Protocol-specified final analysis of the phase 3 KEYNOTE-048 trial of pembrolizumab (pembro) as first-line therapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC).

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Background: KEYNOTE-048 is a phase 3 study of P or P + chemo (C) vs EXTREME (E) as 1L therapy for R/M HNSCC (NCT02358031). At the second interim analysis (IA2), P significantly improved OS in the PD-L1 combined positive score (CPS) ≥20 and ≥1 populations and had noninferior OS in the total population with favorable safety. We present the protocol-specified final results. Methods: 882 pts with locally incurable R/M HNSCC and no prior systemic therapy in the R/M setting who provided a tumor sample for PD-L1 testing were randomized to P 200 mg Q3W for 24 mo (n = 301), P for 24 mo + 6 cycles of C (cisplatin 100 mg/m² or carboplatin AUC 5 Q3W + 5-FU 1000 mg/m²/d for 4 d Q3W) (n = 281), or E (cetuximab 400 mg/m² loading/250 mg/m² QW + 6 cycles of chemo) (n = 300). OS superiority was tested sequentially for P+C vs E in the CPS ≥20 population, then the CPS ≥1 population, and for P vs E in the total population (superiority thresholds: one-sided P = .0023, .0026, and .0059, respectively). Data cutoff was 25 Feb 2019 (~25 mo after last pt randomized). Results: P+C significantly improved OS vs E in the CPS ≥20 (HR 0.60, 95% CI 0.45-0.82, P = .0004; median 14.7 vs 11.0 mo) and CPS ≥1 (HR 0.65, 95% CI 0.53-0.80, P < .0001; median 13.6 vs 10.4 mo) populations. HR (95% CI) for PFS was 0.76 (0.58-1.01) for CPS ≥20 and 0.84 (0.69-1.02) for CPS ≥1. ORR (P+C vs E) was 42.9% vs 38.2% for CPS ≥20 and 36.4% vs 35.7% for CPS ≥1; median DOR was 7.1 vs 4.2 mo and 6.7 vs 4.3 mo, respectively. P did not significantly improve OS vs E in the total population (HR 0.83, 95% CI 0.70-0.99, P = .0199; median 11.5 vs 10.7 mo). HR (95% CI) for PFS was 1.29 (1.09-1.53). ORR (P vs E) was 16.9% vs 36.0%; median DOR was 22.6 vs 4.5 mo. All-cause gr 3-5 AE rates were 54.7% for P, 85.1% for P+C, and 83.3% for E. Conclusion: Overall, KEYNOTE-048 showed that compared with E, P+C had superior OS in the PD-L1 CPS ≥20, CPS ≥1, and total populations with comparable safety and P had superior OS in the CPS ≥20 and ≥1 populations, noninferior OS in the total population, and favorable safety. These results support pembrolizumab and pembrolizumab + platinum + 5-FU as new 1L standards of care for R/M HNSCC. Clinical trial information: NCT02358031.
Ado-trastuzumab emtansine in patients with HER2 amplified salivary gland cancers (SGCs): Results from a phase II basket trial.

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Background: SGCs are rare tumors with no approved therapy for metastatic disease. HER2 amplification occurs in 8% among all SGC histologies, and 25-33% of the aggressive salivary duct carcinoma (SDC) histologic subtype. We hypothesized that ado-trastuzumab emtansine, a HER2 targeted antibody drug conjugate, may be clinically active in these patients. Methods: A cohort of patients with HER2 amplified SGCs were enrolled into a multi-histology basket trial of ado-trastuzumab emtansine, treated at 3.6mg/kg IV every 3 weeks. The primary endpoint was overall response rate (ORR) by RECIST v1.1 or PERCIST. A Simon two-stage optimal design was applied with type I error rate under 2.7%, power of 89%, H0 10%, H1 40%; H0 will be rejected if 6 or more responses are observed in 24 patients. Other endpoints include duration of response (DOR), progression-free survival (PFS), and toxicity. HER2 amplification was identified by next generation sequencing (NGS), and tumors were subsequently tested by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Fluorescence lifetime imaging microscopy - Förster resonance energy transfer (FLIM-FRET) assessed the propensity for HER2-HER3 heterodimerization, which leads to receptor internalization. Results: 10 patients with HER2 amplified SGCs were treated. The median age was 65 (range 36-90 years), 90% were male. The median lines of prior systemic therapy was 2 (range 0-3). ORR was 90% (9/10, 95% CI 56-100%) including 5 complete responses after prior trastuzumab, pertuzumab and anti-androgen therapy. After a median follow up period of 12 months (range 4-20 months), median DOR (range 2-19+ months) and median PFS (95% CI 4–22+ months) were not reached. Toxicities included grade 1 or 2 infusion reaction, thrombocytopenia and transaminitis; there were no treatment related deaths. HER2 amplification by NGS (fold change 2.8 to 22.8) correlated with HER2/CEP17≥2 by FISH (8/8 tested) or IHC3+ (10/10 tested). FLIM-FRET tested positive in 3/3. Conclusions: Ado-trastuzumab emtansine is highly efficacious in patients with HER2 amplified SGCs as identified by NGS. This study has met its primary endpoint, and cohort expansion is warranted to confirm these results. Clinical trial information: NCT02675829.
**Background:** After promising results from the GORTEC TPEx phase II trial, the role of taxane instead of 5FU in 1st-line R/M HNSCC chemotherapy (CT) remained to be confirmed by comparing TPEx to the reference EXTREME regimen. **Methods:** Randomized (1:1), open-label trial. Main inclusion criteria were R/M HNSCC not suitable for locoregional treatment, age 18-70 years, PS $\leq 2$, creatinine clearance $>60$ml/min, prior cisplatin $\leq 300$ mg/m². Reference EXTREME regimen (arm A: 6 cycles every 3 weeks (Q3W) of 5FU–cisplatin-cetuximab (cetux) followed by weekly cetux maintenance) was compared to TPEx regimen (arm B: 4 cycles Q3W of docetaxel 75mg/m²–cisplatin 75mg/m²– cetux 250mg/m² with mandatory G-CSF support followed by every 2W cetux 500mg/m² maintenance). The primary endpoint was Overall Survival (OS). To detect a hazard ratio (HR) of 0.72 (median OS increase from 10.1 to 14.0 months (mo) with 88% power, 2-sided significance level of 0.05, 374 deaths were required. 540 patients (pts) were planned to enroll. **Results:** 539 pts were enrolled in 37 mo. Median age was 60 years, 93% were smokers, 40% had oropharyngeal tumor (p16 or HPV DNA was done in 85%, positive in 28%). In arm A, 44% of pts received all CT cycles vs 72% in arm B. Delays in administration were more frequent in arm A (27% vs 10%). Cisplatin was more frequently switched to carboplatin in arm A (34% vs 9%). Toxicity was lower in arm B: 34% pts had grade $\geq 4$ adverse events during CT in arm B vs 50% in arm A ($p<0.001$). Less pts in arm A started maintenance than in arm B (53% vs 73%). At time of analysis, the median follow-up duration was 30 mo and 406 pts had died. OS was not significantly different between arms: HR=0.87 (95%CI: 0.71-1.05), $p=0.15$. Median OS was 13.4 mo in arm A vs 14.5 in arm B. 2-year OS rate was 21.0% in arm A vs 28.6% in arm B. **Conclusions:** This large randomized trial confirmed the encouraging survival results of the TPEx regimen observed in the first phase II. OS in both arms was higher than observed in previous randomized CT or immunotherapy combination trials. Despite lack of significant OS increase, taxane based TPEx regimen appears to be a new option in 1st line R/M HNSCC, with a shorter time on CT and significantly lower toxicity than the EXTREME regimen. Clinical trial information: NCT02268695.
Gemcitabine and cisplatin (GP) induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT) versus CCRT alone in locoregionally advanced nasopharyngeal carcinoma (NPC): A phase 3, multicenter, randomized controlled trial.

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Background: GP regimen has been established as the standard first-line treatment option for patients with recurrent/metastatic NPC. However, its efficacy in locoregionally advanced disease remains unclear.

Methods: Patients with previously untreated, non-metastatic stage III-IVB (except T3-4N0M0, AJCC 7th) NPC, aged 18–64 years without severe comorbidities were eligible. They were randomly assigned (1:1) to receive GP IC (gemcitabine 1 g/m2 on days 1 & 8, cisplatin 80 mg/m2 on day 1, q3w for 3 cycles) plus CCRT (cisplatin 100 mg/m2, q3w for 3 cycles, concurrently with intensity-modulated radiotherapy) or CCRT alone. The primary endpoint was failure-free survival (FFS). The calculated sample size was 238 per group, with an 80% power (two-sided α 0.05) to detect a treatment failure hazard ratio (HR) of 0.52.

Results: From Dec 2013 to Sep 2016, 480 patients from 12 centers were randomly assigned to IC+CCRT (n = 242) or CCRT alone (n = 238) group. Baseline characteristics were well balanced. After a median follow-up of 39 months, 3-year FFS was 85.8% in the IC+CCRT group and 77.2% in the CCRT alone group (intentio-to-treat population; HR 0.53, 95% confidence interval 0.34–0.81; P = 0.003). In GP+CCRT group, 239 patients started GP IC and 231 (96.7%) completed all three cycles. The most common ≥grade 3 adverse events (AE) in IC+CCRT and CCRT group were mucositis (28.9% vs. 32.1%), neutropenia (28.0% vs. 10.5%) and leukopenia (26.4% vs. 20.3%).

Conclusions: Adding GP IC to CCRT significantly improved FFS in locoregionally advanced NPC and is well tolerated with favorable toxicity profile. Clinical trial information: NCT01872962.

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Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: Long-term results of a phase 3 multicenter randomized controlled trial.

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Background: Initial 3-year results from our clinical trial in locoregionally advanced nasopharyngeal carcinoma (NPC) patients showed that induction chemotherapy (IC) with cisplatin and fluorouracil (PF) resulted in improved disease-free survival (DFS) with a marginally significant effect on distant metastasis-free survival (DMFS), but the effect of IC on locoregional relapse-free survival (LRRFS) and overall survival (OS) did not differ significantly. Here, we present 5-year follow-up results. Methods: Our trial was a randomized, open-label phase 3 trial comparing IC followed by concurrent chemoradiotherapy (CCRT) versus CCRT alone in patients with stage III-IVB (except T3N0-1) NPC. The IC followed by CCRT group received cisplatin (80 mg/m² d1) and fluorouracil (800 mg/m² d1-5) every three weeks for two cycles before CCRT. Both groups were treated with 80 mg/m² cisplatin every three weeks concurrently with radiotherapy. The primary endpoints were DFS and DMFS. We did efficacy analyses in the 476 randomized patients (intention-to-treat population). Results: After a median follow-up of 82.6 months, the 5-year DFS rate was 73.4% (95% confidence interval (CI) 67.7-79.1) in the IC followed by CCRT group and 63.1% (95% CI 56.8-69.4) in the CCRT alone group (P = 0.005). The 5-year DMFS rate was also significantly higher in the IC followed by CCRT group (82.8%, 95% CI 77.9-87.7) than in the CCRT alone group (73.1%, 95% CI 67.2-79.0, P = 0.013). Our updated analysis revealed an OS benefit of IC: the 5-year OS rate was 80.8% in the IC followed by CCRT group versus 76.8% in the CCRT alone group (P = 0.045). There were no significant differences in the rate of grade 3–4 late adverse events during follow-up between the two groups. Conclusions: IC followed by CCRT provides long-term DFS, DMFS, and OS benefits compared with CCRT alone in locoregionally advanced NPC and, therefore, can be recommended for these patients. Clinical trial information: NCT00705627.
A phase II randomized trial for early-stage squamous cell carcinoma of the oropharynx: Radiotherapy versus trans-oral robotic surgery (ORATOR).

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Background: The incidence of OPSCC has risen rapidly, due to an epidemic of human papillomavirus (HPV) infection. Radiation therapy (RT) has historically been the standard treatment, but transoral robotic surgery (TORS) has surpassed RT in the US as the most common approach, based on assumptions of reduced toxicity or improved quality of life (QOL). No randomized trials have previously compared these treatments. Methods: The ORATOR trial (NCT01590355) enrolled patients with T1-T2 N0-2(≤4 cm) OPSCC amenable to TORS. We randomly assigned patients, stratified by p16 status, to RT (70 Gy/35 fractions, with chemotherapy if N1-2) vs. TORS (± adjuvant [chemo]RT based on pathology). The primary endpoint was a definitive comparison of swallowing QOL at 1-year using the MD Anderson Dysphagia Inventory (MDADI), powered to detect a 10-point improvement (a clinically-meaningful change [CMC]) in the TORS arm. Secondary endpoints included adverse events (AEs), other QOL outcomes [including EORTC scales, the Voice Handicap Index-10, Neck Dissection Impairment Index, and Patient Neurotoxicity Questionnaire], overall- and progression-free survival (OS, PFS). All analyses were pre-specified and intention-to-treat. Results: Between 2012 and 2017, 68 patients were randomized (n = 34 in each arm), in Canada and Australia. Primary tumor sites were palatine tonsil (74%) or base of tongue (26%). Arms were well-balanced for baseline factors, including p16 status (88% in each arm). Median age was 59 years; 87% were male. Primary tumor sites were palatine tonsil (74%) or base of tongue (26%). Arms were well-balanced for baseline factors, including p16 status (88% in each arm). Median follow-up was 27 months. MDADI scores at 1-year were statistically superior in the RT arm (mean ± SD: 86.9 ± 11.4 vs. 80.1 ± 13.0 in the TORS arm; p = 0.042), but not meeting the definition of a CMC. For the other QOL metrics, outcomes were similar at 1-year. Feeding tube rates at 1-year were 3% (n = 1) vs. 0% respectively. Rates of treatment-related grade ≥2 AEs were similar (91% vs. 100%, p = 0.24), with more neutropenia, constipation and tinnitus in the RT arm and more trismus in the TORS arm (all p < 0.05). There was one TORS bleeding-related death. OS and PFS were similar. Conclusions: RT had superior swallowing QOL scores at 1 year compared to TORS, but the difference was not a CMC. Toxicities differed between the arms. This study provides the first level 1 evidence to inform patients of the QOL impact of both approaches. Clinical trial information: NCT01590355.
Neck dissections based on sentinel lymph node navigation versus elective neck dissections in early oral cancers: A randomized, multicenter, non-inferiority trial.

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Background: The objective of the study is to evaluate the non-Inferiority of survival, the superiority of postoperative disability, and the complication of the neck in neck dissections based on sentinel lymph node navigation in early oral cancer patients, compared with standard selective neck dissections.

Methods: This study was a randomized, multicenter, non-inferiority trial at 16 institutions in Japan. Eligibility criteria included histologically confirmed squamous cell carcinoma in the oral cavity; clinical categories T1 and T2, N0M0 by UICC TNM classification 7th edition, clinical depth of invasion (DOI) of T1 was over 4mm (defined as late T1); previously untreated; age at least 18 years; and written informed consent. We randomly assigned patients (1:1) to receive either sentinel lymph node biopsy (SNB) or standard selective neck dissections (ND) with stratification of T category (late T1 vs T2) and subsite (tongue vs others). The primary endpoint was 3-year overall survival with a non-inferiority margin of 12%. Sentinel nodes (SNs) were detected using radioisotope method and examined with multislice frozen section analysis intraoperatively, following HE and cytokeratin stain for a final postoperative diagnosis. Patients with positive SNs had neck dissections in a one-stage or back up procedure.

Results: Between November 2011 and January 2016, 271 patients were enrolled and randomized to SNB group (134 patients) and ND group (137 patients) with a median follow-up of 37 months (IQR 36-39). Pathological positive nodal status was 34% (46/132) in SNB group and 26% (34/133) in ND group (Chi-Square p = 0.10). 3-year overall survival in SNB group was 89% (95%CI 82-93%), which was non-inferior to that in ND group (86%, 95%CI 79-91%), 3-year relapse-free survival was 80% (95%CI 72-86%) in SNB group and 81% (95%CI 73-87%) in ND group. Arm abduction of postoperative 1 and 3 months in ND group was disturbed significantly compared with SNB group.

Conclusions: SNB navigated ND could replace elective ND without survival disadvantage and reduce postoperative disability of the neck in patients with early oral cancer. Clinical trial information: 000006510.

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**Background:** Anti-PD-1/PD-L1 are active in metastatic oropharynx squamous cell carcinoma (OPC). Durvalumab (durva) and tremelimumab (tremi) target respectively PD-L1 and CTLA-4, which in combination may be synergistic. Here we report the safety and interim results of durva vs. durva+tremi prior to surgery in a window of opportunity trial in OPC. **Methods:** Pts were randomized 1:1 to durva 1500 mg or durva 1500 mg + tremi 75 mg IV Q4W x 2 cycles. The primary objective was to quantify pre- and post-treatment differences in CD8+ tumor infiltrating lymphocytes for the two arms. Secondary objectives included safety, toxicity, ORR by RECIST, fraction of patients undergoing surgery at 8 wks, and percentage viable tumor cells in the surgical specimen. Serial pre- and post-treatment blood and tumor specimens were collected for ongoing correlative analyses. **Results:** 28 pts enrolled: median age 64y, 27 (96%) male, 19 (68%) newly diagnosed, most (63%) at stage IVA (AJCC 7th Ed), 9 (32%) had locoregional recurrence, 24 (86%) p16 positive, and 22 (79%) had ≥10 PPY smoking history. Median follow-up was 7.6 months. The most common AEs were fatigue (36%), leukopenia/lymphopenia (25%), transaminitis (25%), and rash (21%). Grade 3 AEs occurred in 4 (14%) pts: 2 elevated lipase, 1 diarrhea, and 1 hepatitis, all were manageable. There were no grade 3 AEs. ORR was 43%; 50% had SD (including 29% tumor shrinkage in 1 pt). Treatment effect in the surgical specimen was observed in 19 (79%) of 24 evaluable pts; 2 pts had major pathologic response (<10% viable tumor) at the primary site. Efficacy was equivalent in both arms. The 2 pts with PD and 1 pt with SD were switched to chemotherapy after durva +/- tremi before resection; interestingly, each achieved a pCR in the primary. Most pts (57%) didn’t receive radiotherapy after surgery. There was a statistically significant association between ORR and treatment effect (p=0.014). The median percentage of viable tumor in the primary was 37.5% in pts with PR, and 82.5% in SD (p=0.003). **Conclusions:** Durva +/- tremi prior to surgery was well tolerated in OPC pts. Activity is encouraging with treatment effect seen in 79% of pts. The primary endpoint and complete efficacy data will be presented. Clinical trial information: NCT03144778.
Genomic and transcriptomic landscape of oral pre-cancers (OPCs) and risk of oral cancer (OC).

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Background: The molecular landscape of OPCs and its association with neoplastic progression is largely unknown. We report the results of high throughput DNA/RNA profiling of OPCs from pts in the Erlotinib Prevention of Oral Cancer trial (EPOC), with long-term prospective follow-up. Methods: We performed next generation sequencing of 201 cancer genes (MD Anderson T200 platform) in 170 OPCs from EPOC, and RNA profiling using HTG EdgeSeq Oncology Biomarker Panel containing 2,560 transcripts in a subset of 141 OPCs. 73 pts developed invasive OC during a median follow up of 7.3 years, from whom 23 paired OCs were profiled to characterize the evolutionary trajectory from OPCs to OCs. OPC molecular features were correlated with OC-free survival. Results were compared with TCGA invasive OC DNA/RNA profiles and an independent set of 86 OPCs with RNA data.

Results: Similar to TCGA, C>T was the predominant substitution. The top mutated genes in OPCs were TP53 (29%), CDKN2A (15%), NOTCH1 (11%) and PIK3CA (7%), which were also frequently mutated (albeit at higher rates) in OCs from EPOC or TCGA. There was a progressive increase of tumor mutation burden (TMB, \( P < 0.05 \)) and frequency of high-risk TP53 mutations (\( P = 0.02 \)) from hyperplasia, to dysplasia, to invasive OCs (\( P < 0.05 \)). Median TMB was higher in OPCs from pts who developed OC (2.45 mut/Mb) vs those who did not (1.22 mut/Mb) (\( P < 0.01 \)). Pts with TP53 mutated OPCs had shorter OC-free survival compared to TP53 wild-type (HR 1.81, 95% CI 1.13-2.90, \( P = 0.01 \)). A prognostic score was derived from a Cox regression model which identified 12 mRNA transcripts associated with OC risk (HR 4.72, 95% CI 2.51-8.86, \( P < 0.01 \)), and which was validated in the independent set of 86 OPCs (HR 2.68, \( P < 0.01 \)). This score was also associated with shorter overall survival when applied to invasive OCs from TCGA pts (HR 2.72, \( P < 0.01 \)).

Conclusions: This is the first large-scale cohort of OPC pts with long-term, prospective follow up and comprehensive RNA/DNA profiling. We demonstrated an association between TMB, TP53 mutations, a 12-gene RNA signature score in OPCs, and OC risk. This study may provide a framework for similar efforts of pre-cancer molecular profiling in the oral cavity and other sites, such as the PreCancer Atlas of the NCI.
Evolutionary action score of TP53 analysis in pathologically high-risk HPV-negative head and neck cancer from a phase II clinical trial: NRG Oncology RTOG 0234.

Chieko Michikawa, Pedro A. Torres-Saavedra, Natalie L. Silver, Paul M. Harari, Merrill S. Kies, David Ira Rosenthal, Quynh-Thu Le, Richard C. Jordan, Dzifa Yawa Duose, Saradhi Mallampati, Sanchit Trivedi, Rajyalakshmi Luthra, Ignacio Ivan Wistuba, Olivier Lichtarge, Robert Leonard Foote, Upendra Parvathaneni, David N. Hayes, Curtis R. Pickering, Jeffrey Myers; Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Department of Otolaryngology-Head and Neck Surgery, University of Florida, Gainesville, FL; Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI; Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA; NRG Oncology Biospecimen Bank, University of California, San Francisco, San Francisco, CA; Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Hematopathology, University of Texas MD Anderson Cancer Center, Houston, TX; Departments of Molecular and Human Genetics, Pharmacology, and Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX; Department of Radiation Oncology, Mayo Clinic, Rochester, MN; Radiation Oncology Center, University of Washington Medical Center, Seattle, WA; Division of Medical Oncology, The University of Tennessee Health Science Center, Memphis, TN

Background: An evolutionary action scoring algorithm (EAp53) based on phylogenetic sequence variations and speciation stratifies head and neck squamous cell carcinoma (HNSCC) patients bearing TP53 missense mutations as high-risk (high, $EAp53 \geq 75$), associated with poor outcomes, or low-risk (low), with similar outcomes as TP53 wild-type (wt), and has been validated as a reliable prognostic marker. This study is designed to further validate prior findings that EAp53 is a prognostic marker for locally advanced HNSCC patients, and assess its predictive value for treatment outcomes to adjuvant biochemoradiotherapy. Methods: Eighty one resection specimens from patients treated surgically for stage III or IV human papillomavirus-negative (HPV(-)) HNSCC with high-risk pathologic features, who received either Arm 1) radiotherapy (RT)+cetuximab (CTX)+cisplatin or Arm 2) RT+CTX+docetaxel, as adjuvant treatment in a phase II randomized clinical trial (RTOG 0234) underwent TP53 targeted sequencing, and EAp53 scoring. The EAp53 scores were correlated with clinical outcomes. Due to limited sample sizes, patients were combined into 2 EAp53 groups: wt/low and high/other. Results: At median follow-up of 10 years, there was a significant interaction between treatment and EAp53 group for overall survival (OS) ($p = 0.008$), disease-free survival (DFS) ($p = 0.05$) and distant metastasis (DM) ($p = 0.004$). Within arm 2, high/other showed worse OS [HR 4.69 (1.52-14.50)], DFS [HR 2.69 (1.16-6.21)], and had higher DM [HR 11.71 (1.50-91.68)] than wt/low. Within arm 1, there was no significant difference by EAp53 in OS, DFS and DM. Within the wt/low group, arm 2 had better OS [HR 0.11 (0.03-0.36)], DFS [HR 0.24 (0.09-0.61)], and DM [HR 0.04 (0.01-0.31)] than arm 1 but this was not found in high/other. Conclusions: High/other EAp53 scores were associated with worse survival for patients in arm 2. Arm 2 is associated with better survival than arm 1 for patients with wt/low EAp53. This benefit appears to be largely driven by a reduction in DM. Further validation is required to determine whether EAp53 can be used for personalized post-operative treatment decisions in HPV(-) HNSCC.
PIK3CA mutation as a prognostic factor in HPV-associated oropharynx cancer.

Brian T. Beaty, Gaorav Gupta, Colette J. Shen, Robert J Amdur, Jared Weiss, Juneko E. Grilley-Olson, Shetal Arvind Patel, Adam M. Zanation, Trevor Hackman, Brian Thorp, Jeffrey Blumberg, Samip Patel, Mark Christian Weissler, Wendell Gray Yarbrough, Nathan Christopher Sheets, Joel S. Parker, Neil Hayes, William M. Mendenhall, Roi Dagan, Bhishamjit S. Chera; University of North Carolina, Chapel Hill, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Radiation Oncology, University of Florida, Gainesville, FL; University of North Carolina Hospitals, Chapel Hill, NC; Department of Otolaryngology/Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Otolaryngology, University of North Carolina School of Medicine, Chapel Hill, NC; Rex/University of North Carolina, Raleigh, NC; Lineberger Comprehensive Center. Department of Genetics. University of North Carolina, Chapel Hill, NC; University of Tennessee, Germantown, TN; University of Florida Health Proton Therapy Institute, Jacksonville, FL; University of Florida Proton Therapy Institute, Jacksonville, FL

Background: PIK3CA is the most frequently mutated gene in HPV-associated oropharyngeal SCC (OPSCC), with a prevalence of 20-30%. While PIK3CA mutations have been associated with adverse outcomes in cervical cancer, their prognostic significance in HPV-associated OPSCC remains unknown. We sought to elucidate the significance of PIK3CA mutations in a prospective cohort of HPV-associated OPSCC patients treated with definitive chemoradiation (CRT). Methods: Seventy-eight patients with HPV-associated OPSCC were prospectively enrolled on three protocols: LCCC 1121 (NCT03161821) or two phase II clinical trials of de-intensified CRT (NCT02281955 / NCT03077243). De-intensified regimen was 60 Gy IMRT with concurrent cisplatin (30mg/m²). Next-generation sequencing of tumor samples was performed using a targeted panel-based assay (UNCSeq), including over 200 genes. We estimated disease-free survival (DFS) using the Kaplan-Meier method and compared treatment groups with two-sided log-rank test (Medcalc). Results: Sequencing was performed in 78 patients with a median follow-up of 24 months. Seventy-five patients received 60Gy; three patients received 70Gy. Ten patients had disease recurrence (2 regional only, 5 distant only, 3 regional and distant). Thirty-eight of 78 patients had at least one mutation identified (17 PIK3CA, 4 PTEN, 3 KRAS, 3 FBXW7, 3 FGFR3, 2 TP53, 2 prothrombin 20210, 1 NRAS, 1 BRCA1, 1 factor V Leiden, 1 FLT3, 1 RAD50, 1 PIK3R1). The most common site of PIK3CA mutation was the helical domain (E545K – 8/17, E542K – 2/17). Despite similar T/N staging and tobacco pack years, patients with WT-PIK3CA had significantly higher DFS (93%) compared with 65% for patients with PIK3CA mutations (p = 0.0009). Patients with mutations other than PIK3CA also had improved DFS relative to those with PIK3CA mutations (96% vs. 65%; p = 0.0147). Conclusions: PIK3CA mutation is associated with worse DFS in a prospective cohort of newly diagnosed HPV-associated OPSCC patients treated with definitive CRT. These findings suggest that patients with PIK3CA mutations may not be suitable for de-intensified therapy and investigation of novel treatment strategies may be appropriate.

6012 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 1:15 PM-4:15 PM, Discussed in Poster Discussion Session, Sat, 4:30 PM-6:00 PM

EAGLE: A phase 3, randomized, open-label study of durvalumab (D) with or without tremelimumab (T) in patients (pts) with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

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Background: EAGLE is a phase 3 study evaluating efficacy of D (anti-PD-L1 mAb) monotherapy and D+T (anti-CTLA-4 mAb) vs standard of care (SOC) in pts with R/M HNSCC who progressed following platinum-based therapy (NCT02369874). Methods: Pts were randomized 1:1:1 to D 10 mg/kg IV every 2 weeks (Q2W), D+T (D 20 mg/kg IV Q4W + T 1 mg/kg IV Q4W for 4 doses, then D 10 mg/kg IV Q2W), or SOC (investigator’s choice: cetuximab, taxane, methotrexate, or fluoropyrimidine-based regimen). The primary endpoint was overall survival (OS) with dual primary objectives of D+T vs SOC and D vs SOC. Additional endpoints included objective response rate (ORR), duration of response (DoR), and adverse events (AEs). Results: 240 pts were randomized to D, 247 to D+T and 249 to SOC. An imbalance for Eastern Cooperative Oncology Group performance status (ECOG PS) was seen in favor of the SOC arm (D, PS 0 = 26%, PS 1 = 74%; D+T, PS 0 = 26%, PS 1 = 74%; SOC, PS 0 = 32%, PS 1 = 68%). The risk of death was not statistically significantly different for D compared with SOC (HR: 0.88; 95% CI: 0.72–1.08; P = 0.20) or D+T vs SOC (HR: 1.04; 95% CI: 0.85–1.26; P = 0.76). Efficacy data are provided in the table. Treatment-related AEs Grade ≥3 were 41.4% in the D arm, 16.3% (51.2%) for D+T, and 24.2% (44.2%) for SOC. Following treatment, 2% of pts in D, 5% in D+T and 15% in SOC received immunotherapy. Conclusions: D and D+T did not demonstrate a statistically significant improvement in OS compared to standard chemotherapy in pts with R/M HNSCC. Median OS and ORR of D arm were similar to other studies with checkpoint inhibitors. The SOC arm outperformed what has been seen for SOC arms in previous studies; subsequent immunotherapy may have confounded the OS analyses. The safety profile for D and D + T in R/M HNSCC is consistent with previous trials. Clinical trial information: NCT02369874.

