These genomic alterations or higher TMB may result in a greater neoantigen burden yielding an abundance of activated, effector T cells. We also observed improved outcomes in patients receiving chemotherapy prior to PD-L1 blockade. Further studies are needed to validate these findings.

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TCGA Data on Head and Neck Squamous Cell Carcinoma Suggest Therapy-Specific Implications of Intratumor Heterogeneity

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Purpose/Objective(s): To determine whether the relation of intratumor genetic heterogeneity to outcome in head and neck squamous cell carcinoma (HNSCC) differs depending on the therapy received. Three hundred and five initial HNSCC cases from The Cancer Genome Atlas (TCGA) showed a strong relation of high heterogeneity to shorter overall survival (OS) in HNSCC (PLoS Medicine 12: e1001786, 2015), but were insufficient to determine whether the relation to OS depended on therapy type. More complete TCGA data now allow examination of this issue.

Materials/Methods: Clinical and whole-exome sequencing (WES) data on 528 HNSCC cases in TCGA were obtained from the NCi Genome Data Center and the Broad Institute. Clinical data were reviewed to determine if initial therapy included radiation or chemotherapy as primary or adjuvant therapy. Intratumor genetic heterogeneity was assessed by a modification of the MATH measure (Oral Oncology 49: 211, 2013) that improved handling of differing tumor-cell fractions among samples. Cox multiple regression of OS included age, year of diagnosis, smoking history, anatomic subsite, N and T classifications, HPV status, therapy, MATH, and another WES-derived classification. The interaction of MATH with therapy was evaluated to address the project’s objective.

Results: Three hundred and ninety-three TCGA HNSCC cases (144 deaths) had sufficient data. The interaction of MATH with therapy was significantly related to OS (P = .016). With other clinical variables accounted for, the longest OS was seen for patients with low-MATH tumors who received chemoradiation (baseline for hazard ratio, HR). Intermediate OS was seen for patients with high-MATH tumors receiving chemoradiation (HR, 2.3; 95% CI, 1.1-5.2); patients with low-MATH tumors receiving no adjuvant therapy (HR, 1.7; CI, 0.7-4.2); and patients receiving adjuvant therapy without chemotherapy, with low (HR, 1.6; CI, 0.7-4.1) or high (HR, 1.7; CI, 0.7-4.1) MATH. The shortest OS was for patients with high-MATH tumors not receiving adjuvant therapy (HR=6.6; CI, 2.8-20).

Conclusion: This first report that the relation of intratumor genetic heterogeneity to OS depends on therapy, although based on retrospective analysis and statistical control of other variables, has provocative implications that deserve prospective study. The results suggest that patients with high intratumor heterogeneity might benefit from radiation even when clinical considerations suggest that adjuvant therapy can be omitted. The results also suggest, however, that such patients might not benefit from the addition of chemotherapy, and thus could be spared the morbidity of complications from combination therapy. Intratumor heterogeneity should be evaluated in controlled trials that compare adjuvant radiation against chemoradiation following surgery for HNSCC.

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OPTIMA—A Phase 2 Trial of Induction Chemotherapy Response-Stratified Radiation Therapy Dose and Volume Escalation for HPV+ Oropharyngeal Carcinoma: Efficacy, Toxicity, and HPV Subtype Analysis

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Purpose/Objective(s): This prospective phase 2 de-escalation study used induction chemotherapy to identify favorable HPV+ oropharyngeal cancer (OPC) patients (pts), including those with high-risk tumors, and applied significantly lower radiation or chemoradiation doses than previously reported. We herein report an updated analysis with p16 IHC and HPV PCR genotyping.

Materials/Methods: Pts with HPV+ OPC were classified as low-risk (≤T3, ≤N2B, ≤10 PHY) or high-risk (T4 or ≥N2C or ≥10 PHY). Pts received 3 cycles of carboplatin and nab-paclitaxel induction. Low-risk pts with ≥50% response received low-dose radiation therapy (RT) alone to 50 Gy (RT50). Low-risk pts with 30%-50% response OR high-risk pts with >50% response received low-dose chemoradiation therapy to 45 Gy (CRT45). All other pts received de-escalated RT volumes limited to the first echelon of unmoved nodes. RT50 was delivered in 2 Gy/fx once daily whereas CRT arms used paclitaxel, 5-FU, hydrea, and 1.5 Gy twice-daily RT every other week. Primary site biopsy and neck dissection were performed only after de-escalated treatment (RT50, CRT45) for pathologic confirmation. The primary endpoint was 2-year PFS. Secondary endpoints included pathologic complete response (pCR) rate and toxicity.

