INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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2022 Multidisciplinary Head and Neck Cancers Symposium (February 24-26, 2022) Late-Breaking Abstracts

Oral Scientific Sessions

LBA-1

Cancer-associated Fibroblasts Transform Monocytes Into Protumorigenic Macrophages via IL-22 Signaling in Head and Neck Squamous Cell Carcinoma

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Purpose/Objective(s): The tumor microenvironment (TME) is composed of several cell types that have been shown to play fundamental roles in tumor growth and metastasis. Uncovering landscapes and mechanisms within TME is critical for identifying new therapeutic modalities to improve outcomes in head and neck squamous cell carcinoma (HNSCC). We hypothesized that discrete cell clusters in the pathologic landscape of HNSCC drive tumor growth and result in worsened patient outcomes.
Materials/Methods: To identify motifs that define patient subsets and their clinical outcomes, a multiplexed tissue imaging platform was used to analyze 56 markers in single cells on formalin-fixed paraffin embedded (FFPE) HNSCC tissue samples. Peripheral blood mononuclear cells (PBMC) were isolated from HNSCC patients and co-cultured with normal fibroblasts or HNSCC-associated fibroblasts. A panel of 48 cytokines was assayed in cell-free supernatant collected at day 5. HNSCC cells were stimulated with supernatant obtained from PBMC-fibroblast co-culture in a time- and dose-dependent manner. STAT3 activation was assayed via western blot and cell proliferation was determined using WST-1.
Results: Using the imaging platform, we delineated the single cell pathologic landscape of HNSCC and uncovered an enrichment of macrophage-fibroblast interactions in HNSCC patients that succumbed to disease ($P = 0.01$). *In vitro*, we discovered that HNSCC-associated fibroblast induced PBMC IL-22 secretion (fold change = 43.9, $P = 0.004$), a finding that was not observed with normal fibroblasts. Furthermore, we discovered that supernatant obtained from HNSCC-associated fibroblast/PBMC co-culture activated STAT3, a key driver of head and neck carcinogenesis. Lastly, while supernatant obtained from normal fibroblast/PBMC co-culture inhibited HNSCC growth, HNSCC-associated fibroblast/PBMC supernatant appeared to reverse growth inhibition.
Conclusion: Our findings indicate that fibroblast-macrophage crosstalk within HNSCC TME induces IL-22 secretion and drives tumor growth. These findings suggest that targeting the IL-22 pathway may be beneficial in HNSCC.
Author Disclosure: **T.F. Olonisakin**: None. **A. Mayer**: None. **U. Duvvuri**: None.

LBA-2

Targetable Vulnerabilities of Head and Neck Cancer Cell Lines Detected by the DepMap CRISPR Screens

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Purpose/Objective(s): The DepMap genome-wide loss of function CRISPR screens offer new insight into gene dependencies in HPV(-) head and neck squamous cell carcinoma (HNSCC) cell lines. We aimed to leverage this data to guide preclinical studies by cataloging targetable dependencies that are predicted to offer a therapeutic window. We also aimed to identify targets representing potential synthetic lethalities by testing for associations between genetic alterations and dependency profile.
Materials/Methods: DepMap was queried for gene probability and effect scores in cell lines from 77 tumors, including 62 HPV(-) HNSCCs plus 15 ESCCs, which have comparable etiology and genetic profile. A probability score of ≥ 0.5 was used as the threshold for essentiality. Essential genes were selected for analysis by 3 criteria: (1) presence in ≥10% cell lines, (2) lack of common essentiality in prior CRISPR screens of normal human cell lineages, and (3) designation as druggable by the Drug-Gene Interaction Database. Gene set enrichment analysis (GSEA) was performed using the Hallmark Gene Sets. DepMap gene effect scores were used to prioritize targets likely to have a useful therapeutic window based on median scores greater than for *EGFR* (0.66) but less than for common essential genes (1.0). The Open Targets platform was used to identify targets with inhibitors used in trials for other cancers and/or nonmalignant diseases. Associations between dependencies and genetic alterations were defined using two-sample t-tests, with filter conditions of $p<0.05$ and effect size ≥ 1.
Results: The 231 genes meeting selection criteria had a median gene effect score of 0.56. The criteria captured targets of standard therapeutic agents including *TYMS* (5-FU), tubulin genes (paclitaxel), *EGFR* (cetuximab), plus known oncogenes like *PIK3CA*. GSEA showed enrichment of known oncogenic signaling pathways including PI3K/AKT and JAK/STAT, as well as hallmark cancer processes like DNA repair and apoptosis. 90% were not known oncogenes in the OncoKB Database. 44 genes had a median gene effect score between that of *EGFR* and the median for common essential genes, including 7 without known cancer-promoting roles: *OTOP1, DHRSX*, *UTP11*,*MBTPS1*, *SLC25A3, PPIAL4G*, and *RBM10*. 17% had inhibitors that reached a non-HNSCC phase II trial, including 10 targets not previously tested in cancer. Novel associations between dependencies and genetic alterations included *DDX3X* with *NOTCH1mut*, *ITGB1* with *CDKN2Amut*, and *ATP1A1* with *HRASmut*.