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<th>D+T (n = 247)</th>
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<td>Median OS, mo (95% CI)</td>
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<td>Survival rate, % (95% CI)</td>
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<td>12 mo</td>
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<td>ORR, % (95% CI)</td>
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<td>18.2 (13.6–23.6)</td>
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<td>DOR, mo</td>
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<td>7.4</td>
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Palbociclib plus cetuximab versus placebo plus cetuximab in platinum-resistant, cetuximab-naive, HPV-unrelated head and neck cancer: A double-blind randomized phase II trial (PALATINUS).

Douglas Adkins, Jin-Ching Lin, Assuntina Gesualda Sacco, Jessica C. Ley, Peter Oppelt, Qi Shen, Kenneth Alan Kern, Holger C. Thurm, Shaw-Ling Wang, Jean-Francois Martini, Justin Hoffman, Bohuslav Melichar, Makoto Tahara; Division of Medical Oncology and Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Department of Radiation Oncology, Taichung Veterans General Hospital, Taichung, Taiwan; University of California San Diego Moores Cancer Center, San Diego, CA; Pfizer Inc, Collegeville, PA; Pfizer Inc, New York, NY; Pfizer Inc, San Diego, CA; Fakultni Nemocnice Olomouc/Onkologicka Klinika, Pavlova, Czech Republic; National Cancer Center Hospital East, Kashiwa, Japan

Background: Cetuximab monotherapy results in a median overall survival (OS) of approximately 6 months (mo) in platinum-resistant recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). HNSCC unrelated to human papillomavirus (HPV) is driven by hyperactivation of the CDK4/6 and cyclin D1 (CD1) regulatory complex, resulting in cell cycle progression and tumor growth, suggesting that CDK4/6 inhibition can be a rational therapeutic strategy in this setting. Palbociclib (PAL) is a selective CDK4/6 inhibitor that may reverse cetuximab resistance by countering the actions of deregulated CD1. PAL plus an epidermal growth factor receptor inhibitor synergistically reduced cell viability of HPV-unrelated HNSCC cell lines. In a single-arm, multicenter trial of platinum-resistant, cetuximab-naive, HPV-unrelated HNSCC, PAL in combination with cetuximab resulted in a median OS of 9.5 mo. Methods: In a double-blind randomized phase II trial, patients (pts) with platinum-resistant, cetuximab-naive, HPV-unrelated HNSCC were treated with cetuximab plus either PAL (arm A) or placebo (arm B). Pts were stratified by performance status (PS) and prior immunotherapy (IT). 120 pts were required for 1:1 randomization to have ≥ 80% power to detect a hazard ratio (HR) of 0.6 (corresponding to a median OS of 10 mo in arm A and 6 mo in arm B) using a 1-sided log-rank test \( P = 0.10 \). Key secondary endpoints included progression-free survival (PFS), adverse events (AEs), and p16 status. Results: Pts \( n = 125 \) were randomized (arm A, 65; arm B, 60). PS and prior IT were balanced between the arms. Median (95% CI) follow-up for OS was 15.9 (15.0–19.4) mo. Median OS was 9.7 (7.3–13.9) mo in arm A and 7.8 (6.7–10.6) mo in Arm B (stratified by PS: HR=0.82 [95% CI, 0.54–1.25], \( P = 0.18 \)). Median PFS was 3.9 mo in arm A and 4.6 mo in arm B (stratified by PS: HR=1.00 [0.7–1.5], \( P = 0.5 \)). Hematologic AEs were more common in arm A. Only 11 pts (9%) received IT after being treated on the trial. Conclusions: Among pts with platinum-resistant, HPV-unrelated HNSCC, PAL plus cetuximab resulted in a trend of prolongation of median OS compared with cetuximab. Clinical trial information: NCT02499120.
Results of a phase 2a, multicenter, open-label, study of RM-1929 photoimmunotherapy (PIT) in patients with locoregional, recurrent head and neck squamous cell carcinoma (rHNSCC).

Background: Patients with rHNSCC who have failed standard of care have poor prognoses and limited therapeutic options. In this study, final results are reported of a phase 2a trial of photoimmunotherapy (PIT) with a targeted drug RM-1929, consisting of the EGFR-directed antibody cetuximab conjugated to a photoactivatable dye (IRDye 700DX). Binding of the antibody-dye conjugate to cancer cells followed by photoactivation with nonthermal red light induces selective and rapid necrosis of the cancer cells, with minimal damage to surrounding tissue. Methods: A phase 2a, multicenter, open-label, study of RM-1929 PIT in patients with locoregional, rHNSCC who could not be satisfactorily treated with surgery, radiation, or platinum chemotherapy was conducted to evaluate the safety and efficacy of the drug, RM-1929. For each treatment, nonthermal red light (690 nm) was applied to the tumors 24 hours post IV infusion of the drug. Surface illumination was administered for superficial tumors and interstitial illumination via intratumoral placement of fiber optic diffusers for deep tumors. Therapeutic response was assessed using CT RECIST 1.1 by an independent blinded radiologist. Results: Thirty rHNSCC patients were enrolled. There were no dose-limiting toxicities and one Grade 1 photosensitivity reaction. Most reported AEs were mild to moderate in severity with 96.7% (29/30) of patients with Grade 1 and 83.3% (25/30) with Grade 2, respectively. There were 13 (43.3%) patients who had at least one SAE. 86% (19/22) of SAEs were deemed unlikely related to treatment, including all 3 fatal SAEs. Three SAEs were reported to be possibly/probably related to treatment (site/oral pain, tumor hemorrhage, and airway obstruction). ORR was 50% (15/30) with 16.7% (5/30) CR and 86.7% (26/30) DCR. Median PFS and OS results will be forthcoming. Conclusions: These data indicate that RM-1929 PIT treatment was generally well tolerated with majority of AEs as mild to moderate in severity. Preliminary data showed favorable response rates in a heavily pre-treated population. A global phase 3 clinical trial is currently underway. Clinical trial information: NCT02422979.
Primary analysis of phase 2 results of cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with locally advanced cutaneous squamous cell carcinoma (laCSCC).

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Background: Cemiplimab (REGN2810) produced substantial antitumor activity with durable responses in Phase 1 CSCC expansion cohorts and Phase 2 metastatic (m) CSCC cohort. We now present the primary analysis of the Phase 2 laCSCC cohort (NCT02760498; data cutoff date: Oct 10, 2018). Methods: Pts with laCSCC received cemiplimab 3 mg/kg IV every 2 weeks (Q2W). Tumor measurements were performed Q8W. The primary objective was to evaluate objective response rate (ORR; complete response [CR] + partial response [PR]) according to independent central review (per RECIST 1.1 for scans; modified WHO criteria for photos). Results: 78 pts were enrolled (59 M/19 F; median age: 74 years; ECOG PS: 0 in 38 pts, 1 in 40 pts; primary CSCC site: head/neck in 79.5%; prior systemic therapy: 15.4%; prior radiotherapy: 55.1%). Median duration of follow-up was 9.3 months (range: 0.8–27.9). ORR by central review was 43.6% (95% CI: 32.4–55.3; 10 CRs and 24 PRs); investigator-assessed (INV) ORR was 52.6% (95% CI: 40.9–64.0; 13 CRs and 28 PRs). Median duration of response (DOR) has not been reached. The longest DOR at data cut-off was 24.2 months and was still ongoing. Durable disease control rate (stable disease or response for ≥16 weeks) was 62.8% (95% CI: 51.1–73.5). Median observed time to response was 1.9 months (range: 1.8–8.8). Median progression-free and overall survival have not been reached. Tumor PD-L1 status is available for 48/78 pts, tumor mutational burden analysis (from targeted exome panel) is ongoing for ≥40/78 pts; response correlation analyses are planned. The most common treatment-emergent adverse events (AEs; all grades, Grade ≥3) were fatigue (42.3%, 1.3%), diarrhea and pruritus (both 26.9%, 0%), and nausea (21.8%, 0%). INV grade ≥3 immune-related AEs occurred in 10.3% of pts. One pt died due to an unknown cause that was assessed as treatment-related. Conclusions: Cemiplimab 3 mg/kg Q2W showed substantial antitumor activity, durable responses, and acceptable safety profile in pts with laCSCC. These data strongly support the recent FDA approval of cemiplimab-rwlc for pts with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation. Clinical trial information: NCT02760498.
Discordant treatment response in primary tumors and lymph node metastases after four weeks of preoperative PD-1 blockade in head and neck squamous cell carcinoma (HNSCC).

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Background: Discordant radiographic responses are described in other tumor types in response to immunotherapy with response at some anatomic sites and progression in others. Here we determined the frequency of discordant treatment effects (TE) in HNSCC patients treated with immunotherapy in the context of a neoadjuvant trial. Methods: 23 Patients with resectable primary HNSCC were 1:1 randomized to receive nivolumab (240 mg IV Q 2 weeks x 2) or nivolumab and tadalafil 10 mg daily. Surgery was performed 4 weeks after the first nivolumab infusion. Resection specimens were graded histopathologically by two pathologists. Areas exhibiting TE (defined by fibrosis with chronic inflammation, foamy macrophage reaction and multinucleated giant cells) were expressed relative to the total tumor area. This was assessed in the primary tumor and all lymph nodes (LN). Each primary lesion and individual LN was defined as a) no response 0%TE, b) minimal response 1-19%TE, c) response 20-99% or d) complete response 100%. Concordance was defined if primary lesion and LNs were in the same ordinal data set. Results: 11/23 (48%) of subjects experienced concordant TE in the primary tumor and LNs. Within this cohort, 3 patients had a complete pathologic response both at the primary site and LNs. In contrast, 12/23 patients (52%) revealed discordant TE between the primary tumor sites (average of 17% TE) and involved LNs (average of 62% TE), (p= 0.018; signed rank test). Interestingly, in the discordant group, TE effects in LNs were invariably greater than in primary lesions. In 5 of 11 patients with multiple involved LN, the TE varied between nodes. This included patients with adjacent LNs demonstrating 0% and 100% TE in the same level. Systemic and local immune parameters as they relate to concordant and discordant TEs in individual patients will be presented including a type 1 immune bias. Conclusions: Early histologic evaluation of TE in patients with HNSCC receiving immunotherapy demonstrate a wide variety of response between the primary tumor and LNs. Further investigations will lend insight into complex interactions of cancer cells with the microenvironment. Clinical trial information: NCT03238365.
Recombinant humanized anti-PD-1 monoclonal antibody (JS001) in patients with refractory/metastatic nasopharyngeal carcinoma: Interim results of an open-label phase II clinical study.

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Background: Metastatic nasopharyngeal cancer (NPC) patients progressed after standard therapy have limited treatment options. Toripalimab, also known as JS001, a humanized IgG4 antibody specific for human PD-1, has been approved for 2nd line treatment of metastatic melanoma in China. Here we report the results from a phase II study in metastatic NPC patients treated with toripalimab. (Clinical trial ID: NCT02915432). Methods: This multi-center, open-label, phase II registration study is designed to evaluate the safety and efficacy of toripalimab in metastatic NPC patients who have failed systemic treatment. Toripalimab is given at 3 mg/kg IV Q2W until disease progression or intolerable toxicity. Tumor PD-L1 expression, plasma EBV DNA level and other biomarkers will be correlated with clinical response. Results: Enrollment of 190 chemotherapy-refractory metastatic NPC patients was completed by Feb 2019 from 17 participating centers. The median age was 46 years, with 89.5% patients received at least 2 lines of prior systemic therapies. Treatment related adverse events (TRAE) occurred in 92% patients, which were mostly grade 1 or 2. Common TRAE included anemia, hypothyroidism, AST increased, proteinuria, pyrexia, cough, constipation, ALT increased, hypoalbuminemia and pruritus. Grade 3 or higher TRAE occurred in 25% patients. By the cut-off date of Jan 7 2019, among 135 evaluable patients, 3 complete responses, 31 partial responses and 40 stable diseases were observed for an objective response rate (ORR) of 25.2% and a disease control rate of 54.8%. PD-L1 expression results were obtained from 125 patients and 45.6% (57/125) were PD-L1+. PD-L1+ patients achieved slightly higher ORR than PD-L1- patients, 29.8% versus 22.1%. In addition, an average drop of 47-fold plasma EBV DNA copy number was observed in responding patients, which typically preceded the radiographic identification of clinical benefit. Conclusions: Toripalimab has demonstrated a manageable safety profile and encouraging clinical activity in the largest check-point blockade study in NPC to date. A change in plasma EBV DNA copy number might serve as a predictive marker for favorable clinical response. Patients will be continuously monitored for additional safety and survival readouts. Clinical trial information: NCT02915432.
Activity and tolerability of BLU-667, a highly potent and selective RET inhibitor, in patients with advanced RET-altered thyroid cancers.

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Background: RET alterations are targetable oncogenic drivers in ~90% of advanced medullary thyroid cancer (MTC) and 20% of papillary thyroid cancer (PTC), yet no selective RET inhibitors are approved. BLU-667 is an investigational highly potent and selective RET inhibitor targeting oncogenic RET alterations including those that confer resistance to multikinase inhibitors (MKIs). We provide an update on the expanded experience of BLU-667 in RET-altered thyroid cancer from the registration-enabling ARROW study (NCT03037385). Methods: ARROW is a global DE (30-600 mg daily [QD or BID]) and dose expansion (DX; 400 mg QD) study in pts with advanced solid tumors. Primary objectives are response rate (ORR; RECIST 1.1) and safety. Results: As of 19Dec2018, 60 pts with RET-mutated MTC (M918T [37], C634R/S/W [8], V804M [4], other/pending [11]) and 5 pts with RET-fusion+ PTC (NCOA4 [3], CCDC6 [2]) received BLU-667 (37 DE, 28 DX). 58% had prior MKI therapy. Among 49 response-evaluable MTC pts, ORR is 47% (95% CI: 33, 62; 2 complete and 21 partial responses (PR); 4 PR pending confirmation; 25 stable disease; 1 progressive disease). 96% (22/23) of responding pts continue treatment; 15 with response duration ≥ 6 months. 2/4 evaluable PTC pts had PR; all 5 enrolled PTC pts continue treatment at 8-11 months. Responses in MTC occur regardless of MKI resistance (prior cabozantinib/vandetanib: ORR 46% (12/26)) or RET genotype (PR in 2/3 evaluable pts with V804M). Disease control rate in MTC pts is 98%. Rapid plasma clearance of RET variants and marked reduction in CEA and calcitonin is observed. Treatment-related toxicity in MTC/PTC pts, generally low-grade and reversible (28% had grade 3 events, no grade 4/5 events, no events requiring discontinuation), includes decreased WBC (23%), increased AST (17%), increased ALT, blood creatinine, and phosphate, hypertension, and decreased neutrophils (all 15%). Conclusions: BLU-667 demonstrates potent, durable and broad antitumor activity and is well tolerated in MTC/PTC pts regardless of MKI resistance and may significantly improve outcomes for pts with RET-altered thyroid cancers. Enrollment of the expansion is ongoing with registrational intent. Clinical trial information: NCT03037385.
Anlotinib treatment in locally advanced or metastatic medullary thyroid carcinoma: A multicenter, randomized, double-blind, placebo-controlled phase IIB trial.

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Background: Anlotinib (AL3818) is a novel multi-target TKI, inhibiting tumor angiogenesis and proliferative signaling. Our previous single-arm phase 2 ALTN/MTC trial (NCT01874873) has demonstrated that anlotinib has a durable antitumor activity with a manageable adverse event profile in locally advanced or metastatic medullary thyroid carcinoma (MTC). Here we report results of the phase IIB trial (ALTER01031, NCT02586350) of anlotinib for locally advanced or metastatic MTC with a larger samples. Methods: Between September 2015 and September 2018, 91 patients were enrolled in China. Eligible patients have diagnosed as phase IV MTC with relapsed and measurable disease and without antiangiogenetic target therapy. The patients were randomly assigned in a 2:1 ratio to receive anlotinib or a matched placebo (12 mg QD from day 1 to 14 of a 21-day cycle). Patients who have been diagnosed with disease progression by the Independent Imaging Committee could be unblinded and crossed to the treatment group if the patient previous treated by placebo. The primary endpoint was progression-free survival (PFS). Results: 91 patients were randomized 62 to anlotinib arm and 29 to placebo arm. Until the data cutoff date (1 Feb 2019), median PFS was 20.67 months (95%CI, 14.03-34.63) in anlotinib arm vs 11.07 (95%CI, 5.82-14.32) months in placebo arm (HR 0.53, p = 0.0289). The OS data were not sufficiently mature for analysis. Considerable improvement in ORR was observed over the two arms (48.39% vs 3.45%, p < 0.0001). The adverse events (AEs) were 100% in anlotinib arm and 89.66% in placebo arm. The most common AEs in anlotinib arm were hand-foot syndrome, hypertension, hypertriglyceridemia and diarrhea. Conclusion: ALTER01031 met its primary endpoint of PFS shows that anlotinib treatment is effective and well tolerated. The safety profile was consistent and no new adverse events were identified. These data potentially extend the role of anlotinib monotherapy as a new therapy strategy for MTC patients. Clinical trial information: NCT02586350.
Alliance A091404: A phase II study of enzalutamide (NSC# 766085) for patients with androgen receptor-positive salivary cancers.

Background: A subset of salivary gland cancer (SGCs) express the androgen receptor (AR). This phase II trial evaluated the anti-androgen enzalutamide (Astellas) for patients with AR+ SGCs. Methods: Locally advanced/unresectable or metastatic AR+ SGCs were enrolled (AR status was centrally confirmed). Prior therapy with AR-targeted drugs was allowed. Enzalutamide 160 mg orally once daily was given (1 cycle=28 days). The primary endpoint was confirmed response (RR) according to RECIST v1.1 within the first 8 cycles. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. A Simon-Optimal two-stage design was used to detect a 20% RR (vs. 5%) (alpha = 5%; beta = 90%). >1 response(s) in the first 21 would trigger accrual to 41; >4 responses would be considered promising. Results: 46 eligible patients (pts) were enrolled (40 M, 6 F; median age 65) in 22 months. In the first 21 pts, we initially had 2 confirmed PRs allowing for full study accrual, though one was later changed to stable disease. Among the 46 pts, 7 had PR as best response, though only 2 were confirmed within the first 8 cycles (4% (95% CI: 0.5-15%). Two other PRs did not count towards the primary endpoint due to 1) development beyond 8 cycles (cycles 12-18) and 2) a confirmatory scan completed <4 weeks apart. The other 3 pts with unconfirmed PR developed progression of disease (PD) after the first PR scan. 24 pts had stable disease; 15 pts PD as best response. Among 11 pts previously treated with AR-targeted therapy, best responses were 1 confirmed PR, 7 SD, 3 PD. With a median follow-up of 11.7 months (mo), OS at 12 mo was 66% (95% CI: 52-83%), PFS at 12 mo was 24% (95% CI: 14-42%), and median PFS was 5.5 mo (95% CI: 3.7-7.3). Conclusions: This is the first prospective trial evaluating an antiandrogen alone for AR+ SGCs. The failure to meet the protocol-defined measure of success was due in part to the lack of durability of initial responses. The clinical activity observed suggests the AR-dependence of AR+ SGCs, even among those previously treated with other hormonal therapies. Support: U10CA180821, U10CA180882; Astellas; https://acknowledgments.alliancefound.org. Clinical trial information: NCT02749903.
Longitudinal circulating Epstein–Barr virus DNA response to induction chemotherapy and chemo-radiotherapy to identify biological phenotypes in EBV-associated nasopharynx of head and neck cancer.

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Background: Liquid biopsies have the utility for detecting minimal residual disease in several cancers, but its clinical utility for real-time treatment adaptation remains limited. We adopted Epstein-barr virus (EBV)-associated nasopharyngeal carcinoma (NPC) as a model to investigate its potential. We characterize longitudinal response of circulating EBV DNA to induction chemotherapy (IC) and concurrent chemoradiotherapy (CCRT) in locally advanced NPC (LA-NPC), and investigate the association of complete biological response (cBR, undetectable cfEBV DNA) during treatment to prognoses. Methods: The medical records of 673 LA-NPC cases with serial EBV DNA measurements (pre-treatment, after each IC cycle, post-CCRT) were extracted. Cox regression and landmark analysis were used for survival analyses. Results: Four distinct phenotypes were identified based on their longitudinal cfEBV DNA response: 1) Early responders (200/673[29.7%]) achieved cBR post-IC1; 2) Intermediate responders (332/673[49.3%]) included patients with cBR post-IC2-4, and cBR post-CCRT after two IC cycles or following a temporary bounce (detectable reading following initial cBR); 3) Late responders (75/673[11.2%]) achieved cBR only post-CCRT after 3-4 IC cycles; 4) Treatment-resistant (66/673[9.8%]) patients demonstrated non-cBR post-IC+CCRT. These phenotypes were significantly correlated with prognoses, adjusted for pre-treatment EBV DNA load, N-category and chemotherapy intensity (AHRDFS = 3.46[2.01–6.25], intermediate; 7.50[4.24–14.77], late; 17.33[10.06–33.38], treatment-resistant vs. early responders, \( P_{all} < 0.01 \)). Interestingly, intermediate and late responders without cBR post-IC2 had inferior survival despite more IC (HR DFS = 1.83[1.17–2.84], > 2 vs. >2 IC cycles, \( P < 0.01 \)). For treatment-resistant patients, adjuvant chemotherapy following IC+CCRT reduced risk of distant metastasis (HR DMFS = 0.42[0.24–0.74], \( P < 0.01 \)). Conclusions: We propose investigate risk-adapted chemotherapy de-intensification and intensification strategies based on the four novel phenotypes, which could shape the individualized treatment of LA-NPC. Our study highlights the feasibility of liquid biopsy for real-time therapeutic adaptation.
Mature results of the LCCC1413 phase II trial of de-intensified chemoradiotherapy for HPV-associated oropharyngeal squamous cell carcinoma.

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Background: To report the mature results from a prospective phase II clinical trial of highly de-intensified chemoradiotherapy (CRT) for patients with HPV-associated oropharyngeal squamous cell carcinoma (OPSCC). Methods: The major inclusion criteria were: 1) T0-T3, N0-N2, M0, 2) p16 positive, and 3) minimal/remote smoking history. Treatment was limited to 60 Gy intensity modulated radiotherapy with concurrent weekly intravenous cisplatin 30 mg/m² (second choice was cetuximab). Patients with T0-T2 N0-1 disease did not receive chemotherapy. All patients had a 10 to 12-week post-treatment PET/CT to determine need for planned neck dissection. The primary study endpoint was 2 year progression free survival (PFS). Secondary endpoint measures include 2 year local control (LC), regional control (RC), distant metastasis free survival (DMFS), cause specific survival (CSS) and overall survival (OS), and patient reported symptoms (PRO-CTCAE) and quality of life (EORTC QLQ-C30 & H&N35). Results: 114 patients were enrolled (median f/u of 28.8 months, range 2.6 to 51.4) with 84 having a minimum follow-up of 2 years. Smoking status was as follows: 47% never, 33% ≤ 10 pack years, and 19% > 10 pack years. Post-treatment PET/CT complete response rate was 93% at the primary site and 80% in the neck. Eleven patients had planned neck dissection with 4 having pathological residual disease. Two year LC, RC, DMFS, PFS, CSS, and OS were the following: 96%, 99%, 91%, 88%, 97%, and 95%. Neither smoking status nor receipt of cetuximab correlated with recurrence. Four patients with recurrent disease had PIK3CA mutations. Thirty four percent of patients required a feeding tube (none permanent) for a median of 10.5 weeks. Mean pre- and 2-year post-treatment EORTC QOL scores were: Global 79/83 (lower worse), Swallowing 8/9 (higher worse), Dry Mouth 14/45 (higher worse), and Sticky Saliva 9/28 (higher worse). Mean pre- and 2 year post-treatment PRO-CTCAE (0 to 4 scale, higher worse) scores were: Swallowing 0.5/0.7 and Dry mouth 0.4/1.4. There were no ≥ Grade 3 late adverse events. Conclusions: Clinical outcomes with a highly de-intensified CRT regimen of 60 Gy IMRT with concurrent low-dose cisplatin are excellent in patients with HPV-associated OPSCC. Clinical trial information: NCT02281955.
NRG-HN003: Phase I and expansion cohort study of adjuvant cisplatin, intensity-modulated radiation therapy (IMRT), and MK-3475 (Pembrolizumab) in high-risk head and neck squamous cell carcinoma (HNSCC).

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Background: Pembrolizumab, an anti-PD1 monoclonal antibody, improves survival in advanced HNSCC. Patients with pathologic high risk, HPV-negative HNSCC have a high recurrence rate despite adjuvant cisplatin-IMRT (CRT), the current standard. Immunosuppression is induced by HNSCC and CRT, and may be reversible by targeting PD1.

Methods: We conducted a phase I trial with expansion cohort to determine the recommended phase II schedule (RP2S) for adding fixed-dose pembrolizumab to adjuvant CRT (NCT02775812). Eligibility: oral cavity, pharynx, or larynx primary; HPV-negative; pathologic high risk (positive margin or extranodal extension [ENE]); Zubrod 0-1. During phase I, patients enrolled in descending cohorts of 12 (Table). RP2S was declared if ≤3 dose-limiting toxicities (DLT) occurred. DLT was defined as ≥ Grade 3 non-hematologic adverse event (AE) related to pembrolizumab, immune-related (ir)AE requiring ≥ 2 weeks of systemic steroids, or unacceptable delay in IMRT. The expansion cohort enrolled 20. Results: From Nov 2016-Oct 2018, 34 eligible patients enrolled at 22 NRG institutions. During the first cohort, 1 DLT was observed (Grade 3 fever). RP2S was declared as Schedule 3 and the expansion cohort triggered. Among all 34 patients, median age was 60 years (26-83); 68% were male; 74% had Zubrod 1; 85% had oral cavity; 88% had ENE; 21% had positive margin. During expansion, 3 additional patients with DLT were observed: wound infection; diverticulitis; nausea. No DLT unacceptably delayed IMRT. Twenty-eight of 34 (82%) received 5 doses of pembrolizumab; 17 (50%) got all 8 doses. Thirty-one of 32 (97%) DLT-evaluable patients received all adjuvant RT; 1 withdrew consent after starting protocol. Conclusions: The RP2S is pembrolizumab 200 mg IV q 3 weeks for 8 doses, starting the week before adjuvant CRT. This regimen was safe and feasible in a cooperative group setting. irAE were rare in this population. Clinical trial information: NCT02775812.

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- **IMRT (60 Gy, 2 GY/Fx/day)** – all schedules
- **Cisplatin 40 mg/m²/week IV** – all schedules
- **Pembrolizumab 200 mg IV**

Schedule 3 (Starting): X X X X X X
Schedule 2 (1st De-escalation): X X X X X X X
Schedule 1 (2nd De-escalation): X X X X X X X
Afatinib versus methotrexate as second-line treatment for patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) progressing on or after platinum-based therapy: LUX-Head & Neck 3 phase III trial.

