Spectrum of acquired *KRAS* mutations in driver mutation-positive non-small cell lung cancer

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Background

- With the emergence of effective therapies targeting specific *KRAS* mutations (mt), identifying these unique *KRAS*mts in NSCLC has become increasingly relevant.
- Acquired *KRAS* mutations are a known resistance mechanism in driver mutation-positive (DM+) NSCLC.
- The incidence and diversity of these acquired alterations and whether they differ from those observed in *de novo KRAS*mt NSCLC is unknown.
- We aimed to characterize the distribution of *KRAS*mt between acquired and *de novo KRAS*mt NSCLC, as well as the distribution of unique *KRAS*mt by driver mutation.

Objectives and Methods

- NSCLC samples were analyzed at Caris Life Sciences (Phoenix, AZ) with DNA-based next-generation sequencing (NGS; 592 genes, NextSeq) or whole-exome sequencing (NovaSeq) and with RNA-based whole-transcriptome sequencing (WTS, NovaSeq).
- Demographics were abstracted from medical records.
- *KRAS*mt subgroups were defined as *de novo KRAS*mt NSCLC (*KRAS* only identified driver – DN) and DM+ NSCLC with acquired *KRAS*mt (concurrent *KRAS*mt with other known drivers – ACQ)
- Queried known oncogenic drivers in NSCLC included: *EGFR*, *MET*, *ERBB2* & *BRAF* mutations; *METex14* skipping; *ALK*(overexpression + fusions), *RET, ROS1, NRG1, NTRK1-3* fusions
- Due to the unique biology of NSCLC with class II/III *BRAF* mutations, this subset was excluded from the ACQ subgroup for the final analysis
- Fisher's exact, chi-square and Mann-Whitney U tests were performed where appropriate and p-values were corrected for multiple hypothesis testing (q<0.05)

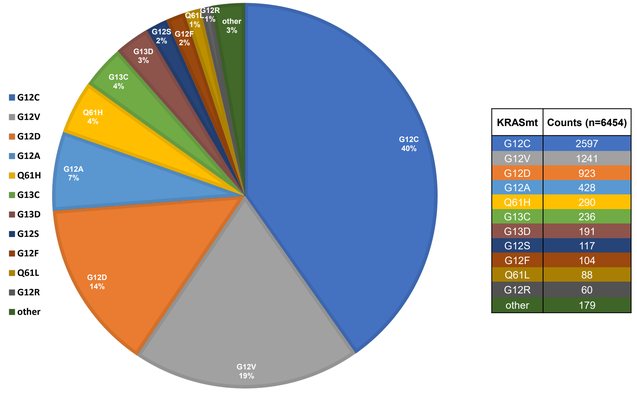
Results

Table 1: Demographic differences between acquired *KRAS*mt- and *de novo KRAS*mt-NSCLC

Features	ACQ (n=57)	DN (n=6433)	Statistic	p-value	q-value
Median Age	72	69	Mann-Whitney U	0.044334	0.088668
Male	59.6% (34/57)	43.0% (2767/6433)	chi-square	0.011578	0.046312
Female	40.4% (23/57)	57.0% (3666/6433)	chi-square	0.011578	0.046312
Smoker	100.0% (8/8)	98.5% (1755/1781)	Fisher's Exact	1	1
Non-smoker	0.0% (0/8)	1.5% (26/1781)	Fisher's Exact	1	1
Adenocarcinoma	78.9% (45/57)	83.5% (5374/6433)	Fisher's Exact	0.533045	0.710727
Squamous Carcinoma	1.8% (1/57)	1.8% (113/6433)	Fisher's Exact	0.533045	0.710727
Sarcomatoid	1.8% (1/57)	0.8% (51/6433)	Fisher's Exact	0.533045	0.710727
Adenosquamous Carcinoma	0.0% (0/57)	0.7% (45/6433)	Fisher's Exact	0.533045	0.710727
Large Cell Carcinoma	0.0% (0/57)	0.2% (13/6433)	Fisher's Exact	0.533045	0.710727
Other/Unclear Histology	17.5% (10/57)	13.0% (837/6433)	Fisher's Exact	0.533045	0.710727

The median age of patients was higher in the ACQ compared to the DN cohort (p<0.05, q>0.05). There was a significantly higher proportion of males in the ACQ subgroup and females in the DN subgroup (q<0.05).

