Characterization of KRAS mutations in non-small cell lung cancer (NSCLC)

Stephen V. Liu[1], Ari M. Vanderwalde[2], Hirva Mamdani[3], Luis E. Raez[4], Yasmine Baca[5], Joanne Xiu[5], W. Michael Korn[5], Misako Nagasaka[3], Sachin Gopalkrishna Pai[6], Mark A. Socinski[7], Jorge J. Nieva[8], Chul Kim[1], Antoinette J. Wozniak[9], Chukwuemeka Ikpeazu Sr. [10], Gilberto Lopes[10], Alexander I. Spira[11], Julia Judd[12], Edward S. Kim[13], Hossein Borghaei[14]

[1]Georgetown University, Washington, DC; [2]University of Tennessee Health Science Center, West Cancer Center, Germantown, TN; [3]Barbara Ann Karmanos Cancer Institute, Detroit, MI; [4]Memorial Cancer Institute, Florida International University, Miami, FL; [5]Caris Life Sciences, Phoenix, AZ; [6]University of South Alabama, Mobile, AL; [7]AdventHealth Cancer Institute, Orlando, FL; [8]University of Southern California, Los Angeles, CA; [9]Hillman Cancer Center University of Pittsburgh, Pittsburgh, PA; [10]University of Miami Health System, Miami, FL; [11]Virginia Cancer Specialists, Fairfax, VA; [12]Temple University Health System, Philadelphia, PA; [13]Levine Cancer Institute/Atrium Health, Charlotte, NC; [14]Fox Chase Cancer Center, Philadelphia, PA

Background

KRAS is the most commonly mutated oncogene in NSCLC and the development of direct KRAS inhibitors has renewed interest in this challenging molecular subtype. However, there are several distinct KRAS mutations, each with a unique biology and a different prognostic and therapeutic impact. A more comprehensive understanding of the genomic landscape relative to each KRAS mutation subset will help guide therapeutic development.

Methods

- Molecular profiles of 17,113 NSCLC specimens were obtained using NGS of 592 genes (Caris Life Sciences) and classified based on specific types of KRAS mutations. Incidence of KRAS mutations were noted across the cohort and by histology.
- PD-L1 IHC testing was performed using the 22c3 antibody clone (Dako). Tumor Proportion Score (TPS) was measured as the percentage of viable tumor cells showing partial or complete membrane staining at any intensity.
- Tumor mutational burden (TMB) was measured from 592 genes (1.4 megabases [MB] sequenced per tumor) by counting all nonsynonymous missense mutations found per tumor that had not been previously described as germline alterations. TMB-high was defined as ≥10 mutations/MB.
- A combination of multiple test platforms including NGS, IHC and fragment analysis was used to determine MSI-H/dMMR status.
- Co-occurring genomic alterations, TMB and PD-L1 TPS were analyzed by KRAS mutation type.

Results

Table 1: Patient characteristics in KRAS subtypes

- Across 17,113 NSCLC samples, KRAS mutations were present in 27% of samples(n=4706)
- KRAS mutations were more prevalent in female patients (31.35%) than male patients (23.7%), p<0.0001

KRAS Categories	Female	Male	Total
WT	5862	6527	12,389
G12C	1102	780	1882
G12V	504	411	915
G12D	386	298	684
G13 Any	184	143	327
Q61 Any	175	138	313
G12A	160	138	298
G12 Other	130	80	210
Other	36	41	77

Table 2: KRAS mutation categories

KRAS protein change	category	N
G12S	G12 Other	71
G12R		62
G12F		62
G12I		6
G12L		3
G12Y		2
G12E		2
G12W		1
G12N		1
G12A	G12A	298
G12C	G12C	1882
G12D	G12D	684
G12V	G12V	915
G13C	G13 Any	186
G13D		117
G13V		9
G13E		8
G13Y		2
G13dup		1
G13F		1
G13H		1
G13P		1
G13R		1
Q61H	Q61Any	227
Q61L		66
Q61K		10
Q61R		9
Q61E		1

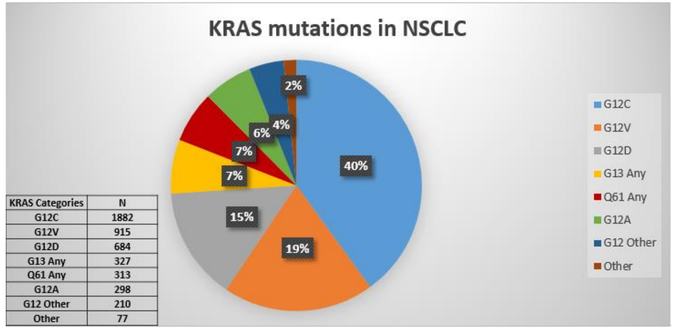
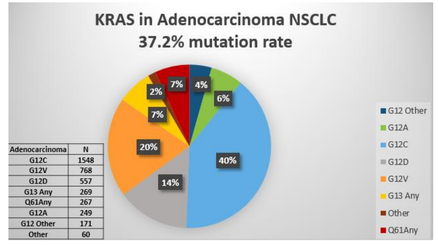


Figure 1: *KRAS* mutational distribution in NSCLC and in adenocarcinoma and squamous subtypes.