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Background: In a previous global phase III trial (LUX-Head & Neck 1), second-line (2L) afatinib significantly improved PFS vs methotrexate (MTX) in pts with R/M HNSCC. Here, we compared efficacy/safety of 2L afatinib vs MTX in Asian pts with R/M HNSCC. Methods: Pts progressing on/after platinum therapy were randomized (2:1) to 40 mg/day afatinib (feeding tube or oral) or 40 mg/m²/week iv MTX. Primary endpoint was PFS by independent review. Secondary endpoints were OS, ORR, and patient-reported outcomes. Results: 340 pts were randomized (afatinib 228, MTX 112). Median (range) duration of treatment (Tx) was 3.0 (0.1–35.9) and 1.4 (0.1–8.8) mos, respectively. Afatinib significantly decreased the risk of progression or death by 37% compared with MTX (HR 0.63; 95% CI: 0.48, 0.82; p = 0.0005, median PFS, 2.9 vs 2.6 mos; landmark analysis at 12 and 24 wks, 58 vs 41%, 21 vs 9%). There was no significant difference in OS (HR 0.88; 95% CI: 0.68, 1.13; median 6.9 vs 6.4 mos). ORR was 28% with afatinib and 13% with MTX (OR 2.8; 95% CI: 1.5, 5.2, p = 0.016). More pts had clinically relevant improvements in global health status/quality of life (GHS/QoL; 40 vs 23%, p < 0.01), swallowing (34 vs 18%, p = 0.01) and pain (34 vs 25%, p = 0.22) with afatinib vs MTX. Post-baseline change in GHS/QoL score was more favorable with afatinib (p < 0.001). Treatment-related adverse events (TRAEs; all/grade ≥3) were reported in 89/16% and 67/23% pts with afatinib and MTX. The most common grade ≥3 TRAEs were rash/acne (4%), diarrhea (4%), and stomatitis (3%) with afatinib, and anemia, leukopenia, and fatigue (all 5%) with MTX. Fatal AEs were reported in 23 and 11% pts with afatinib and MTX. Two (hypoglycemia, pneumonitis/lung infiltration) and 4 pts had fatal AEs considered related to Tx with afatinib and MTX. 11% and 17% pts discontinued Tx due to TRAEs. Conclusions: LUX-Head & Neck 3 achieved its primary endpoint. Two randomized phase III trials have now demonstrated clinical benefit with 2L afatinib vs MTX. Safety data were consistent with the known tolerability profiles of afatinib and MTX. Clinical trial information: NCT01856478.

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Background: CDX-3379, an anti-ErbB3 monoclonal antibody with a half-life-extending YTE modification in its Fc region, binds a unique epitope that locks ErbB3 in an inactive form and inhibits ErbB3 signaling, the latter implicated in tumor growth/resistance to anticancer therapies. CDX-3379 enhances antitumor activity of targeted therapies in preclinical models. In a Phase 1 clinical study, CDX-3379 was well-tolerated alone and in combination with cetuximab. A durable complete response (CR) to CDX-3379 + cetuximab was observed (8.3 months) in a patient (pt) with cetuximab-refractory HNSCC (Falchook ASCO 2016). Methods: This open-label phase 2 study (NCT03254927) was designed to enroll up to 30 pts with advanced, HPV-, HNSCC, previously treated with cisplatin, anti-PD-1 antibodies, and cetuximab-resistant (progression within 6 months), according to a Simon’s 2-stage design (13 evaluable pts in Stage 1 with ≥1 objective response allows enrollment of 14 more pts in 2nd stage). Pts receive CDX-3379 (initial dose 12 mg/kg IV every 21 days) + cetuximab (loading dose 400 mg/m²; 250 mg/m² IV weekly) until disease progression/toxicity. Endpoints include objective response rate (primary), progression-free and overall survival, safety, pharmacokinetics, immunogenicity, and exploratory biomarkers. Results: Stage 1 accrual is complete with 14 evaluable pts treated. All pts were heavily pretreated; prior therapies included surgery (10/14) and chemotherapy (13/14). All pts had prior radiation, cetuximab and PD-1 targeted therapy. One confirmed ongoing CR (8.1+ months) was observed. 7/14 pts experienced stable disease (SD), including 4 with tumor shrinkage (8-27.5% reduction). Three pts continue treatment. Treatment-related adverse events were generally grade 1-2 and included diarrhea (53%), hypokalemia (20%), prolonged QT interval (13%) and rash (13%). Conclusions: CDX-3379 in combination with cetuximab is well tolerated with the primary toxicity of diarrhea. Signs of antitumor activity were observed in these cetuximab-resistant HNSCC pts, including an ongoing, durable CR. Complete stage 1 results will be presented. Clinical trial information: NCT03254927.
Pembrolizumab (pembro) for recurrent head and neck squamous cell carcinoma (HNSCC): Post hoc analyses of phase 3 KEYNOTE-040 prior radiation treatment (RT) and disease state.

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**Background:** The open-label, randomized, phase 3 KEYNOTE-040 study (NCT02252042) showed that pembro vs standard of care (SOC) chemotherapy prolonged survival in patients (pts) with recurrent and/or metastatic HNSCC whose disease progressed during/after platinum-based therapy. Post hoc analyses were conducted to evaluate pembro vs SOC by prior RT and disease state (metastatic, locoregionally recurrent [referred to as recurrent herein], or recurrent and metastatic [R/M]).

**Methods:** Pts (N = 495) were randomly assigned (1:1) to receive pembro (200 mg Q3W) or investigator choice of methotrexate (40 mg/m² QW), docetaxel (75 mg/m² Q3W), or cetuximab (400 mg/m² loading dose, then 250 mg/m² QW). Primary end point was OS; PFS and ORR were secondary end points.

**Results:** 175, 97, and 195 pts had metastatic, recurrent, and R/M disease, respectively (28 pts had unknown disease state); 64 pts had no prior RT; 431 pts had prior RT. As in the ITT population, prolonged survival benefit and trend toward improved PFS and ORR was observed with pembro vs SOC in pts with prior RT (Table), and prolonged survival benefit was observed with pembro vs SOC in pts with metastatic and R/M, but not recurrent, disease.

**Conclusions:** In this post hoc analysis, patients with prior RT benefited from treatment with pembro vs SOC. For patients without RT, sample sizes are too small to draw any definitive conclusions. Survival benefit of pembro vs SOC was observed in pts with metastatic and R/M disease. Clinical trial information: NCT02252042.
Induction chemotherapy with docetaxel, cisplatin and cetuximab versus docetaxel, cisplatin and 5-fluorouracil followed by radiotherapy with cetuximab for locally advanced or inoperable squamous cell carcinoma of the head and neck: Promising results of a randomized phase II AGMT-trial.

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Background: Induction chemotherapy (ICT) with Cisplatin (P), 5-FU (F) and Taxanes (T) is a therapeutical option in patients suffering from locally advanced or unresectable stage III or IV squamous cell carcinoma of the head and neck (SCCHN). The role of ICT is controversial and toxicity and/or delay of radiotherapy may reduce the potential benefit of this treatment regimen. Here we report promising results of a randomized phase II trial comparing TPF with TP and Cetuximab (C) replacing F. Methods: In our trial, N= 100 patients with locally advanced or unresectable stage III or IV SCCHN were randomly assigned to either Arm A (N= 49), receiving TPF, or Arm B (N= 51), receiving TPC, both followed by radiotherapy (RT) + C. The primary end-point of the study was overall response rate (ORR) three months after RT + C was finished. Results: We observed a remarkable response rate (CR + PR) of 86.4% in the TPC-arm that compared favorably with 77.5% responding patients in the TPF-arm three months after RT + C was completed. OS and PFS were similar in both arms. After 400 days we observed an OS rate of 79% in the TPF and 86% in the TPC arm, and a PFS rate of 67% in the TPF and 70% in the TPC arm. TPC containing ICT led to less serious adverse events (SAEs), including blood and lymphatic disorders (40.8% in TPF arm, 27.5% in TPC arm) and metabolism and nutrition disorders (22.4% in TPF arm, 9.8% in TPC arm) during ICT. Interestingly, in HPVp16 positive patients, 88.24% in the TPF-arm and 93.33% in the TPC-arm showed CR or PR three months after RT + C, whereas only 69.57% in the TPF-arm and 82.76% in the TPC-arm showed CR or PR. We only lost one patient because of treatment-related mortality (TRM) and no delay from the end of ICT to local radiotherapy was observed in any patient. All patients received RT + C within three weeks after ICT was completed. Conclusions: In conclusion, TPC is a feasible and tolerable therapy regimen and can be applied within one day with less hematological toxicities. In contrast, more local reactions were observed after TPC. TPC containing ICT leads to improved response rates, while OS and PFS were similar in both arms. TRM was extremely low with 1%. Therefore, we conclude, that TPC containing ICT could be a considerable therapeutical alternative for patients with locally advanced or unresectable stage III or IV SCCHN, who are eligible for ICT. Clinical trial information: 2011-005540-99.

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Background: To assess safety and efficacy of accelerator-based boron neutron capture therapy (AB-BNCT) using cyclotron-based neutron generator, BNCT30, and $^{10}$B-boronophenylalanine (borofalan($^{10}$B)) agent, SPM-011, in patients with recurrent squamous cell carcinoma (R-HNNSCC) or recurrent/locally advanced non-squamous cell carcinoma (R/LA-HNNSCC) of the head and neck. Methods: The multi-institutional open-label, a world-first phase II trial of AB-BNCT in patients with inoperable R-HNNSCC which present resistance to platinum-based chemotherapy, or with inoperable R/LA-HNNSCC, was conducted to assess safety and antitumor activity of AB-BNCT with BNCT30 and SPM-011. SPM-011 was administered at 200 mg/kg/h intravenously for 2 hours, followed by neutron irradiation with continuous infusion of SPM-011 at 100 mg/kg/h. The irradiated dose for tumor was determined passively as a mucosal maximum dose was given 12 Gy-Eq in calculation with a blood boron concentration measured just before the start of neutron irradiation. Primary endpoint was objective response rate (ORR) by central review. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) ver 1.1 every 4 weeks for the first 3 months and every 12 weeks thereafter. Results: Eight R-HNNSCC and thirteen R/LA-HNNSCC patients were enrolled and received AB-BNCT. All R-HNNSCC patients had prior radiotherapy with a median dose of 65.5 Gy (range 59.4–76.0). The median irradiation time was 43 min (range 26–65). The median tumor minimum dose was 31.0 Gy-Eq (range 16.1–42.6). For adverse event, nausea (81%), dysgeusia (71%), parotitis (67%) were observed more frequently. The ORR for all patients were 71.4%, and CR/PR were 50.0%/25.0% in R-HNNSCC and 7.7%/61.5% in R/LA-HNNSCC. At a median follow up of 18.8 months (range 9.2–29.0), 1-year PFS and OS by investigator assessment were 70.6% and 100%, respectively. The data for antitumor activity is still immature and will be further updated. Conclusions: AB-BNCT for R-HNNSCC and R/LA-HNNSCC demonstrated an acceptable safety profile and a promising antitumor activity.
Hyperprogressive disease (HPD) in head and neck squamous cell carcinoma (HNSCC) patients treated with immune checkpoint inhibitors (ICI).

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Background: HPD was described in 9% of cancer patients (pts) treated in phase I trials, in 13.8% of advanced non-small cell lung cancer and 29% of 34 HNSCC pts upon ICI. A better definition of the hallmarks and survival outcomes of HPD pts in a larger cohort of HNSCC is still lacking. Methods: We retrospectively analyzed all advanced HNSCC pts treated with ICI at our Institution between October 2014 and December 2018. Three scans, performed before ICI, at baseline and at first evaluation during ICI, were assessed according to RECIST 1.1. Tumor Growth Kinetics (TGK) pre- (TGKpre) and post-baseline (TGKpost) were measured as previously reported (Saâda-Bouzid E, Ann Oncol 2017). Pts were defined HPD if they had progression at first radiological evaluation and TGKpost/TGKpre $\geq$ 2. Correlation between HPD and clinical characteristics was performed by Fisher or t-student test. Median overall survival (mOS) and progression free survival (mPFS) were estimated using the Kaplan-Meier method and compared between HPD and non-HPD using the log-rank test. Results: Ninety pts were eligible: 18% were female, 4% had ECOG PS $\geq$ 2, 73% smoking history, 37% oropharyngeal cancer (61% HPV+), 65% locoregional disease (89% previously irradiated), 54% received combined immunotherapy, 75% in $\geq$ 2nd line. Two out of 90 pts had TGKpre = 0 and were not evaluable for TGK ratio. HPD was observed in 7.9% (7/88) of pts. HPD pts were significantly younger compared to non-HPD pts (median age 53 ± 3.7 vs 63.3 ± 0.9 years, p = 0.002) and had a significantly higher median neutrophil-lymphocyte ratio (NLR) (11.5 ± 3.5 vs 6.4 ± 0.4, p = 0.004). Overall, mOS and mPFS were 7.5 (95% CI: 4.2-10.8) and 2.2 months (95% CI: 0.9-3.4), respectively. At a median follow-up of 20.9 months (95% CI: 19-22.8), HPD pts had a significantly worse mPFS compared to non-HPD pts [1.8 (95% CI: 1.5-2.2) vs 3.5 (95% CI: 2.2-4.8) months; p = 0.001]. HPD correlated with a not significant trend in lower mOS compared to non-HPD group [3.7 (95% CI: 2.4-5.1) vs 8.3 (95% CI: 4.1-12.5) months; p = 0.348]. Three (43%) out of 7 HPD pts early switched to chemotherapy after PD to ICI having a mOS of 8.1 months (range 3.7-25.3). Excluding these 3 pts, HPD correlated with a significantly worse mOS compared to non-HPD [2.6 (95% CI: 1.9-3.3) vs 8.3 (95% CI: 4.1-12.5) months; p = 0.006]. Conclusions: HPD was identified in 7.9% of HNSCC and correlated with younger age and higher NLR. HPD pts who did not receive a subsequent treatment had poorer mPFS and mOS. The assessment of HPD in a control cohort of advanced HNSCC upon standard chemotherapy is ongoing.
Apatinib for locoregionally recurrent or metastatic nasopharyngeal carcinoma after failure of first-line chemotherapy: A multicenter, phase II trial.

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Background: Concordant programs for patients with nasopharyngeal carcinoma (NPC) who failed to first-line chemotherapy after locoregional recurrence or metastasis are not yet available. Here, we investigated the efficacy and safety of apatinib as an second-line treatment in these patients. Methods: In this multicenter, phase II trial, patients of NPC with disease progression after failure of first-line chemotherapy were treated with apatinib (500mg/d). The primary endpoint of this study was objective response rate (ORR), secondary endpoints included progression free survival (PFS), overall survival (OS) and toxicity. Results: Between January and December 2017, 33 patients were finally enrolled onto the analysis from three centers in China. The baseline characteristics were summarized in Table. Of the 12 patients achieved a partial response and no complete responses were observed, yielding an ORR of 36.3%. Additionally, 6 patients (18.2%) experienced stable disease of at least 5 months in duration, and the disease control rate was 54.5%. At a median follow-up time of 14 months (range 1-22), median PFS was 5.0 months (95% CI, 2.3 to 7.7). The median OS had not reached, and the 1-year OS rate was 83.1%. The most common adverse events (grade 1 to 2) related to apatinib were hypotension (42.4%), hand-foot syndrome (54.5%), proteinuria (12.1%) and oral ulcer (24.2%). Conclusions: Apatinib showed a well therapeutic effect and a manageable safety profile for patients of advanced NPC after previous chemotherapy. Further study in combination with chemotherapy and other targeted agents in patients with NPC is warranted. Baseline demographic and disease characteristics. Clinical trial information: NCT03130270.
Preclinical efficacy of copanlisib in cetuximab sensitive and resistant tumors of HNSCC.

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Background: Copanlisib is a highly selective, pan-class I PI3K inhibitor with preferential activity against the p110α and p110δ isoforms that lead to downregulation of PI3K signaling. Copanlisib has been approved for the treatment of follicular lymphoma in the US. Here, we explored the anti-tumor activity of copanlisib in head and neck squamous cell carcinoma (HNSCC), where PI3K signaling has been defined as alternate signaling in cetuximab resistant tumors. Further, TCGA data show up to 56% of HNSCC display either amplification or mutational changes in the PI3K pathway making PI3K an attractive target.

Methods: Using a mouse-clinical trial set-up we profiled 20 patient derived HNSCC xenograft models for their sensitivity to cetuximab or copanlisib as single agent as well as in combination. Models were selected from our HNSCC PDX platform based on PI3K mutational status, with 6 models harboring hot spot mutations, HPV positivity (n=3) and/or cetuximab resistance based on previous drug screenings (n=12). Treatment response was defined as tumor regression, stabilization or progression expressed as relative tumor volume (RTV) after 3 weeks of treatment: RTV<0.7 responder, RTV>1.2 progressor. Results: Copanlisib single agent treatment resulted in moderate activity with 5 responders (25%). In cetuximab resistant tumors (n=12) combined treatment led to an improved tumor response in 75% (n=9) whereas 41% (n=5) resulted in tumor control. PI3KCA mutation was not predictive for treatment response to either cetuximab or copanlisib. No PTEN mutation was detected in the selected cohort. Increased PI3K signaling activity evaluated through gene expression profiling and computed with GSEA pathway analyses was positively correlated with response. Conclusions: The anti-tumor responses observed in monotherapy or in combination treatment support further investigation for the potential of PI3K inhibition in HNSCC with high expression of PI3K pathway signature as a potential predictive biomarker.
A safety study of nivolumab in patients with recurrent and/or metastatic platinum-refractory squamous cell carcinoma of the head and neck (R/M SCCHN): Interim analysis on 199 patients—The TOPNIVO study on behalf of the GORTEC and the Unicancer Head & Neck Group.

Background: In the randomized phase III Study CA209141, Nivolumab (N) demonstrated significant overall survival (OS) benefit with favorable safety profile for platinum refractory R/M SCCHN and is now approved for these patients (pts). The objectives of the study are to provide additional insight into the frequency of high-grade AEs related to N and the efficacy of N in real life. Methods: Between August and December 2017, 203 pts were included in the multicenter, non-controlled phase II TOPNIVO. The main inclusion criteria were patients with platinum refractory R/M SCCHN with progressive disease, ECOG 0-2. Pts received N 3mg/kg every 2 weeks intravenously over 30 minutes. Four pts did not receive N. We report here the safety during the first 6 months (mo) after inclusion and OS results on the first 199 treated pts. Results: Median age was 62 yr, 83% were male, 84% were ECOG 0-1, 16% 2. The primary site of cancer was oral cavity 26%, oropharynx 38%, larynx 16%, hypopharynx 21%. 33% had loco regional relapse, 32% metastatic disease and 35% both. 49% had received one prior line of chemotherapy and 30% two prior lines. 157 (79%) pts ended their treatment within the first six mo: 5 for AE related to N (pneumonitis 3 pts, hepatitis 1 pt, diarrhea 1 pt), 107 for progression, 33 for death (24 related to progression, 9 to intercurrent disease), 12 other. 132 pts (66%) experienced at least 1 AE grade 3. On the 226 AEs grade 3-4, 21 (mainly pneumopathy, lipase increase and asthenia) were related to N and occurred in 18 pts. On the 51 AEs grade 5, 3 were considered related to N (2 pneumonitis, 1 cardiac arrest). The median OS was 7.7 mo (CI 95% [6.0; 9.5]) in the whole population; 9.2 mo [6.8; 12.1] in the 167 pts with ECOG 0-1, 3.0 mo [1.1; 6.0] in the 32 pts with ECOG 2; 12.1 mo [7.6; NR] in the 64 pts with metastatic disease, 7.7 mo [5.0; 9.6] in the 66 pts with locoregional disease and 4.6 mo [3.1; 7.9] in the 69 pts with both. OS was similar in pts older or younger 70 yr. Conclusions: The interim analysis of the TOPNIVO study shows no additional toxicities of N compared to what has been described previously, confirms the previous results of OS and provides new survival data in subgroups of pts. Clinical trial information: NCT03226756.
An open label, nonrandomized, multi-arm, phase II trial evaluating pembrolizumab combined with cetuximab in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Results of cohort 1 interim analysis.

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Background: Pembrolizumab (a humanized monoclonal antibody blocking programmed death receptor-1 [PD-1]), and cetuximab (a chimeric monoclonal antibody inhibiting epidermal growth factor receptor) are both FDA-approved, second-line monotherapies for R/M HNSCC. This is the first trial to evaluate anti-tumor efficacy of dual therapy with pembrolizumab and cetuximab. Previously reported safety data demonstrated favorable toxicity. An interim futility analysis of cohort 1 (anti-PD-1/PD-L1 and cetuximab naïve) was completed per protocol. Methods: Patients (pts) with platinum-refractory/ineligible, R/M HNSCC were treated with pembrolizumab 200mg IV on day 1 and cetuximab 400mg/m² loading dose followed by 250mg/m² weekly (21-day cycle). Primary endpoint: overall response rate (complete and partial responses) by 6 months (mo). Secondary endpoints: 12-mo progression-free survival (PFS) probability, overall survival, response duration, safety, correlative analyses. Results: 14 evaluable pts were enrolled March 2017-October 2018. Median age 60y (range 47-86y), M:F 6:8, ECOG (0:1) 2:12, 14 mucosal primaries (9 oral cavity, 2 HPV-mediated oropharynx, 2 non-EBV-associated nasopharynx, 1 larynx). 11 pts (79%) had no prior lines of systemic therapy for R/M HNSCC (range 0-1). 6 pts (42.8%) had a partial response by 6 months, meeting pre-planned criteria for trial continuation. 4 pts (28.6%) had stable disease and 4 (28.6%) had progressive disease. Median PFS was 128 days (4.3 mo). Median duration of response was 160.5 days (5.4 mo) for partial responders and 133 days (4.4 mo) for pts with stable disease. Disease control rate (partial + stable) was 71.4%. There were 7 grade 3 treatment-related toxicities. 2 pts discontinued cetuximab due to toxicity, however, both continued pembrolizumab. Conclusions: Interim analysis indicates that pembrolizumab plus cetuximab is potentially active for platinum-refractory/ineligible pts with R/M HNSCC. These results meet protocol specifications for trial continuation. Final results will include PD-L1 expression data. Clinical trial information: NCT03082534.
Clinical implications of hyperprogression with immune checkpoint inhibitors in patients with head and neck squamous cell carcinoma (HNSCC).

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Background: Hyperprogressive disease (HPD) refers to paradoxical acceleration of tumor growth kinetics (TGK) after initiation of treatment with anti-PD-1/PD-L1 agents and has been reported across tumor types in 4-29% of patients using different definitions. Preliminary data suggest that HPD might affect response to subsequent therapies. Methods: We compared TGK prior and TGK upon immunotherapy (IO) in 62 patients (pts) with recurrent/metastatic (R/M) HNSCC treated with PD-1/PD-L1 inhibitors. The TGK ratio (TGKR, ratio of tumor growth velocity before and upon treatment) was calculated. The first imaging assessment was performed 3 months (mo) after IO initiation. HPD was defined as 1. Radiological HPD (TGKR $\geq 2$) or 2. Clinical HPD (Disease-related rapid clinical deterioration post IO).

Results: After median follow-up of 12.3 mo (range, 0.4-28.1), 43 pts progressed and 38 died. Median PFS was 2.8 mo (95%CI, 2.2-3.4) and median OS 8.6 mo (95%CI, 4.2-12.9). HPD was observed in 16 pts (25.8%), while 15 pts had early PD (Time to Treatment failure, TTF < 3 mo) and 31 late PD (TTF > 3mo). Among 16 pts with HPD, 11 had radiological HPD and 10 had clinical HPD. 4 pts had both clinical and radiological HPD. Pts with late PD had median OS 11.3 mo (95%CI, 9.3-13.3), those with early PD 5.2 mo (95%CI, 3.1-7.3 months) and those with HPD 5.1 mo (95%CI, 4.4-5.9) (p < 0.005). Regarding post-progression OS, pts with late PD had median 11.3 mo (95%CI 0-22.8), those with early PD 2.5 mo (95%CI 0.6-4.4) and those with HPD 4.2 mo (95%CI 1.7-6.7) (p = 0.001). Pts with HPD had a trend for longer median post-progression OS compared to pts with early PD (p = 0.121). Median PFS with chemotherapy after immunotherapy failure was 3.0 mo (95%CI 2.4-3.6) for pts with late PD, 2.1 mo (95%CI 0.9-3.4) for pts with early PD and 6.1 mo (95%CI 3.0-9.3) for those with HPD (p = 0.040). HPD was associated with longer median PFS with chemotherapy compared to pts with early PD (p = 0.016), while the difference in median PFS with chemotherapy between pts with HPD and late progressors was non-statistically significant (p = 0.260). Conclusions: Radiological or clinical HPD was observed in 25.8% of patients with R/M HNSCC treated with IO. Early progression to immunotherapy is an important predictor of short survival, while HPD was associated with improved PFS to subsequent chemotherapy.
Efficacy and safety of immune checkpoint inhibitors in elderly patients (≥70 years) with squamous cell carcinoma of the head and neck.

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Background: Recent meta-analysis showed that immune checkpoint inhibitors (ICI) have comparable activity in younger vs older patients (pts) (≥65 years). However, little is known about efficacy and safety of ICI in elderly pts with relapsed/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). The aim of this study is to compare efficacy and grade ≥3 immune-related adverse events (irAEs) of ICI in pts ≥70 y with R/M SCCHN to younger pts. Methods: A retrospective study was conducted at 4 French hospitals. Eligibility criteria were pts treated with ICI for R/M SCCHN between September 2014 and December 2018. Clinical and radiological data and outcome were collected from review of medical records. Results: Two hundred twenty-six pts were enrolled, including 67 pts ≥70 y. Median age of elderly pts was 75y (range 70-87). Elderly pts received ICI as first-line treatment in 21% of pts vs 17% in younger pts. In elderly pts, 9% had ECOG of 0, 72% had ECOG of 1 and 15% had ECOG of 2 at ICI initiation vs 34%, 62% and 4% respectively in younger pts (p = 0.0006). In elderly pts, 22% had only loco-regional relapse at ICI initiation, 30% only distant recurrence and 49% had both vs 42%, 32% and 26% respectively (p = 0.0014). Elderly pts received ICI as monotherapy in 73% of pts vs 52% (p = 0.0027). The ORR in elderly pts was 23% vs 13% in younger pts (p = 0.071). After a median follow-up of 16.8 months (m) (range 10.7-23.7), median OS was 9.7 m in elderly pts vs 8.7 m in younger pts (p = 0.87). Median PFS was 2.7 m in elderly pts vs 1.9 m (p = 0.2). After adjustment for ECOG, type of evolution, number of ICI drugs, time between initial diagnosis and ICI start and number of previous lines, age ≥70 years was significantly associated with a better PFS (HR = 0.66 (95%CI = 0.47;0.93), p = 0.02) but was not significantly associated with OS (HR = 0.91 (95%CI = 0.61;1.34), p = 0.62). Grade ≥3 irAEs occurred in 15% of elderly pts vs 8% of younger pts (p = 0.13). Patients with grade ≥3 irAEs had a significantly higher ORR than pts without Grade ≥3 irAEs (36% vs 14%, p = 0.007). Conclusions: Elderly pts treated with ICI had significantly higher PFS but not OS after adjustment. Grade ≥3 irAEs were associated with significantly higher ORR to ICI in the whole population.
A multicenter prospective observational study of nutritional status on survival in locally advanced nasopharynx cancer treated by induction chemotherapy and chemoradiotherapy.

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Background: We conducted a multicenter prospective study (NCT02575547) to investigate the association between longitudinal nutritional status and survival in locally advanced nasopharynx cancer (LA-NPC) treated with induction chemotherapy and concurrent chemoradiotherapy (IC-CCRT). Methods: All patients with biopsy-proven LA-NPC and planned for IC-CCRT were recruited from ten institutions. IC entailed 2 cycles of docetaxel 75mg/m^2/3w and cisplatin 75mg/m^2/3w; CCRT entailed 2-3 cycles cisplatin 100mg/m^2/3w and IMRT (70-72Gy/30-32fr). Study parameters included weight loss (WL), % of ideal body weight (%IBW), body mass index (BMI), nutrition risk screening 2002 (NRS2002), patient-generated subjective global assessment (PG-SGA), and EORTC QLQ-C30 that were collected at the following time-points: baseline (T1), 1 w pre-2nd IC (T2), 1 w pre-CCRT (T3), 4 w mid-CCRT (T4), end-CCRT (T5), 3 mo post-CCRT (T6), 1 y post-CCRT (T7), 2 y post-CCRT (T8). Results: 186 patients were recruited; 171 were eligible for analysis. Median follow-up was 35.8 mo (range 12.3-46.1 mo). Compliance rates were 97.7% (167/171) and 87.7% (150/171) for IC and CCRT, respectively; all except one completed RT. Longitudinal assessment indicated the worst nutritional status at T5, followed by recovery at T8: 27.1% with %IBW <90%; 69.2% with WL >=5%, which was also associated with a worsened QOL (OR = 6.23 for QOL change >=25.0, P = 0.012). Interestingly, T1 nutritional status was not associated with prognosis (P >0.05 for all). However, nutritional parameters at T5 were significantly associated with survival; %IBW <90% was the strongest predictor for inferior DMFS (HR = 2.669) and OS (HR = 4.661) among all parameters (multivariable-adjusted P <0.05). Subgroup analyses revealed that %IBW <90%, WL >=10% at T5 represented the most adverse subset of patients (Table). Conclusions: Here, we show that poor nutrition despite systemic intensification leads to inferior QOL and disease control in LA-NPC patients. This is counter-intuitive and highlights the crucial importance of paracrine factors in optimising treatment efficacy. Clinical trial information: NCT02575547.

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Metformin treatment of locally advanced head and neck squamous cell carcinoma (LAHNSCC) patients induces an anti-tumorigenic immune response.

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Background: Metformin is a biguanide, widely used oral hypoglycemic agent. Metformin has also shown to inhibit tumor growth and progression in a wide variety of cancers including Head and Neck Squamous Cell Carcinoma (HNSCC). Metformin activates AMP protein kinase (AMPK) related pathways leading to inactivation of mammalian target of rapamycin (mTOR) and suppression of its downstream effectors. In addition, metformin is postulated to alter immune regulation in the tumor microenvironment leading to increased tumor cell killing. Here, we report our findings on the impact of metformin on T cells, NK cells and cytokines from patient peripheral blood mononuclear cells (PBMCs) from a phase I open-label single site dose escalation study combining metformin and chemoradiation (CRT) in HNSCC (NCT02325401).

