Prevalence of *KRAS* Subtype Alterations in Non-Small Cell Lung Cancer (NSCLC) with Brain Metastases

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INTRODUCTION

- *KRAS* alterations (*KRAS*alt) NSCLC accounts for 29% to 33% of lung adenocarcinomas, and 17% to 55% of these patients develop brain metastases.
- *KRAS*alt status appears to have a limited effect on overall survival (OS) in patients with early-stage NSCLC and its affect on prognosis is largely unknown.
- Few studies document the prevalence of brain metastases within each *KRAS* subtype.
- In the current study, we examined the prevalence of patients with NSCLC and brain metastases to determine the prevalence of *KRAS* alterations.

METHODS

- Analyses were completed using Tempus Lens, which aggregates de-identified data from samples tested with the Tempus Database and enables real-time cohort identification and analysis.
- Data from both liquid (xF) and solid tissue (xT) biopsy were included in this study.
- The Tempus xT is a targeted, tumor-normal-matched DNA panel that detects single-nucleotide variants, insertions and/or deletions, and copy number variants in 648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.
- The Tempus xF assay is a targeted liquid biopsy DNA panel that detects single-nucleotide variants and insertions and/or deletions in 105 genes, copy number variants in six genes, and chromosomal rearrangements in seven genes.

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TEMPUS

SUMMARY

- This study details the most prevalent *KRAS* alterations and co-mutations among *KRAS*-altered NSCLC brain metastases.
- *KRAS* p.G12C was the **most frequently observed alteration** and co-mutations were found in *TP53, LRP1B, STK11, KEAP1*, and *CDKN2A*.
- Our findings have **therapeutic implications** as co-alterations with *STK11/KEAP1* are associated with worse outcomes. Further drug development for *KRAS* inhibitors with CNS activity is warranted.

RESULTS

Characteristic	Overall, N = 752[1]	G12A, N = 58[1]	G12C, N = 388[1]	G12D, N = 100[1]	G12V, N = 161[1]	G13C, N = 45[1]	p-value[2]
Age at Diagnosis							0.026
Median (IQR)	65 (59, 72)	68 (62, 74)	64 (58, 71)	65 (60, 71)	66 (61, 72)	64 (60, 71)	
Range	36, 90	51, 87	38, 89	36, 89	36, 90	49, 82	
Unknown	4	0	4	0	0	0	
Gender							>0.9
Female	428 (57%)	31 (53%)	226 (58%)	54 (54%)	92 (57%)	25 (56%)	
Male	324 (43%)	27 (47%)	162 (42%)	46 (46%)	69 (43%)	20 (44%)	
Race							
White	411 (80%)	29 (73%)	213 (82%)	58 (74%)	83 (83%)	28 (88%)	
Black or African American	64 (13%)	7 (18%)	33 (13%)	10 (13%)	12 (12%)	2 (6.3%)	
Other	26 (5.1%)	3 (7.5%)	12 (4.6%)	6 (7.7%)	3 (3.0%)	2 (6.3%)	
Asian	10 (2.0%)	1 (2.5%)	3 (1.1%)	4 (5.1%)	2 (2.0%)	0 (0%)	
Unknown	241	18	127	22	61	13	
Ethnicity							0.5
Not Hispanic or Latino	311 (96%)	28 (100%)	158 (96%)	46 (96%)	62 (93%)	17 (94%)	
Hispanic or Latino	14 (4.3%)	0 (0%)	6 (3.7%)	2 (4.2%)	5 (7.5%)	1 (5.6%)	
Unknown	427	30	224	52	94	27	
Smoker status							0.004
Current/former smoker	666 (97%)	51 (98%)	352 (99%)	87 (92%)	138 (96%)	38 (100%)	
Never smoker	19 (2.8%)	1 (1.9%)	4 (1.1%)	8 (8.4%)	6 (4.2%)	0 (0%)	
Unknown	67	6	32	5	17	7	

[1]n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 1. Cohort Demographics. Using Tempus Lens, 4321 cases of brain metastasis linked to the curated diagnosis of NSCLC were identified. In the overall cohort, *KRAS*alt were identified in 28.93% (1250/4321) of patients. *KRAS* p.G12C was the most prevalent alteration, appearing in 11.32% (488/4321) of cases compared to the most common *EGFR* subtype, p.L858R, at 6.04% (261/4321).

