclusions:** PARP-1 inhibition and PD-1 inhibition combined does not appear to enhance response over PD-1 inhibitor alone in R/M HNSCC who had previously failed PD-1 inhibitor treatment. However, a more focused population including those with DNA damage response (DDR) mutations and PD-1 treatment naïve may benefit. Clinical trial information: NCT04313504. Research Sponsor: GSK provided funding for this trial; Tesaro.

## Molecular breakdown of biomarkers using NGS.

Biomarker	n (%)
<b>TMB</b>	Total n=8
Low (0-9 mut/Mb)	7 (87.5)
High ( $\geq 10$ mut/Mb)	1 (12.5)
<b>PD-L1 CPS</b>	Total n=8
0	2 (25)
$\geq 1$ to 20	5 (62.5)
$\geq 20$	1 (12.5)
<b>DDR</b>	Total n=8
Yes	2 (25)
No	6 (75)

# TCR-T cells armored with immune checkpoint blockade in EBV-positive nasopharyngeal carcinoma: The first-in-human phase 1/2 trial.

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**Background:** Nasopharyngeal carcinoma (NPC) refraction and metastasis is common, but therapeutics are limited. As adoptive immunotherapy has emerged as effective against other cancers, engineered T cells bearing a transgenic Epstein-Barr virus (EBV)-specific TCR (TCR-T) represent a viable approach to treat EBV-associated NPC. Given PD-1/PD-L1 induced T cell hypofunction, we herein report preliminary findings of a phase I trial of EBV-targeting TCR-T cells armored with secreted PD-1 blockade for patients who failed in two or more lines of standard therapies. **Methods:** Patients with advanced NPCs were consented and screened for EBV serotype and HLA haplotype. EBV+/HLA-A\*02+ patients were enrolled in a rapid titration setting to escalate the single infusion dose from  $5 \times 10^6$  to  $1.0 \times 10^7$  and  $5.0 \times 10^7$  /kg TCR-T cells. After safety evaluation, the  $5.0 \times 10^7$  /kg cohort was expanded for further investigation of combining with IL-2 administration. Fludarabine/cyclophosphamide were administered prior to TCR-T cell transfer as pre-conditioning. Patient monitoring and peripheral blood analysis occurred weekly over the first month and then monthly until disease progression or patient withdrawal. The primary objective was to determine safety and a recommended phase 2 dose (RP2D), while the secondary objective was investigator assessed ORR (RECIST v1.1). **Results:** One patient per TCR-T dose was treated, and, as no dose-limiting toxicity (DLT) has been observed, dose level 3 ( $5.0 \times 10^7$  /kg) was expanded with IL-2 administration upon TCR-T cell infusion. As of January 2023, six patients have been treated. One patient (16.7%) exhibited grade 1 CRS (n=6). No grade 4 treatment-related adverse events (TRAEs) have been observed, with leukopenia and fever being the most common AEs. Two patients (33.3%) were assessed as partial response (PR), with one reaching a response duration of 9 months to date. Three patients (50%) were assessed as stable disease (SD). For all patients, pharmacokinetic analysis revealed that levels of TCR-T cells in peripheral blood peak between 3- and 14-days post-infusion, with a maximum duration of 180 days. **Conclusions:** EBV-targeting TCR-T cells armored with PD-1 blockade are well tolerated. Initial results from this ongoing study indicate that EBV proteins may be safe and effective TCR-T targets to achieve superior outcomes in advanced EBV-positive NPC patients. Clinical trial information: NCT04139057. Research Sponsor: Guangdong TCRcure Biopharma Technology Co., Ltd, Guangzhou, China.

Clinical adverse events and efficacy ( $5.0 \times 10^7$ /kg TCR-T cells, n=6).					
Treatment-Related Adverse Events (TRAEs)				Efficacy	
	All grades	Grade 3	Grade 4		
Leukopenia	6 (100%)	2 (33.3%)	0	Complete response (CR)	0 (0)
Fever	5 (83.3%)	2 (33.3%)	0	Partial response (PR)	2 (33.3%)
Chills	3 (50%)	0	0	Stable disease (SD)	3 (50%)
Anemia	4 (66.7%)	0	0	Progressive disease (PD)	1 (16.7%)
Vomiting	2 (33.3%)	0	0	Disease control rate (DCR)	6 (100%)
Hypoalbuminemia	3 (50%)	0	0		
Hypokalemia	1 (16.7%)	0	0		
Hyponatremia	2 (33.3%)	0	0		



**A phase II study of lenvatinib plus pembrolizumab in patients with progressive, recurrent/metastatic adenoid cystic carcinoma.**

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**Background:** Recurrent/metastatic adenoid cystic carcinoma (R/M ACC) is a rare salivary gland cancer (SGC) without standard treatments. The multitargeted, antiangiogenic kinase inhibitor lenvatinib (len) has activity in R/M ACC, but immune checkpoint inhibitor (ICI) therapies lack efficacy. Hypothesizing that VEGFR inhibition can enhance ICI-induced responses, we conducted a phase II trial evaluating len plus the programmed death-1 (PD-1) inhibitor pembrolizumab (pem) in two R/M SGC cohorts: ACC and non-ACC. Here we report results from the completed ACC cohort. **Methods:** Patients (Pts) with R/M ACC were enrolled. RECIST v1.1 measurable disease and evidence of progression on imaging performed within 6 months of enrollment were required; any number of prior therapies was allowed. Pts were treated with len 20 mg orally daily and pem 200 mg intravenously every 3 weeks (21-day cycles). The primary objective was to evaluate best overall response rate (ORR), seeking an ORR improvement with len+pem from 15% (previously reported with len alone) to 35%. In the first stage, > 3 confirmed complete and partial responses (cCRs+ cPRs) were required among 17 pts to continue to the second stage; > 8 responses among 32 total pts would have been considered positive (1-sided alpha 0.1, power 0.9). Secondary objectives included evaluating progression-free survival (PFS) and safety/tolerability per CTCAE v5.0 criteria. **Results:** 17 R/M ACC pts were enrolled and evaluable for the primary objective. One pt had a cPR for an ORR of 6%, failing to meet the rule for progression to the second stage. Thirteen (76%) pts had stable disease and 2 (12%) progression of disease as best response; 1 pt did not have response assessed. Thirteen (76%) pts experienced some degree of regression in RECIST target lesions (TLs; -1.9% to -42.8%), including 5 (29%) with > -20% regression. Eleven (65%) pts were progression-free for > 24 weeks. Twelve (71%) pts experienced at least one > Grade 3 adverse event related to study treatment. Sixteen pts had at least one treatment interruption or len dose reduction; 2 pts received only 1 cycle of therapy. Five pts were treated beyond first progression without observation of subsequent response. Quality of life data and correlative tissue studies are ongoing. **Conclusions:** The trial failed to demonstrate that len+pem produces a greater ORR in patients with R/M ACC than what was previously reported with len alone. Further investigation into the biology mediating ICI-resistance and development of novel approaches to augment the efficacy of immune-based therapies in ACC are needed. (Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA provided lenvatinib and pembrolizumab for the study.) Clinical trial information: NCT04209660. Research Sponsor: Merck Sharp & Dohme Corp and Eisai.

**Low-dose fractionated radiotherapy combined with neoadjuvant chemotherapy for T3-4 nasopharyngeal carcinoma patients: Preliminary results of a phase II randomized controlled trial.**

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**Background:** Over 70% of NPC patients were local advanced NPC (LANPC). The 5-year local recurrence-free survival rate is only 70% in T3-4 patients. Neoadjuvant chemotherapy (NACT) followed with concurrent chemoradiotherapy (CCRT) was recommended for LANPC patients. Low-dose fractionated radiotherapy (LDFRT), which is  $< 100\text{cGy}$ , induces enhanced cell killing by the hyper-radiation sensitivity phenomenon and potentiates effects of chemotherapy. The synergy of LDFRT and NACT has not been used in the clinical practice and few studies focused on it. A single arm study found the ORR of primary site was improved to 90% for head and neck squamous carcinoma patients treated with LDFRT and NACT. Our previous study found the ORR of lymph nodes was higher in LDFRT group for high-risk LANPC patients. However, another study showed there was no significant difference between LDFRT and control group for LANPC patients. So, we aimed to investigate the potential efficacy of this novel neoadjuvant therapy for T3-4 NPC patients. **Methods:** 60 pathological confirmed T3-4 (UICC/AJCC8<sup>th</sup>) NPC patients were prospectively enrolled in our study. They were randomly assigned to two groups. For the LDFRT group, the patients received 3 cycles of NACT (docetaxel  $75\text{mg}/\text{m}^2$  D1, cisplatin  $80\text{mg}/\text{m}^2$  D1) with LDFRT, and followed with CCRT. LDFRT was delivered as  $50\text{cGy}$  per fraction twice a day to primary site on D1,2 for each cycle of NACT. The patients in the control group only received NACT and followed with CCRT. All the patients underwent IGRT. RECIST criteria and CTCAE 5.0 was used to evaluate the ORR and toxicity at post-NACT and the completion of CCRT. **Results:** from Feb 2022 to Dec 2022, 60 T3-4 NPC patients were included, and 30 patients for each group. For the primary site, the median volume reduction rate and the ORR after NACT was significantly improved in LDFRT group (69.27% vs 40.10%,  $p < 0.001$ ; 93.33% vs 73.33%,  $p = 0.038$ ). For the median volume reduction rate of primary site and lymph node, it was also obviously improved in LDFRT group (86.59% vs 55.43%,  $p < 0.001$ ). Though there was a tendency of ORR improvement in LDFRT group, but no significant difference (96.67% vs 83.33%,  $p = 0.195$ ). After the completion of CCRT, the median volume reduction rate of primary site had an increased tendency in LDFRT group (96.16% vs 88.3%,  $p = 0.065$ ), but the ORR had no statistical significance (LDFRT group: CR 45.8%, PR 54.2%; control group: CR 37.5%, PR 62.5%). For the toxicity, the incidence of grade 3-4 adverse events had no difference between two groups ( $p = 0.786$ ). No grade 5 adverse events occurred. **Conclusions:** LDFRT combined with NACT could obviously improve the median volume reduction rate and ORR of primary tumor for T3-4 NPC patients, and the toxicity was similar and tolerable. The novel treatment could be a promising strategy to improve treatment response, and needed to be confirmed further. Clinical trial information: NCT05503914. Research Sponsor: 2022YFS0047.

### Phase I/II trial of durvalumab plus tremelimumab and stereotactic body radiotherapy for metastatic head and neck carcinoma: Final results.

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**Background:** Anti-PD-1/PD-L1 is now part of first line therapy in metastatic head and neck squamous cell carcinoma (HNSCC). Stereotactic radiotherapy (SBRT) to metastatic lesions can reduce tumor burden and could be immune-stimulatory. The combination of SBRT with dual-checkpoint blockade with Durvalumab (D, anti-PD-L1) and Tremelimumab (T, anti-CTLA-4) has not previously been tested in HNSCC. We report on the safety and efficacy of this triple treatment combination (TTC) consisting of SBRT sandwiched between cycles of D and T in oligometastatic HNSCC. **Methods:** This is a phase I/II single arm multi-institutional study powered for 35 patients with oligometastatic HNSCC (2-10 lesions) (NCT03283605). D (1500 mg) and T (75 mg) were given for 4 monthly cycles, followed by monthly D for 8 monthly cycles. SBRT to 2-5 lesions was administered during cycle 2. The safety of the TTC was the primary endpoint of the phase I and was evaluated through assessment of Grade 3-5 TTC-related adverse events (AE), based on CTCAE (v 4.03). The primary endpoint of the phase II portion was 6-month progression free survival (PFS), with a predetermined 6-month PFS (6moPFS) rate greater than 27% considered as a positive signal to conduct further research on this combination. **Results:** A total of 33 evaluable patients were recruited (study accrual was interrupted by the COVID pandemic). The table describes patients' characteristics. Patients had received 1, 2 and 3 prior systemic therapy lines in 48%, 21% and 9% of the cases, including 6 (18%) patients who had received prior anti-PD-1/L1 or anti-CTLA-4 therapies. The median prescribed and maximum SBRT doses were 45 Gy (range: 18-50) and 52.3 Gy (range: 28.1-69) in 3-5 fractions, respectively. Fourteen patients (42%) had Grade  $\geq$  3 AE attributable to D and T. Only 1 patient developed Grade  $\geq$  3 AE attributable to SBRT. This patient, who had mucosal radionecrosis after re-irradiation and refused surgical debridement and flap reconstruction, specifically developed 2 Grade 3, 1 Grade 4 and 1 Grade 5 AE. Our primary efficacy endpoint, 6moPFS, was 69.7% (95% CI: 55.6-87.3). Median PFS was 11.9 months (6.94-14.5) and median OS was 25.1 months (17.9-28.4). Rates of complete response, partial response, stable disease and progressive disease were 9%, 21%, 33% and 12%, respectively, with 8 (24%) patients with no evaluable non-SBRT treated lesion. **Conclusions:** The addition of SBRT to dual-checkpoint inhibition led to 1 (3%) additional patient developing severe AE. Best response rates were encouraging. Our primary efficacy outcome, 6mo PFS was attained and was higher than what was expected in this patient population. Clinical trial information: NCT03283605. Research Sponsor: Astra Zeneca.

Covariate.	n=33	
Gender (N, %)	Female : Male	5 (15%) : 28 (85%)
Age	Median (Min, Max)	63 (42, 84)
Rx lines prior to entering trial (N, %)	0	7 (21%)
	1	16 (48%)
	2	7 (21%)
	3	3 (9%)
Total number of lesions	Median (Min, Max)	4 (2,8)
SBRT treated lesions (N, %)	1	1
	2	21 (63%)
	3	7 (21%)
	4	2 (6%)
	5	1

**Safety and efficacy of time restricted eating (TRE) in improving response to immunotherapy in patients with head and neck cancer (HNSCC).**

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**Background:** Advanced head and neck cancer continues to have very poor prognosis. Only a fraction of patients respond to immune checkpoint blocker therapy (ICB), with no effective treatment options for non-responders. Gut microbiome composition and diversity have been associated with response to ICB in many cancers including HNSCC. We, therefore hypothesized that modulation of gut microbiota may improve response to ICB. Time restricted eating represents an attractive strategy to favorably alter the microbiome and improve ICB responses. We conducted a phase I/II nonrandomized study to evaluate safety, feasibility and efficacy of TRE in improving response rates in treatment naïve metastatic HNSCC patients receiving single agent ICB. **Methods:** TRE is a form of circadian aligned nightly fast of 14 hours without reduction in calories. Patients were assigned to TRE vs control in 1:2 ratio, with first response evaluation at 12+/- 3 weeks as end point. Compliance to TRE was monitored via an app ("my circadian app") and daily food logs. Blood and stool samples were collected at therapy initiation, at 1<sup>st</sup> response assessment and at 6 months. We evaluated stool metagenomics, untargeted stool/plasma metabolomics and serum cytokines as correlatives. We focused on microbial metabolites including indoles and short chain fatty acids (SCFA), which are potent aryl hydrocarbon receptor agonist and immunosuppressive. We also evaluated serum cytokines associated with insulin signaling pathways. **Results:** A total of 43 HNSCC patients receiving single agent pembrolizumab were accrued, 15 in the TRE arm and 28 in control arm. TRE was well tolerated without any study dropouts, weight loss or any adverse events attributable to the intervention. TRE was associated with significant improvement in disease control rate (DCR) at 3 months and at 6 months (3 month DCR 85% in TRE vs 50% in the control arm,  $p < 0.0001$ , 6 month DCR 64% in TRE vs 39% in control arm,  $p = 0.0004$ ). Responders in both TRE and control arm had lower relative abundance of microbial immunosuppressive indole metabolites, butyric acid (NR vs R: 0.67 vs 0.58,  $p = 0.05$ ) and IGF1 (NR vs R: 0.42 vs 0.39,  $p = 0.02$ ). TRE led to a similar change in microbial metabolites including decrease in abundance of 5 Hydroxyindole acetic acid, Indole 3 acetic acid (IAA), Indole Carboxaldehyde, Indole acrylic acid, butyric acid (control vs TRE: 0.68 vs 0.58,  $p = 0.03$ ) and IGF1 (control vs TRE: 0.4 vs 0.3,  $p = 0.03$ .) **Conclusions:** We report a novel phase I/II study of TRE in HNSCC patients and demonstrate excellent safety, feasibility and marked improvement in efficacy of ICB. The effect of TRE may be mediated via changes in microbial metabolome and insulin signaling pathways. TRE represents an attractive and safe strategy to improve treatment responses to ICB and needs to be explored in phase III expansion studies. Humaira Sarfraz, MD, and Shahla Bari, MD, both 1st authors/equal contributors. Clinical trial information: NCT05083416. Research Sponsor: ACSIRG; Moffitt Advent Health Collaborative Award.

**Association of pretreatment lymphocyte-monocyte ratio with survival outcome in patients with head and neck cancer treated with chemoradiation.**

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**Background:** Lymphocyte-monocyte ratio (LMR) from peripheral blood has been suggested as a biomarker to assess the extent of inflammation in several solid malignancies. However, the role of LMR as a prognostic factor in head and neck cancer (HNC) was unclear in several meta-analyses, and there is a paucity of literature including patients in North America. We performed an observational cohort study to evaluate the association of pre-radiation LMR with survival outcomes in North American patients with HNC. **Methods:** A single-institution database was queried for patients with non-metastatic HNC who underwent curative-intent definitive chemoradiation from 6/2007 to 4/2021 at the Roswell Park Comprehensive Cancer Center. Patients were excluded if they underwent induction chemotherapy or postoperative radiation. Primary endpoints were overall survival (OS) and cancer-specific survival (CSS). The association of LMR with OS and CSS was examined using nonlinear Cox proportional hazard model using restricted cubic splines (RCS), Cox multivariable analysis (MVA), and Kaplan-Meier method. LMR was stratified into high and low based on its median. Logistic MVA was performed to identify variables associated with low LMR. Propensity scored matching was used to reduce selection bias. Subgroup analyses were performed among those with available human papillomavirus (HPV) status. **Results:** A total of 476 patients (391 male [82.1%], median [interquartile range] age, 61 [55-67] years) met our criteria. Median follow up was 45.3 months (interquartile range 22.8-74.0). The nonlinear Cox regression model using RCS showed that low LMR was associated with worse OS and CSS in a continuous fashion without plateau and crossed the hazard ratio of 1 at LMR 3.4 for both OS and CSS. On Cox MVA, higher LMR as a continuous variable was associated with improved OS (adjusted hazard ratio [aHR] 0.90, 95% confidence interval [CI] 0.82-1.00,  $p = 0.04$ ) and CSS (aHR 0.81, 95% CI 0.70-0.94,  $p = 0.005$ ). The median value of LMR was 3.8. On logistic MVA, patients with other racial background (adjusted odds ratio [aOR] 0.85, 95% CI 0.74-0.97,  $p = 0.02$ ) and positive HPV status (aOR 0.82, 95% CI 0.72-0.94,  $p = 0.005$ ) were less likely to have low LMR. Higher T staging was associated with low LMR (aOR 1.15, 95% CI 1.04-1.27,  $p = 0.005$ ). A total of 186 pairs were matched with well balanced baseline characteristics. LMR lower than 3.8 remained associated with worse OS (HR 1.60, 95% CI 1.13-2.28,  $p = 0.009$ ) and CSS (HR 1.69, 95% CI 1.07-2.67,  $p = 0.03$ ). In the subgroup of 319 patients (67.0%) with available HPV data, LMR status was not associated with both OS and CSS regardless of HPV status. **Conclusions:** Low LMR was associated with worse OS and CSS. Low LMR was also associated with higher T staging, negative HPV status, and White race. Further studies are warranted to evaluate the role of such prognostic marker to tailor interventions. Research Sponsor: None.

# **Evaluation of tumor mutation burden (TMB) in tumor (tDNA) and plasma cell free DNA (cfDNA) in patients (pts) with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with a combination of cetuximab and nivolumab (C+N).**

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**Background:** High TMB is associated with immune checkpoint inhibitor (ICI) response in many solid tumors. However, obtaining sufficient tumor specimens for testing in a routine clinical setting could be a challenge. We evaluated TMB from whole-exome sequencing (WES) of cfDNA as a surrogate for tDNA TMB in R/M HNSCC pts treated with C+N. **Methods:** Archived formalin fixed paraffin embedded tumors, serially collected plasma (pre-treatment, on-treatment, and time of disease progression/end of treatment), peripheral mononuclear blood cells, and clinical data were obtained from R/M HNSCC pts treated with C+N from a completed clinical trial (NCT03370276). Nucleic acids were extracted using AllPrep DNA/RNA Mini Kit (Qiagen). Libraries were constructed using KAPA HyperPrep Kit with Library Amplification (KK8504) and IDT's duplex UMI adapters. Hybridization and capture were performed using IDT's XGen hybridization kit. Whole exome sequencing was performed using Illumina NovaSeq S4 flowcells (paired 151bp runs). Data preprocessing including point mutation calling, filtering, CNV calling, and purity and ploidy estimation were performed using the Getz Lab CGA WES Characterization pipeline. TMB for each sample was calculated based on the number of mutations with cancer cell fraction > 0.75 as determined by ABSOLUTE and normalized to the 35Mb targeted for exome capture. **Results:** A total of 88 tDNA, 226 cfDNA, and 30 normal DNA (nDNA) from 82 pts were sequenced. To date, sequencing data from 13 matched tDNA/cfDNA/nDNA samples and 34 matched cfDNA/nDNA samples with sufficient tumor purity were available for analyses. The median TMB was 2.4 mut/Mb (range 0.46-17.5) in tDNA and 1.8 mut/Mb (range 1.1-12.6) in cfDNA. There was a high correlation between tDNA/cfDNA pairs in TMB ( $r = 0.826$ ,  $p = 1.5 \times 10^{-16}$ , Pearson correlation). The median TMBs in tDNA and cfDNA obtained at different time points or treatment course did not differ significantly in 22 patients with at least two cfDNA timepoints ( $p = 0.26$  paired t-test of log-transformed TMB). There was no difference between responder (R) vs. non-responder (NR) in cfDNA TMBs (two-sample t-test  $p = 0.7$  between 2 R and 12 NR) and tDNA TMBs (two-sample t-test  $p = 0.25$  between 6 R and 21 NR). However, tDNA TMB was higher in R compared NR in a subset of pts who did not have prior treatment with ICI (two-sample t-test  $p = 0.05$  between 5 R and 2 NR). **Conclusions:** TMB in tDNA and cfDNA is highly correlated and suggests the possible use as a surrogate marker for tTMB. High TMB in cfDNA derived from ICI-naïve patients appears to have a prognostic value. Further evaluation is warranted to determine the role of cfDNA TMB as a biomarker of ICI response. Research Sponsor: Florida Health Department; IBM.

# Association between locoregional failure and *NFE2L2/KEAP1/CUL3* pathway mutations in NRG/RTOG 9512: A randomized trial of hyperfractionation vs. conventional fractionation in T2N0 glottic squamous cell carcinoma (SCC).

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**Background:** Radiotherapy (RT) is the primary treatment for patients with T2N0 glottic SCC. ~30% of these patients experience locoregional relapse despite dose escalation. Mutations in the *NFE2L2/KEAP1/CUL3* pathway have been linked to radioresistance preclinically and in small retrospective studies. We tested the hypothesis that patients with T2 glottic SCCs having these mutations would show radioresistance and more local (LF) and locoregional failures (LRF) when treated with RT compared to those without, using samples from a phase III trial. **Methods:** Of 250 randomized patients with T2N0 glottic SCC receiving definitive RT in RTOG 9512, 119 had available biospecimens that were subjected to amplicon-based next generation sequencing (appropriate to low-input DNA from biopsy specimens) to assess for presence of *NFE2L2/KEAP1/CUL3* mutations without regard to outcomes. The association between binary mutation status and LF, LRF, disease-free survival (DFS), and overall survival (OS) was assessed using (cause-specific) Cox models (2-sided alpha of 0.05). LR/LRF rates were estimated by the cumulative incidence method and DFS/OS rates by the Kaplan-Meier method. **Results:** Nineteen of 119 patients (16.0%; 95% confidence interval [CI] 9.4, 22.6) had mutations in the *NFE2L2/KEAP1/CUL3* pathway. Patient and tumor characteristics were similar between those with and without mutation. There were 32 LF, 37 LRF, and 80 DFS events, and 52 deaths. Patients with mutation compared to those without had significantly higher LF and LRF rates (Table). Median DFS was 0.9 years (95% CI 0.4, not reached) for the mutation group compared to 4.2 years (95% CI 3.2, 6.4) for those without. The hazard ratio (HR) for DFS was significantly higher for the mutated compared to the non-mutated group in the first 2 years after randomization but declined thereafter (Table), likely due to limited events after 2 years in the mutation group. There was no significant difference in OS between the two groups (HR = 0.76; 95% CI 0.35, 1.6; p = 0.48). **Conclusions:** *NFE2L2/KEAP1/CUL3* pathway mutations may predict radiation treatment failure in T2N0 glottic cancer. They may also be a prognostic biomarker for DFS, but the current evidence supports the harmful effect of these mutations only during the first 2 years from randomization. Clinical trial information: NCT00002727. Research Sponsor: This project was supported by grants UG1CA189867 (NCORP), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA196067 (NRG Specimen Bank), CTEP from the National Cancer Institute (NCI).