Methods: In this study, we evaluated the immune cell phenotypes and cytokine profiles of peripheral blood in patients before and after metformin treatment on trial by using flow cytometry and cytokine magnetic bead assays (Luminex). Cytokine profiles were further studied in co-culture experiments combining PBMCs, HNSCC cell lines, and metformin. Results: Patients who received metformin developed expanded NK cell populations, increased NKG2D expression, and a shift in their CD8+ T-cell memory phenotypes. Patient serum ELISA examination revealed increased anti-tumorigenic cytokine profiles. Metformin treatment of HNSCC cell lines in vitro as well as HNSCC PBMCs ex vivo resulted in downregulation of STAT3 compared to healthy controls. Downregulation of STAT3 may be a potential mechanism in which metformin stimulates NK cells. Conclusions: Here we show evidence that metformin treatment has a direct effect on the innate immune system in patients with HNSCC, inducing an anti-tumorigenic immune response suggesting that metformin continues to be a good candidate to yield improved clinical outcomes in patients with advanced stage HNSCC. Clinical trial information: NCT02325401.
High-dose, short-duration, intra-arterial cisplatin therapy for oral cancer.

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Background: We developed a superselective intra-arterial chemotherapy (iaCT) approach for oral cancer wherein an intra-arterial catheter is retrogradely inserted via the superficial temporal artery (STA) and/or occipital artery (OA). In most iaCT cases, high-dose anticancer agents are administrated via the intra-arterial catheter weekly or biweekly with daily irradiation. This approach remarkably improves curative efficiency, but some adverse events, e.g., severe mucositis, dysphagia, dysgeusia, dry mouth, and radiation osteonecrosis, mainly because of irradiation, decrease the quality of life. Methods: Thirty-two patients with stage II, III, or IV oral squamous cell carcinoma were treated using this new iaCT approach. The catheter was superselectively placed in the tumor-feeding arteries by cut-down of STA or OA. The catheter was completely placed under the skin and was connected to an infusion reservoir that was subcutaneously implanted around the mastoid process via the subcutaneous tunnel, ensuring little possibility of catheter-related issues such as infection and displacement of catheter. Anticancer agents (30 mg/m² of cisplatin with/without 10 mg/m² of docetaxel) were intra-arterially administered via the reservoir twice a week for 3 weeks, 180 mg/m²/6 times in total, without irradiation. The treatment effect was assessed using computed tomography, positron emission tomography, and biopsy. Results: The response rate of this approach was 100%, with 31 and 1 case having complete response (CR) and partial response (PR), respectively. Five patients with delayed regional lymph node metastasis or PR underwent salvage surgery; 28 patients (87.5%) had disease-free survival, while 2 (6.2%) died due to local recurrence and 2 due to distant metastasis. All patients developed CTCAE v4.0 Grade 2 oral mucositis in the flow area of the intended artery, most of which disappeared in half a year. No dry mouth, dysgeusia, and eating disorder were observed because the patients did not receive radiotherapy. No systemic adverse events such as hematologic toxicity and renal and/or hepatic injuries occurred. Conclusions: This method improved the adverse event of iaCT with radiotherapy, and the main advantage of superselective iaCT was not lost.
Phase 1b/2, open label, multicenter study of intratumoral SD-101 in combination with pembrolizumab in anti-PD-1 treatment naive patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).

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Background: SD-101, a synthetic CpG-ODN agonist of TLR9, stimulates dendritic cells to release IFN-alpha and mature into antigen presenting cells - activating T cell anti-tumor responses. Pembrolizumab has demonstrated activity in HNSCC. Study DV3-MEL-01 (NCT02521870) assesses safety and efficacy of SD-101 in combination with pembrolizumab in patients with recurrent/metastatic HNSCC. We have previously reported a 27.3% ORR in 22 patients receiving 8 mg SD-101/injection in the modified ITT after at least 2 CT scans due to late responses (Abstract 3560, ESMO 2018). Higher efficacy at a lower SD-101 dose, 2 mg/injection, has been reported in advanced melanoma patients (LBA 45, ESMO 2018). Consequently, this dose is now being assessed in HNSCC. We report preliminary data with the 2 mg/injection dose in 23 patients in mITT at the first CT scan.

Methods: Anti-PD-1/PD-L1 na¾ve patients received 2 mg SD-101 intratumorally in 1 - 4 lesions (weekly x 4 doses then Q3W x 7 doses). Pembrolizumab is was administered IV at 200 mg Q3W. Responses were assessed per RECIST v1.1.

Results: 28 patients enrolled: median age 63 y/o, male 68%; ECOG PS 0-1 (18%/82%); mean prior lines of systemic therapy 1 (0-3); mean treatment duration 70 days (1-253). Primary tumors: 19 (68%) oropharyngeal; 3 (10%) laryngeal; 2 (7%) hypopharyngeal; 4 (14%) unknown. Mean number of target lesions: 1.82 (1 to 5). HPV status: 7 (25%) +, 9 (32%) -, 12 (43%) unknown. 18 (64 %) discontinued treatment: 12 (42%) due to PD, 4 (16%) deaths, 1 (3%) consent withdrawn, 1 (3%) went to hospice. Mean follow up 2.70 months. Safety: 16 non-treatment-related SAEs in 9 patients. 2 treatment-related Grade $3 AEs: sepsis (4%) and lymphopenia (4%). No treatment-related deaths. Efficacy: 23 patients in the mITT population with first CT scan at day 64: ORR: CR: 2, PR: 3 (22%); SD: 6 (26%), PD: 7 (30%), non-evaluable: 5 (22%). Disease control rate (48%). 5 patients on study have not had a CT scan.

Conclusions: SD-101 with Pembrolizumab shows early promising data and is well tolerated. Additional follow-up scans from both dose cohorts are being evaluated and will be presented. Clinical trial information: NCT02521870.
Personalized TPF induction chemotherapy on the basis of stathmin expression in patients with locally advanced oral squamous cell carcinoma.

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Background: A randomized phase 3 trial failed to demonstrate a survival advantage for TPF (docetaxel, cisplatin, and 5-fluorouracil) induction chemotherapy in the overall study population of patients with locally advanced and resectable oral squamous cell carcinoma (OSCC). It is possible that personalized TPF-based induction chemotherapy might improve outcomes in biomarker-defined subsets of patients.

Methods: Immunohistochemical staining against stathmin was performed in pre-treatment biopsy specimens in 170 OSCC patients from our randomized trial. Chemoresistance to TPF chemotherapy drugs regulated by stathmin expression was investigated. The anti-cancer activity of TPF chemotherapy drugs alone, a combination of TPF drugs and PI3K-AKT-mTOR pathway inhibitors, and vincristine were investigated using in vitro and in vivo OSCC models.

Results: OSCC patients with low stathmin expression benefited from TPF induction chemotherapy in terms of overall survival (HR = 0.102, 95% CI:0.013-0.781, P = 0.028), disease-free survival (HR = 0.070, 95% CI:0.009-0.525, P = 0.010), locoregional recurrence-free survival (HR = 0.070, 95% CI:0.009-0.524, P = 0.010), and distant metastasis-free survival (HR = 0.101, 95% CI:0.013-0.767, P = 0.027). Stathmin overexpression promoted cellular proliferation and chemoresistance to TPF drugs in OSCC (P < 0.05). PI3K pathway inhibitors decreased stathmin expression and phosphorylation, and improved the chemosensitivity to TPF drugs in vitro and in vivo (P < 0.05). Vincristine decreased stathmin expression and phosphorylation, and OSCC lines were significantly sensitive to vincristine in vitro and in vivo (P < 0.01).

Conclusions: Our results suggest a potential personalized TPF induction chemotherapy on the basis of stathmin expression in OSCC patients: patients with low stathmin expression in the biopsy samples are suggested to receive TPF induction chemotherapy followed by surgical resection and post-operative radiotherapy. For patients with stathmin overexpression PI3K inhibitor is a good choice to improve the inductive effect of TPF chemotherapy drugs; vincristine is a potential alternative for a chemotherapy drug when a patient is chemoresistant to or unsuitable to receive TPF chemotherapy drugs; however, more clinical trials are warranted to verify this optimization protocol.
Predictors of early immunotherapy response in head and neck cancer: Per lesion analysis of a prospective randomized trial with nivolumab.

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Background: The capacity for radiation and checkpoint inhibitors to elicit clinical responses is impacted by tumor immunogenicity and the immune microenvironment. We sought to determine whether head and neck primary site and metastatic tumor location was associated with initial response in non-irradiated lesions.

Methods: We evaluated response in 144 non-irradiated lesions from 59 patients with metastatic head and neck cancer enrolled on a phase II randomized controlled trial of nivolumab with stereotactic body radiotherapy (n=30) vs. nivolumab alone (n=29). Nivolumab was administered 3 mg/kg intravenously every 2 weeks. Radiated lesions were treated with 27 Gy / 3 fractions to a single lesion within 14 days of the first dose of nivolumab. Non-target lesion progression was defined as ≥30% increase in the greatest axial diameter 8 weeks after enrollment. Fisher’s exact test with nested bootstrap resampling was used for univariate analysis. Logistic regression with a mixed random effects term was used for multivariate analysis.

Results: Primary tumor site, metastatic tumor organ sites, and the unadjusted likelihood of progressive disease by site are listed in the table. On multivariate logistic regression controlling for PD-L1 status (p=0.66) and viral status (p=0.29), lymph node metastases (OR 0.79, p=0.0064) were associated with decreased risk of progression, while liver metastases (OR 1.39, p=0.014) and oral cavity primaries (OR 1.56, p=0.018) were associated with increased risk of progression at 8 weeks, using lung metastases and larynx/hypopharynx primaries as reference.

Conclusions: Primary tumor subsite and metastasis location were predictors of response or stable disease following treatment with nivolumab. Metastases from oral cavity primaries and metastases to the liver were at increased risk of early progression. Clinical trial information: NCT02684253.
COX-2 expression and mesenchymal-transition status on circulating tumor cells to predict survival in patients with nasopharyngeal carcinoma: A prospective analysis.

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Background: The prognostic significance of circulating tumor cells (CTCs) in head and neck cancer is still under active investigation. It remains unclear whether just CTC count alone is sufficient to predict outcomes or whether the functional status of the CTCs is also needed. We investigated the clinical significance of determining epithelial-to-mesenchymal transition status and geno-/pheno-typic biomarkers of aggressiveness of CTCs in predicting outcomes in nasopharyngeal carcinoma (NPC).

Methods: The prospective study enrolled 131 patients with NPC. CTCs were isolated at baseline and at the end of concurrent chemoradiotherapy using the CanPatrol system. Subsequently, the epithelial-mesenchymal transition (EMT) biomarkers and cyclooxygenase-2 (COX-2) expression status of the CTCs were identified by RNA-in situ hybridization (ISH) method.

Results: COX-2 expression was found in 87/131 (66.4%) patients at baseline and 53/115 (46.1%) patients post-treatment. Independent of initial COX-2 expression status, the patients with post-treatment COX-2 expression on CTCs had significantly poorer treatment response (P = 0.011), and higher risk of tumor relapse (P = 0.026) and metastasis (P = 0.007). Similarly, post-treatment mesenchymal transition was also associated with higher risk of tumor relapse and metastasis. In multivariate analysis, post-treatment COX-2 expression on CTCs remained an independent prognostic indicator of poorer overall survival (HR 2.41, 95% CI 1.12-5.19; P = 0.024). Post-treatment COX-2 expression and mesenchymal transition in CTCs was the strongest prognostic indicator of overall survival on multivariate analysis (HR 2.73, 95% CI 1.28-5.83; P = 0.009).

Conclusions: Post-treatment COX-2 expression on CTCs, especially on the mesenchymal subtype, is a novel and promising prognostic indicator for NPC patients treated with chemoradiation therapy. Future studies are needed to validate our findings and further clarify the value of integrating the indicators with current clinical strategies in improving survival of NPC patients.
Development of a clinicomolecular risk stratification system for nonmetastatic nasopharyngeal carcinoma using Epstein–Barr virus DNA and TNM stage: A “Big data” analysis of 9,160 endemic cases.

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Background: To construct a clinicomolecular index integrating circulating Epstein-barr virus (cfEBV) DNA with T- and N- categories for better prognostication in nasopharyngeal carcinoma (NPC).

Methods: Clinical and treatment records of 9,160 biopsy-proven, non-metastatic NPC cases were identified from an institutional “Big-data” platform. Decision tree modeling (DTM), recursive partitioning analysis (RPA) and adjusted hazard ratio (AHR) methods were used to generate clinicomolecular risk models. Outcome prediction of the models were compared against 8th edition TNM stage and two RPA-original models.

Results: We observed linearity between cfEBV DNA and DFS; cfEBV DNA of > 2,000 copies was consistent for risk discretisation (HR > 1.0) for DFS, OS and DMFS in our cohort of 9,160 patients. DTM, RPA-new and AHR modelling using a two-tiered stratification by cfEBV DNA (≤2,000 and > 2,000 copies) and T- and N- categories yielded five risk groups with significantly disparate DFS (P < 0.001 for all subgroup comparisons). AHR model outperformed all other models and the TNM stage classification with better hazard consistency, hazard discrimination, explained variation, sample size balance and likelihood difference. Importantly, our clinicomolecular AHR groupings were significantly associated with the efficacy of different therapeutic regimes. Outcomes were comparable between concurrent chemoradiotherapy and intensity-modulated radiotherapy (IMRT) and IMRT alone for AHR1-2 (3-y DFS [AHR1] = 96.2% [IMRT] vs 95.3% [chemo-IMRT]; 3-y DFS [AHR2] = 91.1% vs 90.4%). Neoadjuvant chemotherapy and chemo-IMRT was superior to chemo-IMRT alone for AHR4-5 (AHR DFS 0.77[0.65-0.93], P = 0.005; 0.77[0.61-0.97], P = 0.027), but not for AHR3 (AHR DFS 1.07[0.86-1.34]).

Conclusions: Here, we present a robust clinicomolecular risk stratification system that outperforms the TNM stage classification in non-metastatic NPC. Our clinicomolecular model is associated with the efficacy of different therapeutic regimes.
Association between human papillomavirus (HPV) status and duration of response of anti-programmed cell death protein-1 (PD-1) inhibitors in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).

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Background: Human papillomavirus status is known to be prognostic for patients with HNSCC. Current data suggests that HPV-positive HNSCC tumors exhibit increased infiltration of immune cells and higher levels of T-cell exhaustion markers compared with HPV-negative tumors, possibly suggesting a difference in response patterns to immunotherapy. We evaluated whether HPV status is associated with duration of response in patients receiving anti-PD-1 inhibitors. Methods: We performed a retrospective chart review of 54 patients at Moffitt Cancer Center who received either pembrolizumab (N = 32) or nivolumab (N = 22) from February 2016 to July 2018 for R/M HNSCC. We collected the following data for our patient population: primary site of disease, stage, smoking status, duration of treatment, and overall survival (OS). Overall survival time was defined as the date of starting anti-PD-1 inhibitors to death. Primary disease site was oropharynx (N = 25), oral cavity (N = 13), larynx (N = 11), nasopharynx (N = 3) and unknown primary (N = 2). HPV status was available for 37 patients. Analysis of survival and time on treatment was done using log-rank test. Results: Overall survival was not different with respect to primary site of disease, smoking, ECOG status, or type of anti-PD-1 inhibitor, but was significantly longer for patients with HPV-positive vs HPV-negative HNSCCs (17 months vs 4.5 months; log rank p < 0.001). Time on anti-PD-1 inhibitor was also significantly longer for patients with HPV-positive HNSCCs (7 months vs 3 months; log rank p < 0.001). Conclusions: Our data suggests patients with HPV-positive R/M HNSCCs have longer duration of response and OS on anti-PD-1 inhibitors compared to HPV-negative patients.
Role of the oral and gut microbiota as a biomarker in locoregionally advanced oropharyngeal squamous cell carcinoma (ROMA LA-OPSCC).

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Background: The ROMA LA-OPSCC (NCT03759730) study prospectively evaluated the oral and gut microbiota in a single-centre cohort of LA-OPSCC patients (pts) receiving chemoradiotherapy (CRT). Methods: LA-OPSCC pts treated with definitive CRT (IMRT plus single-agent cisplatin) were eligible. Oral swabs over the tumor site and stool samples were collected at baseline and end of CRT (EOT). Taxonomic profiles were generated by 16S rRNA sequencing. ANOSIM/Kruskal-Wallis tests were used to identify differences between baseline and EOT samples. Results: A total of 96 samples were collected from 24 evaluable pts (100% compliance). Baseline characteristics: median age = 61 (range, 50-71); smoking status current/former/never = 5/11/8; HPV+/- = 23/1; stage I/II/III/IVA = 7/7/9/1; use of antibiotics = 12 pts. In oral swabs, decreased Shannon diversity (p< 0.01) and changes in abundance (adjusted p value: q< 0.05) of multiple taxa including Prevotella, Veillonella, and Streptococcus were observed at EOT vs baseline. Stool diversity did not differ between baseline and EOT (p= 0.42), but abundance of Ruminococcus and Roseburia decreased (q< 0.05). CRT-associated changes remained significant when controlled for stage, smoking, antibiotics, cisplatin dose and mucositis grade (p< 0.01). In HPV+ pts, stage I-II baseline oral swabs had higher relative abundance of Clostridium IV (p< 0.02) and Escherichia (p= 0.04) than stage III, which had higher Fusobacterium (p= 0.03) and Gemella (p< 0.01). Relative abundance of Actinobacteria (p < 0.01), Proteobacteria (p < 0.01) and Firmicutes (p = 0.03) was higher in stool from stage III pts. Akkermansia muciniphila was present in 57% of the stage I-II stool samples, and 11% in stage III (p = 0.04). Conclusions: CRT in LA-OPSCC is associated with increases in potentially pathogenic genera in the oropharynx. HPV+ stage III disease was associated with higher Fusobacterium in the oropharynx, which has been implicated in tumor metastases, and with decreased prevalence of the immunotherapy-response-associated species Akkermansia in stool. These preliminary observations suggest an opportunity for the evaluation of IO based therapies or manipulation of the gut microbiota in this patient population. Clinical trial information: NCT03759730.
Impact of adjuvant chemotherapy and cumulative cisplatin dose in locally advanced nasopharyngeal carcinoma (LA-NPC) treated with definitive chemoradiotherapy.

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Background: Total cumulative cisplatin dose (CDDP-D) (concurrent/induction/adjuvant) in multimodality therapy for LA-NPC has been associated with survival at centers in Asia. We evaluated the survival impact of adjuvant chemotherapy (adj chemo) and total CDDP-D in a large, single institution Canadian cohort of LA-NPC. Methods: Patients (Pts) with WHO type II and III LA-NPC treated with concurrent IMRT with high-dose CDDP and adj chemo with CDDP/Carboplatin and 5-FU (maximum total/adjuvant CDDP-D= 540/240 mg/m²) between 2003-2016 were analyzed. EBER status was tested by ISH. Staging was classified by UICC/AJCC7th edition TNM. Kaplan-Meier 5-year (5y) for overall survival (OS) and recurrence-free survival (RFS) were calculated and compared by log-rank test between stage, adj chemo (yes vs no) and total CDDP-D (>300 vs ≤300mg/m²). Multivariable analysis (MVA) identified survival predictors. Results: A total of 312 pts were evaluated: median age = 49.8 (range 17.4-75.9); EBER+/unknown=67%/1%/32%; stage II/III/IV=2%/51%/47%; T4=36%; N3=17%; adj chemo=83% (21% switched to carboplatin); median total/adjuvant CDDP-D=380/160 mg/m²; median follow-up 7.6 years (range 0.6-14.9). 5y OS differed by stage II-III vs IV (95% vs 80%, p<0.001) and total CDDP-D (>300 vs ≤300mg/m²) (89% vs 83%, p=0.02). Adj chemo and total CDDP-D impacted 5y OS in stage IV (table). 5y RFS was higher in stage IV with total CDDP-D >300 vs ≤300mg/m² (74% vs 59%, p=0.03), with a trend in locoregional control (LRC) (91% vs 80%, p=0.05) but not significant on distant control (DC) (78% vs 72%, p=0.36). Conclusions: Total CDDP-D >300 mg/m² impacts OS in the overall cohort. The benefit of adj chemo and total CDDP-D on OS and RFS is significant in stage IV but not stage II-III LA-NPC, mainly due to higher LRC rather than DC.

<table>
<thead>
<tr>
<th>5y OS and MVA by stage.</th>
<th>Variables</th>
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<tr>
<td>Stage</td>
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<tr>
<td>II-III</td>
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<tr>
<td>5yOS %</td>
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<td>(95%CI)</td>
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<td>95% (90-99) vs 94% (86-100)</td>
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<tr>
<td>MVA HR</td>
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<tr>
<td>0.71 (0.59-0.92) p=0.02</td>
<td>0.92 (0.84-1.01) p=0.87</td>
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<tr>
<td>0.32 (0.14-0.74, p&lt;0.01)</td>
<td>0.43 (0.23-0.81, p&lt;0.01)</td>
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</table>

Impact of tobacco smoking on radiotherapy outcomes in 1875 HPV-positive oropharynx cancer patients.

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Background: This study investigates the impact of smoking on radiotherapy (RT) outcome and survival in a population based cohort of HPV+ oropharynx cancer (OPC). Methods: We identified all OPC with positive p16 staining from 2007 – 2015 who received curative IMRT according to approved guidelines in two oncology groups. Associations between smoking and locoregional control (LRC) and distant control (DC) were estimated by competing risk regression. Disease free survival (DFS) and overall survival (OS) were estimated by proportional-hazards regression model. Multivariable analyses (MVA) adjusted for age, gender, performance status (PS), T- and N-category, and treatment regimen. Results: A total of 1875 patients were included. Median age was 59.2 [31.3-86.8]; 79% (1481) were males; 96% (1651) had PS ≤ 2; 71% (1337) received concurrent chemo-radiotherapy (CRT) +/- hypoxic modification (Nimorazole); and 538 (29%) received RT alone +/- Nimorazole. 23% (425) were current smokers (at time of diagnosis) and 46% (853) were ex-smokers. Median smoking pack-years (PY) was 20.1 in the total cohort, and higher in current smokers vs ex-smokers (38 vs 20 PY, p<0.001). 63% of current smokers had >30PY. Median follow-up was 4.8 years. Actuarial 5-year univariate analysis showed that current smokers had a reduced probability of LRC (85% vs 92%, p=0.002), DC (88% vs 92%, p=0.046), DFS (69% vs 84%, p<0.001), and OS (73% vs 88%, p<0.001) compared to never-smokers (n=567). Outcomes for ex-smokers and never-smokers were similar. In MVA current smoking retained strong independent significance for LRC (HR 1.73 [1.18-2.53]), DFS (1.79 [1.35-2.36]) and OS (2.06 [1.49-2.84]). However, DC was not significantly influenced by current smoking status (1.27 [0.83-1.95]). Similar observations were found for >30PY. Conclusions: Heavy lifetime and current smoking negatively impacts LRC and survival in HPV+ OPC. While smoking mediated hypoxia could interfere with RT efficacy, a putative impact on tumor biology remains uncertain in the absence of a detriment to distant metastasis risk. The findings support encouraging smoking cessation to improve therapeutic efficacy of RT and to avoid excess smoking related mortality.
Correlation of angiogenic and immunomodulatory proteins with clinical outcomes of durvalumab (anti-PDL1) in recurrent/metastatic head and neck squamous cell carcinoma.

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Background: The potential for durvalumab, a PD-L1 blocking monoclonal antibody, to treat head and neck squamous cell carcinoma (HNSCC) is being evaluated in multiple clinical trials. We assessed circulating protein biomarkers in HNSCC patients prior to treatment to better understand pathways related to clinical outcomes and potentially relevant for targeting in combination with durvalumab. Methods: Sixty-six selected serum proteins were measured by multiplex immunoassay at baseline in HNSCC patients receiving durvalumab treatment: 106 patients with high PD-L1 (≥25% tumor cells; SP263 assay) in phase II HAWK trial and 52 patients with low/no PD-L1 in phase II CONDOR trial. Results: Multivariate Cox modeling demonstrated that higher baseline concentrations of angiogenic, pro-inflammatory, and myeloid-associated proteins (ANGPT2, CRP, IL6, S100A12) were associated with shorter overall survival (OS), while higher concentration of a bone formation marker and immunostimulatory hormone (BGLAP) correlated with longer OS in 158 durvalumab-treated HNSCC patients (P < 0.05). These 4 proteins also showed higher baseline levels in patients with progressive disease (PD) compared to stable disease (SD) and partial or complete responses (PR/CR), while BGLAP had lower levels in PD compared to SD or PR/CR (Mann-Whitney P < 0.05). The 5 proteins remained significantly associated with OS in a multivariate model including PD-L1, ECOG, tumor size, and neutrophil count. Bone metastasis status had no impact on the association of BGLAP with OS, which has not been reported before in HNSCC. Interestingly, ANGPT2 level above median showed the highest hazard ratio (HR = 2.2, P < 0.001) among all evaluated variables. Furthermore, higher levels of VWF, an angiogenesis-related protein, correlated with shorter OS by univariate survival analysis (P < 0.001). Conclusions: Our results suggested an important role of angiogenesis in the resistance of HNSCC patients to durvalumab treatment, and ANGPT2 may have predictive utility for durvalumab combination with an anti-angiogenic agent. The predictive value of BGLAP remains to be evaluated in a randomized clinical study. Clinical trial information: NCT02207530; NCT02319044.
Phase 1b study of chemoprevention with green tea polyphenon E (PPE) and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (Erlotinib) in patients (pts) with advanced premalignant (AP) lesions of the head and neck.

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Background: Based on the strong synergistic effects between green tea polyphenon E (PPE) and EGFR-TKI in our preclinical studies (Int J Cancer, 2008; Cancer Prev Res, 2009; JCO, 2009), we conducted a phase 1b study with PPE and erlotinib combination for APL (mild-, moderate-, severe-dysplasia or carcinoma in situ [CIS]) of the oral cavity and larynx from 2/2011 to 11/2017 at Emory Winship Cancer Institute.

Methods: All pts were enrolled after signing the IRB approved Informed Consent Form. Tissue biopsy before and at 6-months (6-M) treatment was mandatory, and cytobrushed samples of the APL and normal buccal mucosa at 3-, 6-, and 12-M were obtained for biomarker studies. Treatment included fixed dose of PPE (200 mg, P.O., TID) and dose escalation of erlotinib P.O., (50mg [level 1], 75mg [level 2] and 100mg [level 3]) for 6-M. The primary endpoint was safety and toxicity, and secondary endpoints were evaluation of pathologic responses, cancer free survival (CFS) and biomarker modulation.

Results: Out of 27 enrolled pts, 6 control subjects for biomarker studies, 2 ineligible, and 19 were treated with PPE and erlotinib for 6-M. Clinical characteristics of treated patients included median age, 63 yrs. (range,33-78); 9 M/10 F; 10 former or current smokers/9 never smokers; 15 severe dysplasia or CIS, 2 moderate dysplasia, 2 mild dysplasia; 13 had surgical resection; and 2 at larynx. 3 pts were treated at dose level 1, 4 at level 2, and 12 at level 3. Toxicity (G0 or G1 excluded) were: skin rash (1 G3, 1 G2), pruritus/dry skin (1 G2), fatigue (1 G2), diarrhea (1 G2), epistaxis (1 G2), and hypertension (2 G3, 1 G2). Skin rash (associated with erlotinib) may be DLT and MTD has not been reached. The recommend doses for phase 2 or 3 studies will be PPE 200mg TID plus erlotinib 100mg QD. 17 pts were assessed for pathologic responses at 6-M: pCR 7/17 (41%), pPR 2/17 (12%), pSD 5/17 (29%) and pPD (3/17 (18%). The median follow up was 32 months. Median CFS has not been reached. 16 pts are alive at the time of data analyses and 1 pt died (by noncancerous reason). Biomarker studies are ongoing for tissues and/or cytobrushed samples.

Conclusions: The treatment of the combination of green tea PPE plus erlotinib for 6-M was well tolerated in pts with APL of the head and neck, and showed significant pathologic response rates (pCR and pPR, 53%). This combination therefore deserves further investigation for efficacy testing.

Clinical trial information: NCT01116336.
Connective tissue growth factor (CTGF) methylation status is associated with prognosis of patients with head and neck squamous cell carcinoma (HNSCC) treated with radiochemotherapy (RCHT): A multicenter study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG).

