31P Characterization of pre-exhausted / exhausted state of CD8+ T cells in HRAS mutant head and neck carcinomas (HNSCCs). Implications for response to immune checkpoint blockade (ICB).

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Introduction

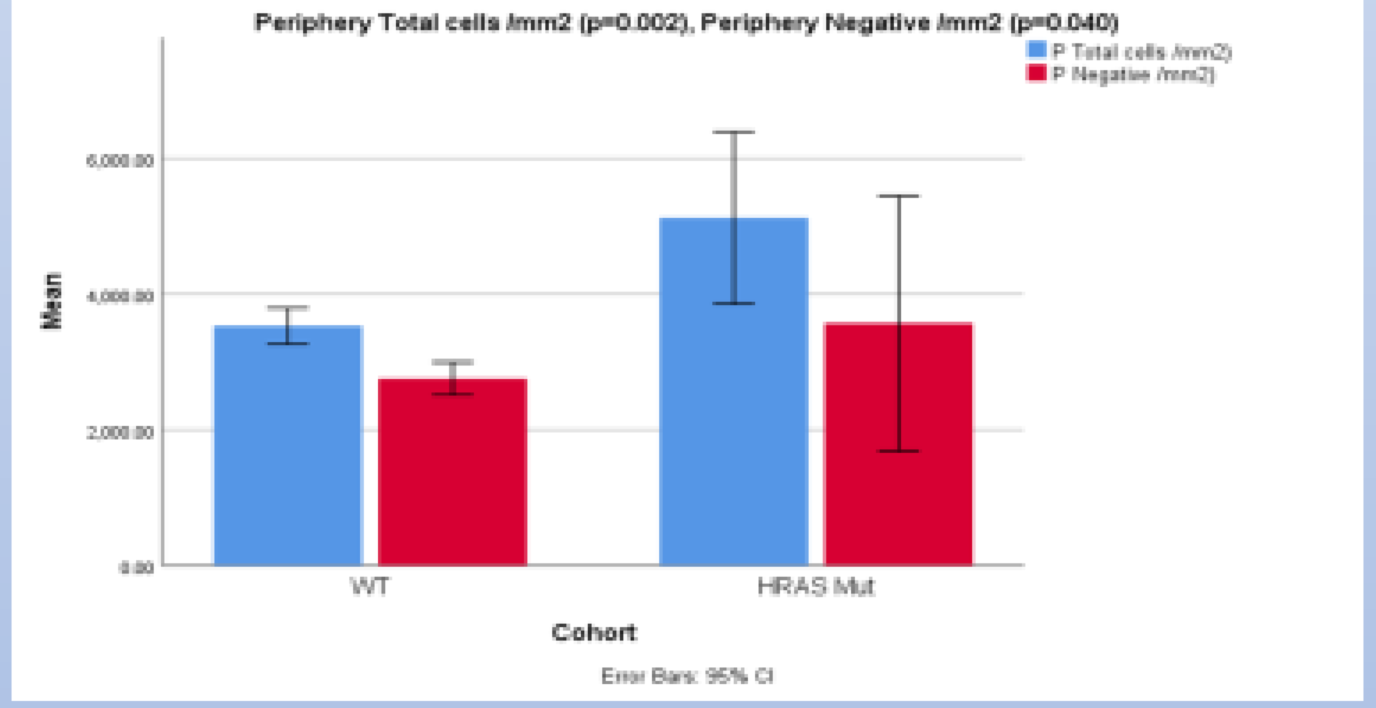
HRAS mutations have been found in approximately 6% of HNSCCs according to emerging molecular analysis data. There is little information about the sensitivity of *HRAS*-mutant tumors to ICB. T cell exhaustion, defined as dysfunctional T cells stimulated by continuous antigen exposure, has a significant impact on ICB response. To guide immunotherapeutic approaches, we sought to assess the immune landscape of HRAS-mutant tumors by investigating the subpopulations of pre-exhausted (PD-1(+) TCF-1(+)) and exhausted (PD-1(+) TCF-1(-)) T cells.