		With Mutation	Without Mutation
<b>LF</b>	2 yr. rate (95% CI)	47.4% (23.5, 68.0)	17.1% (10.5, 25.2)
	HR*, p-value	3.05 (95% CI 1.35, 6.86), p = 0.0071	
<b>LRF</b>	2 yr. rate (95% CI)	57.9% (32.0, 77.0)	20.2% (12.9, 28.6)
	HR*, p-value	3.40 (95% CI 1.61, 7.18), p = 0.0014	
<b>DFS</b>	2 yr. rate (95% CI)	36.8% (15.2, 58.5)	67.7% (58.5, 76.9)
	HR*, p-value	2.66 (95% CI 1.36, 5.20), p = 0.0044 (≤ 2 years)	
		0.08 (95% CI < 0.01, 1.42), p = 0.0851 (> 2 years)	

\*Based on multivariable Cox model with treatment arm, age, race, KPS, primary site and T stage.

**A proteomic signature associated with prognosis in HPV-related locally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC).**

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**Background:** Although HPV-related LA-OPSCC is associated with better prognosis than HPV-negative disease, ~30% of cases relapse despite curative-intent chemoradiotherapy. New prognostic biomarkers are needed to rationalise curative-intent treatment without compromising efficacy. We aimed to develop a proteomic signature associated with risk of recurrence from diagnostic biopsies of patients with HPV-positive OPSCC. **Methods:** We analysed 139 formalin fixed paraffin embedded archival core biopsy specimens from 124 patients with HPV-related (p16 IHC positive) T1-4N0-3M0 LA-OPSCC tumours. All patients were treated with definitive chemoradiotherapy at the Princess Alexandra Hospital (Brisbane, Australia) between 2007-2019. The cohort included 50 patients with recurrence less than five years from diagnosis and 74 age/performance-status matched patients with no recurrence. Proteomic analysis was performed utilizing data-independent acquisition mass spectrometry (DIA-MS). A proteomic prognostic signature associated with recurrence free survival (RFS) at five years was the primary endpoint of interest. It was developed using a computational pipeline comprising an initial univariate Cox model step, followed by multiple runs of multivariate Cox models with Least Absolute Shrinkage and Selection Operator (LASSO) regularization, and then a final step of recursive feature selection. **Results:** A total of 7,597 proteins were quantified and 665 were differentially expressed proteins between tumour and normal adjacent tissues. There were 5,199 proteins remaining in the tumour samples after filtering. RFS was significantly (q-value < 0.05) associated with 252 proteins, whose functions are enriched in adaptive and innate immunity and MAPK6/MAPK4 signalling pathways. A 16-protein signature associated with RFS stratified patients into low, intermediate, or high-risk groups (C-index = 0.885,  $p < 0.0001$ ). The 16-protein signature outperformed clinico-pathological covariates including age, stage, ECOG and smoking history with the highest area under the receiver operating characteristic curve (AUROC 0.95). **Conclusions:** DIA-MS-based proteomics on core biopsies can be used to risk stratify HPV-related OPSCC patients. A 16-protein signature associated with RFS was successfully identified as a basis for future studies. Validation of this proteomic prognostic signature in independent cohorts is required and may be used to inform future clinical trials to better tailor upfront therapy. Research Sponsor: Australian Cancer Research Foundation, Cancer Institute New South Wales (NSW) Cancer Council NSW (IG 18-01); Ian Potter Foundation, NHMRC,; NSW Ministry of Health (CMP-01), European Union grant (GNT1170739, a companion grant to support the European Commission's Horizon 2020 Program, H2020-SC1-DTH-2018-1; The University of Sydney, Queensland Head and Neck Cancer Centre.



**Single-cell RNA and T cell receptor (TCR) sequencing in patients with HPV-positive head and neck squamous cell carcinoma (HNSCC) after induction CTLA4 and PD-1 immune checkpoint blockade (ICB).**

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**Background:** Combination CTLA-4 and PD-1 ICB results in durable responses in patients with recurrent and metastatic HNSCC and therefore justifies further investigation in the induction or neoadjuvant setting. **Methods:** We investigated features of the tumor immune microenvironment (TIME) associated with MHR after induction CTLA-4 and PD-1 ICB in patients with newly diagnosed HPV-positive HNSCC. Tumor samples were collected at baseline and on treatment from 31 patients enrolled in a phase 2 trial of a 6-week cycle of CTLA-4 and PD-1 ICB induction followed by dose/volume-adapted IMRT (50-66Gy) concurrent with cycle 2. Tumors were evaluated for histological response and single-cell RNA sequencing (scRNA-seq) and scTCR-seq were performed on the 10X genomics platform. After stringent clustering and annotation of scRNA-seq data, 76,319 CD8<sup>+</sup> and 78,622 CD4<sup>+</sup> T cells with paired TCR sequence data were evaluable for transcriptomic, TCR repertoire and clonotype differentiation analysis.

**Results:** Percent reduction in tumor viability on histology correlated significantly with reduction in tumor cell proportion in scRNA-seq data ( $R^2 = 0.7$ ). Thirteen (48%) of 27 patients with paired samples (missing data due to COVID) had MHR, defined as  $\leq 10\%$  residual tumor viability on ICB treatment. Through TCR tracing, over 100 T cell clonotypes that expanded significantly ( $p < 0.05$ , Fisher's exact) post-ICB were identified. Highly expanded clonotypes resided mainly in exhausted CD8<sup>+</sup> T cell clusters and exhibited a tissue resident memory (TRM) phenotype. Examination of their functional states revealed a variety of T cell modulatory trajectories, including reverse transition from exhausted to less exhausted states and from memory to functional states. When compared to patients without MHR, those with MHR had significantly higher ICB-induced TCR clonotype expansion ( $p = 0.025$ , Wilcoxon), reductions of activated Tregs ( $p = 0.003$ , Wilcoxon) and terminally exhausted CD8<sup>+</sup> T cells ( $p = 0.003$ , Wilcoxon), and increase of polyfunctional CD8<sup>+</sup> T cells ( $p = 0.014$ , Wilcoxon). A lasso regression model associated T cell expansion, basal 7-gene TRM and 5-gene effector scores, and on-treatment proliferation score and effector cell proportion with percent reduction in tumor viability ( $R^2 = 0.66$ ).

**Conclusions:** In HPV-HNSCC, induction CTLA4 and PD1 ICB lead to extensive reinvigoration of CD8<sup>+</sup> T cell clonotypes with both an exhausted and TRM phenotype, revealing a high degree of plasticity of distinct T cell clones. Paired RNA and TCR profiling facilitated identification of potentially tumor reactive and ICB-responsive T cells and clonotypes and identified several TIME features associated with tumor cell death. Clinical trial information: NCT03799445. Research Sponsor: Cancer Prevention and Research Institute of Texas.

**Introduction of E-Score: A gene expression score to characterize immunogenic versus oncogenic HPV expression in HNSCC.**

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**Background:** Human Papillomavirus (HPV) integration in the human genome occurs in a majority of HPV(+) head and neck squamous cell carcinomas (HNSCC), with direct and indirect effects on host gene expression and tumorigenesis. Although previous studies showed that HPV integration in HNSCC is overrepresented in genes often somatically mutated in head and neck, lung, and urogenital cancers, reports are mixed for whether patients with HPV integration have worse clinical outcomes. These disparate results may be due to differences in how integration is defined. Integration can often lead to partial loss of the viral genome (e.g. HPV genes E1, E2, or E5) with retention of the oncogenes E6 and E7, which led to a low E2/E7 expression ratio being used as a biomarker for integration. Conversely, others have used the direct detection of DNA or RNA HPV-human breakpoints to identify tumors harboring integrated HPV. HPV integration and the retention or deletion of HPV genes can dramatically change the expression of HPV genes, and we hypothesize it also affects the host immune response. **Hypothesis:** Loss of non-oncogenic HPV genes relative to E6 and E7 levels reduces immunogenicity, leading to weakened immune cell infiltration and worse clinical outcomes. **Methods:** Bulk RNA sequencing data from HPV(+) HNSCC tumors (n = 136) was used to characterize the differences in retention or loss of HPV genes and calculate the E-Score as the sum of the logCPM of HPV genes E1, E2, E4, and E5 relative to E7. Cell type deconvolution was performed using ComBat to correct for batch effects, and CIBERSORTx to quantify cell type proportions within the tumor samples. Kaplan-Meier estimates of recurrence and overall survival (OS) were calculated, and Cox proportional hazards tests with covariates were used to test for association with recurrence and OS. To test the correlation between immune cell type inferred proportions and E-Score, T-Tests were performed between samples with high and low E-scores. **Results:** Low E-Score was significantly associated with recurrence (p = 0.012) but not with OS (p = 0.39) in the multivariate model accounting for age, tumor stage (AJCC8), smoking status, drinking status, BMI, marital status, and molecular tumor subtype (defined as IMU or KRT). For integration positive samples (n = 66), higher E-Score, suggesting lower rates of HPV gene loss, was correlated with higher percentages of dendritic cells (p = 0.044), macrophages (p = 0.021), and CD8+ T Cells (p = 0.024), but not CD4+ T cells (p = 0.14). This significance did not hold when looking at integration negative samples. **Conclusions:** These results suggest that HPV+ HNSCC patients with a loss of E1, E2, E4 and E5 tend to have less immune cell infiltration and are more likely to have recurrence. We conclude that E-Score is a potential prognostic biomarker of recurrence in HPV+ HNSCC and potential predictive biomarker for immunotherapy. Research Sponsor: U.S. National Institutes of Health.

**Association of HPV genotype and phylogenetic clade with oropharyngeal cancer outcomes.**

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**Background:** Human papillomavirus (HPV) is a causative agent of oropharyngeal squamous cell carcinoma (HPVOPC). There are multiple different HPV genotypes based on variations in the nucleotide sequence of the L1 capsid, with HPV16 being most common in HPVOPC (85%). HPV genotypes can be further classified into phylogenetic clades, including alpha-9 (A9) and alpha-7 (A7). HPVOPC is associated with a more favorable prognosis than HPV-negative disease, but the impact of specific HPV genotype and phylogenetic clade on patient outcomes is not well understood and has profound implications for de-escalation studies in HPVOPC. **Methods:** A retrospective cohort study was conducted at a large multicenter health system. Patients diagnosed with non-metastatic HPVOPC or unknown primary from 2012-2021 and treated with curative intent were included. Low-risk HPV types (6, 11, etc) and local recurrences were excluded. HPV molecular typing was prospectively performed according to institutional protocol. Cox regressions were used to measure the effect of HPV genotype (16 versus non-16) on overall survival (OS) and event-free survival (EFS). Gender, smoking status, alcohol use, ECOG performance status, T stage, N stage, and subsite (oropharynx versus known primary) were covariates. A secondary survival analysis according to high-risk HPV clade (A9 versus A7) was also performed. **Results:** The total cohort included 520 patients, the majority of whom were HPV16 (86.9%, n = 452), A9 clade (97.1%, n = 505), oropharynx primary (94.8%, n = 493), male (86.9%, n = 452), white (72.5%, n = 377), non-Hispanic (74.2%, n = 386), non-active smokers (88.3%, n = 459), ECOG 0 (75.6%, n = 393), and N2 stage (65.2%, n = 339). The most common non-16 HPV genotypes were 18 (n = 7), 33 (n = 21), and 35 (n = 29). HPV genotype was not associated with OS (HR = 1.64, 95% CI 0.85-3.16,  $p=0.14$ ) or EFS (HR = 1.15, 95% CI 0.64-2.07,  $p=0.65$ ). A7 clade was associated with a worse OS compared to A9 in the univariate analysis (HR = 3.43, 95% CI 1.07-10.97,  $p=0.04$ ), but not in the multivariate analysis (HR = 1.67, 95% CI 0.45-6.17,  $p=0.44$ ). Finally, HPV clade was not associated with EFS (HR = 1.38, 95% CI 0.34-5.60,  $p=0.66$ ). **Conclusions:** While HPV genotype was not associated with survival differences in patients with HPVOPC, HPV A7 clade only predicted worse OS in univariate analysis. Although the total cohort size was large, this analysis was limited by small numbers of subjects with non-16 HPV genotypes and non-A9 clade, which is reflective of the predominance of HPV16 in HPVOPC. Thus, a pooled multicenter collaboration is needed to further address this question. Moreover, future studies should investigate whether outcomes may be related to intratypic HPV16 variants that affect oncoprotein function and/or immunogenicity. Detection of a subgroup of HPVOPC with possible inferior outcomes has important implications for studying treatment de-escalation in HPVOPC. Research Sponsor: Philanthropy.

**Spatial genomics to reveal an immunosuppressive tumor microenvironment after chemoradiation in head and neck cancer patients.**

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**Background:** Although chemoradiotherapy (CRT) remains the cornerstone of management for locoregionally advanced head and neck squamous cell carcinomas (HNSCC), recurrence occurs in ~50% of patients. We sought to characterize the impact of CRT on the tumor microenvironment (TME) and identify factors associated with progression. Emerging spatial biology technologies, such as NanoString GeoMx Digital Spatial Profiler (DSP), enable spatially defined whole-transcriptomic profiling of cells along the tumor-stromal interface in tumor biopsies to resolve immune cell identities, activation states and signaling pathways in adjacent tumor cells. We used a multimodal approach including immunohistochemistry (IHC), bulk tumor gene expression and spatial genomics to characterize paired pre- and post-CRT tumor samples from HNSCC patients. **Methods:** 20 patients with locoregionally advanced HNSCC who had undergone curative intent CRT and developed subsequent recurrence requiring salvage surgery from June 14, 2010 to June 14, 2020 were retrospectively identified at Duke University Medical Center. Matched formalin-fixed paraffin embedded tumor specimens collected prior to CRT and at salvage surgery were compared via IHC for markers of immune infiltration and PDL1 expression, bulk tumor whole transcriptomic profiling, and spatial transcriptomic analysis of tumor and stroma using DSP were further examined in “early” progressors (< 6 months after CRT) and “late” progressors (≥6 months after CRT). **Results:** IHC analyses demonstrated significant reductions in T-cell immune populations (total CD3<sup>+</sup>, CD8<sup>+</sup>, 4-1BB<sup>+</sup> cell density [ $p < 0.001$ ]) after CRT. PDL1<sup>+</sup> expression was similar before and after CRT. Neither T-cell infiltrate nor tumor PDL1 levels at surgery were associated with progression. Bulk tumor gene expression analysis demonstrated that macrophage and fibroblast markers were increased post-CRT. In early progressors, molecular dissection of the tumor-stromal interface using DSP expression profiling revealed macrophage associated genes (*CD68*, *MRC1/CD206*, *CD163*, *F13A1*) at salvage surgery had a more pronounced increase in macrophage markers in stroma with enriched M2 genes compared to late progressors. **Conclusions:** Integrated spatial analysis with high resolution transcriptomics and IHC suggest CRT induces an immunosuppressive environment characterized by decreased T-cell infiltration and an influx of putative immunosuppressive macrophages. We hypothesize that tumor associated macrophages and/or fibroblasts may contribute to immunosuppression due to “reprogramming” of the TME after CRT. This exploratory study suggests that patients with progressive disease after chemoradiation may benefit from additional immunoregulatory therapies that ameliorate the immunosuppressive TME. These findings will be further validated in a larger cohort of patients. Research Sponsor: Genmab US.

### Clinical validity of TTMV-HPV DNA liquid biopsies for the diagnosis and surveillance of HPV-associated oropharyngeal carcinoma.

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**Background:** While there are several HPV biomarker assays, a commercially available assay evaluating tumor tissue modified viral DNA (TTMV-HPV DNA) (NavDx, Naveris Inc, Natick, MA) has shown impressive results in clinical trials and small cohort studies. Our aim was to establish the clinical efficacy of plasma TTMV-HPV DNA testing in the diagnosis and surveillance of HPV-associated OPSCC in a contemporary, real-world clinical setting. **Methods:** In this retrospective analysis, we evaluated the accuracy of the TTMV-HPV DNA assay in detecting HPVOPSCC in the diagnostic (pre-treatment) and surveillance phases of care between April 2020 and October 2022. For the diagnostic cohort, patients with OPSCC and at least one TTMV-HPV DNA measurement prior to initiation of primary therapy were included in the analysis. For the surveillance cohort, all TTMV-HPV DNA tests performed 3 months after completion of primary therapy for pathologically confirmed HPV-associated OPSCC were evaluated, regardless of pre-treatment TTMV-HPV DNA testing. Patients with suspected recurrence, but without pathologic confirmation, were excluded. HPV status was defined utilizing positive p16 staining on immunohistochemistry (93.2% diagnosis; 97.9% surveillance) or HPV polymerase chain reaction/in situ hybridization (79.6% diagnosis; 89.7% surveillance). **Results:** In the diagnostic cohort, 163 patients were included. The cohort included mostly men (87%) with median age 63, of which 93.3% had HPVOPSCC versus 6.7% had HPV negative OPSCC. The sensitivity in pre-treatment diagnosis was 91.5%; its specificity was 100%. In the surveillance cohort, 591 tests conducted in 290 patients were evaluated. 23 patients had pathologically confirmed recurrences. The assay demonstrated 79.2% sensitivity and 100% specificity in detecting the recurrences. Positive predictive value was 100% and negative predictive value was 98.2%. The median lead time from positive test to pathologic confirmation was 28 days, 6/18 (30%) had lead time >50 days (maximum 507 days). **Conclusions:** The commercially available NavDx TTMV-HPV DNA assay demonstrated 100% specificity, and therefore excellent positive predictive value, in both diagnosis and surveillance. However, the sensitivity was lower, 91.5% for the diagnosis cohort and 79.2% for the surveillance cohort, signifying that a negative value may require further work-up. Further studies will be required to determine the optimal timing of testing and how results should inform treatment decisions. Research Sponsor: None.

2x2 Tables for diagnosis (A) and surveillance (B) cohorts.

	A) Diagnosis Cohort (n = 163)		B) Surveillance Cohort (n = 591#)	
TTMV-HPV DNA	HPV+ OPSCC	HPV- OPSCC	Recurrence	Disease Free
Positive	139	0	38	0
Negative	13	11	10	543

#Surveillance cohort analysis performed at the test level; individual patients may have multiple tests.

**Spatial relationships and immune subsets in the tumor immune microenvironment of head and neck cancers.**

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**Background:** The tumor microenvironment provides important insights into cancer behavior and its response to treatment. In particular, the cellular composition and spatial arrangement of tumor immune infiltrates are associated with patient prognosis and survival. We optimized and employed a novel method using readily available hematoxylin and eosin (H&E) slide images, termed the G-cross score, which reflects immune cell infiltration levels and their proximity to tumor cells. The G-cross score is calculated by estimating the probability distribution of immune cells, of any type, within a certain distance from a tumor cell, with higher scores indicating greater immune cell infiltration. However, because G-cross scores are calculated from H&E slides, the method is unable to distinguish among immune cell types. Using head and neck squamous cell carcinoma (HNSCC) patients having both G-cross scores and bulk RNA-seq data, we determined which subset of tumor-infiltrating immune cell types best correlate with G-cross scores, and its predictive and prognostic value. **Methods:** G-cross scores were calculated for 425 HNSCC samples from University of Michigan, of which 64 had paired bulk RNA-seq data. We applied the cell-type deconvolution tool, CIBERSORTx, to identify immune cell type proportions based on RNA-seq data. G-cross scores were correlated against cell-type deconvolution results, immune cell activation expression signatures, and validated gene expression-based radiosensitivity index scores. Pearson's correlation coefficient and p-value using HPV status as a covariate in a linear model was calculated for each comparison. For survival and recurrence analysis, Cox proportional hazards multivariate regression was performed using the entire 425 sample cohort. **Results:** G-cross scores were significantly correlated with total T cells ( $R = 0.52$ ,  $p = 4.63 \times 10^{-5}$ ), B cells ( $R = 0.33$ ,  $p = 2.08 \times 10^{-2}$ ), and dendritic cells ( $R = 0.46$ ,  $p = 7.71 \times 10^{-4}$ ), but not macrophages or mast cells. G-cross scores also had a positive correlation with T cell activation ( $R = 0.46$ ,  $p = 2.17 \times 10^{-4}$ ) and B cell activation ( $R = 0.53$ ,  $p = 1.24 \times 10^{-4}$ ) and were correlated with radiation sensitivity ( $R = -0.44$ ,  $p = 6.67 \times 10^{-4}$ ). Survival analysis showed higher G-cross scores were associated with a longer time to recurrence and improved overall survival ( $p = 3.0 \times 10^{-4}$ ). **Conclusions:** G-cross scores are mainly driven by T cell and dendritic cell levels among tumor-infiltrating lymphocytes and are correlated with B and T cell activation. Importantly, G-cross scores also correlate with gene expression profiles associated with response to radiotherapy as well as time to recurrence and overall survival. G-cross scores may be an important biomarker of radiation response and indicative of protective immune subsets for HNSCC patients. Research Sponsor: U.S. National Institutes of Health.

# Peripheral blood epigenetic immune-profiling and survival outcomes with anti-programmed death (PD)-1 based therapy in recurrent/metastatic (R/M) squamous cell carcinoma of head and neck (SCCHN).

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**Background:** Most patients with R/M SCCHN do not derive durable benefit from standard-of-care anti-PD-1-based therapy. The currently utilized biomarker, PD-ligand-1 combined proportion score is limited by the availability and heterogeneity of tumor samples. There is an unmet need to develop easily accessible peripheral blood-based biomarkers for response to immunotherapy. **Methods:** We are conducting a prospective multi-center study to identify peripheral blood derived DNA-based methylation biomarkers measured in patients with R/M SCCHN on treatment with FDA-approved anti-PD-1 based therapy. DNA isolated from these samples undergo bisulfite conversion, methylation profiling using Illumina EPIC microarray, and cellular deconvolution to generate peripheral blood immune profiles (PMID 35140201), including granulocytic (g) and monocytic (m) myeloid derived suppressor cell (MDSC) scores. Associations between baseline peripheral blood immune profiles before the start of treatment with progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan Meier curves and Cox proportional hazards models adjusted for age and sex. Additionally, logistic regression models adjusted for age and sex were utilized to investigate the baseline immune profiles between subgroups of patients who received anti-PD-1 monotherapy with durable clinical benefit for at least 1 year (Group A) versus progression or death within 100 days (Group B) from start of therapy.

**Results:** 61 patients with R/M SCCHN who received anti-PD-1 based therapy as of Oct 31, 2022, were eligible for this preliminary analysis. Mean (SD) age of the entire population was 66.4 (11.8) years, 82% were male. gMDSC score was the only immune parameter with a statistically significant association with PFS (HR 2.6 (1.40 – 4.87) independent of age and sex, with higher scores stratified by median value associated with shorter PFS (Median PFS: 75 days vs. 145 days). Memory CD4 T cells, total CD4 T cells, percentage of T regulatory /CD4 cells, and absolute memory B cells were significantly associated with OS in this population, independent of age and sex (Table). Among the subgroup treated with anti-PD-1 monotherapy, Group A with durable benefit (n = 7, 86% male, mean age: 64.7 years) had significantly higher proportion of CD4 naïve/total CD4 cells (p = 0.03), and significantly lower gMDSC (p = 0.015) & mMDSC (p = 0.000049) scores, compared with Group B (n = 27, 78% male, mean age: 66.4 years). **Conclusions:** Peripheral blood DNA-based epigenetic immune profiling can recognize clinically relevant methylation biomarkers of benefit from anti-PD-1 therapy before the start of treatment. Research Sponsor: U.S. National Institutes of Health.

	Hazards ratio (HR) for OS	p value
CD4 memory	0.19	0.006
CD4 total	0.19	0.006
Treg/total CD4	3.89	0.018
Absolute B memory	2.88	0.028
Neutrophils	2.54	0.086

**The impact of genetic predisposition to depression on quality of life in patients with head and neck cancer immediately post-treatment: A longitudinal study.**

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**Background:** The primary aim of this study was to investigate the contribution of genetic predisposition to depression, through polygenic risk scores (PRS), on quality of life levels in patients with head and neck cancer (HNC) immediately post-treatment period (i.e., 3 months post-diagnosis). **Methods:** Prospective longitudinal study of 223 consecutive adult patients with HNC (72% participation) newly diagnosed with a first occurrence of primary HNC, including saliva samples analyzed using the Illumina PsychChip, psychometric measures, Structured Clinical DSM Interviews, and medical chart reviews. **Results:** Level of quality of life at 3 months on the FACT-G+H&N was predicted by ( $r^2 = 0.51$ ,  $r^2$  adj. =  $0.33$ ,  $p = 0.001$ ) the polygenic risk score for depression (standardized  $b = -0.28$ ,  $p = 0.01$ ) and a previous history of suicidal ideation (standardized  $b = -0.25$ ,  $p = 0.04$ ). Other variables were non-significant in the analyses: sociodemographic (i.e., age, sex, education, living alone), psychosocial (i.e., SCID current and past diagnoses (trend), past history of abuse), and medical variables (i.e., cancer stage and site, HPV status, functional status/ECOG, treatment). **Conclusions:** Our results outline the importance of attending to genetic predisposition and past history of suicidal ideation as markers for quality of life compromise immediately post-treatment in patients with head and neck cancers. Strategies are needed to address psychosocial vulnerability early-on as part of pre-habilitation in the treatment of patients with head and neck cancer. Research Sponsor: Quebec Health Research Fund (FRQS).