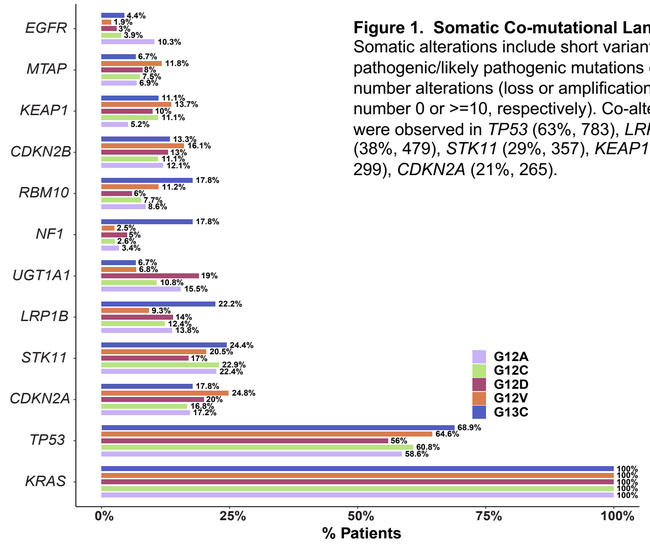

Figure 1. Somatic Co-mutational Landscape. Somatic alterations include short variant pathogenic/likely pathogenic mutations copy number alterations (loss or amplification, copy number 0 or >=10, respectively). Co-alterations were observed in *TP53* (63%, 783), *LRP1B* (38%, 479), *STK11* (29%, 357), *KEAP1* (24%, 299), *CDKN2A* (21%, 265).

Characteristic	Overall, N = 752[1]	G12A, N = 58[1]	G12C, N = 388[1]	G12D, N = 100[1]	G12V, N = 161[1]	G13C, N = 45[1]	p-value[2]
TMB							0.031
Median (IQR)	6.5 (4.2, 9.2)	5.4 (4.1, 8.6)	6.6 (4.6, 9.2)	5.8 (3.3, 8.5)	6.1 (3.9, 9.2)	8.1 (5.0, 11.5)	
Range	0.0, 56.1	0.0, 12.7	0.0, 25.7	1.2, 23.4	0.8, 56.1	1.2, 32.6	
Unknown	132	11	64	19	30	8	
TMB							0.2
<10	502 (81%)	41 (87%)	259 (80%)	68 (84%)	109 (83%)	25 (68%)	
>=10	118 (19%)	6 (13%)	65 (20%)	13 (16%)	22 (17%)	12 (32%)	
Unknown	132	11	64	19	30	8	
MSI Status							>0.9
Stable	614 (82%)	47 (81%)	320 (82%)	80 (80%)	130 (81%)	37 (82%)	
Not detected	137 (18%)	11 (19%)	67 (17%)	20 (20%)	31 (19%)	8 (18%)	
High	1 (0.1%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	
PD-L1 Status							>0.9
Positive	267 (64%)	19 (63%)	142 (65%)	29 (59%)	59 (61%)	18 (67%)	
Negative	146 (35%)	10 (33%)	72 (33%)	20 (41%)	35 (36%)	9 (33%)	
Negative, Positive	6 (1.4%)	1 (3.3%)	3 (1.4%)	0 (0%)	2 (2.1%)	0 (0%)	
Unknown	333	28	171	51	65	18	
MMR Deficiency							
Not Deficient	170 (100%)	12 (100%)	89 (100%)	24 (100%)	37 (100%)	8 (100%)	
Unknown	582	46	299	76	124	37	

[1]n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Table 2. Immunological Markers. PD-L1 status data was available for 732 cases, of which 67.2% (492/732) were positive for PD-L1. The remaining 32.8% were negative and therefore ineligible for first-line IO monotherapy.

Characteristic	N = 287
MUTYH	11 (3.8%)
ATM	8 (2.8%)
NBN	3 (1.0%)
PALB2	2 (0.7%)
PMS2	2 (0.7%)
BRCA1	1 (0.3%)
BRIP1	1 (0.3%)
CHEK2	1 (0.3%)
NTHL1	1 (0.3%)
RAD51C	1 (0.3%)

Table 3. Germline Landscape. Germline sequencing from 287 samples showed a prevalence of pathogenic or likely-pathogenic mutations with a frequency of ~10% (30/287).