0360-3016/$ - see front matter
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Conclusion: We catalog numerous targetable dependencies in cell line models of HNSCC. While well-studied targets were captured, many genes lacked known roles in malignancy. Targets of inhibitors tested in other diseases provide further resources to guide preclinical studies. Association of some dependencies with known molecular subgroups in HNSCC may enhance use of cell line models to personalize therapy.

Author Disclosure: A.C. Cao: None. **P. Rajagopalan**: None. **P.A. Gimotty**: None. **R. Brody**: None. **D. Basu**: None.

LBA-3

Patient-reported Outcomes in Oropharyngeal Cancer Treated With Definitive Chemoradiation vs. Surgery With Postoperative Radiation With or Without Chemotherapy

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Purpose/Objective(s): There are limited data comparing patient-reported outcomes (PROs) between definitive chemoradiation (CRT) and transoral surgery (TOS) among patients receiving proton therapy (IMPT). We compared PROs for pts treated with definitive CRT versus TOS and postop IMPT with or without chemotherapy.

Materials/Methods: We included patients with clinical T0-T2 N0-3 oropharyngeal cancer treated from 08/2019 − 08/2021 with CRT to 70 Gy IMPT or TOS with pathology-directed adjuvant IMPT (60 − 66 Gy) with or without chemotherapy. All received bilateral neck radiation. Patients completed MDADI and MDASI-HN questionaries prior to, weekly during, at 3 mos after and at annual intervals following IMPT. Comparisons between cohorts were made with the Mann-Whitney U test for continuous and $\chi 2$ test for categorical variables.

Results: 42 pts were treated: 23 definitive CRT, 8 TOS + adjuvant IMPT (T+aRT), and 11 TOS + adjuvant CRT (T+aCRT). There were no significant differences in age, comorbidity, smoking history, or tonsil vs base of tongue primary distribution between CRT and TOS cohorts. Chemo was weekly platinum-based (n=31), bolus cisplatin (n=2) or cetuximab (n=1). On baseline imaging, CRT pts had a larger average primary tumor volume (18.3 vs 5.6 cc, p=0.014) with similar nodal disease volume (36.5 vs 21.4 cc, p=0.076) compared to TOS patients. Primary tumor site was omitted from the RT target in 21% of TOS pts. A gastrostomy tube was placed in 39% of CRT patients vs 16% of TOS patients (p=0.17). Prior to adjuvant IMPT, TOS pts had a 19-point lower (worse) average MDADI score (86.1 vs 67.2, p=0.001) and a higher (worse) average MDASI-HN symptom (0.6 vs 2.4, p<0.001) and interference (1.0 vs 3.1, p=0.009) scores compared to non-operative pts prior to CRT. At the conclusion of IMPT, MDADI scores were not significantly different between CRT and TOS cohorts (57.5 vs 64, p=0.14), but were worse in those receiving CRT or T+aCRT compared to T+aRT alone (58.2 vs 70.1, p=0.048). At 3 mos post-IMPT (88% had complete PRO data) TOS pts had a 12-point lower (worse) average MDADI score compared to those treated with CRT (76.8 vs 64.5, p=0.037) with the most pronounced difference in T+aCRT pts (60.4) versus T+aRT (69.7). At 3 mos post-IMPT, there was no significant difference between CRT and TOS in average MDASI-HN symptom (1.5 vs 1.8 p=0.44) or interference scores (1.7 vs 1.6, p=0.8), average percent weight loss from consult (-10.5 vs -9.4%, p=0.53), or residual pain score (1.3 vs 2.9, p=0.066). Patients treated with CRT had fewer average days of hospitalization for any reason (0.5) compared to those treated with T+aRT (3.1, p<0.001) or T+aCRT (6, p<0.001).

Conclusion: Despite smaller average tumor volumes, lower dose RT, omission of chemo in 42% and omission of the primary site in 21%, TOS pts reported worse MDADI scores 3 mos after RT (6 mos after TOS) compared to proton-based CRT.

Author Disclosure: M.W. McDonald: Emory Proton Therapy Center. **J.E. Bates**: None. **M.R. Patel**: Advisory Board; Astra Zeneca. Travel Expenses; Intuitive Surgical. **B.J. Boyce**: None. **S. Rudra**: None. **A.S. Kaka**: None. **C. Steuer**: Research Grant; Vaccinex, Seattle Genetics, Daiichi Sankyo, Infinity Pharmaceuticals. Honoraria; Merck. Consultant; Abbvie, BerGenBio, ARMO BioSciences, Lilly. **D.M. Shin**: None. **S. Tian**: Research Grant; Varian. **M.R. Nathan**: None. **J.M. Waller**: None. **S.E. Thomas**: None. **J.S. Remick**: None. **T. Barrett**: None. **L. Ottenstein**: None. **N.F. Saba**: Research Grant; BMS, Exelixis. Consultant; Eisai, Astra Zeneca, Merck, WebMD, OncLive, Mirati, Reach MD, Vaccinex, Kura, Biontech, GSK, Aduro, Pfizer. **W.A. Stokes**: None.