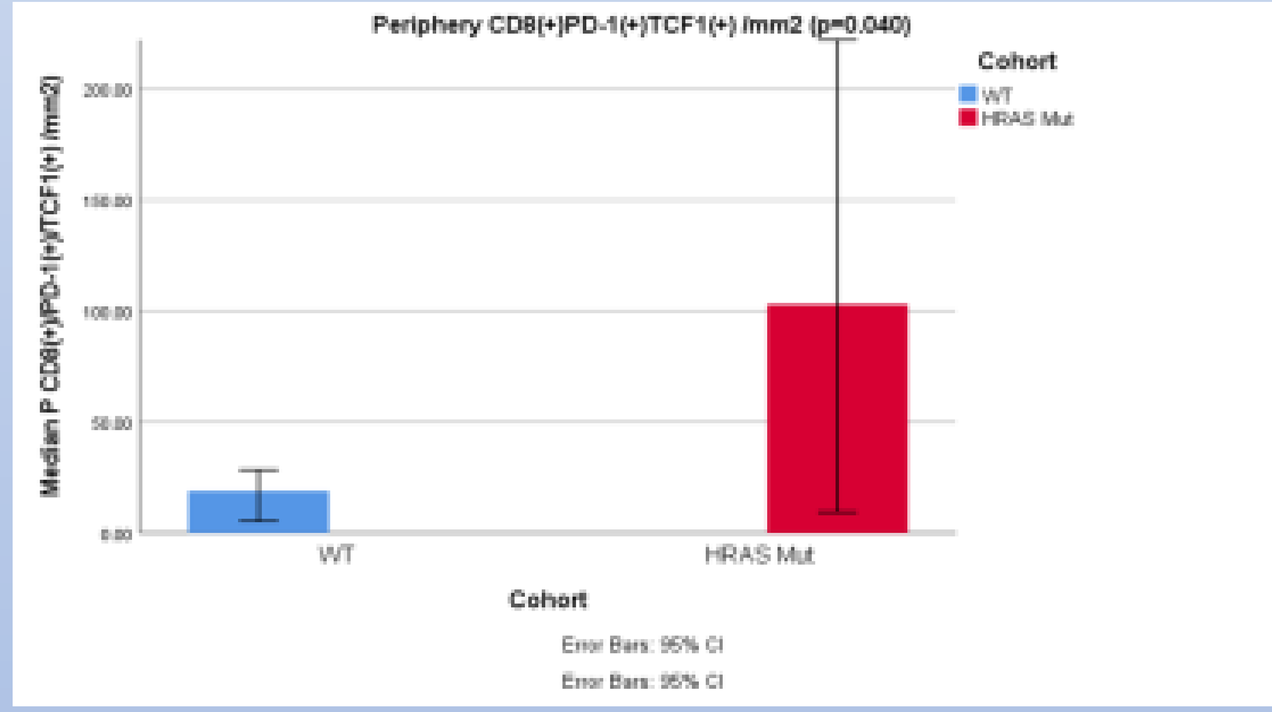
Methods

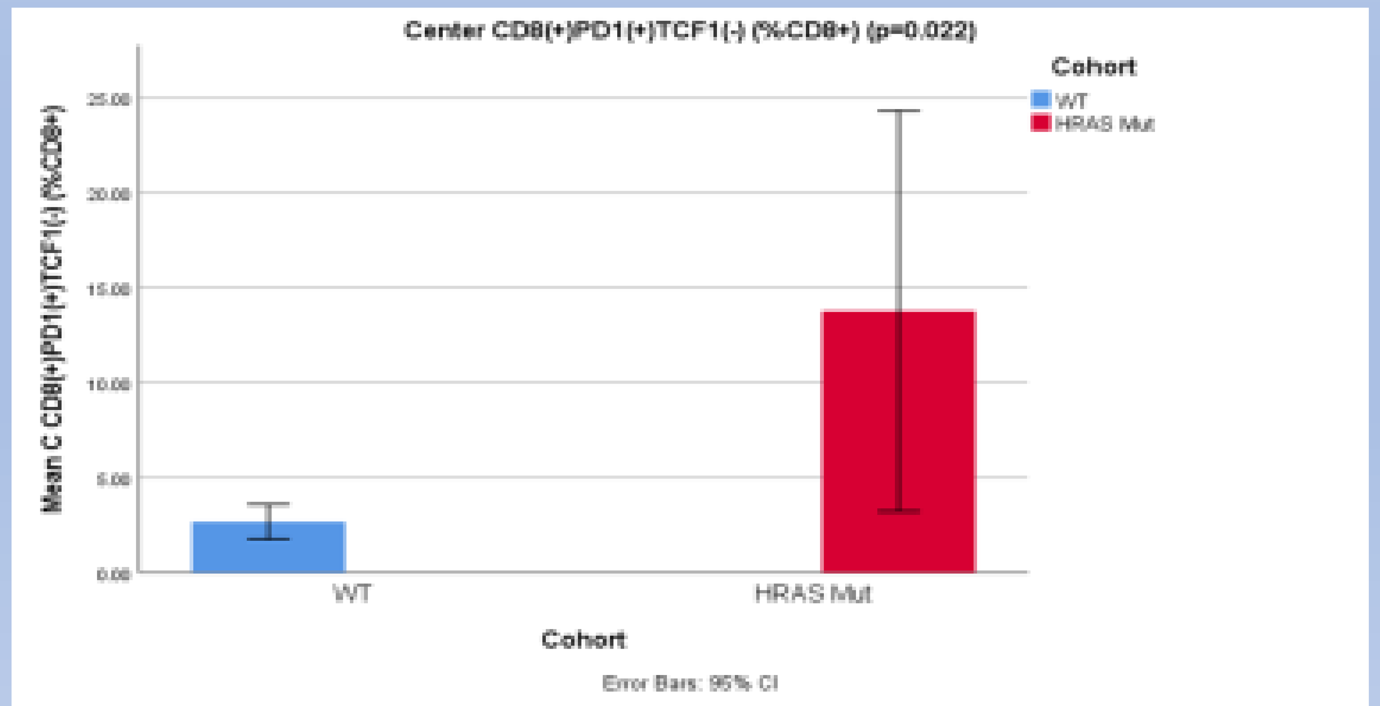
- We found 10 cases of *HRAS* mutant tumors and 39 cases of *HRAS* wild-type (WT) tumors.
- We sought to characterize exhausted CD8+ T cell subpopulations by measuring the expression of T-cell Factor-1 (TCF-1), a marker of T-cell stem-like properties, and PD-1 in the tumor's center (C) and periphery (P).
- Multiplex immunohistochemistry (IHC) was performed in FFPE tissue sections using three primary antibodies (PD1-CD8-TCF1/7), followed by analysis of a manually trained algorithm in Qupath software.

