

## TTLIC 2026 Abstract:

### Clinical, Pathologic, and Genomic Characterization of Non-Small Cell Lung Cancers with *NRAS* or *HRAS* Mutations

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#### Background:

*NRAS* and *HRAS* mutations distinguish rare but clinically relevant molecular subtypes of non-small cell lung cancers (NSCLC). Emerging preclinical and early clinical data suggest that these subtypes may respond to RAS pathway inhibitors; however, their clinical, pathologic, and genomic features remain less well characterized.

#### Methods:

We reviewed a consecutive series of 11,732 patients with NSCLC treated at Memorial Sloan Kettering Cancer Center who underwent tumor molecular profiling using MSK-IMPACT from January 2014 to October 2025. MSK-IMPACT is a hybrid-capture based next generation sequencing assay that targets 341-505 genes. Demographic information, smoking history, PD-L1 status, disease stage and treatment course were collected through manual chart review by medical oncologists. Tumor histology was reviewed and confirmed by thoracic pathologists.

#### Results:

We identified 92 cases harboring *de novo NRAS* (n=68) or *HRAS* (n=24) mutations. Additionally, 15 cases had *NRAS* or *HRAS* mutations that co-occurred with various pre-existing oncogenic drivers (e.g., *EGFR*-sensitizing mutations, *BRAF V600E*, *MET* alterations, *ALK* fusion), suggesting acquired resistance. Among cases with *de novo NRAS* mutations (n=68), the most common subtypes were *NRAS Q61L* (47.1%), *NRAS Q61K* (14.7%) and *NRAS Q61R* (13.2%). Among cases with *de novo HRAS* mutations (n=24), the most common subtype was *HRAS G13V* (25.0%). The most common histology subtypes were lung adenocarcinomas (68.5%) and lung squamous cell carcinoma (14.1%), with less common subtypes including NSCLC NOS, large cell neuroendocrine carcinoma, pleomorphic carcinoma, carcinoid tumor. Overall, the median age was 67 (range: 45-89), 55.4% were female, and 97.8% were former/current smokers. Among cases with PD-L1 testing available (n=71): PD-L1 expression of 0%, 1-49%, and 50-100% were reported in 40.8%, 22.5%, and 36.6% of cases, respectively. Co-occurring alterations were identified in *TP53* (85.9%), *STK11* (14.1%), *KEAP1* (5.4%), and *SMARCA4* (4.3%). At the time of sample collection for molecular profiling, 52.2% of patients had stage IV disease, while 22.8%, 6.5%, and 18.5% had stage I, II, III disease, respectively. Among patients who developed metastatic disease and received first line chemoimmunotherapy (n=14), median time-on-treatment was 7.6 months.

#### Conclusions:

*NRAS*- and *HRAS*- mutant NSCLC represent a rare (<1%) yet clinically relevant disease subset with emerging therapeutic potential. We characterized the clinical, pathologic, and genomic features of NSCLC harboring *NRAS* or *HRAS* mutations, which were associated with tobacco exposure, lung adenocarcinoma histology, and frequent co-occurring *TP53* alterations.