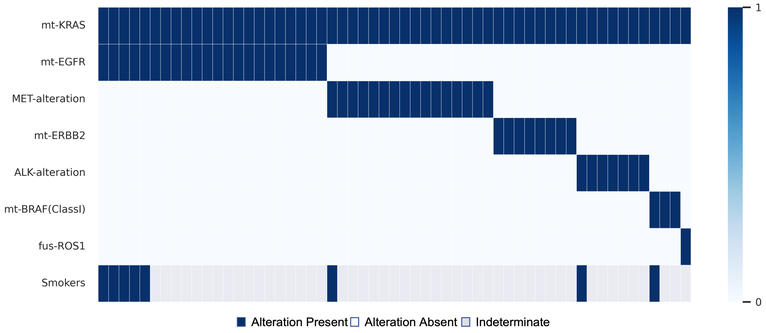
Figure 1: *KRAS* mutation distribution among *de novo KRAS*mt driven NSCLC



KRASmt	Counts (n=6454)
G12C	2597
G12V	1241
G12D	923
G12A	428
Q61H	290
G13C	236
G13D	191
G12S	117
G12F	104
Q61L	88
G12R	60
other	179

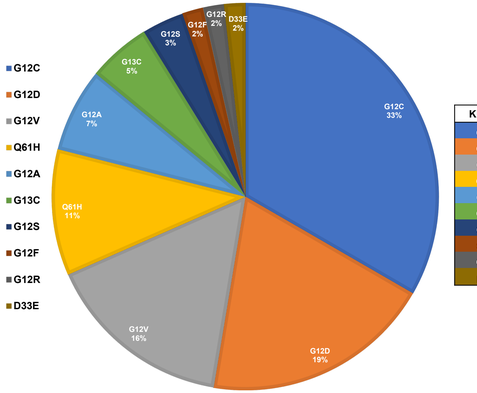
KRAS G12C (40%), G12V (19%) and G12D (14%) were most common and combined for ~73% of the total *KRAS* mutations in the DN subgroup.

Figure 2: Landscape of driver mutations in the ACQ subgroup



Among the oncogenic drivers in the ACQ subgroup, mutations in *EGFR* (38.6%) and *MET* (28.1%) were most prevalent.

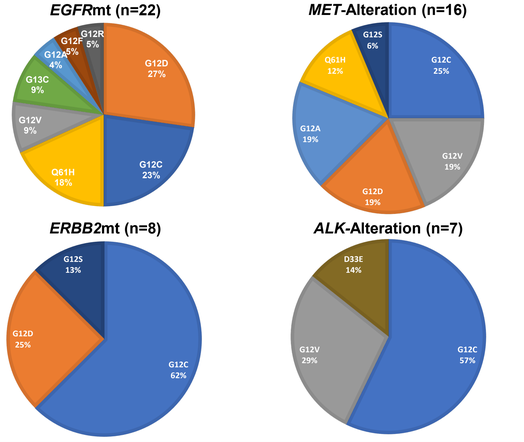
Figure 3: *KRAS*mt distribution among ACQ subgroup



KRASmt	Counts(n=57)
G12C	19
G12D	11
G12V	9
Q61H	6
G12A	4
G13C	3
G12S	2
G12F	1
G12R	1
D33E	1

KRAS G12C (33%), G12D (19%) and G12V (16%) were most common and combined for ~68%% of the total *KRAS* mutations in the ACQ subgroup. The distribution of unique *KRAS* mutations was not significantly different between DN and ACQ groups (p=0.25).

Figure 4. *KRAS*mt distribution among independent drivers in ACQ NSCLC



*KRAS*mt/ Drivers	*EGFR*mt (n=22)	*MET*-alteration (n=16)	*ERBB2*mt (n=8)	*ALK*-alteration (n=7)	*BRAF* Class I (n=3)	*ROS1*fus (n=1)
G12C	5	4	5	4		1
G12V	2	3		2	2	
G12D	6	3	2			
Q61H	4	2				
G12A	1	3				
G13C	2				1	
G12S		1	1			
D33E				1		
G12F	1					
G12R	1					

KRAS G12C and G12V mutations were among the more frequent mutations observed across individual drivers in the ACQ subgroup.

Conclusions

- While the distribution of unique *KRAS* mutations did not differ significantly between DN and ACQ subgroups, acquired *KRAS* mutations at varying frequencies were seen across DM+ NSCLC subsets.
- The functional and immunological significance of these mutations, and their impact on clinical outcomes, warrants further investigation.

Contact Information

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