- *KRAS* mutations were seen in 37.2% of adenocarcinoma and only 4.4% of squamous NSCLC
- *KRAS* G12C was the most common (40% overall) in both adenocarcinoma and squamous NSCLC
- *KRAS* G12V (19%) and *KRAS* G12D (15%) were next most common



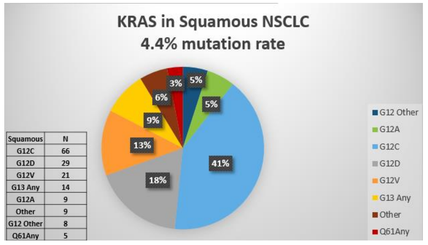


Figure 2: Immune checkpoint therapy associated markers among *KRAS* mutations.

- Incidence of high TMB was significantly different among different *KRAS* mutations (**p<0.001**), most frequent in G13X (68.3%) and least common in G12D (43.2%)
- PD-L1 TPS was significantly different among KRAS mutations across major cutoffs (**p<0.01**). G12C was most likely to be PD-L1 positive (65.5% TPS ≥ 1%) and most likely to be PD-L1 high (41.3% TPS ≥50%)

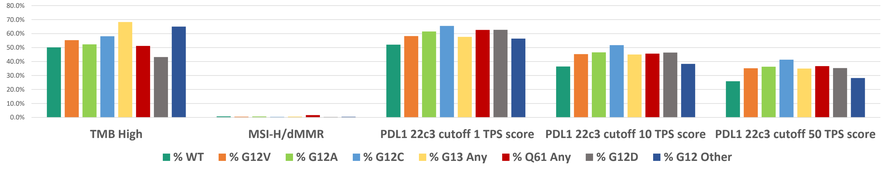


Figure 3: TMB distribution among KRAS mutations.

- TMB distribution values varied among *KRAS* mutations using Kruskal-Wallis Test (**p<0.001**)

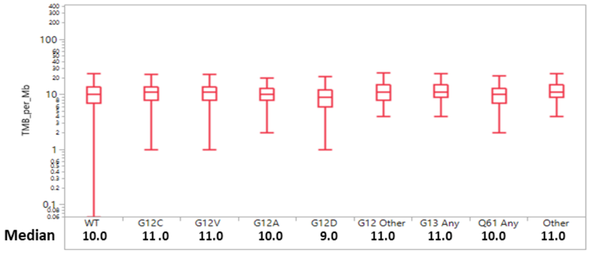
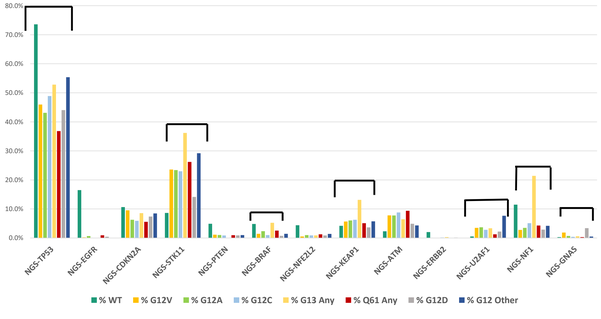


Figure 4: Key biomarkers in *KRAS* mutated cohort.

- **Rate of co-mutations in** *TP53*, *STK11*, *U2AF1*, *BRAF*, *KEAP1*, *NF1* and *GNAS* were all significantly different among the different *KRAS* mutations (p<0.01).



Conclusions

- *KRAS* mutations are relatively common in lung adenocarcinoma with *KRAS* G12C being the most common variant.
- While overall adenocarcinoma carries higher prevalence of *KRAS* mutation, no significant difference in mutation types were seen.
- TMB high (≥10) was significantly different across *KRAS* mutation types.
- *KRAS* G12C was associated with the highest rate of PD-L1 expression.
- Different *KRAS* mutations have unique co-occurring mutations and a different genomic landscape.
- The clinical relevance in the differences of *KRAS* mutations subtypes warrants further investigation in the context of therapeutic intervention.

References

Skoulidis et al (2015). *Cancer Discovery*

Abstract # 9544