**Radiotherapy alone versus concurrent or adjuvant chemoradiotherapy for nasopharyngeal carcinoma patients with negative Epstein-Barr virus DNA post-induction chemotherapy.**

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**Background:** Induction chemotherapy (IC) plus concurrent chemoradiotherapy has been recommended as the standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC). However, concurrent chemotherapy was associated with increased toxicities, poor tolerance, and low completion rates. The aim of this study was to compare the efficacy and toxicity of IC+ radiotherapy (RT) and IC+ concurrent or adjuvant chemoradiotherapy (IC+CCRT/AC) in patients with negative post-IC EBV DNA. **Methods:** A total of 547 NPC patients with negative plasma EBV DNA post-IC were included. Patients were classified into the IC+RT group and the IC+ concurrent or adjuvant chemoradiotherapy (IC+CCRT/AC) group. Locoregional relapse-free survival (LRFS), distant metastasis-free survival (DMFS), overall survival (OS), and progression-free survival (PFS) were estimated and compared using the Kaplan-Meier method. Propensity-score matching (PSM) was performed to balance the variables. **Results:** The median follow-up time was 37 months. The 3-year LRFS, DMFS, OS, and PFS rates for the whole group were 92.2%, 92.4%, 96.4%, and 84.4%, respectively. There was no significant difference in LRFS, DMFS, OS, and PFS between the IC+RT and the IC+CCRT/AC group both before PSM (3-year rates of 91.1% vs. 92.6%,  $p = 0.94$ ; 95.6% vs. 91.5%,  $p = 0.08$ ; 95.2% vs. 96.8%,  $p = 0.80$ ; 85.9% vs. 84.0%,  $p = 0.38$ ) and after PSM (90.7% vs. 92.7%,  $p = 0.77$ ; 96.8% vs. 93.7%,  $p = 0.29$ ; 94.5% vs. 93.9%,  $p = 0.57$ ; 84.7% vs. 85.6%,  $p = 0.96$ ). Multivariate analysis demonstrated that treatment schedule was not an independent predictor for survival rates. Patients in the IC+RT group had fewer treatment-related acute toxicities and better tolerance. **Conclusions:** IC+RT displayed similar survival outcomes as IC+CCRT/AC for NPC patients with negative post-IC EBV DNA. Our current data seems not to support the routine use of concurrent or adjuvant chemotherapy after IC for unselected patients. Research Sponsor: None.

### Multimodal detection in plasma of molecular residual disease (MRD) in locally advanced head and neck squamous cell carcinoma (LA-HNSCC).

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**Background:** Despite intensive therapy, 30% of patients (pts) with LA-HNSCC relapse. Published data shows that MRD detection during follow up (FU) may predict relapse, e.g. human papillomavirus (HPV) DNA in p16+ pts post radiation (RT) or chemoradiation (CRT); or circulating tumor DNA (ctDNA) post surgery. MRD detection using multiple assays after definitive RT/CRT has not been reported. **Methods:** We enrolled pts with high risk LA-HNSCC (stage III HPV+, III-IVB HPV-) treated with curative intent: surgery ± adjuvant therapy, RT or CRT. Plasma was collected pre-treatment at baseline (B), at 4-6 weeks (FU1) and 8-12 weeks (FU2) post-treatment. RaDaR, a personalized liquid biopsy assay that targets patient specific somatic variants identified in whole exome sequencing (WES) from matched tumor tissue, was used to detect ctDNA, reported as estimated Variant Allele Fraction (eVAF). Cancer Personalized Profiling by deep sequencing (CAPP-seq) was used as a tumor naïve assay for ctDNA, reported as mean VAF. HPV sequencing (HPV-seq) in all and digital PCR (dPCR) in p16+ pts were used to detect HPV DNA. Relapse free survival (RFS) was estimated using Kaplan Meier and associations of ctDNA or HPV DNA with RFS using log-rank test. Assays were compared with Spearman correlation.

**Results:** A total of 89 plasma samples from 35 pts were collected prospectively; 32 pts with at least a FU sample were evaluable: 26 had both. Median age was 63 years (34-71). Most pts were stage III HPV + (N = 16, 50%) and received CRT (N = 25, 78%). No pts had clinical or radiological residual disease at FU2. Median FU was 18.3 months (5.1-25.9), there were 7 clinical relapses. RaDaR was applied in 17 pts with WES in matched tissue, including 6 with relapse. ctDNA at B was detected in 15/17 (88%). eVAF at B was not associated with RFS (p = 0.98). Two pts relapsed < 1 year after RT/CRT and had eVAF > 0.001% in FU2 sample; lead time to relapse was 100 and 245 days. FU1 sample of a pt who relapsed > 1 year post-CRT was close to the threshold for ctDNA+ with eVAF 0.0001%; lead time was 494 days. Three pts who received CRT relapsed > 500 days from FU2 sample (ctDNA-). CAPP-seq was applied to 29 pts; mean VAF correlated with eVAF at B (r = 0.75) but not at FU. ctDNA+ at FU using CAPP-seq was not associated with RFS (p = 0.25). HPV-seq was applied to 32 pts; specificity and sensitivity was 100% at B. Among p16+ pts with FU sample (N = 15), HPV DNA was detected in 4/4 with relapse and not in those without, predicting shorter RFS (p < 0.01). dPCR detected HPV DNA in 2/4 pts with relapse. HPV-seq and dPCR correlation was high at B (r = 0.99), lower at FU2 (r = 0.66).

**Conclusions:** HPV DNA and ctDNA can be detected in LA-HNSCC before and after definitive therapy. RaDaR but not CAPP-seq may detect MRD in pts who relapse within 1 year after RT/CRT with a significant lead time. HPV-seq may be more sensitive than dPCR to detect HPV DNA in MRD. Validation in an interception study is planned (NCT04599309). Research Sponsor: Princess Margaret Cancer Centre; BMO Chair of Precision Medicine.

**One-year reductions in cisplatin-related chronic kidney disease (CKD) in patients with head and neck (HNC) cancer treated with avasopasem manganese: A prespecified analysis from the phase 3 ROMAN trial.**

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**Background:** Cisplatin-induced acute kidney injury (AKI), acute kidney disease (AKD), and chronic kidney disease (CKD) are associated with increased production of reactive oxygen species, notably superoxide, in conjunction with alterations in mitochondrial electron transport chain complex activities in tubular epithelial cells (Mapuskar et al. *Antioxidants* 2021;10:1329). These pathologies can be targeted and thereby inhibited by increasing superoxide dismutase activity, which converts superoxide to hydrogen peroxide. The investigational new drug avasopasem manganese (AVA), a selective dismutase mimetic, ameliorated cisplatin-induced kidney injury in mice (Mapuskar et al. *Redox Biol* 2019;20:98). Preclinical results also demonstrate that AVA does not interfere with cisplatin anticancer activity (Mohanty et al. *Cancer Res* 2018;78[13\_suppl]:Abstract 2929). Consistent with this, a retrospective analysis of 1- and 2-year kidney function of a limited subset of patients treated in a randomized, placebo (PBO)-controlled phase 2b trial of AVA to reduce severe oral mucositis (SOM) from radiotherapy and cisplatin (CRT) suggested that AVA prevented or reduced cisplatin-related CKD compared to PBO (Steinbach et al. *J Clin Oncol* 2020;38[15\_suppl]:Abstract 12071). **Methods:** The ROMAN phase 3 trial (NCT03689712; ITT n = 407) of CRT in combination with AVA or PBO demonstrated improved incidence, duration, and onset of SOM by AVA (n = 241) vs PBO (n = 166) (Anderson et al. *J Clin Oncol* 2022;40[16\_suppl]:Abstract 6005). In ROMAN, prospectively defined follow-up of serum creatinine (sCr) and estimated glomerular filtration rates (eGFR) were assessed every 3 months for 1 year following 7 weeks of CRT. **Results:** At 1-year follow-up, AVA was associated with significant improvements in preservation of eGFR ( $P=0.0008$ ) and sCr ( $P=0.006$ ) levels vs PBO. Grade 3+ CKD (eGFR < 60 mL/min) results through 12 months show 10% AVA vs 20% PBO (relative risk 0.55,  $P=0.0043$ ). Regarding cisplatin schedule, patients receiving Q3W therapy show grade 3+ CKD of 12% AVA vs 22% PBO; patients receiving QW therapy show AVA 9% vs PBO 19%. During treatment, nominal reduction of the incidence of AKI adverse events (0.8% AVA vs 3.6% PBO) was also observed. **Conclusions:** At 1-year follow-up, AVA appears to reduce cisplatin-related CKD in the study population and may also reduce cisplatin-related AKI during treatment. These results carry significance beyond CRT for HNC, potentially impacting platinum-containing regimens in other cancers. Clinical trial information: NCT03689712. Research Sponsor: Galera Therapeutics, Inc.

**Induction chemotherapy with nedaplatin, docetaxel and 5-fluorouracil followed by concurrent nedaplatin and radiotherapy in locoregionally advanced nasopharyngeal carcinoma: A single arm, open label, phase II clinical trial.**

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**Background:** To evaluate the efficacy of induction chemotherapy with nedaplatin, docetaxel and 5-fluorouracil followed by concurrent nedaplatin combined with radical radiotherapy in locoregionally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** This is a prospective, single-arm, open-label, phase II trial. Patients with aged 18-65 years, newly diagnosed stage III-IVa (except T3-4N0) nasopharyngeal carcinoma were enrolled. Eligible patients received induction chemotherapy with docetaxel (60 mg/m<sup>2</sup> intravenously on days (D) 1, 22 and 43), Nedaplatin (60 mg/m<sup>2</sup> intravenously on D 1, 22 and 43) and fluorouracil (600 mg/m<sup>2</sup> per day as a continuous 120 hours (h) infusion on D 1-5, 22-26 and 43-47) every three weeks for three cycles, thereafter received intensity-modulated radiotherapy (IMRT) concurrently with nedaplatin (100mg/m<sup>2</sup> intravenously on D 1, 22 and (or) 43) every three weeks for two or three cycles. The primary end point was objective response rate (ORR). The secondary end points included overall survival (OS), progression-free survival (PFS), distant metastasis-free survival (DMFS) and local recurrence-free survival (LRFS). **Results:** Between March 2020 and June 2021, a total of 32 patients with LA-NPC were enrolled. With a median follow-up duration of 14.0 months (IQR 11.7-16.3), 32 patients (100%) achieved ORR at three months after treatment. The 12-month PFS was 95.7% (95% CI 87.3% to 100%) and the 12-month OS was 100%. The most common grade 3 or 4 adverse events during induction chemotherapy were neutropenia (3 [9.4%]), diarrhea (3 [9.4%]) and hepatotoxicity (3 [9.4%]), followed by leucopenia (2 [6.3%]) and fatigue (1 [3.1%]). The most common grade 3 or 4 adverse events during concurrent chemotherapy were mucositis (3 [9.4%]), leucopenia (1 [3.1%]), neutropenia (1 [3.1%]) and thrombocytopenia (1 [3.1%]). All of these adverse events were manageable. **Conclusions:** Induction chemotherapy with nedaplatin, docetaxel and 5-fluorouracil followed by concurrent nedaplatin combined with radical radiotherapy showed promising antitumor activity and manageable toxicities in patients with LA-NPC. Further phase III randomized controlled trials are warranted to validate our findings. Clinical trial information: NCT04834206. Research Sponsor: Affiliated Cancer Hospital & Institute of Guangzhou Medical University Clinical Research 5555 Program, Wu Jieping Medical Foundation (320.6750.2020-13-11).

**Induction chemotherapy and toripalimab for larynx preservation in resectable locally advanced laryngeal/hypopharyngeal carcinoma: Preliminary results of INSIGHT study.**

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**Background:** Previous studies have demonstrated excellent pathological response of induction PD-1 inhibitor with chemotherapy for locally advanced head and neck cancer. To our knowledge, there is scarce evidence on induction chemotherapy (ICT) and PD-1 inhibitor in organ preservation for patients (pts) with laryngeal/hypopharyngeal carcinoma. Hence, the aim of this study is to evaluate the efficacy and toxicities of ICT and PD-1 inhibitor (Toripalimab) followed by radiotherapy or surgery, for pts with resectable locally advanced laryngeal/hypopharyngeal carcinoma. **Methods:** This is a single-arm phase II study. Pts with histopathologic confirmed, resectable locally advanced laryngeal/hypopharyngeal squamous cell carcinoma and ECOG PS 0-1 were eligible. Three cycles of ICT (paclitaxel 175mg/m<sup>2</sup> d1, cisplatin 25mg/m<sup>2</sup> d1-3) combined with PD-1 inhibitor (Toripalimab 240mg d0) were given. Response assessment (RECIST 1.1) was performed post-ICT. Pts with complete response (CR)/partial response (PR) of primary tumor received concurrent chemoradiation, followed by maintenance therapy of Toripalimab for eight cycles. Otherwise, pts were referred to surgery, followed by adjuvant radiation (RT)/chemoradiation (CRT), and then maintenance therapy of Toripalimab. The primary endpoint is larynx-preservation (LP) rate at 3 months post-RT. Forty-two pts were planned. Based on a two-stage Fleming design (one-sided  $\alpha$ :10%, power: 80%), if at least 22 pts attained LP of the first 27 pts in stage I or at least 32 pts attained LP of the 42 pts at the end of stage II, the null hypothesis would be rejected. The cohort would enroll 15 more pts in stage II if 19-21 pts in stage I observed LP, and the study would be terminated if the number of pts with LP were less than 18 in stage I. **Results:** A total of 27 pts were enrolled. By the cut-off date Feb 8<sup>th</sup>, 2023, all reached at least 3 months of follow-up post-RT. Median age was 63 (53-74) years with 92.6% male. Hypopharyngeal cancer accounted for 66.7%. 74.1% were T3 to T4, and 77.7% were N2 to N3. Six cases had primary invasion of esophagus and five pts underwent pretreatment tracheostomy. ORR of ICT was 85.2%. Afterwards, 21 pts were treated with concurrent CRT, while 6 pts received surgery of primary tumor. At 3 months post-RT, 23 pts attained organ preservation and the LP rate was 85.2%. With a median follow-up of 13.5 months, 1-year OS rate, PFS rate and LP survival rate was 83.1%, 79.5% and 79.4%, respectively. During ICT, 22.2% of pts experienced grade 3-4 treatment-related AEs (TRAES). The most common grade 3-4 TRAES were nausea and neutrophil count decreased. **Conclusions:** The primary endpoint LP rate was met. In this cohort of extensive locally advanced laryngeal/hypopharyngeal carcinoma, ICT and Toripalimab followed by radiotherapy or surgery resulted in satisfactory short-term LP rate and encouraging survival. Clinical trial information: NCT04995120. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

### A pilot phase II trial of neoadjuvant camrelizumab plus nab-paclitaxel and cisplatin (NeoCPC) for locoregionally advanced, resectable squamous cell carcinoma of the head and neck.

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**Background:** For resectable squamous cell carcinoma of the head and neck (HNSCC), novel therapeutic approaches are still needed to improve outcomes. Neoadjuvant immunochemotherapy (NICT) is considered as a potentially effective strategy. We therefore conducted a pilot phase II trial to explore the efficacy and safety of neoadjuvant camrelizumab plus nab-paclitaxel and cisplatin (NeoCPC) in patients with locoregionally advanced, resectable HNSCC. **Methods:** In this open-label phase II trial, patients with untreated locoregionally advanced, resectable HNSCC (T2–T4, NO–N3b, MO; AJCC, 8th Edition) received NICT with camrelizumab (200 mg), nab-paclitaxel (260 mg/m<sup>2</sup>) and cisplatin (60 mg/m<sup>2</sup>) on day 1 of each 21-day cycle for three cycles, followed by radiotherapy or surgery. The primary endpoint was objective response rate (ORR) per RECIST version 1.1. Secondary endpoints included pathologic complete response (pCR), major pathologic response (MPR), safety, disease-free survival (DFS), and overall survival (OS). Genomic biomarkers (genetic mutations, tumour mutational burden [TMB] and immune microenvironment) in baseline tumor samples were explored. **Results:** Between April 2021 and January 2022, 48 patients were enrolled (median age, 59 years [range 27–73]; 42 men [87.5%]). After completion of neoadjuvant therapy, patients underwent surgery (27, 56.3%), chemoradiotherapy (15, 31.2%), radiotherapy (five, 10.4%) or continued immunochemotherapy as maintenance therapy (one, 2.1%). At a median follow-up time of 415 days, the ORR was 89.6% (43/45). Of the 27 patients who had surgery, 17 (63.0%) patients had an MPR, including 15 (55.6%) with a pCR. Patients with ORR were more likely to achieve pCR. One patient died of lung metastasis 6 months after completion of treatment. The 1-year OS and DFS rates were both 97.9%. Only 3 (6.3%) patients had grade 3 treatment-related adverse events (AEs): one with pneumonitis and two with neurotoxicity. No unexpected immune-related AEs were observed. For genetic analysis, the most frequently mutated genes were TP53 (77.1%), CDKN2A, FAT1, CCND1 and NOTCH1. The lower radiographic tumor regression percentage was observed in TP53-altered ( $p=0.01$ ) and TERT-altered ( $p=0.002$ ) patients, whereas higher percentage was observed in HPV-positive patients. The median TMB was 3.15 mutations/MB. No significant difference was observed in TMB between patients with ORR and non-ORR (stable disease). There was a significant correlation between density of M1-like macrophage cells, CD8+ T cells in tumor area and radiographic tumor regression percentage ( $p=0.009$ ,  $p=0.0005$ , respectively). **Conclusions:** NeoCPC showed promising efficacy with a high ORR and pathologic response rate for locoregionally advanced, resectable HNSCC, with an acceptable safety profile. Clinical trial information: NCT04826679. Research Sponsor: China Postdoctoral Science Foundation: 2022M713612.

**Induction therapy of toripalimab combined with docetaxel and cisplatin in locally advanced hypopharyngeal squamous cell carcinoma (HPSCC): A single-arm, phase II clinical trial.**

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**Background:** PD-1 (programmed cell death protein-1) inhibitors combination with chemotherapy has a significant efficacy and approved indications in the first-line treatment of head and neck squamous cell carcinoma (HNSCC), but the efficacy of these combination therapies in locally advanced hypopharyngeal squamous cell carcinoma (HPSCC) remains unexplored. We conducted a single-arm, phase II trial to assess the efficacy and safety of toripalimab (a novel PD-1 inhibitor) combined with chemotherapy as induction treatment in locally advanced HPSCC. **Methods:** Patients with locally advanced HPSCC (cT1N+M0 or T2-4NanyM0, AJCC 8.0) were eligible. All patients received 2 cycles of intravenous docetaxel (75mg/m<sup>2</sup>), cisplatin (75mg/m<sup>2</sup>) and toripalimab (240mg) on day 1 every 21 days, followed by radical surgery or concurrent chemoradiotherapy (CCRT) with cisplatin (100mg/m<sup>2</sup>, q21d). The primary endpoint was objective response rate (ORR) assessed by investigators per RECIST v1.1. Secondary endpoints were major pathologic response (MPR), 2 year disease-free survival (DFS) rate in patients received surgery, 2 year progression-free survival (PFS) rate in patients received CCRT and 2 year overall survival (OS) rate in all patients. **Results:** From July 2020 to January 2023, 34 patients (median age: 59, range: 46-72, male: 100%, stag IV: 100%) were enrolled. Patients with stage IVA and IVB disease were 19 (19/34, 55.9%) and 15 (15/34, 44.1%), respectively. 33 patients completed 2 cycles induction treatment and efficacy evaluation (1 patient dropped out). The evaluated ORR was 54.5%, including 3 pts achieving complete response and 15 achieving partial response. PD-L1 status (combined positive score, CPS) were known in 8 patients, ORR were 80% (4/5) and 66.7% (4/6) in patients with CPS $\geq$ 20 and CPS $\geq$ 1, respectively, 2 patients with CPS < 1 had stable disease. Treatment-related grade 3-4 adverse events occurred in 45.5% (15/33) of patients, leukopenia (42.4%) and neutropenia (3.1%). Immune-related AEs were acceptable, 1 patient (1/33, 3.0%) experienced grade 2 interstitial pneumonia and 2 patients (2/33, 6.1%) experienced grade 1 rash. In the following treatment, 27 patients (27/33, 81.8%) performed CCRT. 4 patients (4/33, 12.1%) underwent surgery followed by CCRT and 2 patients (2/33, 6.1%) refused further treatment. Among these 17 patients finished CCRT and radiological assessment, 9 patients (9/17, 52.9%) had complete response, 7 patients (7/17, 41.2%) had partial response and 1 patient (1/17, 5.9%) had progressive disease. Survival data are not mature by cut-off date. **Conclusions:** Induction therapy of toripalimab combined with docetaxel and cisplatin was well tolerated and highly efficient for locally advanced HPSCC. Clinical trial information: NCT04296747. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

# **Nab-paclitaxel plus cisplatin versus docetaxel plus cisplatin and 5-FU induction chemotherapy followed by concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: A multicenter parallel controlled phase III trial.**

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**Background:** Although several large phase III clinical trials and meta-analysis have demonstrated significant clinical benefit of docetaxel combined with cisplatin and 5-FU (TPF) chemotherapy in head and neck cancer, serious adverse reactions are unsatisfactory. Therefore, this study was designed to evaluate the efficacy and safety of nab-paclitaxel plus cisplatin (TP) versus TPF induction chemotherapy (ICT) followed by concurrent chemoradiotherapy (CCRT) for locally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** In this open-label, phase 3 trial, patients were randomized 1:1 to received TP (260 mg/m<sup>2</sup> nab-paclitaxel and 80 mg/m<sup>2</sup> cisplatin on days 1 and 22) or TPF (60 mg/m<sup>2</sup> docetaxel and 60 mg/m<sup>2</sup> cisplatin on days 1 and 22; 3 g/m<sup>2</sup> 5-Fu on days 1-5 and 22-26) every 3 weeks for 2 cycles, both groups of patients received CCRT (100mg/m<sup>2</sup> cisplatin and IMRT on days 43 and 64) every 21 days for 2 cycles. The primary endpoint was failure-free survival. Secondary endpoints included overall survival, objective response rate (ORR), quality of life and safety. **Results:** From January 2019 to July 2021, 281 patients were randomized to TP (n = 142, TP arm) or TPF (n = 139, TPF arm). The median age was 44 years (range, 20-63) in the TP arm and 45 years (range, 18-69) in the TPF arm. The pathological stages were 40.85% stage III and 59.15% stage IVA in the TP arm, while those of the TPF arm were 43.17% stage III and 56.83% stage IVA. There were 99.30% and 97.12% undifferentiated nonkeratinizing carcinoma in the two groups, respectively. All patients had Karnofsky performance status of 90. ICT was completed in 98.93% (100% in the TP arm and 97.84% in the TPF arm). The median relative dose intensity of nab-paclitaxel and cisplatin were 99.96% and 99.81% in the TP arm, 99.83%, 100% and 100% for docetaxel, cisplatin and 5-FU in the TPF arm, respectively. The ORR were 80.28% in the TP arm and 78.26% in the TPF arm after two cycles of ICT. 85.77% (83.10% in the TP arm and 88.49% in the TPF arm) completed the CCRT. After two cycles of CCRT, the ORR were 99.25% and 99.24%, respectively. 3 months after completion of all treatment, the ORR were 99.25% and 99.25%, respectively. During ICT, all treatment-related adverse events occurred in 40.14% of patients in the TP arm and 57.55% in the TPF arm. The most frequent grade 3 adverse events were neutropenia (0.70% vs 2.16%), leucopenia (0 vs 2.88%), diarrhea (0 vs 0.72%) in the TP arm and in the TPF arm. Over the entire course of treatment, the most common was 1 grade adverse events, and no patient developed grade 4 adverse events in the two groups. **Conclusions:** In this study, TP regimen showed similar trends in the ORR but excellent safety profile in patients with LA-NPC compared with TPF regimen, suggesting a potential therapeutic option for this population. Clinical trial information: ChiCTR1800019922. Research Sponsor: CSPC Ouyi Pharmaceutical Co., Ltd.



