

INTRODUCTION

- Lung cancers harboring KRAS^{G12V} accounts for approximately 20% of KRAS mutations in this disease.^{1,2}
- KRAS^{G12V} NSCLC is enriched among individuals with smoking history and are associated with high PD-L1 expression and TMB.³
- Frequently observed co-alterations include TP53, STK11 and KEAP1.³
- Treatment with immunotherapy-based treatments were associated with improved outcomes compared to chemotherapy alone.³
- As pan(K)RAS and G12V selective inhibitors have entered the clinic, further characterization of this disease is imperative to guide optimal treatment selection.

OBJECTIVE

- Comprehensive analysis of clinicopathologic, genomic and immunophenotypic features of KRAS^{G12V} and KRAS^{G12C} NSCLC.

PATIENT CHARACTERISTICS

Characteristics	KRAS ^{G12V} , N=726 (%)	KRAS ^{G12C} , N=1700 (%)
Age, median (range)	70 (19-90)	70 (25-98)
Female, n (%)	488 (67)	1,131 (67)
Race, n (%)		
Caucasian	646 (89)	1,553 (91)
Others	78 (11)	147 (9)
Prior smoking history, n (%)	639 (88)	1,615 (97)
ECOG 0-1, n (%)	553 (76)	588 (93) ¹
Stage at diagnosis, n (%)		
1	214 (30)	443 (29)
2	70 (9)	118 (7)
3	115 (16)	265 (17)
4	267 (37)	726 (47)
Histology, n (%)		
Adenocarcinoma	660 (91)	1,455 (86)
Squamous carcinoma	8 (1)	40 (2)
PD-L1 expression (%)		
<1	133 (18)	405 (30)
≥1	271 (37)	780 (58)

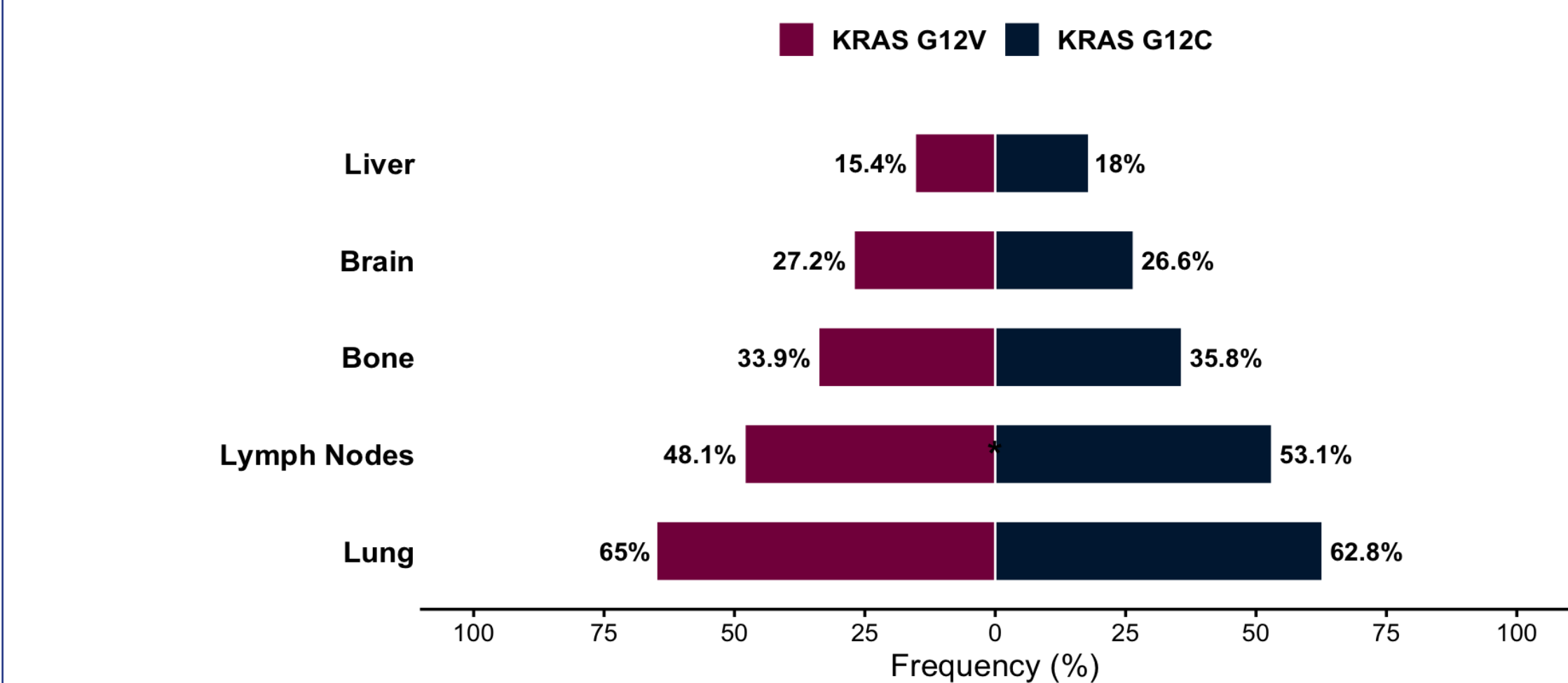
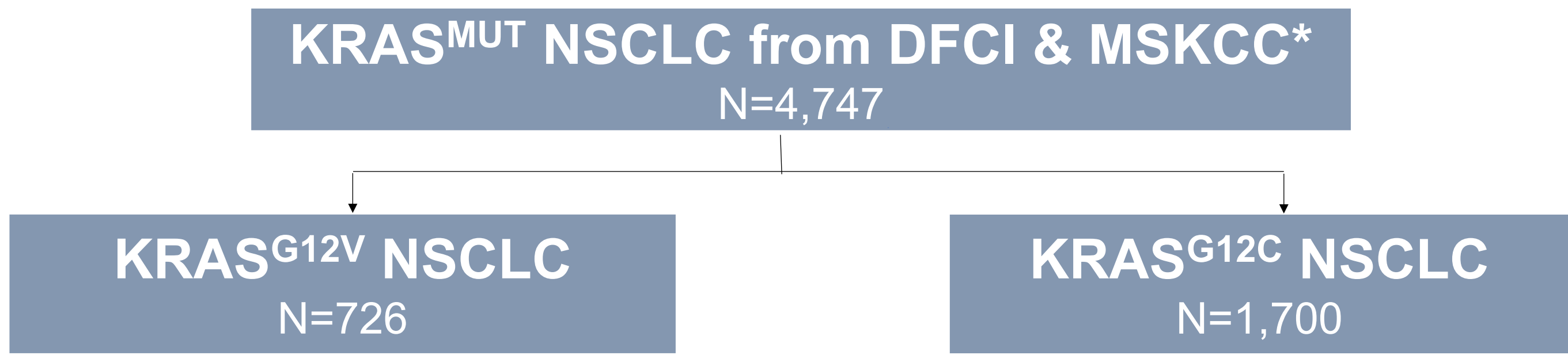


