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Title: Characterization of the immune microenvironment of recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) that progress on or after platinum and anti-PD(L)1 therapies – An EORTC IMMUcan sub-project

Background: R/M SCCHN patients that progress after platinum therapy and PD-1 inhibitors represent an unmet medical need. A better characterization of the tumor molecular landscape and immune micro-environment is needed to guide the rational development of new therapeutic approaches.

Methods: EORTC1559 is a biomarker-driven study including patients with R/M SCCHN. Tumor biopsies are collected at time of patient enrolment to perform WES, RNAseq, multiplex immunofluorescence (mIF) and Imaging Mass Cytometry (IMC).

Results: 95 R/M SCCHN patients were included (oropharynx 50% (HPV+ 13%), oral cavity 23%, hypopharynx 19%, larynx 8%). All patients progressed on/after platinum therapy and 80% of them (n= 76) progressed on/after anti-PD(L)1. Preliminary transcriptomic analyses on 83 patients indicated that the last regimen given before tumor biopsy had a significant impact on the immune infiltrate. For instance, patients treated with anti-PD(L)1 as last treatment before biopsy (n=38) had a significantly (p= 0.001) higher tumor immune score (ESTIMATE immune score) compared to patients that received other systemic therapies such as taxanes as last treatment. LAG3 expression was significantly higher in the tumor of patients treated with anti-PD(L)1 as last treatment compared to patients never exposed to anti-PD(L)1 (n=15) (padj = 0.001) and to patients pre-treated with anti-PD(L)1 in previous line (n=30) (padj = 0.002). Genomic analyses on n=95 showed median TMB was 4.6mut/MB (range 0.8-46.1). Correlation between TMB and tumor immune score was weak (r= 0.25, p= 0.02). The most frequent oncogenic non-synonymous mutations were found in genes *TP53*, *LRP1B*, *PIK3CA*, *FAT1*, and *CDKN2A*. Interestingly, 2 and 3 patients progressing on anti-PD(L)1 had mutations in *TAP2* and *STK11,* respectively, which were not found in anti-PD(L)1-naive patients.

Conclusion: Preliminary results suggest that patients progressing on anti-PD(L)1 administered as last treatment have a higher tumor immune score and LAG3 expression. We will validate our findings on 85 additional patients and integrate our RNAseq and WES analyses with mIF and IMC analyses.

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