Clinicopathologic characteristics of HRAS Mutant Head and Neck Squamous Cell Carcinoma

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BACKGROUND

- RAS mutations are often associated with tumor development and immune evasion and therefore unfavorable clinical outcomes.
- Farnesyl transferase inhibitors (FTI) are an emerging therapeutic option for HRAS mutant HNSCC (Hm)
- Understanding the genomic and immunologic landscape of Hm is important for further development of this therapeutic approach.

METHODS

- A total of 2,407 HNSCC tissue went through tumor molecular profiling at Caris Life Science (Phoenix, AZ).
- Analyses included next-generation sequencing of DNA and RNA, and immunohistochemistry (IHC).
- HPV 16/18 status was assessed using WES.
- MAPK pathway activation and the likelihood of a tumor's response to anti PD1 therapy were tested via MPAS and IFN signatures, respectively.
- Wilcoxon, Fisher's exact were used for statistical significance
- Overall survival was calculated from date of tissue collection to last contact from insurance claims data and compared using Kaplan-Meier method.
- All comparisons were made between Hm and the entire Head and Neck Squamous Cell Carcinoma (HNSCC) general cohort (GC).

RESULTS

- Hm significantly correlated with male gender and older age
- No difference in HPV status was observed.

HnN	Total	HRAS		qvalue
	2407	Positive (N) 69 **(2.87%)**	Negative (N) 2338	
Gender, n (%)				
Male Female	1830 (76.0) 577 (24.0)	41 (59.4) 28 (40.6)	1789 (76.5) 549 (23.5)	<0.01
Age (median)	64.1 (15 - >89)	68.6 (35 - >89)	64.0 (15 - >89)	<0.01
HPV status	1180	38	1142	
HPV16, n (%) + -	347 (29.4) 833 (70.6)	8 (21.1) 30 (78.9)	339 (29.7) 803 (70.3)	ns
HPV18, n (%) + -	11 (0.9) 1169 (99.1)	0 (0) 38 (100)	11 (0.9) 1131 (99.1)	ns

Table 1. Association between Hm and clinico-pathological features.

- Hm had worse prognosis when comparing to HRAS wildtype tumors.
- Hm correlated with more TERT, FAT1 mutations, lower p16 expression, PD-L1 expression and TMB-H
- PIK3CA Hm were mutually exclusive with TMB-H tumors in Hm.

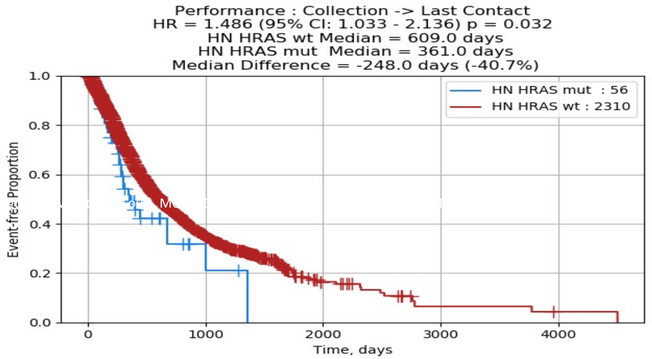

Figure 1. Prognostic value of Hm in HNN patients.

- Hm had higher activation of MAPK signaling, indicated by higher MPAS scores when comparing to GC, The most prevalent point mutation was G13 (Table 2). Q61 and G13 had significantly higher scores with respect to GC.

Cohorts	HNN (total = 2407)			
Alteration Type	**Mutation (total = 69, 2.87%)**			
Mutation type	Q61	G12	G13	others
Cases	21 (30.34%)	22 (31.88%)	24 (34.78%)*	2 (2.98%)

Table 2. Prevalence of different HRAS point mutations in HNN patients

- Hm showed higher immunogenicity, evidenced by higher IFN score, higher fraction of macrophage M1 but higher fraction of macrophage M2, more CD8+ T cells and elevated expression level of MHC1 class I genes .

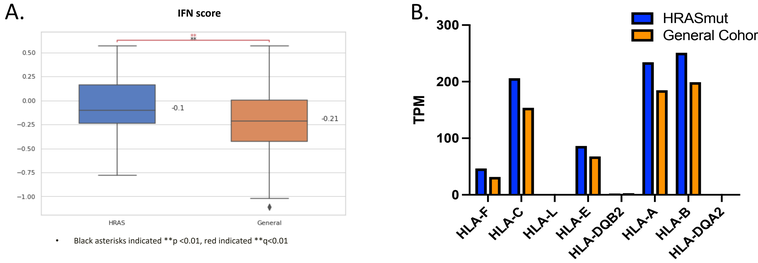

Figure 4. A) IFN scores between Hm and GC; B) mRNA expression levels of HLA genes in Hm and GC

CONCLUSION

- Our findings provide additional evidence for ongoing clinical trials on combinatorial immunotherapy or PI3KCA inhibitors with FTI and demonstrate unique landscape of different point mutations; further evaluation is warranted.