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Background: CTGF plays a central role in tissue remodeling and has emerged as an attractive novel therapeutic target. We sought to investigate the impact of CTGF methylation status (CTGF-M) in predicting outcome of HNSCC patients undergoing RCHT. Methods: CTGF-M was discovered by applying Illumina 450K/850K arrays to DNA extracted from FFPE material of patients homogeneously treated with surgery followed by adjuvant cisplatin-based RCHT in frame of the DKTK-ROG multicenter retrospective trial (n = 194, training cohort). Methylation probes correlating with overall survival (OS) and progression were identified using random forest. Validation was done in 4 cohorts including DKTK-ROG definitive RCHT (n = 110) and 3 RCHT cohorts from Heidelberg, Dresden and Munich (n = 222). CTGF-M and RNAseq data from The Cancer Genome Atlas (TCGA) (n = 206) were analyzed to identify differentially expressed genes (DEG) as a function of CTGF-M. Results: Increased methylation of 2 probes (mapping to CTGF 3’UTR and gene body) was associated with significantly improved OS in the training cohort (HR = 0.51, p = 0.044) and the validation cohort (HR = 0.67, p = 0.016), in multivariate cox regressions adjusting for HPV status, age, T and N stages, location and treatment (adjuvant vs definitive RCHT). In the TCGA, probes’ methylation was significantly inversely correlated with CTGF gene expression (r = -0.18 and -0.51, p < 0.05). 1843 DEGs were found at FDR < 0.05 as a function of CTGF-M. Pathways mapping to tissue remodeling were significantly enriched for among downregulated genes in CTGF hypermethylated tumors. Increased CTGF methylation was inversely correlated with the mesenchymal subtype mRNA gene signature (r = -0.21, p = 0.0026) and correlated with the atypical subtype (r = 0.32, p = 0.000002). Conclusions: Implementation of CTGF-M in routine diagnostic is feasible and correlates well with CTGF gene-expression levels and activation of tissue remodeling pathways. Therefore, CTGF-M might be instructive for stratifying HNSCC patients for CTGF targeting therapies. CTGF emerges as a promising prognostic marker independently of HPV status.

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Background: Despite overall decline in cancer mortality, African Americans suffer from higher mortality in most cancer types including cancers of the head and neck. These differences likely result from a complex interplay of clinical and non-clinical factors. We aim to estimate disparities in overall survival across racial groups in HNSCC in the United States. Methods: This study used SEER-Medicare linked database. We identified all patients aged 66 years or older diagnosed with HNSCC as their first cancer from 1992 to 2011. We excluded those in HMO, diagnosed by death certificate or autopsy, non-SCC, unknown race, and missing month and/or year of diagnosis. Further exclusions included metastatic disease, salivary gland cancers, receiving no treatment in the first 180 days, and unknown stage. Analytic data set included oropharynx, oral cavity, nasopharynx, hypopharynx, and larynx. Primary treatment was defined as any treatment modality received within 180 days after diagnosis. Overall survival (OS) parameters were estimated across ethnic groups by the Cox regression model stratified by site and stage of cancer at diagnosis, adjusted for clinical and demographic characteristics, and propensity score weighted. Results: Our study population included 15, 547 patients. Median OS was 3.5 years (95% CI: 3.4-3.7) across all ethnic groups. African Americans (AA) had inferior outcome with median OS of 2.0 years (95% CI: 1.9-2.3) compared to 3.7 years (95% CI: 3.6-3.8) for Caucasian Americans (CA) (p < 0.0001). This difference was seen despite AA patients receiving comparable treatments and presenting at similar stage of disease, except for cancers of the oral cavity where AA were more likely to present with advanced disease (67% versus 47%; P < 0.001). The difference was most pronounced in the oropharynx where median OS was 1.9 years (95% CI: 1.7-2.1) for AA and 3.8 years (95% CI: 3.5-4.1) in CA (p < 0.0001). AA also had consistently worse OS over time from 1992 to 2011. This study clearly demonstrated AA have inferior outcomes despite similar treatments, comorbidities, age at diagnosis, stage at presentation, tumor location, year of diagnosis and sex. Conclusions: The current study demonstrates inferior overall survival for African American head and neck cancer patients independent of primary site and treatment modalities.
Pretreatment obesity prolongs survival in elderly patients (≥65 years) with head and neck cancer (HNC).

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Background: Pre-treatment Body mass Index (BMI) is an important prognostic factor in HNC with variable survival benefit reported till date. Despite increasing incidence of HNC in geriatric patients there is limited information on prognostic variables in this group. Methods: This is a single center, retrospective cohort study of patients with HNC≥65 years of age at their diagnosis from 2012 to 2016. Patients were stratified by BMI (Class 1- BMI<25 kg/m² (underweight & normal), Class 2- BMI≥25-29.9 kg/m² (overweight), Class 3- BMI≥30 kg/m² (obese) ). Various variables were collected & appropriate statistical analysis was done. Results: 188 elderly HNC patients with non-metastatic disease were stratified into three BMI groups (Table) & found to have evenly distributed co-variates. The Median OS was significantly higher in class 3 patients (53 months) compared to class 1 (21 months) (p =0.02). In multivariate analysis, class 3 was an independent good prognostic indicator (Hazard ratio=0.44; Range-0.21-0.90, p=0.03). Stage, CCI score & gastrostomy tube were adverse prognostic factors in the study. Conclusions: Obese elderly HNC patients have survival benefit over normal/underweight patients. Predictive prognostic models incorporating BMI with other prognostic factors are needed to determine appropriate management in these patients.

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>Class 1 BMI&lt;25 (78 patients)</th>
<th>Class 2 BMI 25-29.9 (57 patients)</th>
<th>Class 3 BMI ≥30 (53 patients)</th>
<th>p-value</th>
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<tr>
<td>MEAN AGE AT DIAGNOSIS (SD) Years</td>
<td>75.12 (7.46)</td>
<td>73.38 (6.13)</td>
<td>73.86 (6.14)</td>
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<tr>
<td>SEX (%)</td>
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<tr>
<td>WOMEN</td>
<td>27 (34.6)</td>
<td>16 (23.9)</td>
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<td>MEN</td>
<td>51 (65.4)</td>
<td>51 (76.1)</td>
<td>28 (71.1)</td>
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<td>PATHOLOGICAL TYPE (%)</td>
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<tr>
<td>SCC</td>
<td>71 (90.3)</td>
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<td>TNM STAGE (%)</td>
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<td>INITIAL TREATMENT (%)</td>
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<td>NONSURGICAL ONYSPHICE</td>
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<td>MEAN SURVIVAL TIME (SD)</td>
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<td>527.08 (319.10)</td>
<td>590.27 (495.62)</td>
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<td>SURVIVED AT LAST FOLLOW-UP (%)</td>
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<td>NO</td>
<td>43 (55.1)</td>
<td>25 (37.3)</td>
<td>15 (34.9)</td>
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</table>
Association of single nucleotide polymorphisms within genes in NF-κB, TGF-β, and JNK signaling pathways with the risks of nasopharyngeal carcinoma in Chinese Han.

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Background: Nasopharyngeal Carcinoma (NPC) is an Epstein-Barr virus (EBV) associated malignancy with remarkable ethnic and geographical distribution. The EBV oncoprotein latent membrane protein 1 (LMP1) is the primary oncogene of EBV infection through its signaling cascade and its connections to other pathways including NF-κB, TGF-β and JNK signaling, which plays an important role in the pathogenesis of NPC. In GWASs (Genome-wide association studies) associations these pathways were also identified. Single nucleotide polymorphisms (SNPs) in the regulatory regions may regulate the expression of genes in these pathways, or affect the function of the coded protein. Methods: Altogether 149 SNPs were covered by the 15 SNPs in the TRAF2, TRAF3, NFKBIA, MAP2K4, and CHUK genes were genotyped in a hospital-based case-control study of 350 NPC cases and 587 healthy controls from the Chinese Han. The observed genotype frequencies in the controls were tested for Hardy–Weinberg equilibrium (HWE) using the chi-square test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for associations between genotypes and NPC risk and tumor characteristics were calculated by logistic regression, and they were adjusted for multiple testing using the SNP spectral deposition (SNPSpD) approach for multilocus analyses. Results: We found one NFKBIA SNP was associated with NPC risk after adjustment for multiple comparisons. Minor allele carriers of the NFKBIA had an increased risk of NPC (P < 0.05). The analyses were adjusted for age and gender. For a polymorphism with a variant allele frequency between 10% and 50%, the study had greater than 90% power to detect an OR of 1.50 at a significance level of 0.05 (PS—software for power and sample size calculation, http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize). The other genotyped SNPs were not associated with NPC risk. Conclusions: Our data suggests that genetic variation especially in the NFKBIA maybe a useful biomarker for NPC screening and further studies are warranted.

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Background: When combined with COX-2 inhibitors, the EGFR tyrosine kinase inhibitor Erlotinib has shown a better antitumor response in preclinical studies. Since high volume hospitals in many countries usually have a longer waiting period for surgery, neoadjuvant targeted therapy may be helpful in reducing disease progression and downstaging oral squamous cell cancers. Methods: Sixty-four treatment-naive operable oral cancer patients were randomized into a four-arm window of opportunity study consisting of treatment with erlotinib 150mg daily, celecoxib 200mg twice daily, the combination of both or observation alone (NCT02748707). Since the regular wait period for surgery at our hospital was four to five weeks, we planned a 21-day drug treatment versus observation followed by definitive surgery in the fourth week. MRI scans and biopsies were done before and after drug treatment. Post-operative adjuvant treatments were given as per the standard guidelines used for regular patients. Results: There were 10 females and 54 males with a mean and median age of 44 and 45 years respectively. Taking a 20% reduction in the maximum tumor dimension after drug treatment (assessed clinically and radiologically) as partial response, the combination arm had a 60% partial response and a 25% stable disease. Whereas, 60% in the control arm had disease progression. The ratio of the longest tumor dimension at day 21 versus day 0 (Clinical & MRI assessment) also showed a significant difference between the observation vs erlotinib arms (p < 0.001) using Mann-Whitney Test. Grade II/III rashes was the commonly observed toxicity predominantly in the combination arm. Though not powered for survival analysis, a significant difference (p = 0.048) was observed for two-year overall survival for celecoxib + control (60%) versus erlotinib + combination groups (86%) using Kaplan Meier estimator. Biomarker analysis (transcriptome sequencing and IHC) is being done on pre and post-treatment tumor specimens and the final results will be presented. Conclusion: Preoperative targeted therapy with erlotinib and celecoxib combination can arrest disease progression and downstage tumors with possible impact on survival. The identified biomarkers can further refine a future cohort for effective neoadjuvant targeted therapy in oral cancers. Clinical trial information: CTRI/2012/07/002828.
Immune signatures associated with response to neoadjuvant PD-1 blockade in oral cavity cancer.

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Background: PD-1 inhibition therapy has revolutionized clinical medicine as it can mediate durable responses in a small cohort of patients. Yet, it remains incompletely understood why these patients respond. To address this question, we studied patients with oral cavity squamous cell carcinoma (OCSCC) to elucidate immune phenotypes associated with response to nivolumab. Methods: We defined the immune profile from the blood and tumor of patients on neoadjuvant nivolumab. We tested if tumor-infiltrating lymphocytes (TIL) could be preferentially expanded ex vivo from nivolumab-responsive patients versus those who were either non-responsive or had never received nivolumab. During the course of therapy, we comprehensively profiled a number of surface markers on patients' T cells to define their activation status, cytotoxic capacity and memory phenotype. Moreover, the immune profile of the peripheral blood was assessed pre- and post-nivolumab using high dimensional mass cytometry. Results: Regardless of PD-1 therapy, TIL were successfully expanded from 11 of the 12 patients. TIL were comprised of both CD4+ and CD8+ T cells. Additional investigation revealed that the frequency of CD4+ T cells and effector memory T cells in TIL correlated with disease progression (CD4: p = 0.04, r = 0.74, effector memory: p = 0.046, r = 0.74). TILs from responders expressed higher CD26 (p = 0.007, r = -0.88) and Tim3 (p = 0.045, r = -0.74) while PD-1, Lag3, and Ox40 were not differentially expressed based on response. Spearman correlation and Mann Whitney U test were used to assess phenotypic differences. Conclusions: We demonstrate, for the first time, that TIL can be reliably expanded from OCSCC patients on neoadjuvant nivolumab. Moreover, individuals who were responsive to PD-1 blockade had TIL expressing high levels of CD26 and Tim3. Future studies will explore if these markers are predictive of responses and if they contribute to treatment outcome.
Risk of mortality varies by type of fat consumed in a longitudinal cohort of head and neck cancer patients.

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Background: Dietary interventions have promise for improving cancer outcomes, but remain an understudied area of cancer care. The relationship between head and neck squamous cell carcinoma (HNSCC) mortality and dietary fat intake has not yet been examined. The objective of this study was to determine how pre- and post-treatment intake of various types of fat are associated with disease-specific and all-cause mortality in adults diagnosed with HNSCC. Methods: Our sample included 472 newly diagnosed HNSCC patients recruited into the University of Michigan Head and Neck Specialized Program of Research Excellence (HN-SPORE) between 2008 and 2012. Participants completed pre-treatment and post-treatment Food Frequency Questionnaires (FFQs) and health surveys. Multivariable Cox Proportional Hazards models were used to test the associations between both the type and quantity of fat intake (categorized into tertiles: low, medium and high intake) and time to mortality, after adjusting for relevant covariates. Fat types included animal, vegetable, medium-chain-fatty-acids (MCFA), long-chain-fatty-acids (LCFA), unsaturated, saturated, and trans. Results: During the study period, there were 144 total deaths and 97 cancer-specific deaths. In considering pre-treatment dietary intake, compared to low intake levels of LCFA, high intake was associated with a reduced risk of all-cause mortality (HR: 0.57; 95% CI: 0.34–0.94). High intakes of unsaturated-fats were associated with a reduced risk of HNSCC-specific mortality compared to low intake (HR 0.52; 95% CI: 0.29–0.93). Considering post-treatment dietary variables, medium (HR: 0.21; 95% CI: 0.08–0.49) and high (HR: 0.41; 95% CI: 0.21–0.78) total fat intakes were associated with reduced risk of all-cause mortality compared to low intake. Medium (HR: 0.25; 95% CI: 0.08–0.67) and high (HR: 0.26; 95% CI: 0.09–0.67) total fat intakes were associated with reduced risk of HNSCC-specific mortality compared to low intake. Conclusions: Our data suggest that HNSCC prognosis may vary depending on both the type and quantity of fats consumed, specifically total fat and long chain fatty acids. Clinical intervention trials are needed to further examine this hypothesis.
Identifying adverse molecular features of HPV+ head and neck cancers using patient-derived models.

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Background: Advancing therapy for human papilloma virus-related (HPV+) head and neck squamous cell carcinoma (HNSCC) is hindered by inadequate preclinical models and risk stratification tools. This study addresses both barriers by characterizing a panel of patient-derived xenografts (PDXs) that includes nine new models of HPV+ disease. Methods: Exome-sequenced genetic features of the PDXs were compared to their growth properties and the outcomes of their patients of origin. Genetic traits with potential prognostic utility were validated in multiple retrospective patient cohorts. Results: The HPV+ PDXs avoided known artifacts in HPV+ cell lines, including 3q amplifications and loss of PIK3CA mutants, while enriching for alterations in H3K4 methyltransferases and Notch pathway genes. A positive association emerged between PDX tumor mutational burden (TMB) and their growth efficiency both in vivo and as organoids. This finding led to identification in The Cancer Genome Atlas (TCGA) of an association between high TMB and worse survival of early-stage HPV-negative cancers but not HPV+ ones. Insight into aggressive HPV+ disease came from a PDX established from a patient before lethal relapse. The reduced levels of viral E7 and p16INK4A present in this model were also detected in early lethal HPV+ cases in TCGA as well as the recurrences in a second HPV+ HNSCC cohort (JHU). This observation suggested a diminished contribution of viral oncogenes to cell cycle dysregulation in aggressive cases. To evaluate this possibility, hierarchical clustering of both cohorts was performed based on expression of E2F target genes. This analysis discovered a distinct cell cycle-related transcriptional pattern in the clusters of cases containing the recurrences and early lethal events. Furthermore, a subset of these transcripts proved to be stage-independent predictors of survival for the HPV+ HNSCCs in both TCGA and JHU cohorts. Conclusions: Characterizing the most HPV+ patient-derived models described to date revealed novel prognostic utility for E2F target expression in HPV+ HNSCCs and TMB in HPV-negative HNSCCs. These features have potential for application to risk stratification, biomarker development, and trial design.
Background: Depth of invasion (DOI) has been incorporated in the new AJCC TNM staging (8th edition) for oral cancers. We hypothesized that the negative effect of increasing DOI on outcomes was a result of an increased propensity to node metastasis and appropriate neck treatment would negate its detrimental effect on outcomes.

Methods: Patients with T1/ T2 oral squamous cell carcinoma, clinically node negative, from a previously reported Randomized Controlled Trial (NCT 00193765) formed the cohort for this study. Patients were restaged according to the new staging system. Overall survival (OS) was estimated by the revised T stage for the entire cohort and separately for those who underwent END and those who did not (TND arm) using Kaplan Meier and log rank test. Multivariate analysis was performed using Cox proportional hazard model making adjustment for neck treatment, T stage, site, prognostic factors and the interaction between revised T stage and neck treatment.

Results: Of the 596 patients 577 were evaluable, with a median follow up of 77.57 months. Initial pT staging was pT1, 389 (67.4%); pT2, 181 (31.4%); pT3, 7 (1.2%) and was modified to pT1, 195 (33.8%); pT2, 280 (48.5%); pT3, 102 (17.7%) on restaging. 288 patients underwent END and 289 did not (TND arm). For the entire cohort 5-year OS rates were 79.0% [95% CI, 73.12-84.88] for pT1, 69.4% [95% CI, 63.91-74.89] for pT2 and 53.0% [95% CI, 43.2-62.8] for pT3 with significant difference between the 3 groups (p = 0.001). In those without upfront neck treatment (TND), OS difference was maintained between the pT1 and pT2 groups [81.1% (95% CI, 73.26-88.94) vs 65.0% (95% CI, 56.77-73.23)], p = 0.004. This difference was not apparent in the END arm, pT1 -76.9% (95% CI, 68.47-85.33) vs pT2 -73.7% (95% CI, 66.25-81.15), p = 0.73. T3 tumours had uniformly poor survival irrespective of neck treatment. On multivariate analysis of the revised pT1/T2 cohort (n = 475), pT stage, neck treatment and grade were independent prognostic factors impacting OS. There was a significant interaction between the T stage and neck treatment (p = 0.03).

Conclusions: When DOI < 10 mm, END supplants the prognostic implication of depth with similar outcomes for T1 and T2 tumours (new AJCC staging). The exact role of DOI on outcomes warrants further research. Clinical trial information: NCT00193765.
Prophylactic gabapentin decreases fatigue and swallowing difficulty in patients undergoing concurrent chemo-radiation (CCR) for head and neck cancer (HNC): Interim results from a randomized controlled trial.

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Background: Preliminary data suggest that gabapentin (G) administered during HNC radiation may decrease treatment associated pain. To confirm this, we undertook a prospective, randomized trial in HNC patients undergoing CCR. Primary outcomes: pain severity (scale of 0-10) and opioid use. Exploratory outcomes: local and systemic symptoms measured by the Vanderbilt Head and Neck Symptom Survey version 2 plus the general symptom survey (VHNSSv2/GSS). We report results of the exploratory endpoints from the interim analysis. Methods: Measures: VHNSSv2 - 50 items, demonstrated reliability/validated, captures acute/chronic local HNC specific symptoms; GSS – 11 item checklist, demonstrated content validity, captures acute/chronic systemic symptoms. Population: HNC patients (≥ stage 2) undergoing primary or adjuvant CCR. Procedures: Randomized to standard pain management (SPM) or SPM + G dose escalated to 900mg tid. VHNSSv2/GSS completed weekly during treatment beginning week 1 and ending the last week of radiation therapy. Results were analyzed using a mixed-effects regression analysis adjusting for baseline levels of each symptom. Results: 71 patients completed a mean of 5.5 surveys. Patients on G experienced a reduction in overall systemic symptoms as measured by the GSS (11-items, p = 0.0073), fatigue (two-items, p = 0.013 ) sleep disturbance (five items, p < 0.0001) , neurosensory eating (3 items, p = 0.026), phlegm-related symptoms (4 items, p = 0.004), and trend to better smell (2 items, p = 0.055). No impact on swallow, xerostomia, voice, dental or musculoskeletal symptoms was noted. Conclusions: This exploratory analysis suggests that G may moderate neurological and neuropsychiatric toxicities in HNC patients undergoing CCR. Further studies are warranted.
Predictive biomarkers for response to nivolumab in head and neck squamous cell carcinoma (HNSCC) (NCT#03652142).

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Background: Tumor immune cell compositions determine response to immunotherapy. For a better understanding of the mechanisms of resistance to nivolumab in HNSCC, we sought to investigate a prospective cohort of longitudinal HNSCC samples from recurrent/metastatic HNSCC pts treated with nivolumab and identify biomarkers of response and resistance. We will specifically focus on modulation of immune markers following two cycles of nivolumab. Methods: Patients with platinum-refractory HNSCC with no contraindication to nivolumab therapy are included in this study. Tumor biopsies are performed at baseline, 24-72 hours after the second cycle and at progression with appropriate written informed consent. Samples were assessed for the presence of Tertiary Lymphoid Structures (TLS), PD-L1 expression (TPS and CPS) and CD8 T cell infiltrates combined with Ki67 (CD8/Ki67 double IHC stain). The primary outcome measure of the study is change in the percentage of immune cells in post treatment compared to baseline biopsies. Secondary endpoints include safety of performing a second biopsy, best overall response rate, biomarker expression in association with response and survival. Evaluation of other biomarkers including tumor mutational burden, HLA class I and II expression and adaptive immunity cell populations using multiplex IF is ongoing. Results: Of 20 patients evaluable for response, 14 had PD (8 of whom showed hyper-progression) and 6 attained disease control (1 with PR). PD-L1 status (CPS or TPS) was not altered by treatment (p = 0.905) and CPS showed a favorable trend towards response (p = 0.117). Absence of tertiary lymphoid structures was associated with disease progression (p = 0.0374). Infiltrating plasma cell count remained unchanged pre- and post-treatment and was unrelated to response (p = 0.458). The percentage of proliferating CD8+ T cells (CD8+/Ki67+) increased in post-treatment biopsies in the entire population (p = 0.022) and especially in progressors (p = 0.039). Pre-treatment CD8+ T cell density was higher in patients with hyper-progression compared to progressors (p = 0.029). Conclusions: Increased percentage of proliferating CD8+ T cells in progressors might represent dysfunctional T cells as has been recently shown in melanoma pts (Li H et al Cell 2019) and clinical efforts to reanimate intratumoral T cells may augment the efficacy of PD1 checkpoint inhibitors. Clinical trial information: NCT03652142.
Prognostic impact of baseline circulating tumor cells (CTCs) detected by the isolation by size of epithelial tumor cells (ISET) in locally advanced head and neck squamous cell carcinoma (LAHNSCC): Results of a prospective study.

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**Background:** The prognostic impact of CTCs in LAHNSCC is yet to be determined, with conflicting results in previous trials, the majority utilizing cytokeratin dependent techniques for identification and counting of CTCs. The primary objective of this study is to determine the detection rates using the ISET method, and the prognostic role of CTCs in LAHNSCC patients (pts) treated with a curative intent. **Methods:** In this prospective study, peripheral blood samples of pts with non-metastatic LAHNSCC, stages III/IV, were analyzed for CTCs using the ISET method, in two scenarios: curative surgical resection and adjuvant radiotherapy (CTCs before RT) and candidates for a non-surgical strategy (unresectable or organ preservation) either with upfront RT concurrent with chemotherapy (CT) or cetuximab (CTCs before RT), or preceded by induction CT (CTCs before ICT). **Results:** Eighty-three pts were included, the majority males (83%), with oropharynx primary (50%) and submitted to ICT (40%). The detection rate of baseline CTCs was 94% (78/83), and CTCs counts were significantly correlated with survival. For each increase of 1 CTC at baseline there was a relative increase of 18% in the risk of death (HR = 1.18; 95%CI: 1.06-1.31; p < 0.001), 16% in the risk of progression (HR = 1.16; 95%CI: 1.04-1.28; p = 0.004) and a reduction of 26% in the odds of complete response to treatment (non-surgical group only - OR = 0.74; 95%CI: 0.58-0.95; p = 0.022). Using the maximum of the standardized log-rank statistic proposed by Lausen and Schumacher we establish cut off points for overall survival (OS) and progression-free survival (PFS). Pts with CTCs < 6.5/ml had an estimated 2y OS of 85.6% versus 22.9% for CTCs ≥ 6.5/ml (HR = 0.18; 95%CI: 0.06-0.49; P < 0.0001) and pts with CTCs ≤ 3.8/ml had an estimated 2y PFS of 71.8% versus 37% for CTCs > 3.8/ml (HR = 0.32; 95%CI:0.15-0.67; p = 0.001). **Conclusions:** The detection rate of baseline CTCs using the ISET method was very high in LAHNSCC and the counts of CTCs were strongly correlated with survival and response to treatment.
Tumor volume, circulating tumor cells, and cfDNA changes during radiotherapy in patients with head and neck cancer.

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Background: Head and neck (HN) cancer treatment response relies heavily on macroscopic clinical findings. Monitoring of circulating markers during treatment may improve detection of responders versus non-responders during radiotherapy (RT). Our work prospectively describes the changes in gross tumor volume (GTV), circulating tumor cell (CTC), and cell-free DNA (cfDNA) enumeration during RT.

Methods: Patients with intact HN squamous cell carcinoma were enrolled in a prospective IRB-approved study. Pre-, after first RT, weekly in-, and post-RT blood samples were collected. Serial pre-, weekly in-, and post-RT magnetic resonance imaging (MRI) was obtained. Serial GTV measurements were recorded. CTC was enumerated using the FDA-approved CellSearch (Menarini Silicon Biosystems) system. Plasma were collected and cfDNA from pre-, mid- and post-RT timepoints were isolated using the MagMAX Nucleic Acid Isolation Kit (Thermo Fisher Scientific), and cfDNA were quantified with Qubit high sensitivity dsDNA assay (Invitrogen).

Results: 40 patients were eligible for analysis. Median age was 60 years and 36 were males. The median pre-RT GTV was 14.1 cc (range 1.3 – 44.9 cc). There was a median reduction of 81% in GTV by week 4 (p < 0.0001). Of the 341 samples analyzed for CTC, 146 (43%) had detectable CTC. 7 patients had detectable pre-RT CTCs (1-3/7.5ml blood). There was no correlation between cancer stage, nodal status, and GTV with detection of CTC. After 1 fraction of RT, 14 patients had CTCs detected, including 11 who had no CTC detected prior. All patients had CTC detected at some point during RT except for 2 patients who had none. In week 4, with significant reduction in GTV, 25 (63%) had detectable CTC. 16 and 11 patients had detectable CTC in final week and post-RT timepoints. The cfDNA levels increased during RT, with its highest level in the final week of RT and lowest at post-RT time-point, inversely correlated with GTV.

Conclusions: Our study showed that CTCs can be detected during RT, suggesting mobilization into peripheral circulation during RT with unknown viability. cfDNA kinetics during RT correlated with CTC release, and may indicate apoptotic change during RT. Combined cfDNA-CTC as an early marker of treatment response should be investigated further.
Biomarker predictors of outcome from a randomized trial of nivolumab +/- stereotactic body radiotherapy (SBRT) in metastatic (M1) head and neck squamous cell carcinoma (HNSCC).

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Background: A minority of patients with M1 HNSCC respond to the anti-programmed death (PD-1) monoclonal antibody, Nivolumab (Nivo). We sought to determine biomarker predictors of outcome to Nivo in M1 HNSCC. Methods: Patients with M1 HNSCC were randomized (n = 60) with stratification by virus status (EBV/HPV+ vs not) to either Nivo alone or Nivo+SBRT to a single lesion. The primary end-point was objective response rate (ORR) in non-irradiated lesions with overall survival (OS) as a secondary end-point. PD-L1 staining in ≥ 1% of tumor cells was regarded as positive. Tumor mutation burden (TMB) was determined using a next generation sequencing assay (MSK IMPACT). Predictive model selection was done to minimize the Akaike Information Criterion (AIC). Results: There was no difference in ORR comparing the two treatment arms (p = 0.86). On univariate analysis, virus status trended towards predicting both ORR (Positive 41.9% vs Negative 20.7%, (p = 0.14)) and OS (1-yr OS for Positive, 65.9% vs 1-yr OS for Negative 40.6%, p = 0.08). In the sub-group of patients for whom PDL1 staining was available (n = 56), there was a trend towards association with ORR: PDL1+ 50% vs PDL1- 23.5% (p = 0.08). PDL1+ patients demonstrated significantly longer OS (1-yr OS 63% vs 47%, p = 0.02). There was no association between virus status and PDL1 staining. IMPACT data was available in 46 patients. TMB was significantly higher in virus negative (mean 8.1 mut/mB) vs. virus positive (mean 4.6 mut/mB) (p = 0.01); TMB was similar comparing PDL1+ to PDL1- (p = 0.47). TMB was higher in responders than non-responders (p = 0.01) and trended towards being higher in virus negative responders (p = 0.10). A model to predict ORR that included PDL1, virus status, and TMB minimized AIC with a C-index of 0.72. A model to predict OS that included PDL1 and virus status minimized AIC with a C-index of 0.62. Conclusions: A multi-variate model including viral status, PDL1 status, and TMB predicts well response to Nivolumab in M1 HNSCC. A model containing PDL1 and virus had moderate predictive value for OS. Clinical trial information: NCT02684253.
Safety and efficacy of docetaxel combined with cisplatin as induction chemotherapy followed by cisplatin concurrent chemoradiotherapy plus gemcitabine as adjuvant chemotherapy in locally advanced nasopharyngeal carcinoma: A prospective and multicenter phase II trial.