**Prospective study of integrating post-radiotherapy [ $^{18}\text{F}$ ] fluorodeoxyglucose-positron emission tomography/computed tomography scan and plasma Epstein-Barr virus DNA in surveillance of locoregionally advanced nasopharyngeal carcinoma.**

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**Background:** To evaluate the role of [ $^{18}\text{F}$ ] fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scan at 12-weeks after the end of Radiotherapy (RT) integrated with plasma EBV DNA in surveillance and standardized implementation of locoregionally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** This prospective study was conducted in patients with stage III-IVa LA-NPC. FDG-PET/CT examination and plasma Epstein-Barr virus (EBV) DNA measurements was performed pretreatment and at 12-weeks after the end RT. The primary study endpoint was the negative predictive value (NPV) and other supporting diagnostic test characteristics of 12-weeks FDG-PET/CT for the surveillance of residual locoregional disease and new distant metastasis. **Results:** From June 2018 to December 2019, 506 eligible patients were enrolled and entered follow-up (median, 45 months). At 12 weeks after the end of RT, there were 22 (4.3%) patients have residual locoregional disease, 30 (5.9%) patients developed distant metastasis and 6 (1.2%) patients presented both residual locoregional disease and distant metastasis. The NPV of 12-weeks FDG-PET/CT for overall residual diseases and distant metastasis was 96.3% (95% confidence interval [CI], 94.0%-97.8%) with sensitivity of 72.4% (95%CI, 58.9%-83.0%), specificity of 93.3% (95%CI, 90.5%-95.4%), positive predictive value (PPV) of 58.3% (95%CI, 46.1%-69.6%) and accuracy of 90.9% (95%CI, 88.4%-93.4%). In EBV DNA-based risk subgroups, the NPV of 12-weeks PDG-PET/CT was 96.8% (95%CI, 94.5%-98.2%) in patients with undetectable 12-weeks plasma EBV DNA and 87.0% (95%CI, 65.3%-96.5%) in patients with detectable 12-weeks plasma EBV DNA. **Conclusions:** 12-weeks PDG-PET/CT was reliable in the surveillance of LA-NPC and could help optimize the follow-up strategy and provide implications for timely and effective therapeutic regimen, especially for patients in different EBV DNA-based risk groups. Clinical trial information: NCT03601390. Research Sponsor: National Key Research and Development Program of China, National Natural Science Foundation of China, Guangdong Major Project of Basic and Applied Basic Research, Sci-Tech Project Foundation of Guangzhou City; the Sun Yat-sen University Clinical Research 5010 Program, Innovative Research Team of High-level Local Universities in Shanghai, Natural Science Foundation of Guangdong Province for Distinguished Young Scholar, Postdoctoral Innovative Talent Support Program, the Pearl River S&T Nova Program of Guangzhou, Planned Science and Technology Project of Guangdong Province, Key Youth Teacher Cultivating Program of Sun Yat-sen University, and Fundamental Research Funds for the Central Universities.

# CT radiomic signature to predict overall survival and chemotherapy benefit in stage I and II HPV-associated oropharyngeal carcinoma.

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**Background:** Chemoradiation is the standard of care for human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC). However, not all patients would benefit from chemotherapy, especially patients with low-risk characteristics. We aim to develop and validate a prognostic and predictive radiomic image signature (pRis) to inform survival and chemotherapy benefit in stage I and stage II HPV-associated OPSCC. **Methods:** Radiographic scans for 491 patients with stage I and stage II HPV-associated OPSCC were acquired from 4 independent sources and divided into three cohorts D<sub>1</sub>-D<sub>3</sub>. D<sub>1</sub> comprised computed tomography (CT) scans from 60 radiotherapy treated patients and was used to identify prognostic features via a LASSO Cox model to predict overall and disease-free survival. The prognostic performance of pRis was evaluated on two test sets (D<sub>2</sub>, n = 162; D<sub>3</sub>, n = 269) using concordance index (C-index). An integrated nomogram was developed to demonstrate the incremental value of the pRis to the existing clinical factors for individualized survival estimation. Patients from D<sub>2</sub> and D<sub>3</sub> who received either radiotherapy alone or chemoradiation were used to validate pRis as predictive of added benefit of chemotherapy. **Results:** Seven radiomic features were selected to construct the image biomarker pRis, which was found to be prognostic of overall survival (OS) on univariate analysis in D<sub>2</sub> (hazard ratio [HR] = 2.14, 95% confidence interval [CI], 1.1–4.16, p = 0.02) and D<sub>3</sub> (HR = 2.74, 95% CI, 1.34–5.62, p = 0.006). Chemotherapy was associated with improved OS for high-pRis patients in both D<sub>2</sub> (radiation vs chemoradiation, HR = 4.47, 95% CI, 1.73–11.6, p = 0.002) and D<sub>3</sub> (radiation vs chemoradiation, HR = 2.99, 95% CI, 1.04–8.63, p = 0.04). In contrast, chemotherapy did not improve OS for low-pRis patients, which indicates these patients did not derive additional benefit from chemotherapy and could be considered for treatment de-escalation. **Conclusions:** The proposed radiomic signature was prognostic of patient survival and the binary pRis group informed chemotherapy benefit for stage I and II HPV-associated OPSCC patients. Research Sponsor: U.S. National Institutes of Health.

Hazard ratios and p values for patients receiving radiation alone vs chemoradiation according to pRis groups.

	Hazard ratio (Confidence interval)	P value
D2, High-pRis	4.47 (1.73 – 11.6)	0.002
D2, Low-pRis	2.56 (0.745 – 8.77)	0.136
D3, High-pRis	2.99 (1.04 – 8.63)	0.04
D3, Low-pRis	0.28 (0.05 – 1.49)	0.135

# Induction chemotherapy with nanosomal docetaxel lipid suspension (NDLS), cisplatin, and fluorouracil in patients with locally advanced head and neck squamous cell carcinoma.

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**Background:** Nanosomal docetaxel lipid suspension (NDLS), a polysorbate-80 and ethanol free formulation, was developed to overcome the toxicity issues and to improve disease outcomes associated with conventional docetaxel. We evaluated the safety and efficacy of NDLS based TPF (NDLS, cisplatin and 5-fluorouracil [FU]) induction chemotherapy in patients with inoperable/unresectable Locally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC). **Methods:** In this multicentric, single arm, open label, Phase IV clinical study, patients with inoperable/ unresectable LA HNSCC received induction chemotherapy with NDLS (75 mg/m<sup>2</sup>; Day 1), cisplatin (75 mg/m<sup>2</sup>; Day 1) and 5-FU (750 mg/m<sup>2</sup>/day for 5 days) based TPF regimen every 3 weeks (q3w) for 4 cycles followed by radiotherapy. The study outcomes were overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS). **Results:** Fifty patients were enrolled in this study. Most of the patients belonged to the age group of 35-64 years (86%) and had a WHO performance status of 1 (66%). In the modified intent-to-treat (mITT) population ( $n = 40$ ), the ORR after NDLS based TPF induction chemotherapy was 42.5%, which increased to 60.0% after loco-regional therapy. In the per-protocol (PP) population ( $n = 14$ ), the ORR was 64.3%, which increased to 80.0% after loco-regional therapy (Table). At 2 years, the PFS and OS rates were 82.5% and 97.5%, respectively, in the mITT population and 85.7% and 100% respectively, in the PP population. The most common grade 3/4 adverse effects reported were neutropenia (10%), leukopenia (6%), febrile neutropenia (4%), asthenia (2%), diarrhea (2%), and thrombocytopenia (2%) respectively. Grade 3/4 infusion-related reactions, hyperglycemia or neuropathy were not reported. **Conclusions:** NDLS based induction chemotherapy was effective and well-tolerated in the treatment of inoperable LA HNSCC and showed high response rates. Clinical trial information: CTRI/2017/12/010938. Research Sponsor: Intas Pharmaceuticals Ltd.

Clinical response rate.				
Parameter	mITT		PP	
	Response to Chemotherapy ( $n = 40$ )	Response to chemotherapy and radiotherapy ( $n = 15$ )	Response to Chemotherapy ( $n = 14$ )	Response to chemotherapy and radiotherapy ( $n = 5$ )
PR, n (%)	17 (42.5)	9 (60.0)	9 (64.3)	4 (80.0)
SD, n (%)	14 (35.0)	3 (20.0)	2 (14.3)	0 (0.0)
ORR, n (%)	17 (42.5)	9 (60.0)	9 (64.3)	4 (80.0)
95% CI	[27.04-59.11]	[32.29-83.66]	[35.14-87.24]	[28.36-99.49]
2-year PFS, n (%)	33 (82.5%)		12 (85.7%)	
2-year OS, n (%)	39 (97.5%)		14 (100.0 %)	

CI, confidence interval; CR, complete response; DCR, disease control rate; mITT, modified intent-to-treat; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PP, per-protocol; PR, partial response; SD, stable disease.

**Neoadjuvant pembrolizumab, GX-188E, and GX-I7 in patients with human papillomavirus-16- and/or 18-positive head and neck squamous cell carcinoma: Single-arm, phase 2 trial with single cell transcriptomic analysis and artificial intelligence-powered spatial analysis.**

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**Background:** With the increasing prevalence of head and neck squamous cell carcinoma (HNSCC) associated with human papilloma virus (HPV) infection, effective treatment strategies for HPV-positive HNSCC are urgently needed. Here, we present the results of neoadjuvant checkpoint blockade of pembrolizumab, therapeutic HPV DNA vaccine of GX-188E, and long-acting interleukin-7 of GX-I7 for patients with resectable HPV-16 and/or 18-positive HNSCC. **Methods:** In this single-arm, phase 2 trial, patients with resectable HPV-16 and/or 18-positive HNSCC were enrolled. Patients were given pembrolizumab 200mg on day 1 and day 22; GX-188E 2mg on day 1, 8, and 22; and GX-I7 1200 ug/kg on day 8 before surgical resection. Major pathologic response (MPR; defined as residual viable tumor of less than or equal to 10%) was primary endpoint with null and alternative hypothesis of MPR rate  $\leq 5\%$  and  $\geq 35\%$ , respectively. Secondary objectives were safety, recurrence, and survival. **Results:** Of the 11 patients included, all underwent surgical resection after neoadjuvant treatment without delays in surgery or increased surgical complications. MPR was achieved in seven patients (63.6%) and pathologic complete response was achieved in four patients (36.3%), which met the primary endpoint. Single cell RNA sequencing of baseline and post-treatment paired specimens revealed that the proportion of follicular helper T cell cluster, featured with *CXCR5* and *BCL6* expression, was significantly increased among tumor-infiltrating immune cells, accompanied with the reinvigoration of CD8 T cell cluster toward less exhausted phenotypes, represented with the upregulation of *TCF7* and *CD28* expression. In addition, artificial intelligence-powered spatial analysis revealed that triple combination significantly increased the density of tumor-infiltrating lymphocytes, completely converting immune-desert and immune-excluded type of tumor to inflamed immune phenotype. **Conclusions:** Neoadjuvant pembrolizumab, GX-188E, and GX-I7 showed promising activity and manageable safety profile in patients with resectable HPV-16 and/or 18-positive HNSCC. Therapeutic induction of brisk immune responses significantly reshaped the tumor microenvironment and associated with pathologic regression, warranting further investigation of pembrolizumab, GX-188E, and GX-I7 for patients with HPV-positive HNSCC. Clinical trial information: NCT05286060. Research Sponsor: None.

### Development of CT-based radiomic model to predict 5-year progression-free survival (PFS) in locally advanced head and neck squamous cell carcinoma (LAHNSCC) treated with definitive chemoradiation.

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**Background:** Definitive chemoradiation is the current standard treatment in LAHNSCC. Prognostic biomarkers that enable to reliably predict LAHNSCC disease progression are needed to stratify the risk of progression to tailor treatment intensity in future clinical trials. Imaging biomarkers have emerged as promising alternatives to non-invasively predict patient outcomes. Aim: to identify an imaging signature to predict progression-free survival (PFS) in LAHNSCC. **Methods:** A single-center, retrospective, observational study was designed. Clinical data and pre-treatment CT images from LAHNSCC patients treated with definitive chemoradiation from 2014 to 2022 were collected. Manual tumor segmentation was performed slice by slice by a qualified image technician and supervised by a radiologist with 20+ years in HNSCC using the DICOM viewer of Quibim platform. A total of 108 radiomic features (shape and textures) were extracted from each region of interest. Feature reduction techniques were applied to select the characteristics used in the classification model. The primary endpoint of this study was 5-year PFS. Random Forest, Support Vector Classifier (SVC), Logistic Regression, Gradient Boosting (GB) and Extreme Gradient Boosting classification models were used. A 5-fold cross validation strategy was followed to evaluate the performance of the models in terms of AUROC, sensitivity, specificity, and accuracy. The importance of each feature in the model was measured by applying the Shapley Additive exPlanations (SHAP) method. **Results:** Baseline CT exams from 102 LAHNSCC patients were included; 50% and 23% were stage IVA and IVB, respectively. The remaining 27% (stage II [3%] and stage III [24%]) were treated in an organ-preservation intention. 67% of patients presented locoregional or distant progression at 5 years. All radiomic features (108) and 6 clinical variables were used in the predictive model, for which a cross-validation was performed. GB as the feature selection technique and SVC as the classification model provided the best results. The final model was able to predict 5-year PFS with an average AUC of 0.82 (95% CI: [0.73, 0.91]), a sensitivity of 0.69 (95% CI: [0.57, 0.81]), a specificity of 0.82 (95% CI: [0.7, 0.94]) and an accuracy of 0.73 (95% CI: [0.62, 0.84]). From most to least important, features contributing to the predictive model were: TNM stage (SHAP: 0.038), glszm Small Area Emphasis (SHAP: 0.026), glcm Idmn (SHAP: 0.023), glszm Large Area High Gray Level Emphasis (SHAP: 0.018) and glrlm Run Entropy (SHAP: 0.015). **Conclusions:** Radiomic biomarkers from pre-treatment CT images in combination with TNM stage were predictive of 5-year PFS to chemoradiation in LAHNSCC patients and might be helpful for patient risk stratification. Further validation of these imaging biomarkers is ongoing. Research Sponsor: INCLIVA Biomedical Research Institute - University of Valencia.

**Neoadjuvant chemoimmunotherapy for the treatment of locally advanced laryngeal and hypopharyngeal squamous cell carcinoma: A single-arm phase 2 clinical trial.**

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**Background:** Standard treatment for patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma (LHSCC) is total laryngectomy, which seriously affects the quality of life. Neoadjuvant treatment with Nab-paclitaxel plus cisplatin (TP) has favorable efficacy with acceptable toxicity for laryngeal preservation in LHSCC. Programmed death 1 (PD-1) blockade plus chemotherapy has shown a survival benefit and recommended as the first-line treatment in recurrent or metastatic head and neck cancer, but the safety and activity in the combination of TP and PD-1 blockade in locally advanced LHSCC need investigation. **Methods:** In this single-center, single-arm, phase 2 trial, newly diagnosed pts with stage T3-4N0-3M0 laryngeal SCC or T2-4N0-3M0 hypopharyngeal SCC were recruited. Eligible patients received chemotherapy [Nab-paclitaxel 240 mg/m<sup>2</sup> plus cisplatin 75 mg/m<sup>2</sup>] and toripalimab [240 mg, d1] every 3 weeks for 3 cycles. After induction treatment, patients achieving clinical partial response (cPR) or complete response (cCR) received definitive radiotherapy, while those with stable diseases (SD) and progression disease (PD) received surgery plus adjuvant radiotherapy. Toripalimab was given intravenously once every 3 weeks for up to 10 cycles, including 3 cycles before. The primary endpoint was the objective response rate (ORR) according to RECIST 1.1 by investigator assessment to neoadjuvant chemoimmunotherapy. The secondary endpoints included laryngectomy-free survival (LFS), disease failure-free survival (DFS) and overall survival (OS) at 2 years, quality of life (QOL) and toxic effects. **Results:** From October 2020 to May 2022, 25 patients received neoadjuvant chemoimmunotherapy (median age 58 years; 23.9% men), 52% (13/25) and 48% (12/25) were hypopharyngeal and laryngeal squamous cell carcinoma. 80% (20/25) were clinical T3/4 and 64.0% (16/25) ≥N2. After neoadjuvant chemoimmunotherapy, 2 patients achieved CR, 21 achieved PR, with an ORR of 92% (23/25), 23 patients with CR/PR of the primary tumor received concurrent radiotherapy and immune maintenance therapy, 2 patients with SD/PD received laryngectomy. At a median follow-up of 17 months (range 8-27 months), 1-year DFS was 88.0%, 1-year OS was 96.0%, 1-year LPS was 92.0%. Respectively, only grade 1-2 adverse events occurred in 100% of patients, including loss of appetite (100%), anemia (92.0%), nausea (84.0%), vomiting (52.0%), hypothyroidism (16.0%), peripheral neuritis (20%), leukopenia (12.0%), rash (12.0%). **Conclusions:** Neoadjuvant treatment with TP plus toripalimab achieved impressive ORR and 1-year LPS rate with manageable toxicities in patients with LHSCC. Further follow-up is needed to confirm the long-term efficacy. Clinical trial information: ChiCTR2000033506. Research Sponsor: None.

**Neoadjuvant low-dose radiotherapy, tislelizumab, combined with albumin-bound paclitaxel and cisplatin in resectable locally advanced head and neck squamous cell carcinoma (NeoRTPC02): The first-stage result from an open label, single-arm, two stage, phase II clinical trial.**

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**Background:** Neoadjuvant immunotherapy and chemotherapy has been explored in phase I/II clinical studies in head and neck squamous cell carcinoma (HNSCC), confirming its safety and efficacy. However, the pathological complete response (pCR) / major pathological response (MPR) rate still needed for improvement. Recent studies revealed that low dose radiotherapy can overcome immunosuppressive tumors by reversing immune desertification when combining immunotherapy. Here, we conducted this clinical trial to explore the efficacy and safety of neoadjuvant low-dose radiotherapy, PD-1 inhibitor, combined with chemotherapy in resectable locally advanced head and neck squamous cell carcinoma. **Methods:** This was an open-label, single-arm, phase II clinical trial. Patients with untreated, histologically confirmed HNSCC staging III-IVB were included. The eligible patients were scheduled to be administrated neoadjuvant low-dose radiotherapy (1GY/1F, D1, D2, D8, D15, Q3W), PD-1 inhibitor tislelizumab (200 mg D1, Q3W), combined with albumin-bound paclitaxel (100mg/m<sup>2</sup>, D1, D8, D15, Q3W) and cisplatin (25mg/m<sup>2</sup>, D1, D8, D15, Q3W) for two cycles. Radically surgical resection was planned to conduct 3-4 weeks after neoadjuvant therapy. The primary endpoint was pCR rate. The second endpoints consisted of MPR rate, objective response rate (ORR), R0 resection rate, safety, non-surgery-delay rate and quality of life. 25 patients will finally be enrolled in this study. Simon's two-stage design was adopted, and 10 patients should be included in the first stage. If 2 or more of the first 10 patients reached pCR, the second stage would be successfully entered. **Results:** By Jan 10, 2023, 10 patients were enrolled. 7 out of 10 patients successfully received the study regimen and finished the operation on schedule. Our primary endpoint of first stage was met. 4/7 (57%) patients achieved pCR at the primary site, 3/7 (43%) patients achieved MPR. The pCR/MPR rate was 100%. R0 resection rate was 100%. Totally 9 patients underwent MRI scan pre and post neoadjuvant therapy, and the assessment per RESCIST criteria were as follow: 0/9 (0%) CR, 6/9 (66%) PR, 3/9 (33%) SD. The treatment-related adverse events (TRAEs) were manageable. The most shared adverse events of grade 1/2 were anorexia (89%), anemia (89%) and nausea (66%). No surgical delay was observed. **Conclusions:** Neoadjuvant low-dose radiotherapy, tislelizumab, combined with albumin-bound paclitaxel and cisplatin contributed to an outstanding pCR/MPR rate of 100% (pCR rate of 57% and MPR rate of 43%) at present, and was generally tolerated in locally advanced HNSCC. The second stage is ongoing. Clinical trial information: NCT05343325. Research Sponsor: BeiGene Co., Ltd. and CSPC Co., Ltd.

# Impact of acute kidney injury on overall survival in postoperative patients with head and neck cancer who received chemoradiotherapy with cisplatin: A supplementary analysis of a phase II/III trial of JCOG1008.

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**Background:** A randomized phase II/III trial of JCOG1008 demonstrated that chemoradiotherapy (CRT) with weekly cisplatin at 40 mg/m<sup>2</sup> (Weekly arm) was noninferior to 3-weekly cisplatin at 100 mg/m<sup>2</sup> (3-weekly arm) in terms of overall survival (OS) for postoperative high-risk head and neck cancer (hazard ratio [HR], 0.69 [99.1% CI, 0.37 to 1.27 < 1.32]; *J Clin Oncol* 2022; 40: 1980-90). Acute kidney injury (AKI) is a major dose-limiting toxicity of cisplatin. Here, we investigated the impact of AKI on OS in patients treated with CRT in JCOG1008. **Methods:** A total of 251 patients who were treated with CRT in JCOG1008 were analyzed. AKI was defined as an increase in serum creatinine of  $\geq 0.3$  mg/dL or a 1.5-fold or more increase from baseline ( $\geq$  stage I) within 30 days after completion of CRT, based on the AKI Network classification/staging system. OS in the two arms was compared by the development of AKI using the log-rank test. **Results:** The total incidence of AKI in the weekly arm was lower than that in the 3-weekly arm (38 of 122 [31.1%] vs. 56 of 129 [43.4%]). The incidence of stage II/III AKI was also lower in the weekly arm (8 of 122 [6.6%] vs. 19 of 129 [14.7%]). Total cisplatin dose was similar in patients who did and did not develop AKI in the weekly arm, but was lower in patients who developed AKI in the 3-weekly arm (Table). Moreover, no difference in OS was observed between patients who did and did not develop AKI in the weekly arm (HR, 1.06 [95% CI, 0.53 to 2.10]), whereas patients who developed AKI in the 3-weekly arm had poorer OS than those who did not (HR, 1.83 [95% CI, 1.04 to 3.21]). **Conclusions:** In this supplementary analysis of JCOG1008, development of AKI impacted OS in the 3-weekly arm, but not in the weekly arm. Consistent exposure to cisplatin through weekly fractionated administration appears of greater clinical significance than cumulative dose, providing maintenance of treatment intensity and better kidney safety, and likely also improving outcomes. Clinical trial information: jRCTs031180135. Research Sponsor: National Cancer Center Research and Development Funds (29-A-3, 25-B-2, and 2020-J-3); AMED under Grant Nos. JP16ck0106055, JP16ck0106093, and JP19ck0106321; and a Grant-in-Aid for Clinical Cancer Research (H23-009 and H26-052) from the Ministry of Health, Labor and Welfare of Japan.

Treatment delivery, compliance, and efficacy outcomes according to treatment arm.						
Parameter	3-weekly arm			Weekly arm		
	AKI (-) n=73	AKI (+) n=56	P-value	AKI (-) n=84	AKI (+) n=38	P-value
Total RT dose (Gy), median (IQR)	66 (66-66)	66 (66-66)	0.72	66 (66-66)	66 (66-66)	0.68
Duration of RT (days), median (IQR)	49 (47-50)	50 (47-52)	0.60	49 (46-50)	49 (47-50)	0.37
Total cisplatin dose (mg/m <sup>2</sup> , IQR)	297.4 (258.9-299.1)	276.3 (219.7-298.0)	0.007	239.2 (199.5-276.7)	238.6 (197.3-277.2)	0.94
Proportion of actual to planned delivery of cisplatin (%), median (IQR)	93.2 (86.4-100.0)	92.4 (73.3-99.9)	0.009	85.7 (71.4-100.0)	85.7 (71.4-100.0)	0.83
3-year overall survival (%; 95% CI)	70.6 (58.6-79.8)	57.9 (43.6-69.7)	0.04	74.7 (63.9-82.7)	76.1 (59.1-86.8)	0.88
3-year relapse-free survival (%; 95% CI)	64.3 (52.2-74.1)	49.5 (35.8-61.9)	0.09	68.9 (57.8-77.7)	65.8 (48.5-78.5)	0.27



**Neoadjuvant tislelizumab combined with APF for patients with locally advanced head and neck squamous cell carcinoma: A prospective single-arm clinical trial.**

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**Background:** Seeking out a more effective and less-toxic regimen is necessary for patients with locally advanced head and neck squamous cell carcinoma (HNSCC). The aim of this study is to evaluate the efficacy and safety of neoadjuvant anti-programmed cell death-1 antibody tislelizumab combined with APF (albumin-bound paclitaxel, platinum and fluorouracil) followed by surgery or concurrent chemoradiotherapy. **Methods:** In this prospective, single-center, single-arm clinical study, previously untreated patients with locally advanced HNSCC, aged 18-75 years without severe comorbidities and contraindications to immunotherapy are enrolled. Eligible patients received A (200 mg/m<sup>2</sup> d1) P (60 mg/m<sup>2</sup> d1- d2) F (600 mg/m<sup>2</sup> CIV120h) induction chemotherapy along with tislelizumab (200 mg d1) every 3 weeks. The curative effect is evaluated (RECIST 1.1) after 3 cycles and a multidisciplinary team discuss whether to perform surgery. For patients undergoing surgery, treatment is completed if there is no residual and extra-capsular lymph node invasion; in case of positive surgical margin, or extracapsular lymph node invasion, or residual lymph nodes, patient will receive concurrent chemoradiotherapy (tumor bed and neck lymph drainage area 66 Gy~70 Gy, P 60 mg/m<sup>2</sup>). Those not suitable for surgery will receive radical concurrent chemoradiotherapy (GTV 66Gy~70Gy, PTV 50Gy, P 60 mg/m<sup>2</sup>) within 3 weeks after neoadjuvant treatment. The primary endpoint of efficacy evaluation is the pathological complete response (pCR) rate. Safety evaluation indicators include vital signs, laboratory indicators and adverse events (NCI CTC AE4.0). **Results:** From Apr 2022 to Jan 2023, 12 patients are screened and enrolled. For the 7 patients who complete 3 cycles of neoadjuvant therapy, 3 patients (42.8%) successfully undergo surgery, with 2 patients (28.5%) achieving pCR and 1 patient (14.3%) achieving major pathological response (MPR). For the other 4 patients, 1 patient (14.3%) achieve pCR by multipoint biopsy of the primary lesion and 2 patients (28.5%) obtain radiologic partial response (PR) by MRI. 1 patient' lymph nodes tend to increase during radiotherapy and that patient withdraw from clinical trial and undergo salvage surgery. The objective response rate (ORR) of neoadjuvant treatment is 85.7% and pCR rate is 42.9%. Grade 2 or higher AEs during neoadjuvant therapy include grade 2 liver function damage (n = 1, 8.3%), grade 3 myelosuppression (n = 1, 8.3%). 1 (8.3%) patient developed radiation-related oral mucositis (RTOG 2). No other obvious adverse reactions of radiotherapy, chemotherapy or immunotherapy are observed. **Conclusions:** Combining Tislelizumab with APF followed by surgery or radical concurrent chemoradiotherapy is feasible and effective in patients with locally advanced HNSCC, and further studies are needed to verify its effectiveness and safety. Research Sponsor: None.

