Abstract # 48

Molecular characteristics of HRAS mutated non-small cell lung cancer

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BACKGROUND

- Alterations in the **RAS pathway** have been linked to tumorigenesis, cellular apoptosis, metabolism and angiogenesis . Mutations of **KRAS in non-small cell lung cancer (NSCLC) are more frequent** and well-studied.
- Other family members such as **HRAS** remain **under investigated,** and RAS remains a challenging therapeutic target.
- HRAS has been indirectly targeted with tipifarnib, a farnesyltransferase inhibitor, rendering HRAS inactive in head and neck tumors
- Here, we characterize the **incidence, genomic landscape, and clinical context of HRAS alterations in NSCLC.**

METHODS

- 29,767 NSCLC tumor tissue samples underwent comprehensive molecular profiling at Caris Life Sciences. Analyses included next generation **sequencing of DNA, RNA and immunohistochemistry (IHC).**
- MAPKinase activation was assessed using the MPAS gene expression signature (Wagle et al., npj Precision Oncology, 2018).
- Survival data was calculated from the date of sample collection to last of contact using insurance claims.

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RESULTS

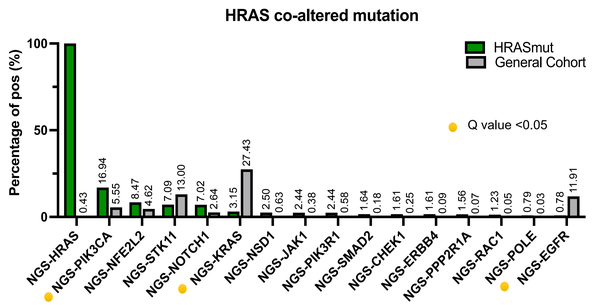

Figure 1. HRAS Co-mutations

Table 1. Hotspot mutations of HRAS in NSCLC.

Cohorts	NSCLC (total = 29767)			
Alteration Type	Mutation (total = 128, 0.43%)			
Mutation type	Q61	G12	G13	other pathogenic/likely pathogenic
Cases with alterations	43 (33.59%)	27 (21.09%)	54 (42.19)	4

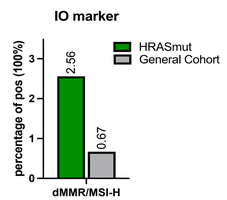

Figure 2. dMMR/MSI status in Hm and GC.

- HRAS mutations (Hm) were detected in 128 of 29,767 NSCLC samples **(0.4%)** and were significantly enriched in **older** patients (median age, 71 vs. 69 years; q<0.01) and in **squamous** histology (57.8% vs 21.8%, q<0.0001) compared to the general cohort (GC). Smoking status was not associated with HRAS mutational status (p=0.19).
- The most prevalent loci of hotspot mutations in Hm tumors were **G13,** followed by Q61 and G12 **(Table 1).**
- Hm-positive tumors harbored significantly **more PIK3CA mutations** but **fewer KRAS** and **EGFR** mutations when comparing to GC **(Figure 1).**
- **Hm are mutually exclusive with EGFR mutations.**
- Hm displayed dMMR/MSI-H deficiency more frequently, but had a comparable percentage of TMB-H tumors (34.2% vs 40.2%, p = 0.16) and similar median PD-L1 expression (54.7% vs 60.3%, p = 0.21) when comparing to GC **(Figure 2).**

Hm Tumors have a **higher frequency of MSI-H** phenotype.

SURVIVAL ANALYSIS

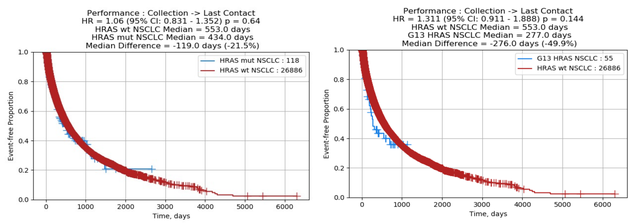

Figure 3. Overall survival of GC compared to Hm (Left) and G13Hm (Right)

- HRAS was not prognostic for overall survival (HR = 1.06, 95% CI [0.83-1.35], p = 0.64)
- for HRAS G13 mutant subset of NSCLC there was a trend towards worse prognosis (HR = 1.31, 95% CI [0.91-1.88], p =0.14).

DISCUSSION

- HRAS mutations are detectable but uncommon in NSCLC and significantly enriched in squamous histology.
- HRAS mutations often occur with PIK3CA co-mutations.
- Hm tumors have a higher frequency of MSI-H phenotype.
- Some samples could have originated from a primary head and neck cancer.
- This warrants further investigation into possible clinical applications of HRAS pathway inhibitors and utility of immune checkpoint inhibitors for this subset of NSCLC.

REFERENCES

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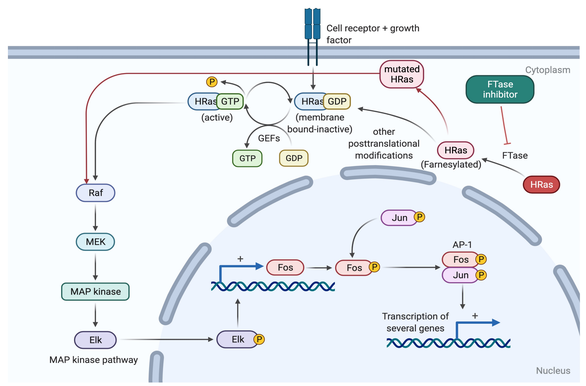
2. *Ho AL, Brana I, Haddad R, et al. . Tipifarnib in Head and Neck Squamous Cell Carcinoma With HRAS Mutations. J Clin Oncol 2021;39:1856-1864.*
3. *Marin-Ramos NI, Ortega-Gutierrez S, Lopez-Rodriguez ML. Blocking Ras inhibition as an antitumor strategy. Semin Cancer Biol 2019;54:91-100.*



Graphical abstract: HRAS pathway. Figure created by BioRender