Tumor Microenvironment (TME) of HRAS Mutated Non-Small Cell Lung Cancer (NSCLC).

Asaad Nabhan, MD
Estelamari Rodriguez, MD, MPH; Samuel A. Kareff, MD, MPH; Jesus Antonio Ocejo Gallegos MD; Jun Yin PhD; Philip Walker, PhD; Patrick C. Ma, MD; Hirva Mammadani, MD; Jorge Nieva, MD; Hossein Borghaei, DO, MS; Chadi Nabhan, MD MBA FACPD; Misako Nagasaki, MD; Sonam Puri, MD; Stephen Liu, MD; Balazs Halmos MD, PhD; Philip Walker, PhD

BACKGROUND

• RAS pathway alterations in NSCLC have been linked to worse prognosis and remains a challenging therapeutic target.
• Other family members such as HRAS are 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.
• Although KRAS has been associated with immune modulation in NSCLC, the role of HRAS remains unclear. We aimed to investigate the relationship of HRAS gene mutations and the TME.

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).
• immune cell fraction (ICF, QuanTiseq) were assessed by mRNA analysis. Wilcoxon, Fisher’s exact were used for statistical significance.
• Survival data was calculated from the date of sample collection to last of contact using insurance claims.

RESULTS

• HRAS mutations (Hm) were detected in 128 of 29,767 NSCLC samples (0.4%) and were mostly smokers.
• HRAS mt showed trending association with worse prognosis in patients(pts) treated with pembrolizumab (pembo) (HR = 1.667, 95% CI [0.921-3.017], p= 0.088) and displayed less B cell, macrophage M2, NK cell, CD4+ and CD8+ Tcells infiltrates compared to GC (Table 1).
• HRAS Q61 was correlated with worse prognosis in pts treated with pembo (HR = 2.779, 95% CI 0.85-8.05, p = 0.08) and displayed less B cell, macrophage M2, NK cell, CD4+ and CD8+ Tcells infiltrates compared to GC.
• HRAS mt SCC also showed an immune-cold TME associated with high MAPK pathway activation and high LAG3 expression.

DISCUSSION

• HRAS mt NSCLC displayed a relatively immune-cold pattern with less CD4+ and CD8+ T cells infiltrates compared to GC with a trend towards inferior OS for patients treated with pembo.
• HRAS mt SCC also showed an immune-cold TME associated with high MAPK pathway activation and high LAG3 expression.

This warrants further investigation, in particular in HRAS Q61 or HRAS mt SCC, with combination therapies targeting MAPK pathway or LAG3 protein.

Graphical abstract: HRAS pathway. Figure created by BioRender.