### Neoadjuvant durvalumab and tremelimumab in resectable locally advanced SCC of the oral cavity: DUTRELASCO study.

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**Background:** Promising rates of response to ICI have been observed in patients with OSCC. This is phase I/II study with focus on biological changes observed in sequential tissue acquisition. **Methods:** Eligibility criteria: Resectable OSCC stage IV Description of each treatment arm: Arm A: durvalumab (1500 mg) on day -14 and 6 cycles adjuvant Arm B: durvalumab (1500 mg) and tremelimumab (75 mg) combination on day -14 and 6 cycles adjuvant Primary endpoint: Biological response in tumor tissue by means of difference in CD8+ lymphocyte infiltration density (TIL) and % remaining viable tumor cells. Secondary endpoints: Recist v1.1 OS PBM and plasma analysis scRNA-seq Statement of study design: open-label, prospective stratified, phase I/II study. **Results:** No ICI related toxicity interfered with surgery. 50 % of patients presented with at least 1 severe AE. There was no difference between both arms. 2 year OS is 64% in arm A and 80% in arm B. Both arms show a significant increase ( $p = 0.01$ ) in TILs. We observed a significant decrease in viable tumor cells ( $p < 0.01$ ). No objective pathological response with  $> 50\%$  decrease of viable tumor cells was observed. T-cell expansion varied although a positive correlation between T-cell expansion and radiologic tumor shrinkage was demonstrated ( $p < 0.001$ ). T-cell expansion was tumor-specific ( $p = 0.749$ ). Differential gene expression analysis comparing expanding T-cells in tumors observed increased expression of effector/activation markers and immune cell homing in expanding T-cells, but reduced expression of naïve and immune regulatory markers. By also profiling tumor-draining lymph nodes, we observe that the addition of aCTLA4 affects the lymph nodes and primes CD4+ naïve T-cells, triggering their expansion. Systemically PD-1 expression in both CD4+ and CD8+ T cells is increased together with an upregulation of activation markers after ICI. 2 baseline plasma factors with predictive capacity for clonotype response were identified: baseline LAG-3 and B7.2(CD86). **Conclusions:** A 14-day window may be considered ethically sound, it might not provide sufficient time for evaluating pathological response. It is both safe and feasible to use neoadjuvant ICI treatment in OSCC. While the initial toxicity is low and does not interfere with standard of care surgical procedures, adjuvant treatment may result in higher toxicity. Response to ICI is not dichotomic but rather a continuous variable which we represent here as clonotype expansion. A positive correlation was demonstrated between T-cell expansion and radiologic tumor shrinkage after one cycle of ICB. T-cell expansion was tumor-specific and gene expression analysis observed increased expression of activation markers here further supporting this as a surrogate marker. Combination therapy facilitates expansion of both CD4+ and CD8+ T-cells versus just CD8+ T-cells with aPD-L1 alone. Clinical trial information: NCT03784066. Research Sponsor: AstraZeneca; VR 2016 2312 Doc.1521/4; EORTC IMMUCan.

**Safety and immunogenicity of TG4050: A personalized cancer vaccine in head and neck carcinoma.**

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**Background:** Despite adjuvant therapy, over 50% of surgically treated head and neck squamous cell carcinoma (HNSCC) patients (pts) experience a recurrence of disease. Systemic stimulation of cellular immunity against tumor mutations using a viral vaccine may be an ideal modality to clear residual cancer cells. For this purpose, we developed a pipeline for the design of TG4050, a personalized cancer vaccine (PCV) using a Modified Vaccinia Ankara (MVA) viral vector. We report here preliminary safety and immunogenicity data from a phase I TG4050 study. **Methods:** Surgically resected stage III or IV, HPV negative HNSCC pts were enrolled in the study. pts must have achieved clinical remission after adjuvant chemoradiotherapy. A PCV for each pt was manufactured with up to 30 neoantigens identified using a state-of-the-art machine learning algorithm, from next generation sequencing (NGS) data. Pts randomized to arm A received the PCV after completion of primary treatment. Pts randomized to arm B received the PCV in the event of relapse, in conjunction with second line therapy. The PCV schedule consisted of an induction period of 6 weekly administrations, followed by booster doses once every 3 weeks for up to one year. Immune cells were collected by leukapheresis at baseline and at day 64. Primary endpoint was safety. Secondary endpoints included feasibility, disease free survival and immune response as assessed by ex-vivo IFNg-ELISPOT. **Results:** At the time of data cut-off, a total of 31 pts were randomized, 15 in arm A and 16 in arm B. A vaccine was successfully designed for all randomized pts. Pts had no evidence of disease at baseline either at the clinical or molecular level, as assessed by ctDNA assessment. All adverse events (AEs) were mild to moderate and most were injection site reactions. Median follow-up was 9.2 months in arm A vs 7.6 months in arm B. None of the pts in arm A experienced relapse vs. 2 in the arm B. Immune monitoring demonstrated priming of a polyepitopic T cell response against the PCV in 100% of pts in arm A, among pts evaluated to date, with a mean of 9 responses per pt (6-19). Responses were observed regardless of HLA genotype, and without cross-reactivity to the wildtype antigen. Baseline tumor analyses revealed challenging genomic and immune profiles such as low TMB (avg of  $3.06 \pm 0.86$  Mut/Mb), a majority of immune-desert tumors, and a low expression of important immune related factors including PD-L1 (16 pts out of 17 had a negative to moderate PD-L1 expression). **Conclusions:** Our preliminary data demonstrate that TG4050 is safe, well tolerated, and capable of inducing T cell responses in cold tumors. In summary viral based, PCVs designed to induce tumor-specific neoantigen may be associated with a safe tolerance and an improved outcome in HNSCC pts. Clinical trial information: NCT04183166. Research Sponsor: Transgene SA, NEC Corporation.

**Combined pulsed radiotherapy (QUAD shot regimen) with immune checkpoint inhibition (ICI) to enhance immune response for LAHNSCC in patients considered ineligible for curative intent therapy.**

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**Background:** Elderly patients with head and neck cancer (HNC) represent a growing population that would benefit from novel, less toxic approaches. Recent negative trial results adding ICI to chemo-RT for LAHNSCC (Javelin, Keynote 412) suggest that total nodal irradiation may create an immunosuppressive tumor microenvironment (TME), blunting the efficacy of ICI. This study was undertaken to use pulsed QUAD SHOT as an in-situ vaccine by stimulating the TME prior to delivery of ICI, excluding elective nodal sites, to enhance the immune response. **Methods:** 33 pts (20 males/13 females), with a median age of 81, seen at two community hospitals, ineligible for curative therapy, were treated with pulsed dose QUAD shot regimen to gross disease (44.4-59.2 Gy) spaced 3 weeks apart with addition of an approved ICI (Pembrolizumab or Cemiplimab). ERT was directed ONLY to GTV p+/-n. ICI was administered in most pts after the 1<sup>st</sup> QUAD shot to enhance immune response. ICI was continued adjuvantly until a > Grade 3 adverse event (AE) or progression of disease (POD). Pts with either advanced cutaneous or mucosal SCC were included (cSCC, mSCC). 39% presented with N1-2 adenopathy, and 24% presented with recurrent disease. PD-L1 status were not routinely obtained. **Results:** The median number of ICI cycles delivered was 5 (range 2-24). All pts completed at least 3 QUAD shots. Overall LRC for all 33 pts was 69.7%, with a mean follow-up of 11 months (1-39). LRC for 33 pts at 1 and 2 years after the end of radiation were 61.07% and 55.52%, respectively. The percentage of pts free from elective regional recurrences at 1 and 2 years was 87.13% for both cSCC and mSCC groups. Six pts (18%) experienced distant failure. Freedom from distant failure at 1 yr after QUAD shot completion by pathology was 100.00% for cSCC and 77.08% for mSCC. DFS for all 33 pts at 1 and 2 yrs were 59.39% and 37.12%, respectively. DFS at 1 year for cSCC was 100% and 53% for mSCC. Median DFS for the mSCC was 13.8 months. Overall survival for all 33 pts was 45.45% with a median OS time of 17.7 months. 1 and 2 year OS rates were 65% and 33%. Overall toxicity was low and manageable. Gr 3 mucositis occurred in 1 patient and 5 (15%) developed Gr 2 AE's. Gr 3/4 IMAR's were observed in 3 pts and included infusion reaction, colitis, and fatigue/FTT and were discontinued. 4 pts required post QUAD PEG's unrelated to radiation toxicity and due to POD. **Conclusions:** In elderly, frail, or comorbidly ill pts with LAHNC, the addition of ICI to involved field pulsed QUAD shot regimen tripled the median OS rate from prior publications with QUAD shot alone from 5.7 months to 17 months in our series. The low percentage of failure in the elective nodal beds was very encouraging based on our hypothesis. This approach represents the next step in an evolution away from conventional RT approaches that engender greater toxicity and warrants further study. Research Sponsor: Gregg and Stacy Bacchieri Philanthropic Fund.

**Are we ready for biomarker driven, radiation dose–adaptable de-escalation studies for HPV+ oropharyngeal cancer?**

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**Background:** Plasma circulating tumor modified viral human papillomavirus (HPV) DNA (TTMV) is a sensitive and specific biomarker of HPV+ oropharyngeal squamous cell carcinoma (HPVOPC). Patients with unresectable locally advanced (LA) HPVOPC are currently treated with induction chemotherapy (IC) and standard (sd) or reduced dose (rd) of chemoradiation (CRT). Post IC TTMV can be used in the future to help assign patients to sdCRT or rdCRT. This approach may help to maintain high efficacy and minimize long-term side effects of CRT in HPVOPC. **Methods:** Patients with LA HPVOPC and High Risk (HR) features (radiographic ECE, T4 primary, >N2c, and isolated lung metastases) were treated with 3 cycles of TPF IC followed by rdCRT to 5600 cGy with weekly carboplatin in responders, sdCRT in clinical non-responders and in M1 patients who also received SBRT to isolated biopsy proven lung metastases. Patients with > 20 pack year smoking history were excluded. Patients were eligible for rdCRT if they had a significant clinical response to IC and were participating in the QB2 trial (NCT02945631). **Results:** Fourteen subjects had pre and post IC TTMV testing available for analysis. 9/14 subjects after IC received rdCRT to 5600 cGy with weekly Carboplatin. 2 subjects were removed from the QB study for clinically inadequate response, 1 withdrew consent and 2 were M1 and treated for cure. All 5 underwent sdCRT 7000 cGy. 13/14 patients had TTMV testing done prior IC, 1 subject had TTMV done after the start of cycle 1 of IC; all 14 of them had a pretherapy or (1 subject) immediate post infusion positive elevated TTMV test. 11/14 subjects developed negative TTMV after 1 or 2 cycles IC. 3/14 subjects after 1 cycle and additional 6/14 subjects after 2 cycles of IC developed negative TTMV. 3/14 subjects still had abnormal TTMV after 3 cycles of IC; 2/3 subjects underwent 7000 cGy. Remaining 1/3 had a negative repeat TTMV prior to CRT and underwent rdCRT with 5600 cGy. TTMV testing was done for all subjects after completion CRT and all were negative. All subjects in addition to standard surveillance had TTMV testing done during their surveillance visits. 2 subjects developed recurrent HPVOPC after CRT: 1 locoregional and 1 metastatic (elevated TTMV after IC; sdCRT). **Conclusions:** In contrast to NCCN guidelines, rdCRT in many academic institutions has become a standard for HPVOPC. We have demonstrated a prompt reduction of TTMV to 0 in a subset of patients receiving 1 cycle and in a majority after at least 2 cycles of IC. The small sample size of our study lacks the statistical power to demonstrate that the failing to attain negative TTMV after/during IC is associated with a poor prognosis and warrants more aggressive therapy. TTMV biomarker response may have important prognostic value in delivering primary therapy and warrants further larger and more structured studies. Research Sponsor: None.

**10-year outcomes of technically unresectable oral cancers with neoadjuvant chemotherapy: Real-world data and implications for clinical practice.**

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**Background:** Neo-adjuvant chemotherapy (NACT) followed by response assessment is the standard treatment algorithm for locally advanced oral cavity squamous cell carcinomas (OCSCC) in the Indian subcontinent. The 3-drug NACT regimen (Docetaxel-Cisplatin-5-FU) has shown improvement in progression free survival (PFS) and overall survival (OS) over 2-drug regimen (Docetaxel-Cisplatin) in a phase-3 randomised study. We have analysed the 10-year outcomes with this treatment algorithm.

**Methods:** This was an institutional review board approved retrospective analysis of a prospectively collected dataset of borderline resectable OCSCC patients who received NACT. Adults with an eastern co-operative oncology group (ECOG) performance status (PS) 0-2 deemed technically unresectable in a multi-disciplinary clinic were included. All patients received 2-3 cycles of 3-weekly NACT. Patients with good general condition (GC) who became resectable underwent surgery followed by appropriate adjuvant therapy. Patients who were unresectable received definitive chemoradiation (CTRT), palliative chemotherapy, radiotherapy or best supportive care based on GC. The OS was calculated from date of diagnosis to date of death. Kaplan-Meier method was used for estimation of 10-year OS and impact of different regimens on OS was calculated using the log-rank method. **Results:** A total of 3266 patients were analysed, of which 2857 (87.5%) were males. The median age was 46 years (IQR: 39 - 54). The most common subsites were buccal mucosa (54.7%), tongue (30.4%) and alveolus (7.9%). Patients presented with either stage IVA (51.3%) or IVB (48.7%). The major indications for NACT were edema up to zygoma (42.2%), involvement of hyoid (22.6%), and high infra-temporal fossa (11.5%). The most common NACT was Docetaxel-Cisplatin (50.2%) followed by Docetaxel-Cisplatin-5-Fluorouracil (29.0%) and Paclitaxel-Carboplatin (13.3%). Planned number of NACT cycles could not be completed by 361 (11.1%) patients. Of 3266 patients, 929 (28.4%) underwent surgery followed by adjuvant CTRT (26.7%) or adjuvant RT (1.3%); 13.1% underwent definitive CTRT, 35.8% received palliative chemotherapy, while 11.7% defaulted for definitive treatment. Pathological complete response was seen in 76 (8.2%) patients, while 871 (93.8%) achieved negative margins and 338 (36.4%) had extra-nodal extension. The median OS was 9 months (95% CI: 8.6 – 9.4). NACT with more than 2-drugs had an OS of 13.2 months (95% CI: 12 – 14.4) vs 7.5 months (95% CI: 7.1 – 7.97) for 2-drug regimens. The 10-years OS was also higher for more than 2-drugs regimen - 21% (95% CI - 17.4% – 24.9%) vs 5.14% (95% CI: 3.28% - 7.6%) ( $p = 0.000$ ). 10-years OS of patients who underwent surgery vs those who did not was 22.28% vs 3.98% ( $p = 0.000$ ). **Conclusions:** NACT with more than 2-drug regimens had survival benefit over 2-drug regimens in technically unresectable OCSCC. Research Sponsor: None.

# Use of machine learning derived features from CT and H&E whole-slide images to predict overall survival in head and neck squamous cell carcinoma.

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**Background:** Computed tomography (CT) and H&E whole-slide images (WSI) have been found to carry rich prognostic information for patients diagnosed with head and neck squamous cell carcinoma (HNSCC). However, most machine learning models aimed for outcome prediction only took advantage of single image modality. In this work, we developed and validated a prognostic machine learning method incorporating both CT and WSI to predict overall survival in HNSCC patients. **Methods:** Matched radiographic CT scans and digitized WSI were acquired from the Cleveland Clinic for 167 HNSCC patients, including 120 HPV-associated oropharyngeal cancer and 47 laryngeal cancer. Both primary tumor and the largest suspicious lymph node were annotated on CT scans and primary tumor was delineated on H&E WSI. We split the dataset into training and validation set using a 7:3 ratio, which resulted in 119 patients in the training set and 48 for hold-out validation. We applied a machine learning model (M\_ML) using both CT and WSI as input to perform end-to-end predictions of overall survival. We used the harrell's concordance index (C-index) to evaluate the prognostic performance. Finally, we performed the multivariable cox proportional hazard analysis adjusting for clinicopathological variables (i.e. age, gender, smoking pack-year [PY], AJCC 7<sup>th</sup> edition overall stage, and treatment modality) to validate the independent prognostic significance of the model. **Results:** The combined machine learning model M\_ML (C-index = 0.81) outperformed the model using CT images alone (C-index = 0.63) and WSI alone (C-index = 0.64) on the validation set. In multivariable analysis, M\_ML is still statistically significant accounting for clinicopathologic factors ( $p = 0.0007$ ). **Conclusions:** This pilot study shows that a multi-omic machine learning model utilizing both radiographic CT and digitized WSI can predict HNSCC overall survival and outperforms models using only a single modality. Research Sponsor: U.S. National Institutes of Health.

Variables	Hazard Ratio (Confidence interval)	p values
Age	1.05 (0.95 - 1.16)	0.36
Gender (Male vs Female)	8.72 (0 - 100)	0.99
Smoking PY	1 (0.97 - 1.03)	0.85
Clinical T stage (3, 4 vs 1, 2)	1.79 (0.32 - 9.98)	0.51
Clinical N stage (2, 3 vs 0, 1)	2.65 (0.32 - 21.76)	0.36
Treatment (CRT vs RT)	0.27 (0.02 - 3.17)	0.30
Cancer subtype (laryngeal vs oropharyngeal)	6 (0.23 - 158)	0.28
M_ML	129.7 (7.69 - 2188)	0.0007

Multivariable cox proportional hazard analysis accounting for clinicopathologic factors.

**Tislelizumab plus chemotherapy as induction treatment followed by chemoradiotherapy or surgery in locally advanced hypopharyngeal squamous cell carcinoma: A single-arm, phase II trial.**

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**Background:** Induction chemotherapy (ICT) followed by chemoradiotherapy (CRT) is the standard of care for locally advanced hypopharyngeal squamous cell carcinoma (LA HPSCC). We aimed to assess whether add immunotherapy to ICT further improving patient outcomes. **Methods:** In this phase II, single-arm study, eligible pts aged 18-70 yrs diagnosed with stage III-IVB (AJCC 8<sup>th</sup>) HPSCC received induction therapy with tislelizumab (200 mg), cisplatin (75 mg/m<sup>2</sup>) and nab-paclitaxel (260 mg/m<sup>2</sup>) Q3W for 3 cycles. After assessment by multidisciplinary team, pts received surgery or CRT. The primary endpoint was objective response rate (ORR). Secondary endpoints include major pathologic response (MPR) in surgery group, disease control rate (DCR), 2-yr PFS rate in CRT group and 2-yr DFS rate. **Results:** 29 pts were enrolled (median age, 61 y; 97% male; stage III/IVA/IVB, 7%/90%/3%) from May to Nov 2022. Median follow-up was 7.3 months, no disease progression occurred in all patients. For all pts, the post-induction ORR and DCR were 82% and 100%. In surgery group (n = 10), all pts achieved R0 resection, and 5 (50%) pts reached pathological complete response (pCR). A patient with stable disease underwent a total laryngectomy achieved pCR by postoperative pathologic evaluation. Grade 3 and 4 treatment-related adverse event (TRAE) reached 82.8%, and mainly come from chemotherapy-related neutropenia. There was no TRAE leading to treatment discontinuation. **Conclusions:** These early data suggested that tislelizumab plus chemotherapy as induction treatment followed by chemoradiotherapy or surgery was safe and had the potential to provide clinical benefits for patients in LA HPSCC. The inconsistency between radiographic and pathological evaluation needs further exploration. Further follow-up is needed to confirm the long-term efficacy. Clinical trial information: ChiCTR2200060094. Research Sponsor: None.



**A multicenter, single-arm phase 2 study of surufatinib plus toripalimab for patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer.**

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**Background:** For patients (pts) with radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC), there presents a considerable therapeutic challenge with poor long-term outcomes. The open-label, multi-cohort, single-arm phase 2 study was performed to evaluate surufatinib (a small-molecule inhibitor of VEGFR 1-3, FGFR1 and CSF-1R) in combination with toripalimab (an anti-PD-1 antibody) in pts with RAIR-DTC. **Methods:** Eligible pts were with locally advanced or metastatic RAIR-DTC who were not amenable for surgery or external beam radiotherapy, with a radiologically confirmed disease progression within 12 months before treatment, and with  $\geq 6$  months since last radioiodine treatment. Enrolled pts received surufatinib 250 mg orally, QD, plus toripalimab 240 mg IV, Q3W, until disease progression or reaching the maximum treatment duration with toripalimab of 24 months, or other protocol-specified criteria. The primary endpoint was objective response rate (ORR) per RECIST 1.1. **Results:** From March 2020 to November 2021, 15 pts were enrolled and received a median duration of 11.1 months of the combination treatment, with a median age of 61 years (range: 37-74). 9 (60%) pts were male, and 12 (80%) had papillary thyroid cancer. Of the 13 pts with PD-L1 immunochemical results, 6 pts had PD-L1 CPS  $\geq 1\%$ . As of 28 Dec 2022, the median follow-up duration was 22.11 months. Of the 15 pts with at least one post-baseline tumor assessment, the confirmed ORR was 33.3% (5 PRs) and DCR was 93.3%. mDoR was 8.34 months. mPFS (95%CI) was 10.91 months (4.01, NA). mOS was not reached, and 12-month OS rate was 100%. 14 (93.3%) pts had treatment-emergent adverse events (TEAEs), and 10 (66.7%) pts reported grade  $\geq 3$  TEAEs, most commonly ( $\geq 10\%$  pts) with hypocalcemia (20%), diarrhea (20%) and hypertension (13%). There was no death due to TEAE in the study. **Conclusions:** Surufatinib plus toripalimab showed encouraging antitumor activity and tolerable safety profile in pts with locally advanced or metastatic RAIR-DTC. Clinical trial information: NCT04169672. Research Sponsor: HUTCHMED Limited.

**Phase II prospective trial of induction chemotherapy for advanced sinonasal squamous cell or poorly differentiated carcinoma.**

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**Background:** The standard treatment for resectable advanced sinonasal carcinoma is surgery followed by adjuvant therapy. Despite aggressive therapy, disease control and survival have historically remained poor. The role of induction chemotherapy (IC) has not been fully assessed. The objective of this study is to prospectively evaluate IC for local disease control, organ preservation, and response-based local treatment selection. **Methods:** This is a phase II, open-label, single-center trial of patients with previously untreated, resectable and nonresectable, locally advanced squamous cell or poorly differentiated carcinoma of the nasal cavity or paranasal sinuses. Eligible patients were  $> 16$  years of age, had an ECOG Performance Status of 0-1, and stage II-IV, M0 disease. Patients were treated with an IC regimen of docetaxel, cisplatin, and fluorouracil (TPF) for 2 cycles, then evaluated for response using clinical (symptoms and nasal endoscopy) and radiographic (RECIST 1.1 and PET) assessments. Those who achieved an objective response received a third cycle followed by chemoradiotherapy (CRT); non-responders underwent surgery with adjuvant radiotherapy. The primary endpoints were overall response rate (ORR) and 2-year local disease control. Secondary endpoints included disease-specific survival (DSS), overall survival (OS), disease-free survival (DFS), organ preservation, patterns of failure, and treatment toxicity. **Results:** 31 patients were enrolled between 2008 and 2020, of which 28 were evaluable for efficacy. Disease was T4a (57%) or T4b (21%), N+ (38%), and would have required maxillectomy (89%), craniotomy (54%), or orbital exenteration (29%). After IC, the ORR was 82.1% (7.1% complete response, 75.0% partial response), and the non-response rate was 17.9% (17.9% stable disease, 0% progressive disease). Patients then underwent CRT (79%) or surgery (21%). Following CRT, salvage surgery was performed for 41% of patients. Grade 3 or 4 adverse events occurred in 18% of patients. The 2-year local control rate was 53.6%. The 2-year DSS rate was 75% (median DSS not reached). For patients alive at 2 years, 63% had organ preservation (avoiding maxillectomy 38%, craniotomy 13%, orbital exenteration 38%). The median DFS and OS were 19.2 and 47.4 months, respectively. Factors associated with worse OS were nonwhite race ( $P = .035$ ), T4 category ( $P = .037$ ), overall stage IV ( $P = .038$ ), and paranasal sinus subsite ( $P = .002$ ). Surgery did not have significantly different OS than CRT ( $P = .86$ ). **Conclusions:** This phase II study demonstrates the validity of induction chemotherapy as a guide for local treatment selection in patients with advanced sinonasal carcinoma. A majority of patients achieved disease control and organ preservation. The median survival was 4 years in a cohort with very advanced locoregional disease, with no survival difference between CRT and surgery. NCT03493425. Clinical trial information: NCT00707473. Research Sponsor: None.