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Background: Radiation therapy is the only curative treatment modality for nonmetastatic nasopharyngeal cancer (NPC). Concurrent chemoradiation (CCRT) is the standard treatment strategy for NPC in locally advanced stages. However, the results after such treatment are suboptimal. Clearly, novel treatment strategies are needed to further improve patients’ survival rates. This trial aimed to determine the safety and efficacy of a new treatment strategy.

Methods: Patients with stage III – IVa-b NPC received TP (docetaxel 75 mg/m², cisplatin 75 mg/m² every 3 weeks for 2-3 cycles) followed by cisplatin chemotherapy concurrently with either 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy plus gemcitabine (1000mg/m² every 2 weeks for 2 cycles) as adjuvant chemotherapy. Objective response rates and acute toxicity were assessed based on RECIST (1.1) and CTCAE v.4.0, respectively. Kaplan-Meier analysis was used to calculate survival rates. This trial is registered with the Chinese Clinical Trials Registry, number ChiCTR-OIC-17011464.

Results: From July 2010 to July 2017, 20 eligible patients with nonmetastatic stage III-IVb NPC were enrolled. The objective response rates were 90% (3 complete responses [CRs] and 15 partial responses [PRs]) after two or three cycles of induction chemotherapy (ICT) and 100% (17 CRs and three PRs) after CCRT plus gemcitabine adjuvant chemotherapy, respectively. With a median follow-up time of 41 months, the 3-year overall survival rates were 90% (18/20, 95% confidence interval [CI], 76.9%-100%). The 3-year progression-free survival, distant metastasis-free survival, and local progression-free survival rates were 80% (16/20, 95% CI, 62.5%-97.5%), 85% (17/20, 95% CI, 69.4%-100%), 95% (19/20, 95% CI, 85.4%-100%), respectively. The most frequent grade 3–4 toxicities were neutropenia (3/20, 15%) and nausea (2/20, 10%) after ICT and thrombocytopenia (6/20, 30%) and leukopenia (6/20, 30%) after CCRT plus gemcitabine adjuvant chemotherapy.

Conclusions: Neoadjuvant TP followed by concurrent chemoradiation plus gemcitabine as adjuvant chemotherapy was well tolerated and produced promising outcomes in patients with LA-NPC in this hypothesis-generating study. The authors concluded that randomized controlled trials are warranted to definitively confirm this aggressive and potentially efficacious strategy. Clinical trial information: ChiCTR-OIC-17011464.
Safety of radiotherapy with concurrent and adjuvant MEDI4736 (durvalumab) in patients with locoregionally advanced head and neck cancer with a contraindication to cisplatin: NRG-HN004.

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Background: MEDI4736 (durvalumab), a PD-L1 inhibitor, has shown promising antitumor activity and safety in head and neck squamous cell carcinoma (HNSCC). A phase II/III trial with lead-in component was designed to evaluate the safety and efficacy of concurrent and adjuvant MEDI4736 with radiation therapy (RT) for HNSCC patients with a contraindication to cisplatin. Safety data for 10 patients on the lead-in study are reported. Methods: Eligible patients had previously untreated locoregionally advanced unresected SCC of the larynx, hypopharynx, oropharynx (OPX), oral cavity, or unknown head/neck primary (AJCC 7th stage III-IVB). Contraindications to cisplatin included renal or hearing impairment, age ≥ 70 with moderate or severe comorbidity/vulnerability to cisplatin, or age < 70 with severe comorbidity/vulnerability, based on 6 validated indexes. Intravenous MEDI4736 1500 mg was delivered at weeks -2, 2, 6, 10, 14, 18, and 22 with RT (70 Gy in 35 daily fractions weeks 1-7). The primary endpoint was dose-limiting toxicity (DLT), defined as a high-grade adverse event (AE; NCI CTCAE version 4.0) definitely/probably related to MEDI4736 up to 4 weeks following completion of RT; 0-2 DLTs in 8 evaluable patients was considered acceptable. Results: Characteristics of the 10 enrolled patients were: 30% age ≥ 70, 90% male, 100% Caucasian, 40% ECOG performance status 0, 60% modified Charlson Comorbidity Index ≥ 1, 60% > 10 pack-years, 20% larynx, 60% p16+ OPX, 50% T3-4 and 80% N2-3 disease. All 10 patients had ≥ 2 contraindications to cisplatin. All 10 patients completed RT and were evaluable. 8 of 10 patients received all 7 doses of MEDI4736 and 1 patient is still on MEDI4736 after 6 doses. 1 patient received 2 doses then discontinued due to AE (diarrhea possibly related to MEDI4736). No DLTs were observed. No grade 4-5 AEs were observed. Grade ≥ 3 AEs possibly related to MEDI4736 were: diarrhea (n=1), nausea (1), and vomiting (1). No grade ≥ 3 AEs were rated as definitely or probably related to MEDI4736. Conclusions: MEDI4736 is safe and feasible to administer concurrently with RT for patients with HNSCC with a contraindication to cisplatin. Clinical trial information: NCT03258554.
A randomized trial of laryngeal organ preservation evaluating two cycles of induction chemotherapy with platinum, docetaxel, and a novel Bcl-xL inhibitor.

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Background: Laryngeal bio-selection with induction chemotherapy (platinum + 5-FU infusion: PF) has been demonstrated to result in impressive rates of survival and organ preservation with moderate toxicities. We sought to reduce the toxicity of PF by substituting docetaxel (T) for 5-FU and improve the tumor response rate with the addition of the Bcl-xL inhibitor AT-101.

Methods: Pts with advanced stage laryngeal cancer were treated with 1 cycle of T 75 mg/m2 + platinum (P) (cisplatin 100 mg/m2 or carboplatin AUC 6) and were randomized 2:1 to the addition of AT-101. Patients with a CR proceeded to chemoradiation (CRT) with concurrent weekly P. All pts with PR or NR underwent a second cycle of induction with TP + AT-101. Pts with a > 50% response (CR or PR) after the second cycle of induction chemotherapy underwent CRT. Pts with a ≤ 50% response (NR) underwent laryngectomy. PET-CT was performed 12 weeks after CRT. Pts with residual disease underwent salvage laryngectomy (SL).

Results: 54 eligible pts were enrolled; 46 M, 8 F; median age 59; 26 T4; stage III 16, stage IV 38; site: 2 hypopharyngeal, 39 supraglottic, 11 glottic, 2 subglottic. After cycle 1 of induction, 2/54 (4%) died prior to assessment by DL and 2 were removed from protocol due to adverse events (AEs). 29/50 pts (58%) had ≥ 50% response, 3 of which had CR; 2 proceeded to CRT & 1 received a 2nd cycle of IC. 21/50 pts (42%) had < 50% response. A total of 48 pts received cycle 2 of IC. After the 2nd cycle, a total of 39/50 pts (78%) had ≥ 50% response & received CRT. No difference in response was seen with addition of AT-101. 11/50 pts (22%) had < 50% response- 8 had laryngectomy & 3 refused. Following CRT, 10 pts underwent SL, 2 for residual disease & 8 late SL. The organ preservation rate was 31/50 (62%). The most common grade 3/4 toxicities associated with IC were nausea 9%, neutropenia 9%, & infection 7%. 1 pt died of CNS hemorrhage unrelated to therapy & 1 from sepsis. The median follow-up time is 28 months. The 2 yr laryngectomy-free survival is 54% (95% CI:38-68) & 2 yr overall survival is 81% (95% CI: 64-90).

Conclusions: AT-101 did not improve responses to P. Treatment with 2 cycles of IC with PT produced similar response rates to our institutional controls, but organ preservation was somewhat less following treatment with weekly P + RT. Toxicities were overall improved with this treatment strategy. Clinical trial information: NCT01633541.
Induction chemotherapy with and without erlotinib in patients with oral cavity squamous cell carcinomas (OCSCCs) amenable for surgical resection.

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Background: We have previously demonstrated activity of erlotinib in head and neck SCCs as monotherapy prior to surgical resection, or in combination with chemotherapy for recurrent/metastatic disease (William et al. ASCO 2011, 2017). The aim of this study was to evaluate the efficacy of induction chemotherapy with a platinum-taxane regimen and explore the potential benefit of erlotinib as part of induction therapy in patients with resectable OCSCCs. Methods: This was a randomized, placebo-controlled, phase II trial of induction chemotherapy (cisplatin 75 mg/m2 or carboplatin AUC 6 with docetaxel 75 mg/m2 every 3 weeks for 3 cycles) with erlotinib (150mg oral daily) or placebo in patients with OCSCCs stage III-IVB amenable for surgical resection. The primary endpoint was major pathological response (MPR, defined as < 10% viable tumor cells in the surgical specimen). Secondary endpoints included safety and long-term efficacy outcomes. Results: From April 1, 2014, to June 7, 2017, 52 patients were enrolled, of whom 47 underwent planned surgery. MPR was achieved in 7/23 (30%) in the erlotinib group and 10/24 (41%) in the placebo group. With a median follow up of 26.5 months, the 2-year long-term progression-free survival (PFS) were estimated at 75% (95% CI: 59.5-94.5) in the erlotinib arm, and 58.6% (95% CI: 40.9-84.1) in the placebo arm, and 2-year overall survival at 73.5% (95% CI: 57.2-94.5) for the erlotinib group and 73.1% (95% CI: 55.9-95.6) for the placebo group. In patients who achieved MPR (n = 17), the 2-year PFS was 77.4% (95% CI: 57.3-100), compared to 64.5% (95% CI: 49.0-84.8) in patients who did not achieve MPR (n = 29, p = .16). All 7 patients in the erlotinib group who achieved MPR remained disease-free. The majority of patients (87%) completed all 3 cycles of induction chemotherapy. The common side effects were expected and distributed similarly between erlotinib and placebo groups. As expected, rash, diarrhea and dehydration were more common in the erlotinib group. Conclusions: Platinum and docetaxel-based induction chemotherapy induced major pathological response in 17/47 (36%) of resectable OCSCC patients. Two-year overall survival was 73%. Responders had improved long-term outcome. Addition of erlotinib did not improve the rate of MPR, but might have contributed to improved PFS. Clinical trial information: NCT01927744.
Impact of smoking cessation in locally advanced head and neck cancers undergoing radiation.

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Background: Multiple studies have highlighted the negative outcomes associated with smoking during radiation (XRT) for locally advanced head and neck cancer. However, there has been little research investigating the potential benefit of smoking cessation prior to XRT and the effect on response rates, relapse, distant metastases, secondary malignancies, and overall survival. Methods: We reviewed 680 patients at the University of Texas MD Anderson Cancer Center from 2005-2012 with locally advanced head and neck cancer undergoing XRT. 127 were referred to the Tobacco Treatment Program (TTP) based on provider referrals, self-referrals, or screening. Of those referred and retrospectively reviewed, 89 were identified as current smokers and 41 of them participated in the TTP for smoking cessation. Among these 89 patients, 50 patients (18 participated in the TTP) quit smoking prior to XRT and 29 patients (19 participated in the TTP) continued to smoke, which are referred to as Quitters and Smokers, respectively. 10 patients (2 participated in the TTP) had incomplete data and were excluded from further analysis. Results: Quitters had 100% complete response (CR) on initial assessment following XRT. 7/50 (14%) developed relapsed disease with 4 local recurrences (LR) and 3 distant metastases (DM). 6/50 (12%) developed secondary malignancies. By contrast, Smokers had 96.5% CR on initial assessment following XRT. 8/29 (27.5%) developed relapsed disease with 6 LR and 2 DM. 6/29 (20.6%) developed secondary malignancies. The median follow ups for Quitters and Smokers were 57.5 and 54 months with overall survival rates of 82% and 79%, respectively. Conclusions: Current smokers that achieved smoking cessation prior to XRT demonstrated lower rates of relapse, DM, and secondary malignancies compared to those that continued to smoke. Thus, smoking cessation is an integral part of head and neck cancer treatment and needs to be further incorporated in cancer care to improve cancer treatment outcomes. As a future direction, a comparable group of patients who did not smoke from the same time range will be compared for response rates, LR, DM, secondary malignancies, and survival.
Hafnium oxide nanoparticles NBTXR3 activated by radiotherapy as a new therapeutic option for elderly/frail HNSCC patients.

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**Background:** New therapeutic approaches are needed for elderly or frail head and neck squamous cell carcinoma (HNSCC) patients (pts) ineligible for standard of care treatment. NBTXR3, a crystalline solution of hafnium oxide nanoparticles may represent such an option. Injected intratumorally, NBTXR3 enters tumor cells and yields an increased cell-localized energy deposit upon exposure to radiotherapy (RT), leading to increased tumor cell death compared to the same dose of RT alone. **Methods:** Phase I study of NBTXR3 activated by RT in pts ≥70 years old or ≥65 years old and unable to receive cisplatin, eligible for exclusive RT with stage III or IV HNSCC of the oral cavity or oropharynx [NCT01946867]. A 3+3 dose escalation design was implemented with dose levels corresponding to 5%, 10%, 15% and 22% of baseline tumor volume, followed by an expansion phase. Pts received an intratumoral (IT) injection of NBTXR3 and intensity modulated RT (IMRT; 70 Gy/35 fractions/7 weeks). Determination of Recommended Phase 2 Dose (RP2D) and Dose Limiting Toxicities (DLT) were primary endpoints of phase I. Absence of NBTXR3 leakage and preliminary efficacy using RECIST 1.1 principles were also evaluated. **Results:** The dose-escalation is complete. Nineteen pts were enrolled: 3 at 5%, 3 at 10%; 5 at 15% and 8 at 22% with no observed DLT or SAE related to NBTXR3 or IT injection. One grade 1 NBTXR3-related AE (asthenia at 22%) and four IT injection-related AE (grade 2 oral pain; grade 1 tumor hemorrhage; grade 1 asthenia, and grade 1 injection site hemorrhage) were reported. RT-related toxicity was as expected with IMRT. RP2D has been determined to be 22%. CT-scan assessment between 24h and 7 weeks post-IT injection demonstrated absence of NBTXR3 leakage in the surrounding tissues. Among 13 evaluable pts treated at doses ≥10%, 9 achieved a complete response of the injected lesion. **Conclusions:** These results show that NBTXR3 activated by RT is safe and well tolerated at all doses with preliminary encouraging efficacy results. It thus represents a promising future treatment for frail and elderly pts with locally advanced HNSCC with limited therapeutic options. Expansion phase has started at the RP2D. Clinical trial information: NCT01946867.
Safety of nivolumab and ipilimumab in combination with radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN).

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Background: Standard cisplatin-based chemoradiotherapy for LA SCCHN is associated with toxicity and less than desirable survival in high-risk patients (pts). The combination of the anti-PD1 antibody nivolumab (nivo) and the anti-CTLA-4 antibody ipilimumab (ipi) has been effective in melanoma and renal cell carcinoma and is under investigation in other solid tumors including SCCHN. Combining RT and immunotherapy (IO) has a strong preclinical rationale and is being evaluated in the clinic. This pilot trial combines IO and RT to build upon these observations.

Methods: We enrolled previously untreated high-risk pts with AJCC 7th edition stage IVA-IVB SCCHN of the oral cavity, oropharynx (OP), hypopharynx, larynx. HPV+ OP tumors were T4, or N2c or N3 by AJCC 7th edition criteria. Nivo 3 mg/kg was administered every 2 weeks IV x 17 doses and ipi 1 mg/kg every 6 weeks x 6 doses beginning 2 weeks before IMRT 2 Gy/fraction/day given to total dose 70 Gy. The primary safety endpoint was acute in-field toxicity. Exploratory correlative studies include tumor PD-L1 expression, tumor immune bias, and exosome quantity and composition. The total sample size is 24 pts with 12 enrolled in the first stage and 12 in the expansion cohort. Results: A planned safety analysis was performed in the first 12 pts (8 OP; 1 hypopharynx; 3 larynx). No acute grade (G) 4 or dose-limiting toxicities were seen. Acute G 3 in-field toxicity occurred during RT in 50% of pts: dysphagia (4 pts), mucositis (3), odynophagia (2), hoarseness (1), dermatitis (1). 50% of pts had immune-related toxicity at any time. 3 pts discontinued treatment at > 3 months post RT: 1 for an immune-related cause (G 3 colitis that resolved with steroids), and 2 for non-immune-related causes (1 G 5 bleeding due to carotid rupture secondary to an in-field ulcer at 4 months post RT in a pt with complete response and 1 G 3 OP ulcer resolving with hyperbaric oxygen). 1 pt with a laryngeal primary developed a solitary lung metastasis vs new primary 6 months post RT. 10 of 12 pts are alive with no evidence of disease (follow up 7.2-18.4 months). Conclusions: Preliminary results with this non-platinum-containing RT plus IO regimen are encouraging. Longer follow-up is needed for assessment of late effects and efficacy. Enrollment is ongoing in the expansion cohort. This study is supported by BMS. Clinical trial information: NCT03162731.
Long-term survival of adjuvant high-dose (HDC) vs weekly cisplatin (WC) for human papilloma-virus (HPV) and non-HPV head and neck squamous cell carcinoma (HNSCC).

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Background: Phase III data suggests a benefit of HDC in the adjuvant setting, but the effect of HDC and WC on long term survival and for HPV+ HNSCC is unknown. Methods: Data from a published retrospective study (Geiger Oral Onc 2013) of HDC vs WC in resected HNSCC was updated. Overall survival (OS) and recurrence-free survival (RFS) was assessed by Kaplan-Meier method for all pts and by HPV status. Multivariate analyses were performed to assess impact of HPV status, smoking, age, HDC vs WC, and cumulative cisplatin dose (≤ 200mg/m² vs > 200 mg/m²). Results: 51 patients (pts) received HDC and 53 WC. Median follow-up was 8.7 yrs (0.8-13.7). For the whole cohort, HDC had significantly improved OS over WC (p = 0.0095; 5- and 10-yr OS 84% and 80% vs 72% and 60%). No OS benefit for HDC was seen in pts with HPV+HNSCC (5- and 10-yr OS 90% and 87% for HDC and 81% and 81% for WC; p = 0.51). For HPV-negative HNSCC, OS had borderline significance with HDC vs WC (5- and 10-yr OS 73% and 68% vs 65% and 44%; p = 0.06). For the whole cohort, there was no difference in 5- and 10-yr RFS (78% and 74% for HDC vs 72% and 62% for WC; p = 0.32). When analyzed by HPV status, there was no difference in RFS with HDC or WC for either HPV+ (p = 0.43) or HPV-negative HNSCC (p = 0.97). On multivariate analyses of OS for all pts, only HPV status was significant (p = 0.0011; HR 0.27, CI 0.12-0.62). For HPV+ HNSCC, there was no significant predictor of OS. For non-HPV HNSCC, the benefit of HDC approached significance with a decreased risk of death (HR 0.38; p = 0.07). For all pts, those who received ≥200mg/m² had significantly improved OS (5-yr 90% vs 72% and 10-yr 86% vs 61%; p = 0.004). By HPV status, cumulative dose had no significant effect on OS. Conclusions: OS is better with HDC and with cumulative dose > 200 mg/m² in unselected patients. The benefit of cisplatin is likely higher for non-HPV HNSCC. A difference in OS with no difference in RFS suggests non cancer-related causes of death in the WC cohort. Ability to receive HDC could be a surrogate marker of comorbidity.

<table>
<thead>
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<th>Original study cohort characteristics.</th>
<th>HDC</th>
<th>WC</th>
<th>p-value</th>
</tr>
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<tr>
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<td>53</td>
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<tr>
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<tr>
<td>HPV+</td>
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Phase II study: Induction chemotherapy and transoral surgery as definitive treatment (Tx) for locally advanced oropharyngeal squamous cell carcinoma (OPSCC)—An update and retrospective review of non-study patients.

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Background: The standard of care for OPSCC includes chemoradiation (CRT) or surgery with adjuvant radiation (RT). However, RT is associated with significant life long morbidity. We assessed the efficacy of a two-drug induction regimen, followed by transoral robotic assisted surgery (TORS) & neck dissection for locally advanced OPSCC. Methods: This is an IRB approved single-arm phase II study for untreated stage III or IVA (AJCC 7th edition) OPSCC patients (pts) with an ECOG < 2 and GFR > 50 cc. Induction cisplatin 75 mg/m2 and docetaxel 75 mg/m2 was administered every 21 days for 3 cycles. Patients then underwent TORS and neck dissection(s). At post-op visits, flexible laryngoscopy, blood tests, and imaging with PET/CT and/or MRI were done. Short and long term toxicity, progression-free survival, overall survival, and quality of life (QOL) were evaluated in all pts. Results: Twenty oropharyngeal pts were treated, 19 were male, 17 were Caucasian, and 19 were HPV+. Median age at dx was 57. Three pts were stage III, and 17 were stage IVA. Pathologic CR at the primary site occurred in 15 pts and CR among LN neck dissections occurred in 13 pts. Four pts were given dose-reduced chemo and 1 pt was changed to carboplatin per protocol because of renal dysfunction. Pre vs post tx QOL scores did not change. At a mean follow-up of 33 months (range 19.6 to 44.1), 18 pts are alive and NED. Three pts recurred a mean of 2.2 mos after surgery, and were treated with salvage CRT. Two pts died of metastatic disease, the third is alive and well. All 3 pts had positive LN (9 LN, 3 LN and 1 LN) at surgery. A fourth pt had 12 pos LN and received radiation. He has not recurred. A retrospective review of an additional 20 pts treated in the same way, were also reviewed for efficacy. Mean age was 61.5. Two pts died of metastatic disease. Fourteen pts have been followed for > 7 mos, and their mean overall survival is 44 mos. Conclusions: Cisplatin + docetaxel followed by TORS & neck dissection(s) appears to be an effective model for the definitive treatment for OPSCC, while avoiding the adverse effects of RT.
Safety and disease control achieved with the addition of nivolumab (Nivo) to chemoradiotherapy (CRT) for intermediate (IR) and high-risk (HR) local-regionally advanced head and neck squamous cell carcinoma (HNSCC): RTOG Foundation 3504.

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**Background:** Nivo, which inhibits the programmed death-1 (PD-1) receptor, improved survival for pts with platinum-refractory recurrent/metastatic HNSCC. A clinical trial evaluated the safety of adding nivo to 4 standard intensity modulated (chemo) radiotherapy (RT) regimens (see table) for pts with newly diagnosed IR/HR HNSCC. Primary endpoint was safety and feasibility. **Methods:** Eligibility included IR (p16+ oropharynx [op], T1-2N2b-N3/T3-4N0-3, >10 pack-years [pys], or T4N0-N3/T1-3N3, ≤10 pys) & HR HNSCC (oral cavity, larynx, hypopharynx, p16- op, T1-2N2a-N3/T3-4N0-3). 10 pts/arm (8 evaluable; 0-2/8 DLTs acceptable). Nivo (dose & schedule varied per arm) started 2 wks pre-RT & continued 3 months post-RT. Feasibility of adjuvant nivo months 3-12 post-RT defined as ≥4 of 8 pts/arm received 7 doses. Arm 4 limited to age ≥70, Zubrod performance status (PS) 2, CrCl <50 ml/min, grade ≥2 hearing loss or ≥ grade 3 neuropathy. **Results:** Characteristics of 39/40 treated pts: median age 62, 79% male, 49% PS0, 38% HR, 67% >10 pys, 62% p16+ op, 72% T3-4, 85% N2-3. Grade ≥3 nivo-related AEs: adrenal insufficiency, diarrhea-3, anemia, fatigue-2, mucositis-3, nausea, vomiting, lipase increase-6, amylase increase-2, lymphocyte/neutrophil/WBC decrease-4, hyponatremia-3, anorexia, maculo-papular rash. SAE in 4/10, 4/9, 5/10 & 4/10. DLTs, adjuvant chemo feasibility, median follow-up (mo), progression or death events per arm shown in table. **Conclusions:** Nivo concomitant with all (chemo)RT regimens was safe for patients with newly diagnosed IR/HR HNSCC but adjuvant nivo was infeasible after high-dose cisplatin or in cisplatin-ineligible patients (NCT02764593). Preliminary data on progression/death is provided. Acknowledgements: Support for this study was provided by Bristol-Myers Squibb Company. Clinical trial information: NCT02764593.

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<th>Arm</th>
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<th>Follow-up</th>
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<tr>
<td>1</td>
<td>cisplatin 40mg/m²/wk x 7</td>
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<td>2</td>
<td>cisplatin 100mg/m²</td>
<td>0/8</td>
<td>3/8</td>
<td>16</td>
<td>1/9</td>
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<tr>
<td>3</td>
<td>cetuximab 400 mg/m² load, 250 mg/m²/wk x 7</td>
<td>1/8 (mucositis)</td>
<td>4/8</td>
<td>10</td>
<td>1/10</td>
</tr>
<tr>
<td>4</td>
<td>RT alone</td>
<td>2/8 (lipase/mucositis; fatigue)</td>
<td>2/7</td>
<td>6</td>
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Is there a benefit of adding surveillance imaging to frequent history and physical exams in patients treated definitively for head and neck squamous cell carcinoma?

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Background: In head and neck squamous cell carcinoma (HNSCC) patients (pts) who completed curative-intent definitive treatment (tx), close surveillance is important. Across all centers, pts are closely monitored for symptoms and undergo frequent dedicated head and neck evaluation. Role of surveillance imaging after the initial 12 week post-treatment PET/CT however is less clear. Our institutional practice is to follow pts with regular interval imaging for two years after treatment. However this carries a financial cost, and risk for false positives and unnecessary biopsies. Methods: This is a retrospective chart review of pts treated definitively for HNSCC at our institution from 2012 to 2016. Pts who had a biopsy (bx) post-tx due to suspicion for recurrence were included. Pts belonged to 3 groups: In the first group (A), biopsy was prompted by findings on surveillance imaging (SI); in the second (B), biopsy was prompted by symptom triggered imaging (STI) and in the third (C), biopsy was based on physical exam (PE). We recorded the aggregate results of bx in each group and calculated the positive predictive value (PPV) for each. Results: Of 353 HNSCC pts, 66 underwent post-tx bx for suspected recurrence of which 46 were positive. Of the 30 pts in group A, 21 had positive bx (PPV = 70%). Within this group, PPV was highest with PET/CT (81.82%) followed by magnetic resonance imaging (66.67%) and CT (62.5%). 20 out of 20 pts in group B had bx-proven recurrence (PPV = 100%). 27 out of 36 pts in group C had positive bx (PPV = 75%). While there was no overlap between groups A and B, there was some overlap between groups A and C; and B and C. 45.45% of all recurrences were captured because of SI. When both imaging and PE conducted were positive simultaneously, 54.35% of recurrences were detected first by PE and 45.65% by imaging. Conclusions: Bx triggered by STI has the highest PPV. SI has the lowest PPV, but 45.65% of recurrences were diagnosed because of SI alone. Our study suggests that routine SI for at least two years post treatment for HNSCC patients may add to the surveillance value of frequent PE but larger studies are needed to determine the optimal frequency and type of SI modality.
Cost-effectiveness analysis of chemoradiation compared to radiation alone in the treatment of nonmetastatic oropharyngeal cancer.

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Background: Using concurrent chemoradiation (CRT) to treat oropharyngeal cancer (OPC) has increased since 2000. However, there is limited information regarding the cost-effectiveness of CRT compared to radiation alone (RT) especially given the approval of cetuximab (cetux) in 2006. We conducted a cost-effectiveness analysis of 1) platinum-based CRT compared to RT and 2) cetuximab plus RT (cetux+RT) compared to RT to determine the value of CRT over time. Methods: In this retrospective cohort study, we identified non-metastatic OPC patients aged 66 years or older diagnosed between 2000-2011 using the linked Surveillance, Epidemiology and End Results -Medicare dataset. We defined two cohorts based on the diagnosis period: 2000-2005 (Cohort I) and 2006-2011 (Cohort II). Cetux+RT was identified in Cohort II only. We matched the platinum-based CRT and cetux+RT groups to the RT groups using propensity score models that included age, race, marital status, income, Charlson Comorbidity Index and stage at diagnosis. The outcomes were incremental cost, incremental life-year gained (LYG) and incremental cost-effectiveness ratio (ICER) during the 3 years after diagnosis. Costs were estimated from the Medicare perspective and using 2017 USD. Results: 2,646 OPC patients were eligible for the study. The estimated parameters with the corresponding 95% confidence intervals (CI) are shown in the table. Conclusions: From 2000-2005, platinum-based CRT was a cost-effective option compared to RT. From 2006-2011 and compared to RT, platinum-based CRT provided a survival benefit at higher costs while cetux+RT patients incurred higher costs with no survival benefit.