Figure 1: Distribution of metastatic sites at diagnosis in stage IV KRAS^{G12V} and KRAS^{G12C} NSCLC.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N, number; PD-L1, programmed death-ligand 1; ¹ n=1065 missing data

METHODS

- Retrospective, multicenter analysis of patient-level data from two academic institutions in the US.



- Detailed clinicopathologic and genomic data were collected.
- Multiplex immunofluorescence (mIF) performed on subset of available biospecimens at DFCI with regions of interest, including intratumoral (IT), tumor stroma interface (TSI) and total (IT+TSI), used for quantitative analyses.
- Clinical outcomes including progression-free survival (PFS) and overall survival (OS) to immune checkpoint inhibitors (ICI) +/- chemotherapy were analyzed.

*Data collected from MSK-Chord (CBioPortal)

IMMUNOPROFILE

Multiplex Immunofluorescence	KRAS ^{G12V} , N=32 (range)	KRAS ^{G12C} , N=96 (range)	P-value
Intratumoral CD8 ⁺ T cells, median (range)	168 (95-317)	269 (108-451)	0.2
Tumor stromal interface CD8 ⁺ T cells, median (range)	423 (145-459)	401 (423)	0.6
Total CD8 ⁺ T cells, median (range)	190 (95-342)	272 (113-459)	0.2