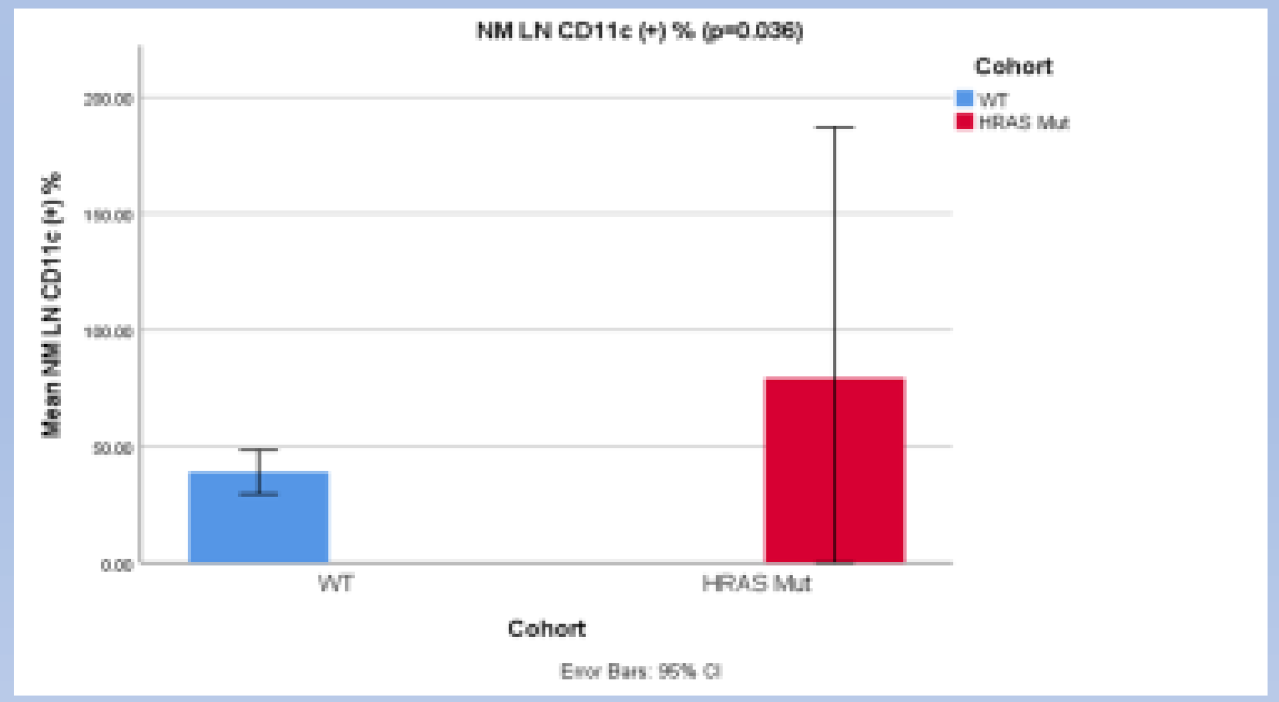
Results

- *HRAS* mutant tumors present higher numbers of total immune cells both in the C and the P , that reached statistical significance only in the P (p=0.002).
- The density of CD8+ T Cells was increased in both the C (694.10/mm^2 vs. 356.02/mm^2) and the P (851.10/mm^2 vs. 333.30/mm2) in *HRAS* mutant tumors.
- The percentage of pre-exhausted CD8 (+) T Cells was elevated in the P of *HRAS* mutant tumors (p=0.040), indicating a possible association of response to ICB, since pre-exhausted T cells mediate the proliferative response to immunotherapy.
- Exhausted T cells, were more abundant in the C of *HRAS* mutant tumors compared to WT (13.77% vs. 2.67% of total CD8+ cells, p=0.022).
- Increased area occupied by CD11c+ dendritic cells and CD8+ T cells were found in regional LNs from *HRAS* mutant patients (p=0.036), consistent with data showing that maintenance of TCF1 by intratumoral T cells requires continuous migration from draining LNs.


Periphery Total cells /mm2 (p=0.002), Periphery Negative /mm2 (p=0.040)
P Total cells /mm2)
P Negative /mm2)
Mean
WT
HRAS Mut
Cohort
Error Bars: 95% CI


Periphery CD8(+)PD-1(+)TCF1(+) /mm2 (p=0.040)
Cohort
WT
HRAS Mut
Median P CD8(+)PD-1(+)TCF1(+) /mm2)
Error Bars: 95% CI
Error Bars: 95% CI


Center CD8(+)PD1(+)TCF1(-) (%CD8+) (p=0.022)
Cohort
WT
HRAS Mut
Mean C CD8(+)PD1(+)TCF1(-) (%CD8+)
Error Bars: 95% CI


NM LN CD11c (+) % (p=0.036)
Cohort
WT
HRAS Mut
Mean NM LN CD11c (+) %
Error Bars: 95% CI

Conclusions

Pre-exhausted PD-1(+) TCF-1(+) T cells are significantly increased at the periphery of *HRAS* mutant tumors, suggesting a potential sensitivity of these tumors to ICB.

COI Disclosure Information
Presenter: Ioannis Kotsantis
I have the following financial relationships to disclose:
Honoraria for advisory board activities: AMGEN HELLAS.

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