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CA209-9KY: Phase II Study of IMRT Re-Irradiation and Concurrent/Adjuvant Nivolumab (Nivo) in Patients With Loco Regionally Recurrent or Second Primary Head and Neck Squamous Cell Carcinoma (HNSCC) – Toxicity and Quality of Life (QoL) Results

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Purpose/Objective(s): Approximately 30-40% of patients irradiated for HNSCC will develop locoregional recurrence or second primary tumors (RSPT). Treatment of RSPT originating within a previously radiated field presents a technical challenge and typically portends worse outcomes than an initial course of RT. Anti-PD-1 therapy has shown promise in the treatment of advanced HNSCC. CA209-9KY aimed to investigate the potential benefit of nivo during and after IMRT based re-irradiation in RSPT. We report here the toxicity and QOL data for 44 enrolled patients.

Materials/Methods: Following IRB approval at 3 participating institutions, patients were enrolled if they had RSPT arising in a previously irradiated field (> 40 Gy) and met criteria for reirradiation classes I or II (Ward et al, IJROBP 2018); prior salvage resection was allowed regardless of HPV status provided patients had positive margins, extranodal extension, gross residual disease, N2/3 or T3/4 disease, multifocal perineural invasion, and/or lymphovascular space invasion. IMRT reirradiation with photons was delivered in 60-66 Gy in 30-33 daily fractions over 6-6.5 weeks with Nivo (240 mg) two weeks prior to and every 2 weeks during IMRT for a total of 5 doses then at 480 mg every 4 weeks for a total of 52 weeks. The Functional Assessment of Cancer Therapy (FACT-G) (Version 4) was assessed pre-therapy and weeks 6, 18, 30 and 52. The sum of FACT-G subscales (SUMQOL) score was also computed. Median and interquartile range (IQR) for each subscale and SUMQOL were recorded per cycle visit. FACT-HN was assessed at the same time intervals. Internal consistency reliability was measured using Cronbach's alpha and reported for each FACT sub-scale at each cycle

Results: As of 1/2021, a total of 44 patients have completed IMRT with nivolumab with a median follow up duration of 6.3 mos [95% CI (4.5-11.2)]. The most common toxicities of any grade-(CTCAE version 4.0) were fatigue (77%), dermatitis (54%), and dysphagia (52%). Grade 3 or 4 toxicities occurred in 47% of patients, with lymphopenia being the most common (11%), followed by diarrhea (7%). Serious Adverse Event (SAEs) occurred in 20% of patients with the most reported being dyspnea (4%). The median total sumQoL scores for FACT-HN per visit were 71 (61-80), 73 (67-77), 70 (67.8-76.2), 74 (66.2-79.7) and 71 (66-79), respectively. Similar observations were seen for FACT-G Scores for subscales with a median total FACT-G sumQoL scores per visit 54 (46.2-56.8), 55 (53.5-59.2), 54 (50-57), 55.5(52-58.2), and 55 (52.5-57.5), respectively. FACT-G and FACT-H&N QOL scores remained consistent across all time points analyzed. The internal consistency and reliability for the FACT scores per sub-scale, per cycle and for all response items had a Cronbach's alpha of > 0.7.

Conclusion: Reirradiation with IMRT with concurrent and adjuvant nivo in patients with RSPT appears to be well tolerated with preservation of QOL measures during and following completion of therapy. Follow up for clinical efficacy measures of IMRT-nivo continues.

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NBTXR3 Activated by Radiotherapy in Combination With Nivolumab or Pembrolizumab in Patients With Advanced Cancers: A Phase I Trial

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Purpose/Objective(s): Immune checkpoint inhibitors (ICIs) have led to improved treatment outcomes in a variety of cancers; however, the majority of patients exhibit resistance to ICIs. Overcoming this resistance is a major challenge in immune-oncology. Radiation therapy (RT) has emerged as a promising combination with ICIs since it may act synergistically with ICIs by producing an immunomodulatory effect. NBTXR3, composed of functionalized hafnium oxide nanoparticles, is injected intratumorally and activated by RT. NBTXR3 increases RT energy deposit inside tumor cells and subsequent tumor cell death, without adding toxicity to healthy tissues. Preclinical data demonstrate NBTXR3/RT can trigger a local and systemic anti-tumor immune response and overcome anti-PD-1 resistance. NBTXR3/RT combined with anti-PD-1 may prime the immune system to increase the proportion of ICI responders or convert ICI non-responders to responders.

Materials/Methods: This multicenter, open-label, phase I trial [NCT03589339] is evaluating NBTXR3/RT/anti-PD-1 in 3 cohorts: (1) Locoregional recurrent or recurrent and metastatic head and neck

squamous cell carcinoma (HNSCC) amenable to HN re-irradiation and (2) lung or (3) liver metastases from any primary cancer eligible for anti-PD-1. Stereotactic body RT (SBRT) is delivered at tumor-site selective doses per standard practice. The primary objective is to determine the NBTXR3/RT/anti-PD-1 recommended phase 2 dose in each cohort. Secondary objectives are anti-tumor response (objective response rate), safety, and feasibility of NBTXR3 injection.

Results: Nine patients have been treated: 3 HNSCC, 4 lung, 2 liver. Overall tumor regression was observed in 8/9 patients of which 7 were anti-PD-1 non-responders. A complete response lasting over 1 year was observed in the injected lymph node in 1 anti-PD-1 naïve patient. 2 SAEs related to anti-PD-1 and possibly related to NBTXR3 (G5 pneumonitis, G4 hyperglycemia) were observed in 1 anti-PD-1 naïve HNSCC patient and considered DLTs. This patient also experienced 2 other G4 SAEs related to anti-PD-1 (diabetic ketoacidosis, acute kidney injury). SBRT-related safety profile was as expected. Updated safety and efficacy results with additional patients and longer follow-up will be presented.