### Larotrectinib (laro) long-term efficacy and safety in patients (pts) with tropomyosin receptor kinase (TRK) fusion thyroid carcinoma (TC).

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**Background:** Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a variety of tumor types, including TC. Larotrectinib (laro) is a 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 a rapid, robust, and durable objective response rate (ORR) in both adult and pediatric pts with various cancers. Here, we report data on the subset of pts with TRK fusion TC treated with larotrectinib with long-term follow-up. **Methods:** Pts with TRK fusion TC enrolled in three laro clinical trials (NCT02576431, NCT02122913, NCT02637687) were included. Larotrectinib was administered at 100 mg twice daily to most pts; two pediatric pts received 100 mg/m<sup>2</sup>. Responses were assessed per independent review committee (IRC) using RECIST v1.1. Data cut-off: July 20, 2022. **Results:** As of data cut-off, 30 pts were eligible for efficacy assessment by IRC. The median age was 61.5 years (range 6–80) and the median time since initial cancer diagnosis was 5.0 years (range 0–46). The gene fusions involved *NTRK1* (n=14; 47%) or *NTRK3* (n=16; 53%). Fifteen pts (50%) received no prior systemic therapies, and six (20%) received ≥2; 23 (77%) received prior radioiodine. ORR was 63% (95% confidence interval [CI] 44–80); three (10%) complete response, 16 (53%) partial response (PR), five (17%) stable disease, four (13%) progressive disease, and two (7%) not evaluable. For pts classified as differentiated TC (DTC; n=23), the ORR was 78% (95% CI 56–93). For pts classified as anaplastic TC (ATC; n=7), the ORR was 14% (95% CI 0–58). All four pts with CNS metastases at baseline had a PR. Median time to response was 1.9 months, and median duration of response (DoR) was 43.3 months (95% CI 21.6–not estimable [NE]) at a median follow-up of 32.3 months. Median progression-free survival was 35.5 months (95% CI 23.4–NE) at a median follow-up of 34.0 months. Median overall survival (OS) was not reached (NR; 95% CI 48.7–NE) at a median follow-up of 46.4 months; the 48-month OS rate was 71% (95% CI 54–88). Median OS was NR (95% CI 48.7–NE) in DTC and 8.8 months (95% CI 2.6–NE) in ATC. At data cut-off, five pts who had disease progression continued treatment for ≥4 weeks due to continued clinical benefit. Treatment-related adverse events (TRAEs) were predominantly Grade 1–2. Grade ≥3 TRAEs were reported in two (7%) pts (anemia and decreased lymphocyte count). There were no treatment discontinuations due to TRAEs. **Conclusions:** Larotrectinib continues to demonstrate a rapid and durable response, 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 next generation sequencing panels, which include *NTRK* gene fusions, in pts with advanced TC prior to the initiation of any systemic therapy. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

### A phase II trial of nivolumab for patients with platinum-refractory recurrent or metastatic salivary gland cancer.

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**Background:** Salivary gland cancer is rare and has various pathological subtypes. With this rarity and heterogeneity, the therapeutic contribution of chemotherapy, including immune checkpoint inhibitors, for recurrent or metastatic salivary gland cancer (RM-SGC) has not been elucidated. The purpose of this trial was to investigate the efficacy and safety of nivolumab for patients with platinum-refractory RM-SGC. **Methods:** This open-label, single-arm, multicenter phase II trial was conducted at 9 centers in Japan. Eligible patients had platinum-refractory recurrent or metastatic salivary gland cancer with measurable lesions by RECIST v1.1 and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2. Nivolumab 240 mg/body was administered intravenously every 2 weeks until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). We set the null hypothesis at 3% and the expected at 15% with a one-sided  $\alpha$  of 0.1 and power of 80%. Secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Twenty-four patients (16 males; median age, 65.5 years [range, 34-78 years]) were enrolled between March 2018 and January 2022. Pathological types were salivary duct carcinoma (n = 10), adenoid cystic carcinoma (n = 6), adenocarcinoma not otherwise specified (n = 5), mucoepidermoid carcinoma (n = 2), and acinic cell carcinoma (n = 1). In the majority of cases the primary site was a major salivary gland (n = 21), namely the parotid gland in 16 patients and submandibular gland in 5. The primary endpoint of ORR was 8.3% (2/24, 80% CI, 2.2-20.6%), with 2 partial responses (PR) in patients with salivary duct carcinoma (2/10, ORR: 20.0%). DCR was 29.2% (7/24, 2 in PR and 5 in stable disease), and all of the other 17 patients (70.8%) showed progressive disease (PD) on first disease evaluation at 12 weeks. With a median follow up for survivors of 32.0 months, median PFS and OS were 3.0 months (95% CI, 2.8-3.2 months) and 25.0 months (95% CI, 10.9-39.1 months), respectively. There was no new safety concern with nivolumab monotherapy. **Conclusions:** This phase II trial of nivolumab monotherapy for patients with platinum-refractory RM-SGC did not meet its primary endpoint of ORR. Although nivolumab monotherapy may be worth further development in salivary duct carcinoma, these results may raise concerns over nivolumab monotherapy for RM-SGC. Translational research to elucidate the immune microenvironment of each pathological type is under investigation. Clinical trial information: UMIN000029636. Research Sponsor: None.

**Darolutamide for patients with androgen receptor positive salivary gland cancers (DISCOVARY): The results of phase 2 study of darolutamide monotherapy.**

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**Background:** There is no standard first-line treatment for recurrent/metastatic (R/M) or unresectable locally advanced (LA) salivary gland cancer (SGC). Androgen receptor (AR) overexpression is known to be particularly high (43-92%) in SDC, depending on histology, and has been identified as a potential molecular target for SGC treatment. However, the clinical utility of this approach has not been well investigated. Here, we evaluated the efficacy and safety of darolutamide for patients with AR-positive SGC. **Methods:** Eligibility included LA or R/M, SGC histologically confirmed positive for AR by the central laboratory; PS 0-1; adequate organ function; and no suitable local therapy. The study consists of two sequential components: a monotherapy part with darolutamide alone (monotherapy part) and a combination part with darolutamide and goserelin (combination part). Darolutamide was given orally at 1,200 mg daily until disease progression or unacceptable toxicity. Primary endpoint for the monotherapy part was overall response rate (ORR) as determined by the investigator. Secondary endpoints were ORR by independent central review (ICR), clinical benefit rate (CBR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. (ClinicalTrials.gov NCT05694819). **Results:** From Mar 2020 to Jan 2021, 24 patients were enrolled in the monotherapy component. Median age was 64.6 years and 23 were male. ECOG PS was 0/1 in 18/6 cases. Pathological diagnosis was salivary duct carcinoma, adenocarcinoma NOS, and carcinoma ex pleomorphic adenoma in 16, 4 and 4 patients, respectively. ORR by investigator was 8.3% (90% CI 1.5–24.0) and ORR by ICR was 20.8% (95% CI 7.1–42.2). CBR and DCR were 41.7% (95% CI 22.1–63.4) and 58.3% (95% CI 36.6–77.9), respectively. Median PFS and OS were 5.7 months (95% CI, 1.9–15.2) and not reached (95% CI, 15.5–not estimable [NE]), respectively, with a median follow-up period of 19.1 months. Nine patients (37.5%) had grade 3 or 4 treatment-related adverse events. There were no treatment-related fatal adverse events. **Conclusions:** This is the first prospective trial of darolutamide for AR-positive SGC. The response rate by ICR and other secondary endpoints confirmed clinically meaningful activity and a well-tolerated safety profile. Patient enrollment to the combination component is now ongoing to evaluate additional benefits. Clinical trial information: NCT05694819. Research Sponsor: Bayer pharmaceutical company.

**Clinical and genomic characterisation of adenoid cystic carcinoma of the head and neck, lung, and breast.**

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**Background:** Adenoid cystic carcinoma (ACC) arises most commonly within the major salivary glands and other exocrine glands. ACC is typically a slow growing disease with high rates of recurrence many years after diagnosis. To inform post-operative surveillance and to provide comparator data for non-randomised studies, we sought to perform clinical and genomic characterisation of a cohort of 450 ACC patients, comparing outcomes between salivary ACC and other primary sites. **Methods:** 450 patients with ACC underwent clinical review at 4 UK NHS institutions. Electronic records were reviewed to extract clinical and demographic data. In 225 patients, DNA-based next-generation sequencing was performed to identify alterations in the most frequently altered genes in ACC (NOTCH1, ARID1A, KDM6A, SETD2, or TP53). Kaplan-Meier survival analyses calculated the time to first confirmed recurrence (TTFR) and overall survival from diagnosis (OS-diag) and from first confirmed recurrence (OS-rec). **Results:** Of 450 ACC patients, the primary site was most frequently the major salivary gland (44.7%; 201/450) comprising parotid (86), submandibular (96), sublingual (9) and salivary NOS (12). Other primary sites were sinonasal (99/450; 22.0%), upper aerodigestive (69/450; 15.3%), tracheobronchial (46/450; 10.2%), breast (16/450; 3.6%), skin (10/450; 2.2%), lacrimal (7/450; 1.6%), and other (2/450; 0.4%). Complete survival data were available in 440 patients. Recurrent/metastatic disease was confirmed in 69.8% (314/450). For these patients, the median TTFR was 4.5 yrs and for those with recurrence, the median OS from recurrence (OS-rec) was 4.8 yrs. The median TTFR in major salivary ACC was 5.8 yrs (95% CI 4.3 – 7.0). In comparison, the shortest median TTFR was seen in tracheobronchial (2.9 yrs, 95% CI 1.6 – 6.8;  $p = 0.019$ ) and sinonasal ACC (3.8 yrs, 95% CI 2.9 – 5.0;  $p = 0.004$ ). Breast ACC showed a differing survival pattern compared with major salivary ACC. Although the OS-diag in these two groups was not significantly different (9.75 yrs and 11.3 yrs respectively,  $p = \text{ns}$ ), breast ACC showed a significantly increased TTFR (9.8 versus 4.4 yrs,  $p = 0.067$ ), and a significantly reduced OS-rec (0.75 versus 4.8 yrs,  $p = < 0.001$ ). KDM6A mutation was seen more frequently in primary sites outside the major salivary glands ( $p = 0.005$ ). However, there was no relationship between primary tumour site and mutations in NOTCH1, ARID1A, SETD2 or TP53. **Conclusions:** In this real-world multi-centre UK study, tracheobronchial and sinonasal ACC have significantly shorter TTFR than major salivary ACC. This study suggests that breast ACC has a similar OS from diagnosis to major salivary ACC, but has an increased TTFR and shorter OS following recurrence. This may have implications for follow-up protocols after primary treatment of breast ACC, and initiation of systemic therapy following recurrence. Research Sponsor: The Christie Charity, Syncona Foundation, The Infrastructure Industry Foundation and Bayer.

**Safety and early efficacy results of phase 1 study of affinity tuned and trackable AIC100 CAR T cells in ICAM-1 positive relapsed and/or refractory advanced poorly differentiated and anaplastic thyroid cancers.**

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**Background:** ICAM-1, a cell surface glycoprotein, is overexpressed in most ATC and PDTC. AIC100 is a 3<sup>rd</sup>-generation CAR T cell with micromolar affinity to ICAM-1, tuned lower than most CARs used to date in pre-clinical studies. Affinity tuned AIC100 are expected to selectively bind and kill tumor cells while safely sparing healthy cells. AIC100 also co-expresses somatostatin receptor 2 (SSTR2), which enables *in vivo* monitoring of AIC100 distribution and expansion by DOTATATE PET/CT scan. **Methods:** The objectives of this phase 1 dose escalation study are to assess the safety, preliminary efficacy and to determine RP2D of AIC100 in patients with ICAM-1<sup>+</sup> relapsed/refractory PDTC or ATC. 3 dose levels (DL) are being explored-DL1 at  $1 \times 10^7$ , DL2 at  $1 \times 10^8$  and DL3 at  $5 \times 10^8$  AIC100. AIC100 is received as a single infusion two days after completing lymphodepletion with Fludarabine/Cyclophosphamide. FDG and DOTATATE PET/CT scans are used to assess response and to track AIC100 *in vivo*, respectively. Response is assessed by RECIST1.1, starting at end of treatment (day 42 post AIC100). AIC100 is manufactured using AffyImmune's Tune and Track CAR T cell platform. **Results:** As of Feb 14, 2023, 6 pts (4 ATC; 2 PDTC) with a median age of 59.5 yrs (48-70) were infused with AIC100, 3 each in DL 1 and 2. AIC100 was successfully manufactured for all patients and all infusion products met target transduction efficiency. No serious adverse events or DLTs were reported. Two patients had grade 1 CRS. No ICANs was reported. In 3 evaluable patients in DL1, 1 patient had stable disease with decreased FDG activity in PET that correlated with increased activity in the DOTATATE scan. From the 3 pts infused in the DL2, one is evaluable for efficacy at day 42. This is a patient with relapsed ATC who achieved PR with 42% reduction in target tumor lesion and remains in PR at 3 mths. The target lesion in this patient showed increased DOTATE avidity at d14 post AIC100 infusion. This was followed by decreased FDG and DOTATE avidity at d42 post AIC100 infusion, concomitant with decreased size, suggesting biological activity 42 days after CAR T infusion. Evaluation of CAR transgene demonstrated transient peripheral blood CAR T cell expansion. The second patient couldn't be assessed due to early withdrawal for disease-related toxicity. The 3rd patient in DL2 remains in the DLT period, pending efficacy evaluation. **Conclusions:** AIC100 demonstrated an excellent safety profile in DL1/DL2 treated patients with ATC and PDTC with no DLTs observed. The objective and relatively durable partial response in the first evaluable patient in the DL2, a patient with metastatic ATC who failed multiple lines of therapy, is unprecedented and very encouraging. Further investigations of AIC100 are ongoing at DL2 and DL3 to determine the RP2D. Clinical trial information: NCT04420754. Research Sponsor: AffyImmune Therapeutics, Inc.

**Predictive biomarkers of benefit to axitinib plus avelumab in patients with recurrent/metastatic adenoid cystic carcinoma (R/M ACC).**

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**Background:** ACC is a heterogeneous malignancy with no standard treatment for patients (pts) with R/M disease. Two distinct ACC subtypes have been identified proteogenomically, which contribute to ACC's biological variability. ACC-I is enriched with NOTCH activating mutations and MYC overexpression and has a poor prognosis (median survival [mOS] = 3.4 years). ACC-II has upregulation of TP63 and presents with an indolent disease course (mOS = 23.2 years). In a phase II trial of axitinib (VEGFR inhibitor) plus avelumab (PD-L1 inhibitor) in R/M ACC, clinical benefit was heterogenous. We hypothesized that ACC subtype and gene expression profile are associated with benefit to axitinib plus avelumab. **Methods:** Cohort of 28 R/M ACC pts with radiological or clinical progression within 6 months (mos) of enrollment in the axitinib plus avelumab trial (NCT03990571). Target transcriptome profile including 19,616 probes was generated using HTG Transcriptome Panel [HTP]. Gene expression was used to identify ACC subtypes (ACC-I vs. ACC-II). Confirmed overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) per RECIST v1.1 was assessed for each ACC subtype. An analysis of genes associated with benefit vs. no benefit from axitinib plus avelumab was conducted for the overall population and per ACC subtype. Benefit was defined as disease control (partial response [PR] or stable disease [SD]) and PFS longer than the median PFS. PFS > 6 mos was not used to define benefit due to the significant differences in PFS between ACC subtypes. **Results:** Out of 28 pts, 14 (50%) were classified as ACC-I and 14 (50%) were ACC-II. For ACC-I, ORR was 14.3% (2/14; 95%CI: 1.8-42.8%), DCR was 35.7% (2 PR + 3 SD; 95%CI: 12.8-64.9%) and median PFS was 1.86 mos (95%CI: 1.81-8.61 mos). For ACC-II, ORR was 21.4% (3/14; 95%CI: 4.7-50.8%), DCR was 100% (3 PR + 11 SD; 95%CI: 76.8-100%) and median PFS was 10.5 mos (95%CI: 7.40-NA). PFS was significantly longer for ACC-II vs. ACC-I (HR 0.19 [95%CI: 0.08 – 0.49], p = 0.0002). Through the previously defined benefit vs. no benefit cutoff, ACC-I had a 42.9% (6/14) and ACC-II had a 50.0% (7/14) benefit rate. Benefit in all ACC pts, ACC-I and ACC-II was associated with high expression of immune-related genes, especially B and T-lymphocyte function. Angiogenesis-related genes were not significantly upregulated in the benefit group as previously reported in renal cell carcinoma pts treated with the same combination. **Conclusions:** Clinical outcomes to axitinib plus avelumab were distinct between ACC-I and ACC-II subtypes, with ACC-II pts demonstrating an improved DCR and significantly longer PFS. Gene expression analysis revealed high expression of immune function-related genes in patients who benefited from axitinib plus avelumab in both ACC subtypes, indicating possible biomarkers predictive of benefit from the combination in ACC. Clinical trial information: NCT03990571. Research Sponsor: U.S. National Institutes of Health; Pfizer.



**Monitoring epithelial, epithelial-mesenchymal, and mesenchymal circulating tumor cells on papillary thyroid cancer following thyroidectomy: A prospective cohort study.**

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**Background:** Monitoring the effectiveness of cancer-removal surgery is challenging in most cases. Therefore, robust and non-invasive techniques have been developed, and liquid biopsy is an apparent method for that purpose. In this prospective cohort study, we examined whether one type of liquid biopsy, an enumeration of circulating tumor cells (CTCs), can monitor the effectiveness of thyroidectomy in patients with papillary thyroid cancer (PTC). **Methods:** From January 2021 to January 2022, we recruited 62 PTC patients who had operated on isthmectomy, lobectomy, and total thyroidectomy for this study at Seoul National University Bundang Hospital. The blood samples from the recruited patients were collected before surgery and two weeks and three months after the surgery for CTC detection. We collected peripheral blood samples by venipuncture from each patient in EDTA tubes and stored them at 4°C until isolation and characterization of CTCs (within 6 hours). **Results:** We found the CTCs in 87% (54/62) of PTC patients, with an average number of 8.0. This number significantly decreased after thyroidectomy, with an average of 5.3 and 4.3 post-operation of two weeks and three months, respectively. In the peripheral blood of PTC patients, the CTCs with epithelial-mesenchymal and mesenchymal phenotypes were significantly more frequent than the epithelial phenotype of CTCs. Furthermore, PTC patients with lymphatic invasion, lymph node metastasis, or BRAF V600E mutation showed significantly decreased CTC count after surgery. **Conclusions:** PTC patients had a significantly higher number of CTCs undergoing epithelial-mesenchymal transition and showed a significant decrease in CTC count after surgery. This indicates that liquid biopsy using CTC enumeration can satisfy the purpose of monitoring the effectiveness of cancer-removal surgery. Clinical trial information: KCT0008179. Research Sponsor: CytoDx Inc.

**Retrospective analysis of genetically matched therapies in salivary gland cancer entities using a real-world database in a tertiary salivary gland cancer expertise center.**

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**Background:** Salivary gland cancer (SGC) is a rare cancer and includes twenty-two different entities. In the Radboudumc SGC expertise center, a real-world database was set up to uniformly collect data of SGC subtypes. More than 500 SGC patients have been enrolled and collection of data for 261 patients is currently completed. Here, we describe the retrospective analysis of genetic aberrations found in different SGC entities and the treatment of selected recurrent/metastatic (R/M) patients with genetically matched therapies (GMT). **Methods:** All SGC patients in the SGC registry of Radboudumc between 2017 and 2022 whose tumors underwent next generation sequencing (NGS) and/or gene fusion analysis within standard of care or clinical trial were included in this analysis. Both primary tumor specimen and metastatic tissue have been used for molecular analyses. GMT was given in basket trials or on basis of compassionate use for clinically relevant genetic aberrations that are considered actionable nowadays. **Results:** NGS and/or gene fusion analysis data was available for 162 out of 261 patients, and most frequently in salivary duct carcinoma (SDC) patients (82/162). The number of patients with genetic aberrations differed between SGC entities. In 112 patients at least one genetic aberration and/or gene fusion was detected regardless of whether the target was druggable. Ninety-three patients out of 112 patients had R/M disease. Both a gene fusion and one or more mutations were found in six patients (adenoid cystic carcinoma [AdCC], n = 3; SDC, n = 2; and secretory carcinoma [SC], n = 1;). Depending on the SGC subtype, in 14.3 – 100% of the R/M cases with genetic aberrations and/or gene fusions a GMT was started (SDC, 14/60; AdCC, 3/21; SC, 2/2; mucoepidermoid carcinoma, 2/4). The most given GMT among patients were monoclonal antibodies and tyrosine kinase inhibitors (TKI), respectively in nine and eleven patients, moreover immunotherapy was started in one patient. For example, eight SDC patients were treated with ERBB2 targeting agents (4/8 mutations; 4/8 copy number variants in ERBB2), showing a complete response in three patients. Additionally, one partial response and two stable diseases were observed, two patients were lost of follow-up. Two SC patients treated with a TKI based on the presence of the *ETV6-NTRK* gene fusion showed radiologically a partial response. **Conclusions:** In 69% of the SGC patients at least one genetic aberration and/or gene fusion was found, and in 23% of the R/M cases GMT was administered. Response differs between entities and GMT; a complete response was achieved after initiation of GMT in several patients. These data justify the use of NGS and gene fusion analysis in all salivary gland cancer entities, notably in subtypes lacking standard systemic therapies as this could offer other therapeutic options. Research Sponsor: None.

### **<sup>177</sup>Lu-PSMA radioligand therapy for patients with recurrent/metastatic (R/M) salivary gland cancer (SGC): A phase II pilot study.**

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**Background:** New treatments are warranted due to limited systemic treatment options for SGC patients (pts). Gallium [68Ga]Ga prostate-specific membrane antigen (PSMA) PET imaging results in SGC pts have demonstrated PSMA expression of SGC and thus indicated that PSMA radionuclide therapy may be a useful option, especially in the case of adenoid cystic carcinoma (AdCC) and salivary duct carcinoma (SDC) subtypes. Therefore, this study (EudraCT number 2019-003857-27) evaluated the safety and efficacy of PSMA-targeted radionuclide therapy in AdCC and SDC pts. **Methods:** This was a single-center, single-arm, phase II pilot study. R/M AdCC (n = 10) and SDC (n = 5) pts with sufficient PSMA tracer uptake on [<sup>68</sup>Ga]Ga-PSMA PET imaging, i.e.,  $\geq 1$  lesion  $\geq 1.5$ cm with PSMA expression above mean liver level, were treated with 2-4 cycles of 7.4 GBq [<sup>177</sup>Lu]Lu-PSMA-I&T, with an interval of  $6 \pm 1$  weeks. Baseline imaging was repeated for evaluation 4 weeks after cycle 2; in case of progressive disease (PD) per RECIST 1.1 the treatment was discontinued; otherwise, pts received the full treatment (4 cycles). All pts received whole body post-therapeutic imaging after 1, 24, 48, 72 h and 7d after each cycle. The primary endpoint was safety. Secondary endpoints include the objective response rate, progression-free survival (PFS), and overall survival (OS). **Results:** Between 6-2020 and 2-2023, 15 AdCC pts and 10 SDC pts were screened for eligibility. Five AdCC pts and 8 SDC pts were screen failures due to insufficient PSMA expression in 11 pts (AdCC n = 4; SDC n = 7) or due to brain metastases in 2 pts (AdCC n = 1; SDC n = 1). Ten AdCC and 2 SDC pts received at least one cycle of 7.4 GBq [<sup>177</sup>Lu]Lu-PSMA-I&T. The most observed adverse events (grade 1-2) included: nausea (75%), dry mouth (75%), fatigue (67%), and anemia (58%). Two pts (17%) developed grade 3 toxicity; lymphocytopenia (n = 1) and hyponatremia (n = 1). No grade 4-5 toxicities were observed. Two pts (AdCC n = 1; SDC n = 1) received only 1 treatment cycle due to early PD. The interim-treatment evaluation resulted in the discontinuation of treatment after 2 cycles in an additional 3 AdCC and the second SDC pts due to PD. Six AdCC pts received the full treatment (4 cycles); no responses were observed; 3 pts (75%) showed stable disease of more than 3 months after treatment completion (5, 15 and 21 months); 3 pts showed PD at 3 months after treatment completion. Median PFS in 10 AdCC pts was 6.7 months (95%CI: 0.0-15.1); OS was not reached after a median follow-up of 11.9 months. **Conclusions:** [<sup>177</sup>Lu]Lu-PSMA-I&T treatment in SGC pts is well-tolerated. The efficacy in AdCC was limited; only stable disease was achieved in 3 out of 10 pts. In most screened SDC pts, PSMA expression was insufficient to undergo [<sup>177</sup>Lu]Lu-PSMA-I&T treatment; the 2 SDC pts included showed early PD. Dosimetry analyses will be performed to calculate the delivered radiation doses to organs at risk as well as tumor lesions. Clinical trial information: EUCTR2019-003857-27. Research Sponsor: Dutch Cancer Society; ACC-RF.

