

**POSTER PRESENTATION**

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# Level of PD-1 expression on CD8<sup>+</sup> T cells influence prognosis and respond to PD-1 therapy in a murine model

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## Introduction

Prognosis varies dramatically in head and neck squamous cell carcinoma (HNSCC) based on HPV status. In HPV<sup>+</sup> patients, programmed death (PD)-1 expression has been linked to a better clinical outcome. We hypothesized that extent of PD-1 expression may differentially impact T cell phenotype, patient prognosis and response to anti-PD-1 immunotherapy in a murine HPV<sup>+</sup> cancer model.

## Material and methods

Freshly isolated tumor infiltrating lymphocytes (TIL) from HNSCC patients were stained by flow cytometry for expression level of PD-1 expression (PD-1<sup>high</sup> vs. PD-1<sup>low</sup>), granzyme B, or IFN- $\gamma$  secretion by ELISPOT. The prognostic impact of PD-1<sup>high</sup> vs. PD-1<sup>low</sup> T cells was determined in a cohort of HNSCC patients (n=56, median follow up=19 mo). In a murine HNSCC model, PD-1<sup>high</sup> and PD-1<sup>low</sup> fractions were compared from CD3<sup>+</sup> CD8<sup>+</sup> PD-1<sup>+</sup> cells and analyzed according to different treatment groups (untreated, anti-PD-1 mAb, radiotherapy and 3 different anti-PD-1/radiotherapy combinations).

## Results

CTLA-4 and PD-1 were significantly upregulated on both HPV<sup>+</sup> and HPV<sup>-</sup> HNSCC patients' TIL, whereas PD-1<sup>+</sup> CD8<sup>+</sup> cells were significantly enriched in TIL from HPV<sup>+</sup> patients (p=0.006). Interestingly, PD-1<sup>high</sup> cells represented a more dysfunctional phenotype, with severely

compromised IFN- $\gamma$  secretion (phigh CD8<sup>+</sup> TIL were more likely to be HPV<sup>-</sup> and had a worse disease free survival (HR = 2.25; 95% CI = 1.46 – 3.15; p < .0001), while high fractions of PD-1<sup>low</sup> T cells were associated with better clinical outcome (HR= 0.19, 95% CI = .07 - .49, p = .0006), and were seen preferentially in HPV<sup>+</sup> HNSCC patients. In the murine HNSCC model, anti-PD-1 mAb plus radiotherapy resulted in optimal tumor elimination, which was associated with an elimination of PD-1<sup>high</sup> CD8<sup>+</sup> T cells and – most importantly – increase in PD-1<sup>low/intermed</sup> T cell frequencies (p < 0.5).

## Discussion

Consideration of different PD-1 expression levels on TIL segregates PD-1 expression as a marker of activated, competent tumor reactive T cells on the one hand (low/intermed expression), and as a marker of exhausted, dysfunctional cells in the tumor microenvironment on the other hand (high expression). These results emphasize the crucial role of differential PD-1 expression levels on HNSCC patients' effector T cells for prognosis and as a potential novel biomarker for anti-PD-1/PD-L1 based immunotherapy.

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