<table>
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<tr>
<th>Cohort / Comparison groups</th>
<th>Incremental cost (95% CI)</th>
<th>Incremental life-year gained (95% CI)</th>
<th>Incremental cost-effectiveness ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>I: Diagnosis year 2000-2005</td>
<td></td>
<td></td>
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<tr>
<td>Platinum-based CRT vs. RT</td>
<td>$18,097 (6,012 to 31,051)</td>
<td>0.26 (0.09 to 0.43)</td>
<td>$70,318 / LYG (21,559 to 213,994)</td>
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<td>II: Diagnosis year 2006-2011</td>
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<tr>
<td>Platinum-based CRT vs. RT</td>
<td>$23,521 (9,734 to 36,332)</td>
<td>0.16 (0.01 to 0.31)</td>
<td>$148,224 / LYG (34,470 to 1,284,469)</td>
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<tr>
<td>Cetux+RT vs. RT</td>
<td>$31,869 (17,694 to 44,959)</td>
<td>-0.13 (-0.30 to 0.05)</td>
<td>Cetux+RT is more expensive with no survival benefit (dominated)</td>
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</table>
Analysis of hydration and antiemetics policies in preventing cisplatin-related gastrointestinal and renal toxicities in low-risk human papillomavirus positive-oropharyngeal cancer (HPV+OPC) patients undergoing chemoradiation in De-ESCALaTE trial.

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Background: The De-ESCALaTE trial confirmed the superiority of cisplatin over cetuximab in combination with radiotherapy for the treatment of low risk human papillomavirus positive oropharyngeal cancer (HPV+OPC). The most common serious adverse events (SAEs) for cisplatin were due to vomiting and nausea, in contrast with oral mucositis and vomiting for concurrent cetuximab. In this study, we examined the efficacy of different hydration and anti-emetic policies in preventing cisplatin-related gastrointestinal and renal toxicities as well as related SAEs in the cisplatin arm of the De-ESCALaTE trial. Methods: This was a post-hoc pre-specified analysis of data collected within the De-ESCALaTE trial including pre-hydration, diuretics, the amount of intravenous (IV) fluids before, during and after chemotherapy, whether oral fluid hydration was advised and type of antiemetic regimen prescribed, if any, after chemotherapy administration, including if a triple antiemetic regimen with a NK1 receptor antagonist, steroids and a serotonin 5-HT3 antagonist was given before and after chemotherapy. The primary outcome was number of SAEs per patient; secondary outcome was number per patient of cisplatin-induced severe toxicity events of interest: nausea, vomiting, dehydration or renal toxicity. Results: 166 (mean age 57 yrs; 132 m, 34 f) patients received cisplatin. Hydration and anti-emetics policies for cisplatin treatment are significantly correlated with the rate of SAEs and acute severe nausea, vomiting, dehydration or renal toxicities. Using stepwise backwards multivariable ordinal logistic regression in the presence of baseline characteristics, use of a triple anti-emetics regimen (OR 0.41, p = 0.032) and 2.5 to 3L IV fluids given before and during cisplatin chemotherapy (OR 0.161, p = 0.009) as well as oral fluids advised post chemotherapy (OR 0.365, p = 0.03) were associated with a significantly lower incidence of SAEs and severe toxicities of interest. We will also present data on relative cost-effectiveness of the different regimens. Conclusions: Based on our results, we recommend the use of a triple anti-emetic regimen, adequate hydration of 2.5-3L before and during chemotherapy as well as advising patients to take oral fluids advised to reduce cisplatin toxicities related to nausea, vomiting, dehydration and/or renal injury. Clinical trial information: ISRCTN33522080.
Randomized phase II study with or without induction chemotherapy combined with accelerated high dose radiotherapy and cetuximab in locally advanced unresectable HPV positive squamous cell carcinoma of the head and neck.

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Background: Concomitant chemoradiotherapy (CT/RT) is the standard treatment for locally advanced non-resectable squamous cell carcinoma of the head and neck. Acute side effects can be serious and late effects important. Patients with HPV+ tumors carry a better prognosis than other patients. De-escalation studies are explored with respect to RT, dose, fractionation, target volumes, adjuvant pharmacotherapy, with encouraging results. However, several patients still recur locoregionally, also in high dose RT volumes. Some patients have distant metastases, often with massive tumor burden and late during follow up (FU).

Purpose of the study: 1. To evaluate the effect of induction chemotherapy (IC) on (a) progression free survival (b) distant metastases as first site of failure (c) locoregional failure (d) pattern of tumor response, spatial and timely, exploring the possibility to reduce RT dose and/or target volume(s) in future protocols. 2. to address the impact of high dose RT for bulky disease, T3/T4 given concurrent with cetuximab (E).

Methods: Patients had previously untreated stage III/IV (>80% st IV; TNM 7th), MO disease, WHO 0-1, unresectable squamous cell carcinoma of the head and neck, HPV positive as evaluated with p16 and/or PCR. Pts were randomised between 2 arms. Pts in arm A were scheduled for 2 cycles of TPF : T (docetaxel) 75 mg/m2 day 1, P (cisplatin) 75 mg/m2 day 1 and F (fluorouracil) 1000 mg/m2 over 24 hours day 1-4. RT was delivered with IMRT to all pts: 68 Gy in 6 weeks for T1/T2 tumors, 76 Gy in 6.5 weeks for T3/T4 tumors with E given one week before and weekly during RT. Tumor response was evaluated according to RECIST with CT, MRI or PET/CT after IC, at 6-8 weeks, 1 and 2 years FU. Results: From January 2011 to February 2016, 152 consecutive pts were enrolled, 77 in arm A. All pts had oropharyngeal cancer. In arm A, 7 pts had CR after TPF, 19 had PR out of 36 evaluable pts. At 2 years FU 70/77 pts (91%) were alive in arm A, 69/75 (92%) in arm B. Distant metastases as first site of failure was 3 (3.9%) in arm A and 7 (9.3%) in arm B. Adverse events grade 3-4, ever registered, were seen in 71 pts in arm A and 63 in arm B, were transient, most often related to RT.

Conclusions: Survival and locoregional control at 2 years was high and similar in both arms. Distant metastases as first site of failure was more than doubled in arm B, not having induction chemotherapy (IC). Clinical trial information: EudraCT number: 2009-013438-26.
Impact of antiviral prophylaxis in HSV positive patients treated with concurrent chemoradiotherapy for head and neck cancer.

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Background: Chemoradiotherapy used for the treatment of locally advanced head and neck cancer (HNC) causes a high incidence of mucositis that may be accentuated by a reactivation of herpes simplex virus (HSV). To date, no study has evaluated the impact of antivirals used as prophylaxis to prevent mucositis or their severity. Methods: This is a retrospective observational study including patients who received at least one cycle of concurrent chemoradiotherapy for the treatment of head and neck cancer between January 2014 and June 2017 at the Centre hospitalier de l’Université de Montréal (CHUM). HSV negative patients were excluded. After approval by the IRB, we compared the incidence and severity of mucositis in HSV positive patients who started an antiviral prophylaxis before cycle 1 or 2 (prophylaxis group) to HSV+/unknown HSV patients who did not receive antiviral prophylaxis (control group). Emergency visits and hospitalizations related to mucositis were collected. Mucositis were assessed regularly by radiation oncologists during the treatment. Results: Of 482 patients who received concurrent chemoradiotherapy for HNC, 75 were HSV negative and 407 were included in this study. In the group with (n = 94) and without prophylaxis (n = 313), patients received carboplatin and 5-FU (77% vs 62%) and cisplatin (23% vs 38%) with concurrent radiation respectively. The rate of all grade mucositis in patients with and without prophylaxis (99% vs 96%; p = 0.19) was not statistically significant. The rate of grade 3 and 4 mucositis (42% vs 49%; p = 0.29), the rate of emergency visit (29% vs 28%; p = 0.91) and hospitalization (9% vs 8%; p = 0.80) were not statistically significant between each group. However, in a subgroup of patient receiving carboplatin and 5-FU, antiviral prophylaxis seems to decrease significantly the rate of grade 3 (49% vs 63%; p = 0.04). Conclusions: The addition of antiviral prophylaxis in HSV positive in patients undergoing concurrent chemoradiotherapy for locally advanced HNC didn’t decrease the rate of all grade mucositis. In the subgroup of patients receiving carboplatin and 5-FU mainly of oropharynx origin, HSV prophylaxis decreased the severity of mucositis.
A retrospective analysis of cisplatin dosing strategies when used with radiation on outcomes in head and neck squamous cell carcinoma of the oropharynx.

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Background: Cis is the gold standard radiosensitizer for CRT to treat head and neck cancer. Prospective trials have required that cis be administered early in the week (Mon/Tues) to optimize radiosensitization without evidence to support this practice. This retrospective analysis considers the impact of cis day of week (DOW) administration and other variables on OPSCC pt outcomes.

Methods: We reviewed OPSCC cases treated with primary CRT at our center. Pts treated with non-cis or induction chemotherapy were excluded. Data collected includes age, DOW (Mon/Tues vs Wed/Thurs/Fri), smoking status, total dose (TD) of cis ($\leq 200\text{mg/m}^2$ vs $> 200\text{mg/m}^2$), single dose (SiD) [100\text{mg/m}^2 \times 1 \text{ day}] vs split dose (SpD) [50\text{mg/m}^2 \times 2 \text{ days}] administration, T stage (0-2b vs 2c-3), N stage (0-2b vs 2c-3), overall survival (OS) (from start of RT), local/regional/distant failure, KPS and HPV/p16 status. Univariate Cox proportional hazards regression was used to analyze OS and multivariate Cox proportional hazard model investigated the relationships between OS and cis dosing variables while controlling for other factors. Results: 745 pts with OPSCC were treated with CRT from 7/31/2001-2/7/2014. 459 used cis based regimens and were included. Median age at start of RT was 55. 311 pts (67.8%) received SpD, 124 (27%) received SiD, 8 (1.7%) received weekly cis and 16 (3.5) received mixed cycles. 269 (58.6%) received $\leq 200\text{mg/m}^2$. 232 (50.5%) were HPV/p16 positive, 40 (8.7%) were negative and 187 (40.7%) were unknown. Median f/u was 7.9yrs (1.8m -18.9yrs). There were 92 (20%) deaths, and 75 (16.4%) recurrences (local/regional and distant) with 44 (9.6%) competing events. In univariate analysis, age, N stage, T stage, KPS and HPV/p16 status were significantly associated with OS, while DOW, TD, and SiD/SpD were not. In multivariate analysis (MVA), none of the associations between cis dosing and OS were significant (although MVA was limited by low number of events and total variables included).

Conclusions: This retrospective analysis suggests that the DOW cis is given has no impact upon CRT outcomes for OPSCC pts. SpD cis represents an alternative administration approach.
Outcomes of postoperative treatment with concurrent chemoradiotherapy (CRT) in high risk resected oral cavity squamous cell carcinoma (OCSCC): A multi-institutional collaboration.

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Background: Adjuvant CRT with high-dose cisplatin remains standard treatment for OCSCC with high risk pathologic features of positive surgical margins (SM+) and/or extranodal extension (ENE). High-dose cisplatin is associated with significant toxicities, and alternative dosing schedules or treatments are used. We evaluated outcomes associated with different systemic therapies concurrent with RT and the effect of cumulative dosing of cisplatin. Methods: An IRB-approved collaborative database of patients (pts) with primary OCSCC (Stage I-IVB AJCC 7th edition) treated with primary surgical resection between 1/1/2005 and 1/1/2015 with or without adjuvant therapy was established from 6 academic institutions. Pts were categorized by systemic therapy received, and resultant groups compared for demographic data, pathologic features, and outcomes by t-test and Chi-squared tests. Kaplan-Meier curves, log-rank p-values, and multivariate analysis (MVA) for disease free survival (DFS) and freedom from metastatic disease (DM). Results: From a total sample size of 1282 pts, 196 pts were identified with high risk features (SM+, ENE) who were treated with adjuvant CRT. Median age was 56 years, 63.3% of pts were men, 81.1% were Caucasian, 70.9% had significant tobacco history. 35.7% of pts had SM+, 82.7% ENE, 65.3% with perineural invasion (PNI), 49% had lymphovascular space invasion (LVSI). There was a trend associating higher cisplatin dose delivered with improved locoregional control, DM, and overall survival (OS) (p-values 0.131, 0.084, and 0.187, respectively). DFS was significantly better with higher cisplatin dose (HR = 0.95 per 100 mg/m² increase in cisplatin). Administration schedule of cisplatin (weekly versus high-dose) was not significantly associated with DFS. On MVA, PNI and higher cisplatin dose remained statistically significant for DFS (p < 0.001 and 0.007). Median OS by cisplatin dose was 10.5 (< 200 mg/m²) vs. 20.8 months (> = 200 mg/m²). Conclusions: This multi-institutional analysis demonstrated cumulative cisplatin dose > = 200 mg/m² was associated with improved DFS in high risk resected OCSCC pts. It remains unclear by this analysis if cisplatin administration schedule has any prognostic implication. Further study is warranted to elucidate the optimal cisplatin schedule for this population.
Influence of tumor size and Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline on patient (pt) outcomes in lenvatinib-treated radioiodine-refractory differentiated thyroid cancer (RR-DTC).

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Background: In SELECT, lenvatinib significantly improved progression-free survival (PFS) of pts with RR-DTC versus placebo (18.3 vs 3.6 months; hazard ratio [HR]: 0.21 [99% CI: 0.14, 0.31]; P<0.001). Here we examine the treatment of RR-DTC with lenvatinib in relation to tumor size (sum of all targeted lesions) and ECOG PS.

Methods: In this post hoc analysis of SELECT with pts randomized to receive lenvatinib, Kaplan-Meier estimates of time to ECOG PS ≥2 were calculated for subgroups of pts according to baseline ECOG PS or tumor size. Objective response rate (ORR) and Kaplan-Meier estimates of overall survival (OS) and PFS according to ECOG PS (0 or 1) at baseline were calculated. Correlations between ECOG PS at baseline (0 or 1) and maximum tumor shrinkage were calculated using one-way analysis of variance.

Results: Pts with ECOG PS 0 or 1 at baseline had similar demographic and disease characteristics. ORR was 78.5% and 51.0% for pts with ECOG PS 0 and 1 at baseline, respectively (odds ratio [95% CI]: 3.508 [2.018, 6.097]). Mean maximum percent decrease in tumor size was significantly greater in pts with baseline ECOG PS 0 (-46.13%) versus pts with ECOG PS 1 (-37.16%; P=0.0017). For pts with ECOG PS 1 at baseline, time to ECOG PS ≥2 was numerically shorter with tumor size >60 mm versus tumor size ≤60 mm (HR [95% CI]: 1.450 [0.708, 2.967]). Additional results are summarized in the table.

Conclusions: Among pts with RR-DTC, PFS, OS, ORR, and time to ECOG ≥2 were generally better for patients with lower ECOG PS or smaller tumor size at baseline. These results may indicate that it is beneficial to start lenvatinib in pts with RR-DTC early, before ECOG PS worsens and tumor size increases. Clinical trial information: NCT01321554.

<table>
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<th>Baseline population</th>
<th>Baseline ECOG PS</th>
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<td>Tumor size* ≤ 35 mm</td>
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<td>PFS</td>
<td>ECOG PS 0 or 1</td>
<td>104</td>
<td>22.1</td>
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*Sum of all targeted lesions at baseline.
A randomized phase II study of pembrolizumab with or without radiation in patients with recurrent or metastatic adenoid cystic carcinoma.

Jonathan Daniel Schoenfeld, Umair Mahmood, Yu-Hui Chen, Raymond H. Mak, Jochen H. Lorch, Glenn J. Hanna, Vishwajith Sridharan, Andrew Bang, Paul Martin Busse, Henning Willers, Harvey J. Mamon, Hyung-Jin Yoo, Sara I. Pai, Lori J. Wirth, Robert I. Haddad, Nicole Grace Chau; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Center, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Brigham Womens Hospital/Dana Farber Cancer Institute, Boston, MA; Harvard Medical School, Boston, MA; Harvard Medical Faculty Physicians, Boston, MA; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard University, Boston, MA; Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA

Background: Adenoid cystic carcinoma (ACC) is a salivary gland malignancy characterized by a high rate of distant recurrence. Systemic therapy has generally failed to produce durable benefit. Radiation (RT) is used for localized disease and as directed treatment for metastases. Here, we report the safety and efficacy of pembrolizumab (pembro) administered with or without hypofractionated RT in a phase II randomized study. Methods: Eligible patients (pts) had recurrent or metastatic ACC with evidence of progressive disease (PD) within the last 12 mos and $\geq$1 measurable non-CNS lesion, along with 1-5 additional lesions deemed appropriate for RT to 30 Gy in 5 fractions. Pts were randomized to pembro alone (200 mg IV q3 weeks) or in combination with RT given within 7 days of cycle 1, day 1. The primary endpoint was objective response rate (ORR) outside the RT field by RECIST 1.1. Using a parallel two-stage design, if $\geq$1 response out of 10 was observed in either arm, 10 more pts would be enrolled to that arm. If $\geq$3 responded, the null hypothesis (ORR=5%) would be rejected in favor of a 25% ORR. Predefined secondary endpoints included progression free survival (PFS) and toxicity. Analyses of tumor growth rate (TGR) excluding RT lesions and immune biomarkers were exploratory. Results: Ten pts per arm were randomized into the trial's first stage with median age 65 (45-79). No objective responses were seen. Stable disease (SD) was observed in 13 pts; 6 had PD as best response, 1 was unevaluable. Median PFS was 7 mos 95% CI (3 - 13 mos), with 9 pts without progression at 6 mos. 3 pts remain on study treatment (range 8-11 mos). In pts with SD, TGR decreased by $>25\%$ in 7 of 12 pts and by $>75\%$ in 4 pts. There was no difference in likelihood of SD or PFS between arms. Treatment related AEs (TRAEs) occurred in 18 pts but there were no G3-5 TRAEs. Among 8 biopsies analyzed, PD-L1+ tumor/immune cells ranged from 12-52%. Conclusions: Pembro alone or with hypofractionated RT was well tolerated. We observed no objective responses, but 65% of pts with PD prior to study entry achieved SD, the majority with decreased TGR, and 15% had prolonged SD. Additional strategies are needed to further delay progression and effect response. Clinical trial information: NCT03087019.
NISCAHN: A phase II, multicenter nonrandomized trial aiming at evaluating nivolumab (N) in two cohorts of patients (pts) with recurrent/metastatic (R/M) salivary gland carcinoma of the head and neck (SGCHN), on behalf of the Unicancer Head & Neck Group.

Jerome Fayette, Caroline Even, Laurence Digue, Lionel Geoffrois, Frederic Rolland, Didier Cupissol, Joel Guigay, Christophe Le Tourneau, Anne-Francoise Dillies, Sylvie Zanetta, Laurence Bozec Lemoal, Christian Borel, Aurélie Guynennon, Sophie Couchon-Thaunat, Valerie Costes, Isabelle Jallut, Jessy Delaye, Audrey Lardy-Cleaud, Sylvie Chabaud; Centre Léon Bérard, Medical Oncology, Lyon, France; Gustave Roussy, Villejuif, France; CHU Saint Andre, Bordeaux, France; Institut de Cancérologie de Lorraine, Vandoeuvre-Lès-Nancy, France; Institut de Cancérologie de l’Ouest, Department of Medical Oncology, St Herblain, France; Institut du Cancer de Montpellier, Montpellier, France; Department of Medical Oncology, Antoine Lacassagne Comprehensive Cancer Centre, FU OncoAge, Université Côte d’Azur, Nice, France; Institut Curie, Paris, France; Centre Jean Perrin, Clermont-Ferrand, France; Centre Georges-François Leclerc, Dijon, France; Institut Curie-Hôpital René Huguenin, Saint-Cloud, France; Centre Paul Strauss, Strasbourg, France; Centre Léon Bérard, Lyon, France; CHU Hôpital Gui de Chauliac, Montpellier, REFCOR, Paris, France; UNICANCER, Paris, France; Centre Léon-Bérard, Lyon, France; Statistician - GINECO - Centre Léon-Bérard, Lyon, France

Background: SGCHN are rare tumors including adenoid cystic carcinoma (ACC) and non-ACC, with no standard systemic treatment for R/M pts. We evaluated N monotherapy in R/M SGCHN pts. Methods: R/M SGCHN pts (ACC or non-ACC) not eligible to local treatment and with centrally confirmed RECIST 1.1 disease progression over the last 6 months were enrolled and received N 3 mg/kg IV, every 2 weeks for a maximum of 12 months (mo). Possibility was given to re-start N in case of progression during the 2-year follow-up phase. Primary endpoint was 6-mo non-progression Rate (NPR6m) as per RECIST 1.1. Secondary endpoints included ORR, PFS, OS, and safety. Considering that N would be uninteresting if NPR6m ≤ 20% and promising if ≥ 40% and using a Fleming’s single-stage design (α: 5% unilateral, power: 90%), at least 14 successes/42 evaluable pts were required for each cohort to be positive. Results: 46 ACC and 52 Non-ACC pts (median age 61 yrs (range 29-81), 43.9% female, 55.1% PS1 and 2.0% PS2) were enrolled and received at least one dose of N. Median treatment duration was 5.5 mo (ACC) and 3.3 (Non-ACC). Median FU was 10.8 mo (ACC) and 8.3 mo (Non-ACC). 95 patients were evaluable for the primary endpoint. NPR6m was 15/45 pts (33.3%, 90%CI:18.8;46.6) and 7/50 pts (14.0%, 90%CI:6.8;24.7) for ACC and non-ACC pts respectively. 4 (8.7%) partial responses (PR) and 26 (56.5%) stable diseases (SD) were observed in ACC cohort while 2 (3.8%) PR and 22 (42.3%) SD were observed in non-ACC. Median PFS was 4.9 mo (95%CI = 3.4;5.6) in ACC pts and 1.8 mo (95%CI = 1.7;3.5) in non-ACC pts. The most common related adverse events (AE) (> 10% by cohort) were asthenia, hyperthyroidism, diarrhea, rash, pruritus and hypothyroidism. 7/98 pts (7.1%) presented at least one related AE Grade 3-4 (mainly hepatic) and 9 pts (9.2%) prematurely discontinued Nivolumab due to toxicity. Conclusions: Limited efficacy was observed with N in R/M SGCHN pts. N in combination might be of interest and deserves exploration in ACC pts. Clinical trial information: NCT03132038.
A phase II trial cohort of nivolumab plus ipilimumab in patients (Pts) with recurrent/metastatic adenoid cystic carcinoma (R/M ACC).

Vatche Tchekmedyian, Eric Jeffrey Sherman, Lara Dunn, James Vincent Fetten, Loren S. Michel, Anuja Kriplani, Luc Morris, Irina Ostrovnaya, Nora Katabi, Sofia Haque, Crystal Tran, Julian Azar, David G. Pfister, Alan Loh Ho; Memorial Sloan Kettering Cancer Center, NY, NY; Memorial Sloan Kettering Cancer Center, New York, NY; Washington University School of Medicine, St. Louis, MO; Mount Sinai School of Medicine, New York, NY; Memorial Sloan-Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York City, NY

Background: R/M ACC is a malignant neoplasm most commonly of salivary gland origin with no standard treatment. The impact of combined PD-1/CTLA-4 checkpoint blockade in R/M ACC is unknown.

Methods: In a two-stage minimax phase II trial, pts with progressive R/M ACC (non-salivary primaries allowed) were enrolled and treated with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (1 cycle = 6 weeks). Imaging, using RECIST v1.1 response assessment, was scheduled to be performed approximately every 12 weeks. The primary endpoint was overall response rate (ORR = complete response [CR]+partial response [PR]) per RECIST v1.1. To detect a difference between an unacceptable ORR of 5% and a desirable ORR of 20% (one-sided type I error of 10%, power of 90%), at least 1 in the first 18 pts required an observed response. At least 4 responses of 32 total pts were needed to meet the primary endpoint. Treatment beyond progression of disease (PD) was allowed at the discretion of the investigator. A second cohort of pts with non-ACC salivary cancer is still accruing for separate analysis.

Results: From 6/12/2017-6/20/2018, 32 pts were enrolled and evaluable for the primary endpoint. There was 1 confirmed PR in the first 18 pts, therefore enrollment of the second stage continued. ORR was 6% (2/32). One additional pt had an unconfirmed PR (-31% regression before CNS PD). For best overall response, there were 2 PRs, 15 SD, and 11 PD. Four pts never reached a first disease assessment: 3 due to death from clinical PD and 1 was removed for toxicity. Six pts discontinued the trial for toxicities: Grade 4 (G4) neutropenia/sepsis and G3 adrenal insufficiency (1), G2 hypophysitis (2), G3 arthritis > 7 days (1), G3 colitis (1), and G3 hepatitis/G4 creatinine kinase (CK) elevation (1)). The 2 confirmed PRs consisted of -73.1% and -58.4% regressions, with a duration of therapy of 18.4 and 7.8 months, respectively (treatment ongoing for both). Conclusions: The study did not meet its primary endpoint, though the responses observed were dramatic. Paired biopsy and peripheral blood samples will be analyzed to elucidate insights into mechanisms of response and resistance to dual checkpoint blockade. Clinical trial information: NCT03172624.
Development and validation of a prediction-score model for distant metastases in major salivary gland carcinoma.

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Background: We developed and validated a prediction-score for distant metastases (DM) in major salivary gland carcinoma (SGC). Methods: Patients with SGC treated with curative-intent surgery +/- postoperative radiation therapy (PORT) at 4 tertiary cancer centers were divided into discovery (institution A&B) and validation (institution C&D) cohorts. Multivariable analysis using competing risk regression was used to identify predictors of DM in the discovery cohort and create a prediction score. The optimal score cut-off for high vs low-DM risk was determined using a minimal p-value approach. The results were subsequently evaluated in the validation cohort. The cumulative incidence and Kaplan-Meier methods were used to analyze DM and overall survival (OS), respectively. Results: Overall, 1035 patients were included (Table). In the discovery cohort, DM predictors (risk score coefficient) were: positive margin (0.6), pT3-4 (0.7), pN+ (0.7), lymphovascular invasion (LVI; 0.8), and high risk histology* (1.2). High DM-risk SGC was defined by sum of coefficients greater than 2. In the discovery cohort, the 5-year cumulative incidence of DM for high vs low risk SGC was 50% vs 8%; p < 0.01; these results were similar in the validation cohort (44% vs 4% at 5 years; p < 0.01). In the combined cohorts, this model predicted distant-only failure (40% vs 6%, p < 0.01) and late (> 2yr post surgery) DM (22% vs 4%; p < 0.01). Patients with high DM-risk SGC had an increased incidence of DM in the subgroup receiving PORT (46% vs 8%; p < 0.01) or concurrent chemotherapy (71% vs 34%; p < 0.01). Conclusions: This validated prediction score model may be used to identify SGC patients at increased risk for DM and select those who may benefit from prospective evaluation of treatment intensification and/or surveillance strategies. Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Discovery (n=619)</th>
<th>Validation (n=416)</th>
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<tbody>
<tr>
<td>Median follow up, yrs</td>
<td>5.3</td>
<td>5.0</td>
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<tr>
<td>Median age, yrs</td>
<td>56</td>
<td>57</td>
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<tr>
<td>Parotid subsite</td>
<td>510 (84)</td>
<td>329 (79)</td>
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<tr>
<td>LVI</td>
<td>92 (15)</td>
<td>47 (11)</td>
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<tr>
<td>Positive margin</td>
<td>210 (35)</td>
<td>158 (38)</td>
<td>0.6</td>
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<tr>
<td>High risk histology*</td>
<td>372 (60)</td>
<td>224 (54)</td>
<td>0.01</td>
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<tr>
<td>pT3-4</td>
<td>224 (36)</td>
<td>129 (31)</td>
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<tr>
<td>pN+</td>
<td>145 (24)</td>
<td>89 (21)</td>
<td>0.45</td>
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<td>PORT</td>
<td>475 (76)</td>
<td>285 (69)</td>
<td>&lt;0.01</td>
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<td>5-yr DM (95% CI)</td>
<td>20% (17-24%)</td>
<td>14% (11-18%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*High risk histology: adenoid cystic carcinoma, salivary duct carcinoma, carcinoma, undifferentiated carcinoma, grade (G) 2-3 adenocarcinoma, G2-3 mucoepidermoid carcinoma, G2-3 carcinoma ex-pleomorphic adenoma, other G3 histology.
PROSPERO: A study to determine the utility of focused genomic profiling to guide selection of drug therapy in salivary gland cancer.