**Artificial intelligence (AI) analysis of tumor-infiltrating lymphocytes (TILs) in hematoxylin and eosin (H&E) slides to explore immune phenotypes in papillary thyroid cancer.**

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**Background:** Different biomarkers have been discovered to predict response to immunotherapy but the variability of response exists. TILs are a potential biomarker as infiltration of CD8+ T cells in the tumor microenvironment (TME) was related to treatment response to PD-1 blockade. Advanced well-differentiated papillary thyroid cancer (PTC) has limited standard-of-care treatment options and can exhibit a poor prognosis when exhausted. Our study aimed to classify the TME of PTC according to TILs. **Methods:** Using the TCGA PTC data, samples were classified into three immune phenotypes (immune-'desert', immune-'excluded', and 'inflamed') based on peri-tumor lymphocyte density from analysis of H&E slides using an AI model (Lunit SCOPE). Immune and stromal cell infiltration was inferred using xCell. Cytolytic scores (CYT) and thyroid differentiation scores (TDS) were calculated using mRNA expression. **Results:** Total of 383 samples were included. Immune phenotype analysis showed 183 (47.7%) 'desert', 133 (34.7%) 'excluded', and 67 (17.4%) 'inflamed'. Median age at diagnosis was the lowest in 'inflamed' (inflamed 41.5 vs excluded 47 vs desert 50,  $p = 0.002$ ). TNM stages were as follows in the order of stages 1 to 4: inflamed 49/4/8/3, excluded 64/13/32/16, and desert 86/28/40/19. BRAF V600E mutation was most prevalent in 'excluded' (97/133, 72%), followed by 'inflamed' (32/67, 47.7%) and 'desert' (51/183, 27.8%). CYT was the highest in 'inflamed' (median: inflamed 186 vs excluded 53 vs desert 39,  $p < 0.001$ ). TDS was the highest in 'desert' (median: inflamed -0.3 vs excluded -0.69 vs desert 0.73,  $p < 0.001$ ). The 6 cell types with the most statistically significant difference in infiltration were activated dendritic cells (aDCs), DCs, B cells, epithelial cells (EpCs), CD8+ central memory T cells, and CD4+ memory T cells. The 'inflamed' showed the highest median value for all of these cells except EpCs. The cells with the highest median value in 'excluded' included EpCs, sebocytes, and immature DCs. The cells with the highest median value in 'desert' were lymphatic endothelial cells (ECs), ECs, and osteoblasts. Three immune phenotypes were associated with differential outcomes in disease-free survival (log-rank for trend,  $p$ -value = 0.01). There was no difference in overall survival. **Conclusions:** Our results suggest that 15% of PTC can have immune features which were related to a higher rate of response to immunotherapy across different tumor types. A previous study showed that PTC with a low TDS or BRAF V600E mutation is related to increased immune response indices. In our study, TDS or BRAF V600E mutation status could not distinguish the 'inflamed' from other phenotypes. This suggests that immune phenotype classification through TILs can provide distinct information about the TME of PTC. Research Sponsor: None.

**XRay Vision: A phase 3 study of xevinapant plus radiotherapy (RT) for high-risk, cisplatin-ineligible patients with resected, locally advanced squamous cell carcinoma of the head and neck (LA SCCHN).**

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**Background:** The current standard of care for patients with resected LA SCCHN who are at high-risk of disease recurrence and are cisplatin eligible is chemoradiotherapy (CRT; cisplatin + RT). For patients at high risk of disease recurrence who cannot receive cisplatin, treatment options are limited, and there is currently no treatment specifically recommended by international guidelines. Xevinapant is a first-in-class, small-molecule IAP (inhibitor of apoptosis protein) inhibitor that has been shown to restore cancer cell sensitivity to apoptosis, thereby enhancing the effects of chemotherapy and RT. In a randomized phase 2 study in patients with unresected LA SCCHN, treatment with xevinapant + CRT was associated with a 53% lower risk of death after 5 years of follow-up and reduced the risk of death or disease progression by 67% after 3 years of follow-up vs placebo + CRT. In preclinical SCCHN models, xevinapant + RT alone also demonstrated antitumor activity. These promising clinical and preclinical data provide a strong rationale for combining xevinapant and RT in cisplatin-ineligible patients with LA SCCHN. **Methods:** XRay Vision (NCT05386550) is a randomized, double-blind, placebo-controlled, phase 3 study comparing xevinapant or placebo in combination with intensity-modulated RT (IMRT) in patients with resected LA SCCHN who are ineligible for cisplatin and have a high risk of relapse. Eligible patients must have histologically confirmed cancer of the oral cavity, oropharynx, hypopharynx, or larynx; undergone surgery with curative intent 4 to 8 weeks before the start of treatment; high risk of relapse; no residual disease by computed tomography scan; and ineligible for cisplatin (meeting  $\geq 1$  of the following criteria: estimated glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>; hearing loss [grade  $\geq 2$  audiometric hearing loss or grade  $\geq 2$  tinnitus]; grade  $\geq 2$  peripheral neuropathy; and if aged  $\geq 70$  years old, unfit according to the G8 questionnaire [score  $\leq 14$ ]). Other eligibility criteria include ECOG performance status of 0 or 1 and adequate hematologic and hepatic function. Approximately 700 eligible patients will be randomized to oral xevinapant (200 mg/day on days 1-14 of a 3-week cycle) or placebo for 3 cycles + standard fractionation IMRT (66 Gy in 33 fractions, 2 Gy per fraction, 5 days per week) followed by 3 cycles of xevinapant or placebo. The primary endpoint is disease-free survival. Secondary endpoints include overall survival, time to subsequent cancer treatments, safety, and health-related quality of life. Patients will be followed up for a minimum of 60 months. Enrollment is planned in 27 countries, including the US, and countries in South America, Europe, and Asia. The study started in October 2022, and recruitment is ongoing. Clinical trial information: NCT05386550. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

**A phase 2 study of magrolimab combination therapy in patients with recurrent or metastatic head and neck squamous cell carcinoma: ELEVATE HNSCC.**

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**Background:** Novel combination therapies are needed to extend survival in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC). Magrolimab is a monoclonal antibody that blocks CD47, a "don't eat me" signal often overexpressed on HNSCC cells. CD47 blockade by magrolimab induces macrophage-mediated phagocytosis of tumor cells and has shown preclinical activity and promising clinical efficacy in hematologic malignancies. Certain chemotherapies, including taxanes, enhance prophagocytic signals on tumor cells, leading to potential synergistic antitumor activity when combined with magrolimab. This study is evaluating the safety, tolerability, and efficacy of magrolimab combination therapy in pts with RM-HNSCC. **Methods:** This open-label study includes 2 safety run-ins and 2 phase (ph) 2 cohorts. Safety run-in 1 includes pts with RM-HNSCC untreated in the RM setting to receive magrolimab + pembrolizumab (pembro) + platinum (cisplatin or carboplatin) + 5-fluorouracil (FU); safety run-in 2 enrolls pts with locally advanced or RM-HNSCC treated with 1-2 lines of prior systemic therapy in the locally advanced or RM setting who received magrolimab + docetaxel. Magrolimab is given intravenously as a 1-mg/kg priming dose on cycle 1 day 1 (C1 D1) to mitigate on-target anemia and 30 mg/kg on D8 and D15. Magrolimab 30 mg/kg is given on C2 D1, D8, and D15 and 60 mg/kg on D1 of C3+. Once the recommended ph 2 dose is determined, the ph 2 cohorts will follow the same dose schedules. In ph 2 cohort 1, pts receive magrolimab + pembro + platinum + 5-FU (arm A), pembro + platinum + 5-FU (arm B), or magrolimab + zimberelimab (anti-PD-1) + platinum + 5-FU (arm C). Pts enrolled in ph 2 cohort 3 receive magrolimab + docetaxel. An optional safety run-in and ph 2 cohort (cohort 2) of magrolimab + pembro in PD-L1+ RM-HNSCC may be opened at sponsor's discretion. Pembro, platinum, 5-FU, and docetaxel are given per standard of care. Reasons for treatment discontinuation may include unacceptable toxicity or disease progression. Safety is monitored throughout the study. Primary endpoints of the safety run-ins cohorts were incidence of adverse events and dose-limiting toxicities per CTCAE v5.0. Primary endpoints for the Ph 2 cohorts are progression-free survival (PFS) by independent central review (cohort 1 arm A vs B) and investigator-assessed objective response rate (ORR) by RECIST 1.1 (cohorts 2, 3). Secondary endpoints include magrolimab pharmacokinetics and antidrug antibodies (safety run-in, ph2 all cohorts), ORR assessed by independent central review, investigator-assessed PFS by RECIST 1.1 (all cohorts) and overall survival (all cohorts), duration of response, and pt-reported outcomes. Planned enrollment is ~230 pts. Clinical trial information: NCT04854499. Research Sponsor: Gilead Sciences, Inc.

**Palbociclib + cetuximab versus cetuximab in patients with *CDKN2A*-altered, anti-PD-1 resistant, HPV-negative head and neck squamous cell carcinoma (HNSCC): A phase 3 trial.**

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**Background:** Cell cycle deregulation is ubiquitous in HNSCC. In HPV-negative HNSCC, the most common genomic cell-cycling alteration involves *CDKN2A*, which results in loss of p16 expression, hyper-activation of CDK4/6-cyclin D1, unrestrained cell cycling and tumor progression. The modest antitumor activity of cetuximab in HPV-negative HNSCC may be due to unregulated cell-cycling events downstream of EGFR. In cell-line, xenograft, and PDX models of HPV-negative HNSCC, selective CDK4/6 inhibition arrested cell cycling and inhibited tumor growth. *CDKN2A* alterations were predictive of efficacy. Palbociclib, a selective CDK4/6 inhibitor, in combination with an EGFR inhibitor synergistically reduced the viability of HPV-negative HNSCC cell lines. An exploratory analysis of a double-blind, randomized, phase 2 trial (PALATINUS) showed that overall survival (OS) was numerically superior in patients with *CDKN2A* altered, HPV-negative recurrent/metastatic (RM) HNSCC treated with palbociclib + cetuximab vs those treated with placebo + cetuximab (median 9.7 vs 4.6 months, HR 0.38); however, OS was similar between the two treatment arms in patients without *CDKN2A*-altered disease. Also, the TAPUR trial showed that palbociclib decreased target lesions in 25% of patients with *CDKN2A*-altered HN cancers. These data provide justification for a randomized trial of palbociclib + cetuximab vs cetuximab in patients with *CDKN2A*-altered, HPV-negative RM-HNSCC. Enrollment was limited to patients with anti-PD-1 resistant disease, since current treatments fail to improve OS in these patients. **Methods:** The primary aim of this open-label, phase 3 trial is to determine the OS of patients with *CDKN2A*-altered (mutation or deletion), anti-PD-1 resistant, HPV-negative HNSCC treated with palbociclib + cetuximab (Arm 1) vs cetuximab (Arm 2). Eligibility also requires 1-3 lines of prior therapy and no cetuximab for RM disease. Patients are randomized (2:1) to Arms 1 or 2, stratified by prior platinum or cetuximab (if given with curative-intent therapy). Patients receive 28-day cycles of palbociclib 125 mg/d orally on days 1-21 + cetuximab 400 mg/m<sup>2</sup> IV cycle 1 day 1, then 250 mg/m<sup>2</sup> weekly (Arm 1) or cetuximab (Arm 2). Tumor response is assessed using RECIST 1.1. A two-stage sequential design, including one interim and a final analysis, was planned. We hypothesized that the median OS of Arm 1 will be 9.7 months and of Arm 2 4.6 months. O'Brien-Fleming method was used to calculate the sample size at each stage and derive the boundaries of two-sided hypothesis with early stopping to reject or accept H<sub>0</sub> (HR = 1). Assuming 22 months enrollment and 12 months follow-up, 66 patients (Arm 1: 44; Arm 2: 22) will be enrolled in the first stage. If the study continues, an additional 15 patients will be enrolled (total Arm 1: 54; Arm 2: 27) which achieves 80% power at a two-sided  $\alpha$  0.05. Clinical trial information: NCT04966481. Research Sponsor: Pfizer; Joseph Sanchez Foundation.

**Phase 2 trial of retifanlimab (anti-PD-1) in combination with INCAGN02385 (anti-LAG-3) and INCAGN02390 (anti-TIM-3) as first-line treatment in patients with PD-L1-positive recurrent/metastatic squamous cell carcinoma of the head and neck.**

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**Background:** Anti-PD-(L)1 therapies have improved clinical outcomes in PD-L1+ squamous cell carcinoma of the head and neck (SCCHN). However, many patients either do not respond or develop resistance, partly due to additional immune checkpoint receptors including LAG-3 and TIM-3, which are frequently coexpressed with PD-1 on tumor-infiltrating lymphocytes. In preclinical studies, LAG-3 and TIM-3 blockade showed synergistic activity with PD-1 inhibition, and triple blockade improves T-cell reinvigoration and antitumor efficacy over single/double combinations. Emerging clinical evidence also supports blockade of PD-1, LAG-3, and TIM-3 as a promising combination approach in checkpoint inhibitor-naïve patients. This study aims to assess the efficacy and safety of the anti-PD-1 antibody, retifanlimab, in combination with INCAGN02385 (anti-LAG-3) and INCAGN02390 (anti-TIM-3) antibodies as first-line treatment in PD-L1+ recurrent or metastatic SCCHN. **Methods:** This randomized, double-blind, multicenter, phase 2 study (NCT05287113) includes patients with previously untreated, recurrent or metastatic, PD-L1+ (combined positive score [CPS]  $\geq 1\%$ ) SCCHN and ECOG status of 0 or 1. Approximately 162 patients will be randomized 1:1:1 to receive (1) intravenous (IV) retifanlimab 500 mg every 4 weeks (Q4W) plus placebo controls, (2) retifanlimab plus IV INCAGN02385 350 mg Q2W plus placebo, or (3) retifanlimab plus INCAGN02385 plus IV INCAGN02390 400 mg Q2W. Patients will be stratified at randomization by LAG-3 expression (tumor proportion score  $\geq 5\%$  vs  $< 5\%$ ), PD-L1 CPS ( $1\%$ - $19\%$  vs  $\geq 20\%$ ), and human papillomavirus p16 status (positive vs negative; oropharyngeal tumors only). Treatment will be administered in 4-week cycles for up to 2 years. The primary endpoint is progression-free survival (PFS; defined per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1). Secondary endpoints are objective response rate per RECIST v1.1, duration of response, disease control, overall survival, and safety. Sample size calculation is based on a median PFS of 3 months, based on historical data for anti-PD-1 monotherapy in the first-line treatment setting for PD-(L)1+ advanced/metastatic SCCHN. PFS, overall survival, and duration of response data will be analyzed by the Kaplan-Meier method. Patient enrollment is ongoing. Clinical trial information: NCT05287113. Research Sponsor: Incyte Corporation.



**A phase 2 study of neoadjuvant lenvatinib in locally advanced invasive thyroid cancer.**

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**Background:** Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor that has demonstrated meaningful benefit in radioiodine (RAI)-refractory differentiated thyroid cancer (DTC). In SELECT, lenvatinib significantly prolonged progression-free survival (PFS) and was associated with an overall response rate (ORR) of 65% in patients with RAI-refractory DTC, with the greatest degree of tumor shrinkage occurring in the first 2 cycles. The robust activity of lenvatinib in DTC suggests that neoadjuvant treatment in patients presenting with bulky neck disease may make surgery more feasible, allows for optimal surgical outcomes and less aggressive surgical management. Neoadjuvant lenvatinib to improve surgical outcomes in locally advanced DTC has not been studied to date. This phase 2 study will examine the efficacy and safety of lenvatinib prior to thyroidectomy, with the goal of achieving more favorable surgical outcomes. **Methods:** This is a Simon two-stage Phase 2 open-label multicenter clinical trial for adult patients who meet the following criteria: have been diagnosed with locally advanced or persistent/recurrent thyroid and/or cervical nodal DTC, deemed at risk for R2 resection (surgical margins with macroscopic tumor) (as evident by vocal cord paralysis by laryngoscopic exam, imaging documenting extrathyroidal/extranodal extension, or major vessels involvement), have measurable disease per RECIST v1.1, have an ECOG performance status  $\leq 1$ , and no contraindication to surgery. A total of 28 patients will be enrolled from three centers (Massachusetts General Hospital/Massachusetts Eye & Ear Infirmary (MGH/MEEI), Memorial Sloan-Kettering Cancer Center (MSKCC), and MD Anderson Cancer Center (MDACC)). Participants will receive up to 6 cycles of lenvatinib prior to surgery depending on response. Participants will undergo restaging at the end of cycle 2, 4, and 6. Participants with sufficient response to treatment who projected to achieve an R0 or R1 resection will stop lenvatinib and proceed to surgery within 7-10 days from the last dose. Participants who do not have a sufficient response who are tolerating treatment, will receive an additional 2-4 cycles of lenvatinib, followed by surgery. The primary objective is the R0 (surgical margins free from tumor)/R1 (surgical margins free from macroscopic tumor) resection rate. Secondary outcome measures include R0/R1 resection rates in each of 5 pre-specified anatomic target interfaces (perithyroid muscles, cartilage, esophagus, recurrent laryngeal nerve, major vessels), evaluation of the change in surgical morbidity complexity MGH/MEEI-MSKCC-MDACC (MMM) score and the Invasive Thyroid Class, ORR prior to surgery per RECIST v1.1, and the safety of lenvatinib in this patient population. The study is currently accruing with 11 patients enrolled at time of submission. Clinical trial information: NCT04321954. Research Sponsor: Eisai.

**A phase 2, open-label, multicenter study investigating efficacy and safety of RP3 oncolytic immunotherapy combined with other therapies in patients with locoregionally advanced or recurrent squamous cell carcinoma of the head and neck.**

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**Background:** Head and neck (HN) cancers were estimated to account for > 50,000 new cancer diagnoses and > 11,000 deaths in the US in 2022. Squamous cell carcinoma of the head and neck (SCCHN) comprises about 90% of HN cancers. For locally advanced (LA) SCCHN, standard initial therapy is concurrent chemoradiation therapy (CCRT) or definitive resection followed by adjuvant radiation  $\pm$  chemotherapy; > 50% of patients (pts) relapse within 2 years. For recurrent/metastatic (R/M) SCCHN, standard first-line therapy includes immune checkpoint inhibitors (anti-PD-1)  $\pm$  chemotherapy or cetuximab, chemotherapy  $\pm$  cetuximab, or salvage surgery; prognoses are poor, and benefit of anti-PD-1 therapy is generally limited to pts with positive PD-L1 combined positive score (CPS). RP3 is an enhanced potency, modified version of herpes simplex virus type 1 expressing the fusogenic gibbon ape leukemia virus glycoprotein with the R sequence deleted (GALV-GP-R-), an anti-CTLA-4 antibody-like molecule, and costimulatory CD40- and 4-1BB-activating ligands. Intratumoral (IT) RP3 delivery may promote immunogenic tumor cell death and systemic antitumor response (abscopal effect), both of which may be further enhanced by standard therapies (eg, chemotherapy, anti-PD-1). This phase 2 study will evaluate the efficacy and safety of RP3 combined with other therapies in pts with advanced, inoperable LA or R/M SCCHN. **Methods:** Pts in the LA cohort (up to ~100 pts) must have inoperable, previously untreated, high-risk SCCHN eligible for curative intent CCRT and will be randomized 1:1 to receive RP3 + standard of care cisplatin-based CCRT, followed by nivolumab (nivo), vs CCRT alone. A formal safety assessment will be performed 3 weeks after the tenth patient randomized to RP3 + CCRT + nivo has completed CCRT. RP3 will be injected IT into primary tumor sites and/or superficial or deep nodal lesions. Pts in the RP3 group will receive up to 4 doses of RP3 every 3 weeks (Q3W; first dose at a concentration of  $1 \times 10^6$  plaque-forming units [PFU]/mL; subsequent doses  $1 \times 10^7$  PFU/mL). Nivo will be given at 240 mg Q2W or 480 mg Q4W (after CCRT completion, concurrent with fourth RP3 dose, for up to 1 year). The primary endpoint for the LA cohort is progression-free survival. Pts in the R/M cohort (up to ~30 pts) must have R/M SCCHN eligible for first-line systemic therapy for locoregional recurrence and/or distant metastases and PD-L1 CPS < 20, and will receive RP3 + nivo + carboplatin/paclitaxel. RP3 will be injected IT as described above for up to 8 doses Q3W (first dose  $1 \times 10^6$  PFU/mL; subsequent doses  $1 \times 10^7$  PFU/mL; carboplatin/paclitaxel started at first RP3 dose). Nivo will be given as above, concurrent with third RP3 dose, for up to 2 years. The primary endpoint for the R/M cohort is overall response rate. Clinical trial information: NCT05743270. Research Sponsor: Replimune Inc.

**A phase 2 open-label study of conditionally active biologic ozuriftamab vedotin (BA3021) in failed PD-1/L1 treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck.**

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**Background:** Ozuriftamab vedotin (BA3021) is a conditionally active biologic (CAB) anti-receptor tyrosine kinase orphan receptor 2 (ROR2) humanized monoclonal antibody (IgG1) conjugated to monomethyl auristatin E (MMAE) using a cleavable linker (CAB ROR2 ADC) (Short, et al., 2014, Chang, et al. 2021). Conditional and reversible binding by CABs is designed to reduce off-tumor toxicity and immunogenicity, avoid tissue-mediated drug deposition, and improve pharmacokinetics (PK). ROR2 is a cell-surface transmembrane receptor protein tyrosine kinase highly expressed in several tumor types including head and neck squamous cell cancer (HNSCC). Increased ROR2 expression has been associated with tumor resistance to chemotherapy, programmed death-1 (PD-1) inhibitors, molecular targeted therapy, and radiation therapy. A pronounced unmet need exists as the majority of patients with recurrent or metastatic HNSCC experience disease progression with existing therapies (Chow 2020). **Methods:** BA3021-002 is a multi-center, open-label, single-arm Phase 2 study (n=40) designed to evaluate the efficacy and safety of BA3021 in patients previously treated with PD-(L)1 with ROR-2 expressing recurrent or metastatic HNSCC. Eligible patients include those with measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 criteria. Failure to prior treatment is defined as documented disease progression after no more than one PD-1/L1 inhibitor either administered as monotherapy or in combination therapy. Pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity, and biomarker assessments will be performed. Enrollment is ongoing (NCT05271604) References: Chang, H.W., Frey, G., Liu, H., Steinman, L., Boyle, W.J. and Short, J.M. Proc. Natl. Acad. Sci. 2021 Mar. 2; 118(9). Chow LQ. Head and neck cancer. *N Engl J Med*. 2020 Jan 2;382(1):60–72. doi: 10.1056/NEJMra1715715. Short, J.M. Nature Biotechnology 2014 Nov 8, 13(20). Clinical trial information: NCT05271604. Research Sponsor: BioAtla.

**Oral NRC-2694-A in combination with paclitaxel as therapy for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) that progressed on or after an immune checkpoint inhibitor (ICI): A multi-center, single-arm, phase 2 trial.**

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**Background:** HNSCC is the seventh most common cancer worldwide. Patients with R/M disease have limited treatment options and a poor prognosis. The USFDA has approved two ICI agents to treat R/M-HNSCC: pembrolizumab given as monotherapy or with platinum-based chemotherapy for first-line treatment of R/M disease and nivolumab (or pembrolizumab) monotherapy for treatment of disease that progressed on or after platinum-containing chemotherapy. In each setting, the ICI improved overall survival (OS); however, the absolute magnitude of the OS benefit was modest and most patients experienced disease progression within one year. There are no agents with regulatory agency-approval that are used to treat R/M-HNSCC that progressed on or after an ICI. Drugs commonly used in this setting have limited activity and include cetuximab (an epidermal growth factor receptor [EGFR] inhibitor), paclitaxel, docetaxel, a platinum, or 5-fluorouracil. Hence, there is an important unmet medical need to develop more effective treatments for R/M-HNSCC that progressed on or after an ICI. NRC-2694-A is an orally administered EGFR tyrosine kinase inhibitor, discovered and developed by NATCO Pharma Ltd., India. Based on the responses from Phase-I and Phase-II trials of NRC-2694-A in India, NAT2694US study is designed to evaluate the safety and efficacy of Oral NRC-2694-A in combination with paclitaxel in patients with R/M-HNSCC, who progressed on or after ICI therapy.