Results: Sixty-two pts were enrolled; p16 IHC was positive in all cases. Confirmatory HPV DNA PCR showed HPV16 in 94.9%, HPV18 in 1.7%, and HPV33 in 3.4%. 28 pts (45.2%) were low-risk and 34 pts (54.8%) were high-risk. 71.4% of low-risk pts received RT50 and 21.4% received CRT45. 70.6% of high-risk pts received CRT45. The pCR rate was 94.7% after RT50 and 89.3% after CRT45. Median follow-up is 1.5 years. The 2-year PFS and OS were both 100% for low-risk pts, and 93.5% and 97.0% for high-risk pts. A single in-field failure occurred in a high-risk pt at 11 months after treatment with CRT45 and was surgically salvaged. Acute toxicity was significantly improved including grade ≥3 mucositis (15.8% RT50, 46.4% CRT45, 60.0% CRT75, P = .033) and grade ≥3 dermatitis (0% RT50, 21.4% CRT45, 30.0% CRT75, P = .056). Long-term PEG-tube dependence was also significantly improved (1-year rate: 0% RT50, 3.5% CRT45, 9.1% CRT75, P = .0001).

Conclusion: Use of 50 Gy limited-field RT alone in low-risk HPV+ pts or 45 Gy CRT in high-risk HPV+ pts with favorable response to induction chemoradiation resulted in excellent pCR and survival outcomes with reduced acute and late toxicity rates; long-term follow-up is ongoing.


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Initial Results from a Phase 2 Prospective Trial of De-Intensified Chemoradiation Therapy for Low-Risk HPV-Associated Oropharyngeal Squamous Cell Carcinoma

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Purpose/Objective(s): To report initial results from a prospective phase 2 clinical trial of highly de-intensified chemoradiation therapy (CRT) for patients with favorable risk HPV-associated oropharyngeal squamous cell carcinoma (OPSCC).

Materials/Methods: The major inclusion criteria were: 1) T0-T3, N0-N2c, M0, 2) HPV or p16 positive, and 3) minimal/remote smoking history. Treatment was limited to 60 Gy intensity modulated radiation therapy with concurrent weekly intravenous cisplatin 30 mg/m2 (second choice was cetuximab). Patients received neither induction chemotherapy nor definitive surgery. Patients with T0-T2 N0-1 disease did not receive chemotherapy (i.e. received 60 Gy alone). All patients had a 10- to 12-week posttreatment PET/CT to determine need for planned neck dissection. The primary study endpoint is 2-year progression-free survival (PFS). Secondary endpoint measures include 2-year local control (LC), regional control (RC), distant metastasis free survival (DMFS), and overall survival (OS), and patient reported symptoms (PRO-CTCAE) and quality of life (EORTC QLQ-C30 & H&N35). Data analysis was performed for patients with a minimum of 1 year of follow-up.

Results: One hundred and thirteen patients have enrolled, with 82 having a minimum follow-up of 1 year. Smoking status was as follows: 49% never, 35% <10 pack-years, and 16% >10 pack-years. Forty-four percent were HPV and p16 positive and 56% were HPV negative/unknown and p16 positive. Posttreatment PET/CT complete response rate was 97% at the primary site and 81% in the neck. Eight patients had planned neck dissection with 1 having pathological residual disease. Two-year PFS, LC, DMFS, CSS, and OS are the following: 98%, 99%, 95%, 96%, and 95%. Sixteen patients were treated with RT alone and received neither induction chemotherapy nor definitive surgery. Patients with T0-T2 N0-1 disease did not receive chemotherapy (i.e. received 60 Gy alone). All patients had a 10- to 12-week posttreatment PET/CT to determine need for planned neck dissection. The primary study endpoint is 2-year progression-free survival (PFS). Secondary endpoint measures include 2-year local control (LC), regional control (RC), distant metastasis free survival (DMFS), and overall survival (OS), and patient reported symptoms (PRO-CTCAE) and quality of life (EORTC QLQ-C30 & H&N35). Data analysis was performed for patients with a minimum of 1 year of follow-up.

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