Conclusion: Safety data from this first-in-human phase I trial evaluating NBTXR3/RT/anti-PD-1 in patients with advanced cancers, show NBTXR3 intratumoral injection is feasible and well-tolerated in HNSCC, lung, and liver. NBTXR3/RT/anti-PD-1 demonstrated promising signs of efficacy and led to tumor regression in patients having progressed on prior anti-PD-1. These data support further development of NBTXR3 in combination with anti-PD-1 as well as other ICIs.

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Predicting Pathologic Lymph Node Positivity in cN0 Pharynx and Larynx Cancers in the Modern Imaging Era

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Purpose/Objective(s): Neck dissection is a standard of care for pharynx and most larynx cancer patients undergoing surgery even with clinically node-negative (cN0) necks. This is based largely on historical series showing high rates of occult pathologic node-positivity (pN+) in cN0 patients. However, in the modern era with more sensitive imaging modalities, it is possible that certain patients with sufficiently low risk of pN+ could have elective neck dissection omitted, thereby reducing toxicity.

Materials/Methods: Patients with cN0 oropharynx, larynx (excluding T1-2 glottic), and hypopharynx cancers diagnosed from 2010-2015 and undergoing primary surgery were identified in the National Cancer Data Base. Multivariable logistic regression was performed to assess predictors of pN+. Predictive nomograms based on these predictors were generated.

Results: 4117 cN0 patients met inclusion criteria, including 2033 larynx (L), 293 hypopharynx (HP), 503 HPV(-) oropharynx (OP), and 1288 HPV(+) OP patients. The overall rate of pN+ among cN0 patients was 29.4%. Probability of pN+ was > 25% for all anatomic subsites (L: 26.9%; HP: 27.6%: HPV(-) OP: 32.4%; HPV(+) OP: 32.7%). In multivariable logistic regression, the presence of lymphovascular invasion (LVI) was the strongest predictor of pN+ (odds ratio [OR] = 4.19, 95% confidence interval [CI] 3.56-4.93, $P < 0.001$). Histologic grade also strongly predicted pN+ (high- vs. low-grade: OR 2.58, 95% CI 1.88-3.59, $P < 0.001$; intermediate- vs. low-grade: OR 1.90, 95% CI 1.40-2.62, $P < 0.001$). However, increasing pT-classification was not associated with increased rate of LN positivity. A nomogram predicting the probability of pN+ for cN0 patients was created. Using this nomogram, < 2% of patients had an estimated pN+ risk below 10%, < 10% of patients had pN+ risk below 15%.

Conclusion: LVI and histologic grade are the strongest predictors of pN+ among patients with cN0 pharynx and larynx cancers. Even with modern imaging, pN+ rates are high for cN0 patients, and the benefits of neck dissection likely outweigh the risks in virtually all patients undergoing surgery.

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Concurrent Immunotherapy With Chemoradiation for Definitive Management of Locally Advanced Laryngeal Cancer: A Prospective Trial

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Purpose/Objective(s): Cisplatin-based chemoradiation is an established organ-preserving strategy for locally advanced laryngeal squamous cell carcinoma, but long-term survival remains suboptimal, warranting an improved approach. Immunotherapy has been studied in the metastatic and unresectable recurrent setting, but additional data are needed to assess its role in definitive therapy. The study hypothesis was that the use of immunotherapy in conjunction with chemoradiation would be safe and result in improved laryngectomy-free survival (LFS) compared to standard of care chemoradiation.

Materials/Methods: This trial was an open-label, single-arm, prospective, multi-institutional study. The study included a Phase I run-in portion to assess safety in the first 6 enrolled patients and a planned subsequent Phase II component. Due to slow accrual, the study was closed after enrollment of 9 patients and the data were allowed to mature. The primary endpoint of the Phase II portion was LFS at 18 months. Study patients had Stage III or IV (T1-3; N0-3; M0) laryngeal squamous cell carcinoma and were candidates for larynx preservation. Pembrolizumab was given as a 200 mg flat dose 3 weeks prior to the start of chemoradiation and was then given q21 days until the completion of chemoradiation. Cisplatin was given at a dose of 100 mg/m^2 q21 days during radiation with allowed dose modifications for toxicities. Radiation was prescribed to a total dose of 70 Gy in 35 daily fractions using IMRT with an elective nodal dose of 56-63 Gy.

Results: A total of 9 patients with a median age of 54 were enrolled from 2017 to 2019. The median follow-up time was 30.1 months. None of the enrolled patients required laryngectomy, resulting in 100% LFS at 18 months for evaluable patients. The 18-month overall survival (OS) rate was 66.7%; of the 3 patient deaths, 2 were due to co-morbid conditions (diabetes, peripheral arterial disease) rather than malignancy. The remaining 6 patients were alive at the time of last follow-up and the median duration of OS was not reached. There were 27 Grade 3 toxicities, with 2 attributable to pembrolizumab. Nearly all Grade 4 (n = 4) and Grade 5 (n = 1) toxicities occurred in a single patient with poorly-controlled diabetes; the Grade 5 toxicity was due to diabetic ketoacidosis. One patient had late Grade 4 laryngeal edema requiring tracheostomy 8 months after chemoradiation; the edema has since resolved and the tracheostomy was reversed.

Conclusion: The use of concurrent pembrolizumab with chemoradiation for locally advanced larynx cancer resulted in high LFS. Most toxicities were attributable to chemoradiation and the majority of Grade 4 and 5 toxicities occurred in a patient with poorly-controlled diabetes. A case of late Grade 4 laryngeal edema could have been related to immunotherapy. Future studies with concurrent immunotherapy with chemoradiation should account for this possibility.