**Methods:** NAT2694US is a multi-center, single-arm, Phase 2 study (NCI ClinicalTrials.gov Identifier: NCT05283226) with an estimated enrolment of 46 patients. Eligible patients are >18 years of age with an ECOG performance status of 0-2 and histologically confirmed unresectable, measurable R/M-HNSCC (of the oral cavity, oropharynx, hypopharynx, and larynx), radiological disease progression on or after ICI therapy, and no prior taxane for R/M disease. Patients receive 300 mg of oral NRC-2694-A once daily and 175 mg/m<sup>2</sup> of paclitaxel IV infusion once every 21-day cycle for 6 cycles or more. Tumor response assessment with CT/MRI scans is performed every 6 weeks. The primary endpoint is objective response rate (ORR) using RECIST v1.1 performed by the investigator. The study uses a Simon's 2-stage design with ORR H<sub>0</sub>: 30% and H<sub>1</sub>: 50% using a one-sided Type-1 error rate = 0.05). In Stage 1, fifteen patients are to be enrolled for tumor assessment. If objective response is observed in at least 6 of these 15 patients, then Stage 2 would be opened with the inclusion of 31 additional patients, leading to a total enrolment of 46 patients. The observation of objective response in at least 19 of 46 patients would reject the null hypothesis in favour of the alternative hypothesis. Enrolment to the NAT2694US trial is currently ongoing in USA. Clinical trial information: NCT05283226. Research Sponsor: NATCO Pharma Ltd.

## Phase 2 trial of three schedules of CUE-101 administered before surgery or chemoradiotherapy in HLA-A\*0201 positive patients with HPV16+ OPSCC.

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**Background:** Patients with locally advanced HPV+ OPSCC have a favorable prognosis; however, 10-40% will experience disease recurrence after curative-intent therapy (CIT). 80-90% of cases are caused by HPV genotype 16. HPV16 E7 is a promising HPV target as there is little variation among isolates and high epitope affinities for HLA-A\*0201 have been identified. HLA-A\*0201 is the most common class I allele in the USA, expressed in 40-50% of people of European descent. We aim to lower the recurrence rate in these patients by activating tumor antigen-specific CD8<sup>+</sup> T cells. CUE-101 is a novel fusion protein comprised of HLA-A\*0201, an HPV16 E7 epitope (aa residues 11-20), a reduced affinity human IL-2 variant, and an effector attenuated human IgG1 Fc domain. In pre-clinical models, CUE-101 demonstrated selective binding, activation, and expansion of HPV16 E7<sub>11-20</sub>-specific CD8<sup>+</sup> T cells. In the murine TC-1 tumor model, a murine surrogate of CUE-101 (mCUE-101) increased the frequency of tumor-infiltrating E7-specific CD8<sup>+</sup> T cells and improved survival. Animals that remained tumor-free rejected TC-1 tumors upon re-challenge, demonstrating functional immunologic memory. In an ongoing phase 1 trial (NCT03978689) of HLA-A\*0201+ patients with recurrent HPV16+ OPSCC, CUE-101 was well tolerated, resulted in expansion of target HPV16 E7<sub>11-20</sub>-specific CD8<sup>+</sup> T cells, and showed durable disease control in some patients. In this Phase 2 trial (NCT04852328), CUE-101 will be administered to HLA-A\*0201+ patients with HPV16+ OPSCC before CIT. The aims of the trial are to evaluate the safety, tolerability, and pharmacodynamic and immunologic activity of CUE-101 in these patients. **Methods:** This is a non-randomized Phase 2 trial of three schedules of CUE-101 administered before CIT to HLA-A\*0201+ patients with HPV16+ OPSCC. HPV16 status of tumor will be assessed by PCR. Safety assessments will be performed, and blood and tumor samples collected, at baseline and after CUE-101 administration. Following CUE-101, CIT will be administered. Each schedule will enroll 10 patients. CUE-101 (4 mg/kg IV) will be administered 14 days (Schedule A), 14 and 7 days (Schedule B), or 7 days (Schedule C) before day 1 of CIT. If Schedule A is safe and tolerable, Schedule B and then C will commence. A schedule will be deemed safe and tolerable if ≤2 patients experience grade 3-4 TRAEs and/or treatment-related delays of >7 days from the planned date of CIT. Immunologic activity is defined as measurable observation of or increases in HPV16-specific T cells in post-CUE-101 blood and/or tumor samples, relative to baseline, as assessed by either ELISpot or tetramer staining and flow cytometry. Exploratory measures of immune activity will be assessed by single-cell RNAseq and immunofluorescence in tumor samples. A schedule will be considered active if immunologic activity is observed in ≥3 patients. Clinical trial information: NCT04852328. Research Sponsor: Cue Biopharma, Inc.

**A phase II trial of neoadjuvant nivolumab, docetaxel, and cisplatin therapy followed by surgery and radiation therapy for resectable high-grade salivary gland carcinoma.**

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**Background:** Salivary gland carcinomas (SGCs) are rare entities that contribute to approximately 5% of head and neck malignancies. The current standard therapy for resectable SGC is complete surgical resection with adjuvant radiotherapy or chemoradiotherapy. However, the patients with high-grade histological subgroup tumors have the highest risk of regional and distant metastasis as the primary cause of treatment failure. The previous evidence demonstrates that neoadjuvant chemotherapy showed a statistically significant advantage in survival for patients with head and neck cancer. Based on the success of neoadjuvant immune checkpoint inhibitors (ICI) in preventing disease recurrence and achieving pathologic complete response (pCR) in different types of cancer, we designed this study by incorporating nivolumab combined with neoadjuvant cytotoxic chemotherapy in patients with potentially resectable high-grade SGCs. **Methods:** This study is the phase II, open-label, single-center study of nivolumab in combination with docetaxel, and cisplatin as a neoadjuvant therapy in high-grade resectable SGCs. All the patients must be confirmed with pre-defined high-grade histology and clinically node-positive. As the representative inclusion/exclusion criteria, all the patients must not receive prior cancer therapy in advance to study enrollment, including another kind of immunotherapy, cytotoxic chemotherapy, or radiotherapy. Three cycles of nivolumab (360mg), docetaxel (60mg per m<sup>2</sup>), and cisplatin (60mg per m<sup>2</sup>) are applied every three weeks. Three weeks after the last treatment, the patient is re-evaluated for the surgery and will undergo surgery within seven weeks after the last treatment. Based on the surgical pathologic outcome, additional radiotherapy will be initiated between 4 to 8 weeks after the surgery per the following guidance; R0: 59.4Gy/25fx; R1 or R2: 59.4Gy/25fx with optional boost 6.6Gy/3fx. The primary objective is the major pathologic response rate defined by  $\leq 10\%$  of tumors composed of viable tumors. Complete resection rate, response rate, downstaging at pathologic staging, two-year distant metastasis free-survival, disease-free survival, overall survival, safety results, surgical outcomes of facial nerve function, completeness of post-neoadjuvant surgery will be analyzed as the secondary objectives. The sample size was calculated using  $H_0$  of mPR  $\leq 25\%$  and  $H_1$  of mPR  $\geq 50\%$ , according to the one-arm binomial model (power of 90% and one-sided alpha of 0.05). A total of 50 patients will be recruited, include 40 evaluable patients. This study is currently recruiting patients at Samsung Medical Center, South Korea. The first subject received treatment in Nov. 2022 and three patients received the treatment. The time point for the primary analyses is Q3.2025. (ONO-4538-X78). Clinical trial information: NCT05727410. Research Sponsor: None.

**A single-arm, multi-institutional, phase 2 study of a pembrolizumab-based organ preservation strategy for locally advanced larynx cancers: SMART-KEY (LACOG 0720) trial.**

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**Background:** Standard treatments for locally advanced larynx cancers include concurrent cisplatin/radiation therapy, or induction chemotherapy followed by radiation therapy alone, with the goal of organ preservation. Both strategies have been shown to achieve similar laryngectomy-free survival (LFS), but failed to improve overall survival (OS) compared with radiation therapy alone or surgery followed by radiation therapy. Although cisplatin given concurrently with radiation therapy is commonly used for organ preservation, there are concerns regarding long-term outcomes, such as late toxicities. Pembrolizumab with chemotherapy has been shown to improve OS in recurrent/metastatic head and neck squamous cell carcinomas (HNSCCs). Additionally, pembrolizumab combined with radiation therapy has been shown to be safe in locally advanced HNSCC. LACOG 0720 is designed to evaluate a pembrolizumab-based, cisplatin-free, and concurrent chemoradiation therapy-free regimen for larynx preservation, in an attempt to improve outcomes and avoid late toxicities. **Methods:** LACOG 0720 is a phase 2, single-arm, multicentric trial assessing patients with newly diagnosed squamous cell carcinoma of the larynx (glottic or supraglottic) and clinical stages III, IVA, or IVB (AJCC 8th Ed.). Patients with large volume T4 disease (invasion through the cartilage or extension > 1 cm to the base of the tongue) or T1 disease are excluded. Patients receive 3 cycles of induction chemo-immunotherapy (carboplatin AUC6, paclitaxel 175 mg/m<sup>2</sup>, and pembrolizumab 200 mg, IV every 21 days [q21D]), followed by concurrent radioimmunotherapy (Intensity-modulated radiation therapy with pembrolizumab 200 mg IV q21D for 3 cycles), followed by consolidation immunotherapy (pembrolizumab 200 mg IV q21D for 11 cycles). The primary endpoint is two-year LFS rate. Secondary endpoints include two-year larynx dysfunction-free survival, OS, overall response rate, short-term and long-term toxicities, causes of death, patterns of failure, and quality of life. Predictive biomarkers of response and survival will be evaluated as exploratory analysis. The sample size was calculated based on the primary endpoint. Using the Chi-square Test for One Proportion and considering a one-sided 10% significance level, 39 patients are needed to achieve 80% power to detect the difference between the null hypothesis; that the true laryngectomy-free survival at two years is 59%, and the alternative hypothesis that the laryngectomy-free survival at two years is 75%. From Feb 2022 to Feb 2023, 24 patients were enrolled in 10 Brazilian centers. Results are expected in July 2024. NCT04943445. Clinical trial information: NCT04943445. Research Sponsor: Merck & Co.; Merck Sharp & Dohme (MSD).

**Response-adapted therapy for locally advanced nasopharyngeal carcinoma based on clinical response and circulating Epstein-Barr virus DNA level post induction chemotherapy.**

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**Background:** For locally advanced nasopharyngeal carcinoma (NPC), the mainstay treatment is cisplatin-based concurrent chemoradiation (CCRT). Recent phase III clinical trials have demonstrated that induction chemotherapy (ICT) plus CCRT, compared with CCRT alone, further improved progression-free survival (PFS). However, not every patient has good response to ICT. Evidence has accumulated that those with poor response to ICT, or those with detectable Epstein-Barr Virus (EBV) DNA post ICT, correlated with poorer PFS. In addition, real-time monitoring of plasma EBV DNA response adds prognostic information, and has the potential utility for risk-adapted treatment intensification in NPC. The aim of this study is to clarify whether response-adapted strategy based on clinical efficacy and EBV DNA response confers survival benefit to patients with locally advanced NPC.

**Methods:** This is an open-label, 3-arm, phase II study. Patients with pathologically confirmed, locally advanced NPC (III-IVA, excluding T3N0M0, 8<sup>th</sup> AJCC staging system), with pretreatment detectable plasma EBV DNA level and ECOS PS 0-1 were eligible. Patients will receive one cycle of GP-based ICT. After one cycle of ICT, plasma EBV DNA and head and neck MR are performed. Based on clinical efficacy (evaluated per RECIST 1.1 criteria) and changes of plasma EBV DNA after one cycle, patients will be divided into three arms. Patients with good response (Arm A: Early Responders, undetectable EBV DNA level and CR/PR) will directly receive CCRT. Patients with intermediate response (Arm B: Intermediate Responders, detectable EBV DNA and CR/PR/decreased SD; or undetectable EBV DNA yet without CR/PR) will be randomized to experiment subgroup (GP combined with Toripalimab for two additional cycles then CCRT and maintenance Toripalimab treatment) and standard subgroup (GP for two additional cycles then CCRT). Patients with poor response (Arm C: Treatment Resistant, increased EBV DNA level, or PD/enlarged SD) will be switched to TP regimen combined with Toripalimab, followed by CCRT and maintenance Toripalimab treatment. Sample size calculation is based on 2-year PFS rate for arm B as the primary endpoint (one-sided  $\alpha = 0.10$ , power = 0.80). Our target sample size is estimated to be 198-240, among them 168 for arm B. Secondary endpoints include adverse events determined by CTCAE v5.0, ORR at 3 months post-CRT, 2-year locoregional recurrence-free survival (LRFS) rate, 2-year distant metastasis-free survival (DMFS) rate, 2-year overall survival (OS) rate, as well as quality of Life for arm B. Exploratory endpoints include 2-year PFS rate, LRFS rate, DMFS rate, OS rate, ORR at 3 months post-CRT, adverse effects, and quality of life for arm A and arm C. This trial opened to accrual in July 2022 and the recruitment is ongoing. Clinical trial information: NCT05628922. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.



**KEVLAR: A phase 2b, multi-institutional, randomized, blinded, controlled trial to assess the safety and efficacy of two schedules of RRx-001 vs. standard of care in attenuating severe oral mucositis (SOM) in patients receiving concomitant chemoradiation (CRT) for the treatment of locally advanced squamous cell carcinomas (SCC) of the oral cavity (OC) or oropharynx (OPC).**

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**Background:** The results of an open-labeled Phase 2a trial suggested that infusion of RRx-001 (bromonitroimidazole), a nitrogen-containing NLRP3 inhibitor and Nrf2 activator, attenuated the course and severity of SOM associated CRT (cisplatin/IMRT) in cancers of the mouth or OPC without impeding tumor response. The primary efficacy objectives of KEVLAR are to replicate the findings of the earlier trial and to determine if a higher dose of RRx-001 (8 mg x 4 doses prior to CRT) will favorably impact overall SOM incidence. **Methods:** KEVLAR is a planned Phase 2b study to be conducted at about thirty sites in North America. Approximately 216 patients with pathologically confirmed SCCs of the OC or OPC will be randomized equally into one of 3 cohorts: Arm 1 will receive RRx-001, 8 mg/dose infusions twice weekly during the 2 weeks prior to CRT start; Arm 2 will receive RRx-001, 4 mg/dose in the same schedule; Arm 3 will receive best supportive care only. All patients will receive intensity modulated radiation therapy (IMRT) in 2.0-2.2 Gy fractions/weekday to a cumulative radiation dose of up to 72 Gy. CRT must include cisplatin administered either weekly (40 mg/m<sup>2</sup>) or tri-weekly (100 mg/m<sup>2</sup>). Radiation fields must include at least two oral sites at SOM risk planned to receive at least 55 Gy. Mucositis indicators will be assessed twice weekly by trained evaluators. OM will be scored centrally using WHO criteria from the first day of CRT until resolution of ulcerative OM (WHO grade ≤1). Adverse events will be evaluated using NCICTCv5 criteria. Patients will be followed for 24 months post the last day of radiation and tumor response will be recorded quarterly using RECIST criteria. Research Sponsor: None.

### CCTG HN11: SPECT-CT guided elective contralateral neck treatment (SELECT) for patients with lateralized oropharyngeal cancer—A phase III randomized controlled trial.

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**Background:** Lymphatic mapping identifies neck lymph nodes at risk for cancer spread in patients with lateralized oropharyngeal (OPC) squamous cell carcinoma. We hypothesize that a lymphatic mapping guided approach to radiotherapy (RT) treatment of the contralateral neck will enable safe de-escalation of therapy with acceptable disease control with potential benefits in RT related toxicity, QOL, swallowing function and economics. **Methods:** HN.11 is a Canadian Cancer Trials Group international multi-centre, non-inferiority randomized phase III trial comparing a lymphatic mapping-guided approach for management of the contralateral neck (experimental) vs. bilateral neck radiation therapy (RT) (control). The primary objective is to determine if a lymphatic mapping-guided approach for management of the contralateral neck has a non-inferior disease-free survival (DFS) compared to bilateral neck RT. Secondary objectives: To compare swallowing related QOL, xerostomia, isolated contralateral neck failure, overall survival, loco-regional failure, distant metastases, RT-related toxicities, patient reported adverse events (PRO CTCAE), gastrostomy tube usage, and economics indicators (resource utilization, lost productivity, financial toxicity, EQ5D). Exploratory objectives: Swallowing function using video fluoroscopic swallow studies, head and neck-cancer specific QOL, patterns of lymphatic drainage, radiomic prediction of contralateral lymphatic drainage, correlation of tumour somatic mutations and ctDNA with disease recurrence. **Statistical Design:** The target sample size is 510 patients. The experimental arm will be considered non-inferior if the upper limit of the one sided 95% confidence interval (CI) of the estimated hazard ratio (HR) does not exceed 1.46 (non-inferiority margin of 6.5% for 2-year DFS). In the primary intention-to-treat (ITT) analysis, the study has 81% power, with a one-sided type I error rate of 5%, assuming 5 years of accrual, 3-years of follow up to observe 178 DFS events, and a 5% loss to follow up. If non-inferiority is demonstrated in the ITT analysis, a secondary per-protocol analysis will be performed, analyzing those patients treated as per their allocation, with 80% power to detect non-inferiority of the experimental arm assuming a conservative 10% cross-over from the experimental to the control arm (i.e. failed lymphatic mapping). **Conduct to Date:** Study activation September 29, 2022. First enrollment was February 10, 2023. Supported by Canadian Cancer Society, Canadian Institutes of Health Research, National Cancer Trials Network (NCTN). Clinical trial information: NCT05451004. Research Sponsor: Canadian Cancer Society, Canadian Institutes of Health Research, National Cancer Trials Network (NCTN).

**Randomized phase I/II trial of TheraT vectors expressing HPV16 specific antigens with neoadjuvant chemotherapy followed by transoral robotic surgery (TORS) or risk/response stratified chemoradiotherapy (CRT) for locoregional HPV16+ oropharyngeal cancer (OPC).**

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**Background:** HPV+ OPC is associated with excellent survival, yet standard therapy leads to substantial treatment-related toxicity. Among various de-escalation strategies, response adaptive de-escalation which selects pts based on neoadjuvant response is promising with excellent survival and reduced toxicity. Strategies to further deepen responses may allow more pts to be de-intensified which may improve survival and further reduce toxicity. As generation and maintenance of the HPV16+ malignant state of a cell requires the consistent expression of HPV-specific E7 and E6 oncoproteins, they represent a potential immunotherapy target, inspiring the development of HPV-specific immune activators, such as HB-200 platform. This platform contains two replicating live-attenuated vectors based on either lymphocytic choriomeningitis virus (HB-201) or Pichinde virus (HB-202), which express the same non-oncogenic (but highly antigenic) HPV16 E7E6 fusion protein and infect antigen presenting cells to induce and activate tumor-specific T cell responses. Data from in vivo models and early phase clinical studies indicate that HB-201 monotherapy and HB-201/HB-202 alternating two-vector therapy induces a robust antigen-specific circulating T cell response and anti-tumor activity, suggesting potential to provide therapeutic benefit to pts with HPV16+ OPC. Based on these studies we hypothesized that incorporation of the HB-200 platform with neoadjuvant chemotherapy followed by risk/response-stratified de-escalation in our ongoing randomized phase I/II study may deepen responses and facilitate de-escalation in a greater proportion of pts (NCT05108870). **Methods:** Eligible pts must have previously untreated HPV16+ OPC with T3-4 or N2-3 (AJCC-7<sup>th</sup> edition). Very low-risk disease with T1-2 and N0-1 are excluded. Pts receive neoadjuvant therapy with either HB-201 or HB-201/HB-202 alternating two-vector therapy for 3 doses in combination with carboplatin AUC 5 day 1 and paclitaxel 100mg/m<sup>2</sup> on days 1/8/15 of 21-day cycle for three cycles followed by risk/response adapted locoregional therapy with transoral robotic surgery (TORS) or RT to 50Gy (single-modality), CRT to 50Gy with cisplatin (intermediate de-escalation), or CRT to 70Gy with cisplatin (regular dose CRT). Eight pts have been enrolled in phase I portion with planned 74 pts (37 pts per arm) in phase II. The primary endpoint is deep response rate defined as proportion of patients with  $\geq 50$  shrinkage per RECIST v1.1. Secondary endpoints include OS, PFS, locoregional and distant control, and safety/tolerability. Exploratory analyses will include cell free HPV-DNA, and tissue/blood-based assessment of specific anti-tumor immunity. Clinical trial information: NCT05108870. Research Sponsor: Hookipa Pharma.

**Phase 2 study of bintrafusp alfa in recurrent/metastatic olfactory neuroblastoma.**

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**Background:** Olfactory neuroblastoma (ONB, esthesioneuroblastoma) is a rare malignant tumor of the nasal cavity, believed to arise from the basal cells of the olfactory neurosensory epithelium. ONB is often locally advanced at diagnosis with high rates of spread both locoregionally and systemically. Current therapy for locoregional disease is local resection with adjuvant (chemo-) radiotherapy. Actionable mutations are rare, and treatment options for recurrent or advanced, non-resectable, disease are limited and include off-label combination chemotherapy (most frequently platinum-containing) and somatostatin-directed therapies (ONB expresses somatostatin receptors). These are based on limited data, with response rates poorly characterized. Bintrafusp alfa is a first-in-class, bifunctional TGF- $\beta$  “trap”/anti-PD-L1 fusion protein. Analysis of ONB has demonstrated both PD-L1/PD-L1 (London et al, 2018) and TGF- $\beta$  ligand expression (Romani et al, 2021). Pre-clinical and clinical data in advanced solid tumors demonstrate enhanced antitumor activity with combination PD-L1/TGF- $\beta$  blockade, with responses observed independently of high PD-L1 levels (Strauss et al, 2020). Thus, combination PD-L1/TGF- $\beta$  blockade in ONB is a rational approach in a setting of unmet clinical need. **Methods:** This study is a Phase 2 single-site, single-arm clinical trial of bintrafusp alfa (1200mg IV every 2 weeks for up to 26 doses) for patients with recurrent or metastatic ONB. Participants must co-enroll to the ONB Natural History study at the NCI (NCT4755205). Patients must not be candidates for local therapy, have received at least 1 line of systemic therapy (including a platinum salt), have RECIST 1.1 measurable disease and have adequate organ function. Prior checkpoint inhibitor therapy is permitted with patients cohorted according to checkpoint exposure; up to 21 checkpoint-naïve and 8 checkpoint-resistant patients will be enrolled. The primary objective is objective response rate by RECIST 1.1 with secondary endpoints including safety and tolerability, duration of response and overall survival; exploratory endpoints include pharmacokinetic analyses, PD-L1 and immune cell correlative analyses. The trial follows a Simon two-stage design, requiring  $\geq 1$  response in the first 12 patients. Tumor biopsy at enrollment is optional. Imaging for response assessment is planned for 8-week intervals and PET scan (preferably  $^{68}\text{Ga}$ -DOTATATE) will be obtained for all patients at baseline and first restaging, then on an individualized basis per radiology advice. This study is presently open at the NCI with 5 patients enrolled as of January 2023. Clinical trial registry: NCT05012098. Clinical trial information: NCT05012098. Research Sponsor: U.S. National Institutes of Health.

**IMRT followed by pembrolizumab in the adjuvant setting in anaplastic cancer of the thyroid (IMPAACT): Phase II trial adjuvant pembrolizumab after IMRT in ATC.**

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**Background:** Anaplastic thyroid carcinoma (ATC) has historically been an almost uniformly rapidly fatal disease. In patients with loco-regional disease with no distant metastasis (stage IVB), and without a targetable mutation, a combination of external beam radiation delivered via intensity modulated techniques (IMRT) +/- concurrent cytotoxic chemotherapy is the current standard of care. However, the relapse rate is very high within the first year of diagnosis. Our data show that 90% of ATCs express PD-L1, with 43% having expression levels greater than 50%. A clinical trial with an anti-PD1 drug in ATC patients with active disease showed that patients with ATC had a response rate of 19%. Additionally, as tumor PD-L1 expression has been linked to radioresistance and there is a need to target micro-metastatic disease, using adjuvant checkpoint inhibitor is a rational strategy in these patients. **Methods:** This is an open label, single center, phase 2 trial of adjuvant pembrolizumab after external beam radiation to the primary tumor in patients with stage IVB ATC. The primary cohorts will include those with gross, locoregional disease who have completed treatment with IMRT +/- concurrent radiosensitizing chemotherapy. Patients will be treated with adjuvant pembrolizumab (400mg IV Q6 weeks for up to 9 cycles), 2-6 weeks after completion of radiation. Patients will be enrolled based on dose of radiation in cohort 1 (high dose group, > 51 Gy), cohort 2 (palliative dose group, < 50 Gy). Cohort 3, consisting of those who underwent surgery followed by IMRT plus concurrent chemotherapy will be an exploratory cohort. Restaging scans will be performed every 12 weeks after enrollment. MRI brain will be repeated every 6 months in the absence of evidence of progression. The primary endpoint is median PFS (from the start of adjuvant pembrolizumab) in cohorts 1 and 2. Secondary endpoint is median overall survival in cohorts 1 and 2. Cohort 3 (5 patients) will have an exploratory endpoint, to estimate the median disease-free survival (DFS). **Statistics:** Survival analyses will be performed using the Kaplan-Meier method. Based on historical data, the median PFS for unresected patients is 6.8 months. For an expected improvement of median PFS by 3.7 months, with a combined total of 30 evaluable patients in cohorts 1 and 2, we anticipate having 80.0% power using 1-sided 10% alpha for a one-sample log rank test. The trial began enrollment in July 2022. This trial is sponsored by philanthropic funds and Merck. ClinicalTrials.gov ID NCT05059470. Clinical trial information: NCT05059470. Research Sponsor: Merck; Philanthropic funds.