THE IMMUNOLOGIC LANDSCAPE OF HRAS MUTANT HEAD AND NECK SQUAMOUS CELL CARCINOMA

Economopoulou P.[1], Rampias T.[2], Spathis A.[3], Kotsantis I.[1], Kyriazoglou A.[1], Anastasiou M.[1], Pantazopoulos A.[1], Gomatou G.[1], Kavourakis G.[1], Margeli A. , Papageorgiou M. [1], Boulouta A.[1], Moutafi M. [1], Gavrielatou N.[1], Kirkasiadou M.[1], Zazas E.[1], Caglar C.[1], Frantzi T.[1],Gkaralea L.[1], Kalfoutzou A.[1], Rouboutsou M.[1], Foukas P.[3], Psyrri A.[1]

[1]Oncology Unit, 2nd Department of Internal Medicine, National and Kapodistrian University of Athens, Attikon University Hospital, [2]Biomedical Research Foundation Academy of Athens, [3]Second Department of Pathology, National and Kapodistrian University of Athens, Attikon University Hospital

INTRODUCTION

- *HRAS* mutations define a distinct biologic subset of head and neck squamous cell carcinoma (HNSCC). There is limited data regarding *HRAS* mutant (*HRAS* mut) tumors' sensitivity to immunotherapy.
- In this translational study, we sought to a) analyze the genomic landscape of *HRAS* mut HNSCC to assess the prognostic impact of concurrent mutations in *HRAS* mut tumors and their potential impact on modulating the T-cell inflamed phenotype, and b) assess the immune microenvironment of *HRAS* mut tumors by exploring the subpopulations of pre-exhausted and exhausted T cells to provide the conceptual framework for combinatorial strategies.

METHODS AND MATERIALS

- We analyzed mutational and transcriptome data from The Cancer Genome Atlas (TCGA).
- In addition, genomic DNA from baseline tumor biopsies was targeted for sequencing.
- Our study included 10 patients with *HRAS* mut and 40 with *HRAS* wild-type (WT) HNSCC.
- PD-L1 expression in FFPE tumor samples was assessed using the PD-L1 IHC 22C3 pharmDx assay.
- We characterized subpopulations of exhausted CD8(+) T cells by measuring the expression of T-cell Factor-1 (TCF1) and PD-1 in both the center and the periphery of the tumors using multiplex immunohistochemistry, followed by analysis using a manually trained algorithm in Qupath software.

RESULTS

- The analysis of TCGA HNSCC mutation and mRNA expression data demonstrated that 6% of HNSCC harbor mutant *HRAS.* whereas 4.7% of HNSCC overexpress WT *HRAS* (HRAS WT^{OV}group).
- Transcriptome analysis showed that *HRAS* mut HNSCCs are infiltrated by immune cells (CD8A, CD8B, CD2) and have higher expression levels of CXCL11, CXCL10, CXCL9, and CCL4 chemokines.
- Moreover, the percentage of *HRAS* mut samples increased in higher PD-L1 score groups (11% vs. 20% vs. 100% in Tumor Positive Scores (TPS) <1%, 1-49% and ≥50% respectively, *p*=0.006).

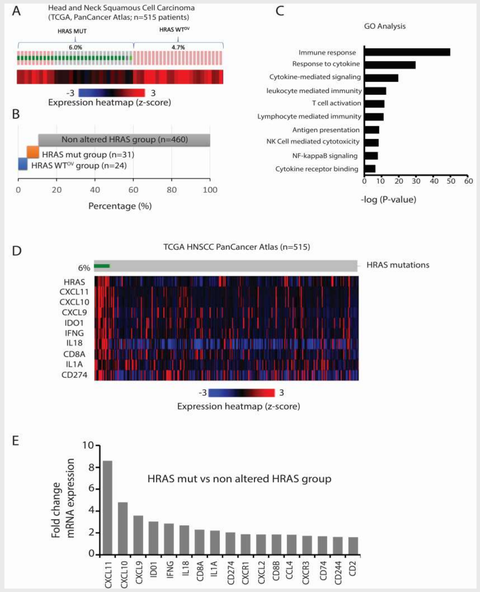

Figure 1. HRAS alterations in HNSCC

RESULTS

- The analysis of TME showed that *HRAS* mut tumors have statistically significant higher numbers of total immune cells (5123.17/mm^{2}vs. 3527.93/mm^2, p=0.002) and a higher percentage of pre-exhausted CD8 (+) PD-1(+) TCF1(+) T Cells in the periphery (384.67/mm2vs. 51.18/mm2, *p*=0.040) than *HRAS* WT tumors.

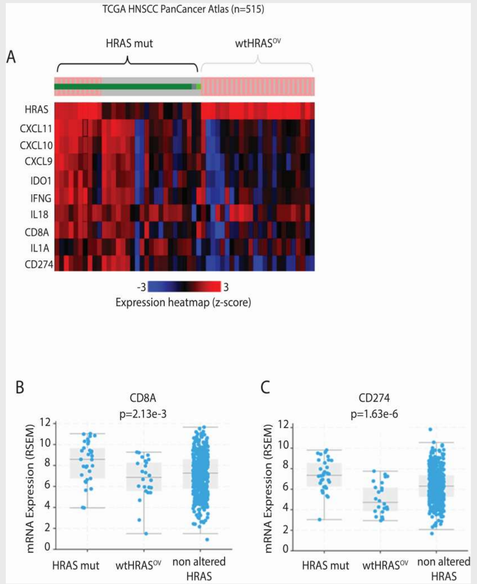

Figure 2. Immune profile of tumors with *HRAS* alterations in HNSCC

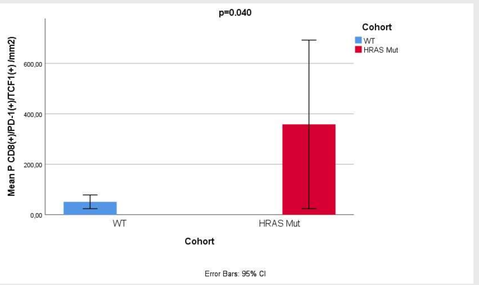

Figure 3. Bar graph showing that the percentage of pre-exhausted CD8 + T Cells, is elevated in the P of *HRAS* mut tumors .

DISCUSSION- CONCLUSIONS

- Our study represents a pioneering effort to evaluate the immune context of *HRAS* mut HNSCCs.
- We show for the first time that *HRAS* mut tumors are characterized by a significantly higher number of total immune cells, pre-exhausted PD-1(+) TCF1(+) T cells, and PD-L1 expression, suggesting a potential sensitivity of these tumors to immunotherapy alone or in combo with tipifarnib

REFERENCES

Funding: Kura Oncology, Inc., supported the work.

Kareff SA, Trabolsi A, Krause HB, et al. The Genomic, Transcriptomic, and Immunologic Landscape of HRAS Mutations in Solid Tumors. Cancers. 2024;16(8).

Coleman N, Marcelo KL, Hopkins JF, et al. HRAS Mutations Define a Distinct Subgroup in Head and Neck Squamous Cell Carcinoma. JCO precision oncology. 2023;7:e2200211.

CONTACT

P Economopoulou, MD, OhD
Attikon Univeroty Hosiptal
Email: panagiota.oiko@gmail.com