Samuel Rack, Yonghan Li, Craig McKay, Andrew Wallace, Robert Metcalf; University of Manchester, Manchester, United Kingdom; The Christie NHS FT, Manchester, United Kingdom; Manchester University NHS FT, Manchester, United Kingdom; Cancer Research UK Manchester Institute, Manchester, United Kingdom

Background: For most patients with recurrent or metastatic salivary gland cancer (RM-SGC), there are no standard therapies. Many patients undergo genomic profiling to guide selection of targeted therapy. The MSK-IMPACT study applied a 468 gene next generation sequencing (NGS) panel, identifying actionable mutations in 34/114 patients (30%) with RM-SGC. Minimising cost will facilitate application within publically funded healthcare systems. We therefore sought to determine the utility of genomic profiling using a focused 24 gene targeted NGS panel to identify actionable mutations in RM-SGC with a sub-group analysis in adenoid cystic carcinoma (ACC) and non-ACC sub-types. Methods: From January 2017 to 2018, 125 patients with RM-SGC provided informed consent to an ethically approved study. Clinical and demographic characteristics were collected. DNA was extracted from FFPE samples and analysed using Qiagen GeneRead DNAseq Targeted Panel V2 in the Manchester Centre for Genomic Medicine Diagnostic Laboratory, an NHS clinically accredited lab. A custom bioinformatic pipeline was validated to detect single nucleotide variants and indels (<40bp) to 5% mutant allele frequency. Alterations were categorised following American College of Medical Genetics guidelines and Association for Molecular Pathology tiering. Results: DNA from 101 tumours (69 major, 32 minor salivary gland) was sequenced with 95% coverage at >350x read depth over the target enrichment. 65 patients had adenoid cystic carcinoma (ACC) and 36 had non-ACC SGC. Median age was 55 years (range 18-80). 43 actionable alterations were identified in 33 patients within the following genes: TP53 (21%), PIK3CA (8%), ERBB2 (6%), PTEN (3%), BRAF (2%), EGFR (T790M) (1%), and AKT1 (1%). Targeted therapy was selected based on genomic findings in 12% of these patients. In ACC patients, actionable alterations were seen in 25% compared with 55% of non-ACC patients (9 adenocarcinoma, 5 salivary duct carcinoma, 3 carcinoma ex pleomorphic adenoma, 2 mucoepidermoid carcinoma and 1 myoepithelial carcinoma). Conclusions: This study identified actionable alterations in 33% of SGC patients using focused genomic profiling, demonstrating comparable utility to larger research panels. This focussed panel is being expanded to include emerging biomarkers such as NOTCH gene mutations, with NOTCH inhibitors currently in trials in ACC. Greater access to basket studies incorporating therapies matched to genomic alterations will maximise the clinical utility of this approach.
Genomic landscape of FNAs positive for medullary thyroid cancer (MTC) and potential impact on systemic therapy.

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Background: Systemic therapies targeting specific genomic alterations in advanced MTC are available or under investigation. The Afirma Genomic Sequencing Classifier (GSC) uses RNA sequencing to assess FNA specimens from cytologically indeterminate thyroid nodules, which are also tested for specific molecular aberrations associated with thyroid cancer via a suite of highly accurate malignancy classifiers. This suite can be applied independently to Bethesda V/VI nodules. The Afirma Xpression Atlas (XA) is an additional test that can be combined with Afirma GSC to report nucleotide variants and fusions across 511 cancer-associated genes. Here we report the prevalence and genomic landscape of MTC classifier positive (MTC+) FNA samples.

Methods: All Afirma GSC and malignancy classifier tests run in the Veracyte Clinical Laboratory between July 2017 and January 2019 were deidentified and examined for MTC+ cases. Afirma XA was run on all such cases, and all variants and fusions were tabulated.

Results: Examination of 29,895 FNAs revealed 90 MTC cases. Of 22,793 Bethesda III cases, 32 (0.14%) were MTC+. Of 5,491 Bethesda IV cases, 33 (0.60%) were MTC+. Provider-ordered testing was done on an additional 16 and 9 MTC cases from Bethesda V and VI nodules, respectively. 58% of all MTC+ samples harbored a \( RET \) variant (+/- others), 9% contained a \( KRAS \) variant (+/- others), 6% included an \( HRAS \) variant, 1% had a \( BRAF \) fusion, 1% demonstrated other fusions, and 26% held no variant/fusion.

Conclusions: In our cohort, Afirma XA identified a variant or fusion in 74% of MTC+ FNAs. Currently approved or investigational therapies exist for cancers with \( RET, BRAF \) and \( HRAS \) alterations, suggesting that 64% of our series might be eligible for treatment based on genomic information from FNA. In advanced MTC, noninvasive FNA sample collection at the time of diagnosis may ultimately impact on targeted therapy selection, with the option to repeat FNA testing should the disease progress. Future studies may investigate how finding a genomic alteration by FNA can inform the management of MTC and, in the case of progressive disease, improve our understanding of the mechanisms of disease progression and drug resistance.
Background: ATC is a rare and aggressive cancer with very limited treatment options. The thyroid is one of the most immunogenic organs in the body and PD-L1 is commonly expressed on ATC tumor cells and PD-1 in the inflammatory cells in the ATC microenvironment. However, antibodies to PD-1 as single agents have a poor record in this disease. Methods: This study evaluated the addition of T (75 mg every 4 weeks up to 4 doses) to D (1500 mg every 4 weeks). SBRT 9Gy × 3 fractions was given within the first 2 weeks of treatment to produce an "abscopal" effect. Major inclusion criteria: Metastatic ATC; ECOG PS 0-2; No prior immunotherapy; Last anti-cancer treatment > 7 days prior to starting study. Primary objective 1-year overall survival with target of ≥ 2 out of 12 patients. Results: 12 patients were accrued. Male – 50%; Median PS 1; Median Age – 71 (49-82); Prior radiation to neck (75%); Prior chemotherapy (75%). MSI-High was noted in 2/11 subjects. BRAF V600E mutation in 3/12 subjects. There were 0 confirmed responses and only 1 subject with SD for 4 cycles or longer. Median time on treatment was 11 weeks (1-28+ weeks). MSI status did not affect treatment response. MSI-High patients were on treatment before progression for 8-14 weeks. Median overall survival was 14.5 weeks with only one person alive past 1 year. Neither the presence of a BRAF or p53 mutation appeared to affect either outcome. Conclusions: T/D with SBRT was not active in metastatic ATC. Future studies looking at other novel immunotherapy combinations in ATC should be evaluated. Biopsies done on study are being analyzed. Clinical trial information: NCT03122496.
A multicenter, randomized, double-blind, placebo-controlled phase III study of anlotinib or placebo in combination with gemcitabine and cisplatin (GP) as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC).

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Background: GP is the standard first-line chemotherapy for R/M NPC. However, the outcome of patients who are refractory to first-line chemotherapy is poor. There remains an unmet need for more effective first-line treatment. Overexpression of vascular endothelial growth factor (VEGF) is common in NPC and the higher expression is related to lower OS. This feature makes NPC potentially suitable for antiangiogenic treatment. Anlotinib is a novel multitarget tyrosine kinase inhibitor that targets VEGFR 1 to 3, fibroblast growth factor receptor 1 to 4, and platelet-derived growth factor receptor α and β. Our phase I study of anlotinib in R/M NPC patients who failed from standard treatment had shown a manageable safety profile and promising antitumor activity with an ORR of 25%. This phase 3 trial aims to compare the efficacy and safety of anlotinib versus placebo in combination with GP in patients with R/M NPC in the first-line setting. Methods: Key eligibility criteria of this study are that the patient has metastatic disease after curative radiotherapy, or is primarily metastatic; has an ECOG PS of 0 or 1; has adequate organ function; and has at least 1 measurable lesion according to RECIST 1.1. Eligible patients will be randomized in a 1:1 ratio to receive intravenous gemcitabine at 1 g/m² on days 1 and 8, cisplatin at 75 mg/m² on day 1, plus anlotinib or placebo 12 mg daily orally on days 1–14 every 3 weeks for a maximum of 6 cycles followed by anlotinib or placebo 12 mg daily on days 1–14 every 3 weeks as maintenance therapy. The primary endpoint is PFS. Secondary endpoints include OS, ORR, quality of life and safety profile. Independent Data Monitoring Committee and Independent Review Committee will be used in this study. We assume that the median PFS will be 10 mos in anlotinib group and 7 mos in placebo group. To detect a 3-month improvement of PFS in anlotinib group at a two-sided significant level of 0.05 and power of 0.8, allowing for a dropout rate of 10%, a total of 336 patients will be enrolled. From August 2018, 58 patients have been enrolled. Clinical trial information: NCT03601975.
KEYNOTE-689: Phase 3 study of adjuvant and neoadjuvant pembrolizumab combined with standard of care (SOC) in patients with resectable, locally advanced head and neck squamous cell carcinoma.

Ravindra Uppaluri, Nancy Y. Lee, William Westra, Ezra E.W. Cohen, Robert I. Haddad, Stephane Temam, Christophe Le Tourneau, Rebecca Chennock, Sufia Safina, Arkadiy Klochikhin, Amichay Meirovitz, Irene Brañà, Joy Yang Ge, Ramona F. Swaby, Behzad Bidadi, Douglas Adkins; Dana-Farber Cancer Institute and Brigham and Women’s Hospital, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Icahn School of Medicine, New York, NY; University of California, San Diego, La Jolla, CA; Gustave Roussy, Villejuif, France; Institut Curie, Paris, France; Washington University School of Medicine, St. Louis, MO; Republican Dispensary of Tatarstan MoH, Kazan, Russian Federation; Yaroslavl Regional Clinical Oncology, Ulitsa Chkalov, Yaroslavl, Russian Federation; Hadassah-Hebrew University Medical Center, Jerusalem, Israel; Hospital Vall d’Hebron, Barcelona, Spain; Merck & Co., Inc., Kenilworth, NJ

**Background:** Evidence of efficacy and pathological response at the time of surgery was reported in two phase 2 studies (NCT02296684 and NCT02641093) of preoperative pembrolizumab in patients with high-risk, resectable, locally advanced (LA) head and neck squamous cell carcinoma (HNSCC). The randomized, open-label, phase 3 KEYNOTE-689 trial (NCT03765918) will evaluate efficacy and safety of pembrolizumab as neoadjuvant and adjuvant therapy in combination with SOC (radiotherapy ± cisplatin) in patients with previously untreated, resectable LA HNSCC. **Methods:** Patients with newly diagnosed LA HNSCC will be randomly assigned 1:1 to two treatment arms. Patients in arm A will receive neoadjuvant pembrolizumab (200 mg Q3W for two cycles) followed by surgical resection then SOC plus adjuvant pembrolizumab (15 cycles). Patients in arm B will undergo only surgical resection followed by adjuvant SOC. Eligibility criteria will include age ≥18 years; newly diagnosed, resectable, stage III/IVA HNSCC (AJCC Cancer Staging Manual, 8th edition); and ECOG performance status 0-1. Randomization will be stratified by primary tumor site (oropharynx/oral cavity vs larynx vs hypopharynx), tumor stage (III vs IVA), and HPV p16 status (oropharynx p16 positive vs oropharynx p16 negative or larynx/hypopharynx/oral cavity). Treatment will continue until disease progression, unacceptable toxicity, or decision to withdraw. Patients in arm A will undergo the first radiologic imaging assessment after two cycles of neoadjuvant pembrolizumab and before surgery. In both arms, postoperative imaging will be performed 12 weeks after SOC, then every 3 months until the end of year 3, and then every 6 months until the end of year 5. Dual primary end points are major pathological response, defined as ≤10% invasive squamous cell carcinoma within resected primary tumor and sampled regional lymph nodes per blinded central pathology, and event-free survival. Secondary end points include overall survival, pathological complete response, and safety and tolerability. Recruitment is ongoing and will continue until ~600 patients are enrolled. Clinical trial information: NCT03765918.
EACH: A randomised phase II study evaluating the safety and anti-tumour activity of the combination of avelumab and cetuximab relative to avelumab monotherapy in recurrent/metastatic head and neck squamous cell cancer.

Martin David Forster, Joseph J. Sacco, Anthony Hee Kong, Graham Wheeler, Sharon Forsyth, Reshma Bhat, Kameka Blair, Helen Lowe, Victoria J Spanswick, Leah Ensell, John A. Hartley, Laura White; University College London Hospitals, London, United Kingdom; Clatterbridge Cancer Centre, Merseyside, United Kingdom; University of Birmingham, Birmingham, United Kingdom; Cancer Research UK & University College London Cancer Trials Centre, London, United Kingdom; Cancer Research UK & UCL Cancer Trials Centre, London, United Kingdom; University College London Hospitals NHS Foundation Trust, London, United Kingdom; University College London Cancer Institute, London, United Kingdom; University College London, London, United Kingdom

Background: Patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) have low response rates to licensed second line therapies, including PD-1 inhibitors nivolumab and pembrolizumab, and represent an area of unmet clinical need. The chimeric IgG1 epithelial growth factor receptor (EGFR) monoclonal antibody cetuximab potentiates the activity of radiotherapy in locally advanced HNSCC and chemotherapy in R/M HNSCC and is also licensed with modest activity as a single agent. Cetuximab initiates Natural Killer (NK) cell antibody-dependent cell-mediated cytotoxicity (ADCC), resulting in an anti-tumour immune response and the potential to augment the activity of PD-1/PD-L1 inhibition. EACH aims to examine the safety and efficacy of the potentially synergistic interaction between cetuximab and avelumab, a fully human IgG1 anti-PD-L1 monoclonal antibody in R/M HNSCC.

Methods: EACH is a randomised phase II trial preceded by a safety run-in phase. Eligible patients have histologically or cytologically confirmed measurable recurrent or metastatic squamous cell carcinoma of any site in the safety run-in phase, and HNSCC in phase II, that is considered incurable by local therapies. The safety run-in has a single arm de-escalating design, aiming to establish the safety of cetuximab with avelumab and determine the optimal dose of cetuximab within this combination. The safety run-in has a dosing schedule of avelumab (10 mg/kg) + cetuximab (500 mg/m²) intravenously every 2 weeks, with de-escalation of cetuximab to 400 mg/m² and 300 mg/m² if necessary. The safety run-in phase commenced recruitment in July 2018 and is ongoing. The phase II component will randomize 114 HNSCC patients between either avelumab + cetuximab at the dose determined by the safety run-in phase or avelumab (10 mg/kg) alone. Treatment will be in 4-week cycles for up to one year. The primary endpoint in the safety run-in phase is the occurrence of dose limiting toxicities, and in phase II is Disease Control Rate at 24 weeks, using iRECIST. Blood and fresh tissue will be collected for exploratory translational studies, which will focus on the identification of potential novel predictive biomarkers for response. Clinical trial information: NCT03494322.
Tabelecleucel in combination with pembrolizumab (Pembro) in platinum-pretreated, recurrent/metastatic Epstein-Barr virus (EBV)-positive nasopharyngeal carcinoma (EBV+NPC).

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Background: Approximately 25% of patients (pts) with NPC develop RM disease, which has a poor prognosis (median overall survival [mOS]: 12–16 mo), despite standard treatments with radiation and/or chemotherapy. NPC is an EBV-associated cancer in which programmed cell death ligand 1 (PD-L1) expression is upregulated upon EBV activation. Pembro showed antitumor activity in a phase 1b study of pts with RM-NPC (objective response rate [ORR]: 26%; mOS: 16.5 mo) (Hsu, J Clin Oncol 2017;35:4050-56). Targeting RM EBV+ NPC with tab-cel immunotherapy (off-the-shelf, allogeneic EBV-specific T cells) in pts has also shown promise, with 2-yr OS rates of 84% (Prockop, ASCO 2016;34:3012). The favorable safety profile of tab-cel offers the opportunity for combination immunotherapy with pembro for increased efficacy.

Methods: This multicenter, open-label, single-arm phase 1b/2 study evaluates safety and efficacy of tab-cel in combination with pembro. Study participants are $\geq 12$ yrs of age with incurable, locally recurrent or metastatic EBV+ NPC previously treated with platinum-containing therapy. Pts are checkpoint-inhibitor naive (phase 1b/2) or refractory to anti-PD-1 or anti-PD-L1 therapy (phase 1b). Tab-cel is selected from a bank based on matching $\geq 2$ HLA alleles, including $\geq 1$ restricting HLA allele, between pts and donors. Tab-cel will be administered intravenously (IV) on days 1, 8, and 15 of a 21-day cycle. Initial tab-cel dose is $2\times10^6$ cells/kg and the de-escalated tab-cel dose (if needed) is $1\times10^6$ cells/kg. Pembro is administered at 200 mg IV Q3W in adults and 2 mg/kg IV Q3W in pts aged 12 to 17 yrs. Primary outcomes of phase 1b are to characterize dose-limiting toxicities, identify the maximum tolerated dose (MTD) or in the absence of MTD, the recommended phase 2 dose, and assess safety. Primary outcomes for phase 2 are ORR and safety. Secondary endpoints include progression-free survival, OS, and duration of response. Enrollment is ongoing for 12-24 participants in the phase 1b portion of the study with a 6+6 design. Phase 2 is expected to enroll 36 pts. Clinical trial information: NCT03769467.
Comparative effectiveness trial of transoral head and neck surgery followed by adjuvant radio(chemo)therapy versus primary radiochemotherapy for oropharyngeal cancer (TopROC).

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Background: For locally advanced, transorally resectable oropharyngeal cancer (OPSCC), both, surgical resection and risk-adapted adjuvant (chemo)radiotherapy or definite chemoradiotherapy with or without salvage surgery are considered the current standard of care. To date, these two different therapeutic approaches for transorally resectable OPSCC have not been compared head to head in a randomized trial yet. The goal of this study is to compare primary transoral surgery followed by adjuvant treatment with definitive chemoradiation for resectable OPSCC, especially with regards to loco-regional control as well as organ function. Methods: TopROC is a prospective, two-arm, open label, multicenter, randomized controlled comparative effectiveness study. Eligible pts. are ≥18 years old with treatment-naïve, histologically proven OPSCC (T1, N2a-c, M0; T2, N1-2c, M0; T3, N0-2c, M0 TNM 7th ed.) which are amenable to transoral resection, ECOG PS ≤2 and no distant metastasis. p16 immunohistochemistry by local pathology or FFPE tissue must be available for central diagnostic. 280 pts. will be randomly assigned (1:1) to surgical treatment (arm A) or chemoradiation (arm B). Standard of care treatment will be done according to daily clinical practice. Arm A consists of transoral surgical resection with neck dissection followed by risk-adapted adjuvant (chemo)radiation. Pts. treated in arm B receive standard chemoradiation, residual tumor may be subject to salvage surgery. Follow-up visits are planned until three years after treatment. Primary endpoint is time to local or locoregional failure or death from any cause (LRF). Secondary endpoints include overall and disease-free survival, toxicity, patient reported outcomes and cost-effectiveness analysis. Approximately 20 centers will be involved in Germany. This trial is supported by the German Cancer Aid and accompanied by a large scientific support program. Recruitment started in January 2018. Clinical trial information: NCT03691441.
A global phase III multicenter, randomized, double-arm, open label trial of ASP-1929 photoimmunotherapy versus physician’s choice standard of care for the treatment of patients with locoregional, recurrent head and neck squamous cell carcinoma (rHNSCC).

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Background: rHNSCC commonly affects local or regional sites and is associated with considerable morbidity and mortality. Outcomes of these patients remain poor with limited curative treatment options and low response rates. New modalities that are targeted, minimally invasive, and provide improved tumor response and control while having limited systemic side effects are needed. Photoimmunotherapy (PIT) is a new cancer-targeted platform technology. It is a combination drug and device treatment that utilizes monoclonal antibodies conjugated to a dye (IRDye 700DX) that is photoactivated using nonthermal red light to induce rapid and selective tumor cell death. The objective of this phase 3 study is to evaluate the efficacy and safety of ASP-1929 (EGFR-directed antibody cetuximab-IR700 conjugate) PIT treatment as a monotherapy in patients with locoregional rHNSCC. Methods: A global, multicenter phase 3, randomized, double-arm, open-label, controlled trial of ASP-1929 PIT vs physician’s choice standard of care (SOC) for the treatment of locoregional, rHNSCC in patients who have failed or progressed on or after at least two lines of therapy, of which at least one line must be systemic therapy, is currently underway. Primary endpoints of the study are PFS and OS and the key secondary endpoint is ORR. Key inclusion criteria include: disease not amenable to curative therapy; tumor(s) accessible for PIT light treatment and measurable by CT or MRI; male or female ≥ 18 yrs old with life expectancy > 6 months; ECOG score of 0 to 1. Key exclusion criteria include: history of ≥ Grade 3 cetuximab infusion reaction; distant metastatic disease; tumors invading a major blood vessel unless embolized. The study will include ~275 subjects in a 2:1 randomization (ASP-1929 PIT: Physician’s choice SOC). The physician’s choice SOC arm includes cetuximab, methotrexate, or docetaxel. Tumor(s) are illuminated with 690 nm PIT light treatment 24 hrs following completion of ASP-1929 infusion (640 mg/m²). Clinical trial sites will be in the USA, EU and Asia. Clinical trial information: NCT03769506.
Multicenter randomized controlled phase III study of nivolumab alone or in combination with ipilimumab as immunotherapy vs standard follow-up in surgical resectable HNSCC after adjuvant therapy.

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Background: Surgically treated locally advanced head and neck squamous cell carcinoma (LA HNSCC) often requires postoperative chemoradiation with high risk of acute and late toxicity. Disease-free survival (DFS) after 2 years is approximately 70%. Combining Nivolumab (N), a PD-1 inhibitor, and Ipilimumab, a CTLA4 inhibitor, as maintenance therapy may improve DFS due to anti-tumor effects of immunotherapy by enhancing cross-presentation of tumor antigens. The IMSTAR HN study compares neoadjuvant N and N+I 6 months after adjuvant therapy vs the standard therapy as first-line treatment for LA HNSCC.

Methods: Eligible pts are ≥18 years old with treatment-naive LA HNSCC (oral cavity, oropharynx p16-, hypopharynx, and larynx), ECOG PS ≤1, and no distant metastasis. 276 pts will be randomized (2:1) into 2 arms and approximately 10 centers in Germany will be involved. Standard of care (arm II) consists of surgical resection followed by risk-adapted adjuvant (chemo)radiation. The experimental arm I receives neoadjuvant N 3mg/kg. After treatment according to standard arm a second randomization will be performed: In arm Ia N 3mg/kg will be given every 2 weeks until progression or up to 6 months. In arm Ib I 1mg/kg will be applied additionally every 6 weeks also until progression or up to 6 months. Primary endpoints is DFS in arms I and II. Secondary endpoints: Local regional control (LRC), distant metastasis free survival (DMFS), overall survival (OS), quality of life (QoL), survival depending on PD-L1 status, comparison of arm Ia vs arm II and Ib vs. II. AEs, graded per CTCAE v4.03, are evaluated for at least 12 months after randomization. The translational program includes investigations concerning immunomodulation, mutational load in general, but also specific mutations in targets involved in immune function and antigen presentation. Recruitment started in August 2018. Clinical trial information: NCT03700905.
Roman: Reduction in oral mucositis with avasopasem manganese (GC4419)—Phase 3 trial in patients receiving chemoradiotherapy for locally-advanced, non-metastatic head and neck cancer.

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Background: Approximately 70% of patients receiving intensity-modulated radiotherapy (IMRT) plus cisplatin for locally advanced head and neck cancer (HNC) develop SOM, defined as WHO Grade 3 or 4, which limits patients' ability to eat solids (Gr 3) or liquids (Gr 4, requiring enteral nutrition). An RT-induced burst of superoxide initiates oral mucositis (OM) development. GC4419, a superoxide dismutase mimetic, interrupts this process by converting superoxide to H2O2. It showed promising reduction of SOM in a published open-label Phase 1b/2a trial (IJROBP 1 Feb 2018). In a subsequent randomized, double-blind placebo-controlled trial in 223 patients receiving IMRT/cisplatin for HNC (ASCO 2018), 90 mg of GC4419 administered M-F prior to IMRT demonstrated statistically significant reduction in SOM duration (p=0.024, median 1.5 days @ 90 mg vs 19 days placebo) and meaningful reductions @ 90 mg in SOM incidence (43% vs 65%) and severity (incidence of Grade 4, 16% vs 30%). The safety profile was acceptable and consistent with the known toxicities of IMRT/cisplatin. Methods: 335 patients at multiple centers in the U.S. and Canada with locally-advanced, nonmetastatic head and neck cancer (oral cavity/oropharyngeal) receiving 70 Gy IMRT (>50 Gy to > 2 oral sites) plus cisplatin (40 mg/m2 qwk x 6-7, or 100 mg/m2 q3wk x 3) are being randomized (double-blinded) 3:2 to 90 mg of GC4419 or placebo, M-F before each RT fraction. Enrollment is stratified by cisplatin schedule and treatment setting (definitive vs post-op). OM by the WHO scale will be assessed twice weekly during RT & weekly for 2 weeks post RT. The primary efficacy endpoint is incidence of SOM through the end of IMRT. Secondary efficacy endpoints include severity (incidence of Grade 4 OM through the end of IMRT), & days of SOM (days from first to last SOM for all patients, with patients never developing SOM having 0 days of SOM by definition). Days of SOM for the subset developing SOM will be analyzed descriptively. Patients will be followed for one year post IMRT for tumor progression/recurrence and for two years for survival. Supported by Galera Therapeutics, Inc. Clinical trial information: NCT03689712.
A phase 3 (COSMIC-311), randomized, double-blind, placebo-controlled study of cabozantinib in patients with radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) who have progressed after prior VEGFR-targeted therapy.

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Background: Treatment options are limited for patients with RAI-refractory DTC that is resistant to VEGFR-targeted therapy. Cabozantinib inhibits receptor tyrosine kinases including VEGFR2, MET, AXL, and RET, which are implicated in the development of DTC, and has shown clinical activity in early-phase studies of patients with RAI-refractory DTC. This study evaluates the efficacy and safety of cabozantinib in patients with RAI-refractory DTC who have progressed during or after prior VEGFR-targeted therapy. Methods: This is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT03690388). The co-primary endpoints are progression-free survival and objective response rate evaluated by blinded independent radiology committee (BIRC) per RECIST v 1.1. Additional endpoints include safety, overall survival, quality of life, and changes in relevant biomarker levels (eg, thyroglobulin). Approximately 300 patients will be randomized in a 2:1 ratio to receive either cabozantinib (60 mg QD orally) or placebo. Randomization is stratified by prior treatment with lenvatinib and age (≤ 65 yrs vs > 65 yrs). Eligible patients must have a pathologic diagnosis of DTC and must have been previously treated with or deemed ineligible for treatment with iodine-131 for DTC. Patients must have received lenvatinib or sorafenib for DTC and progressed during or following treatment with a VEGFR inhibitor. Up to 2 prior VEGFR-targeting TKI agents are allowed. Patients randomized to placebo may be eligible for real time on-study crossover to cabozantinib based on BIRC confirmation of disease progression. Unblinded patients randomized to cabozantinib may continue on study treatment if there is clinical benefit per investigator. Key words: Radioiodine-refractory differentiated thyroid cancer, cabozantinib, VEGFR-targeted therapy, trial-in-progress. Clinical trial information: NCT03690388.
ACCURACY: phase (P) 2 trial of AL101, a pan-Notch inhibitor, in patients (pts) with recurrent/metastatic (R/M) adenoid cystic carcinoma (ACC) with Notch activating mutations (Notch\textsuperscript{act mut}).

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Background: Notch signaling plays a key role in tumorigenesis. Notch cleavage by \( \gamma \)-secretase frees the Notch intracellular domain, which promotes the expression of target genes involved in cancer. AL101, a small molecule, is a \( \gamma \)-secretase inhibitor that potently inhibits Notch1-4, resulting in robust antitumor activity in vivo (PMID 26005526), including ACC xenograft models with Notch\textsuperscript{act mut} (Ferrarotto, AACR 2019, Abstr 4885). Three P1 trials tested AL101 as monotherapy or in combination regimens in > 200 solid/hematologic cancer pts. In the P1 trial of AL101 monotherapy, conducted in 94 pts with advanced/metastatic solid tumors refractory to standard therapies (Tx), AL101 was generally well tolerated, with manageable AEs, and the recommended P2 dose was 4 mg IV once weekly (QW; El-Khoueiry, ASCO 2018, Abstr 2515). 4 pts had objective responses, 2 of those had Notch\textsuperscript{act mut} (1 of which had ACC). ACC, a rare cancer that most commonly develops in the major salivary glands, but can also arise in minor salivary glands in the trachea, lacrimal gland, and other sites, is refractory to chemotherapy, with a high recurrence rate. Notch\textsuperscript{act mut} are found in a subset of ACC pts (11\%–22\%), with particularly aggressive disease and poor prognosis. There is no proven active treatment for R/M ACC pts (PMID 27870570).

Methods: ACCURACY (NCT03691207) is an open-label, single-arm, multicenter study of AL101 (4 mg IV QW) in pts with R/M ACC (bone-exclusive disease included) with known Notch1-4\textsuperscript{act mut}. Pts with disease progression within 6 months of enrollment or newly diagnosed metastatic pts are allowed; pts who received \( \geq 3 \) prior systemic Tx are excluded. Primary endpoint: ORR by RECIST v1.1 (or modified MDA bone criteria), by independent review committee (IRC). Secondary endpoints: ORR by investigator review (IR), duration of response by IRC and IR, PFS by IRC, OS, and safety. Per the Simon optimal design, 12 pts are enrolled in stage 1; if \( \geq 2 \) pts respond, 24 additional pts are enrolled in stage 2. If \( \geq 4 \) pts in stage 2 respond, the trial is deemed positive. This design yields 5\% type I error rate and 80\% power, if ORR is 25\%. 4 of planned 36 pts have been enrolled as of 2/12/19. Clinical trial information: NCT03691207.