CONCLUSION

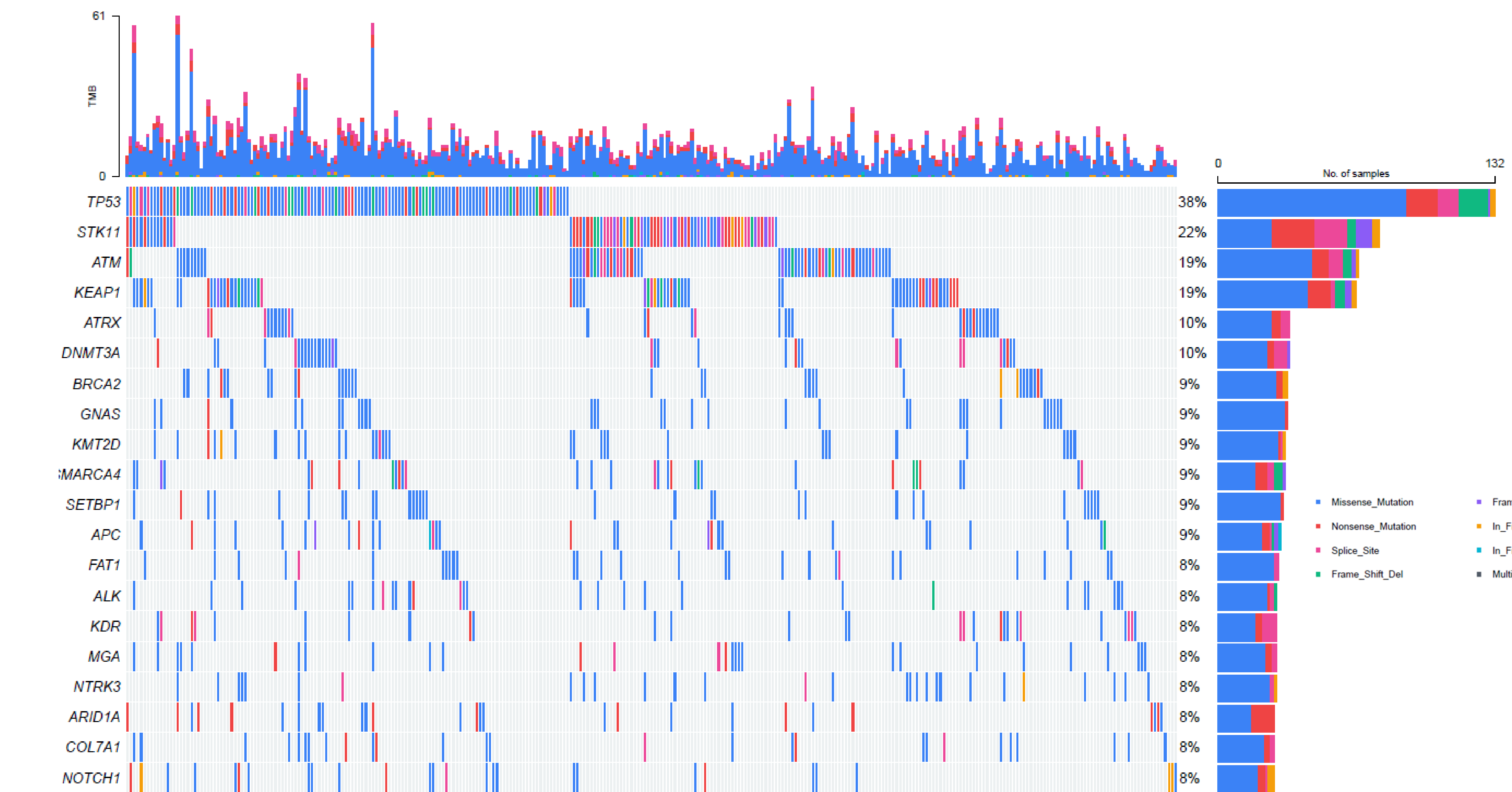
- KRAS^{G12V} NSCLC has **similar clinicopathological features and immunoprofile** as KRAS^{G12C} NSCLC.
- KRAS^{G12V} NSCLC **derive clinical benefit from immunotherapy-based therapies**, consistent with findings of immunoprofile of 'inflamed' tumor microenvironment and high tumor mutation burden (TMB).
- The **genomic co-alterations observed in KRAS^{G12V} are similar to KRAS^{G12C} NSCLC**.
- Novel therapies, such as **RAS inhibitors**, are urgently needed given dismal outcomes with standard of care treatment regimens.

REFERENCES

- Judd, J., et al., *Characterization of KRAS Mutation Subtypes in Non-small Cell Lung Cancer*. Mol Cancer Ther, 2021. **20**(12): p. 2577-2584.
- Punekar, S.R., et al., *The current state of the art and future trends in RAS-targeted cancer therapies*. Nat Rev Clin Oncol, 2022. **19**(10): p. 637-655.
- John, F., et. al., *Molecular and Clinical Characteristics of Patients with Non-Small Cell Lung Cancer Harboring KRASG12V Mutations*. Clin Cancer Res, 2026. **32**(10):2110-2119.

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RESULTS



*In available tissue sample in DFCI cohort

Figure 2: Genomic landscape of KRAS^{G12V} NSCLC (DFCI cohort; N=348)

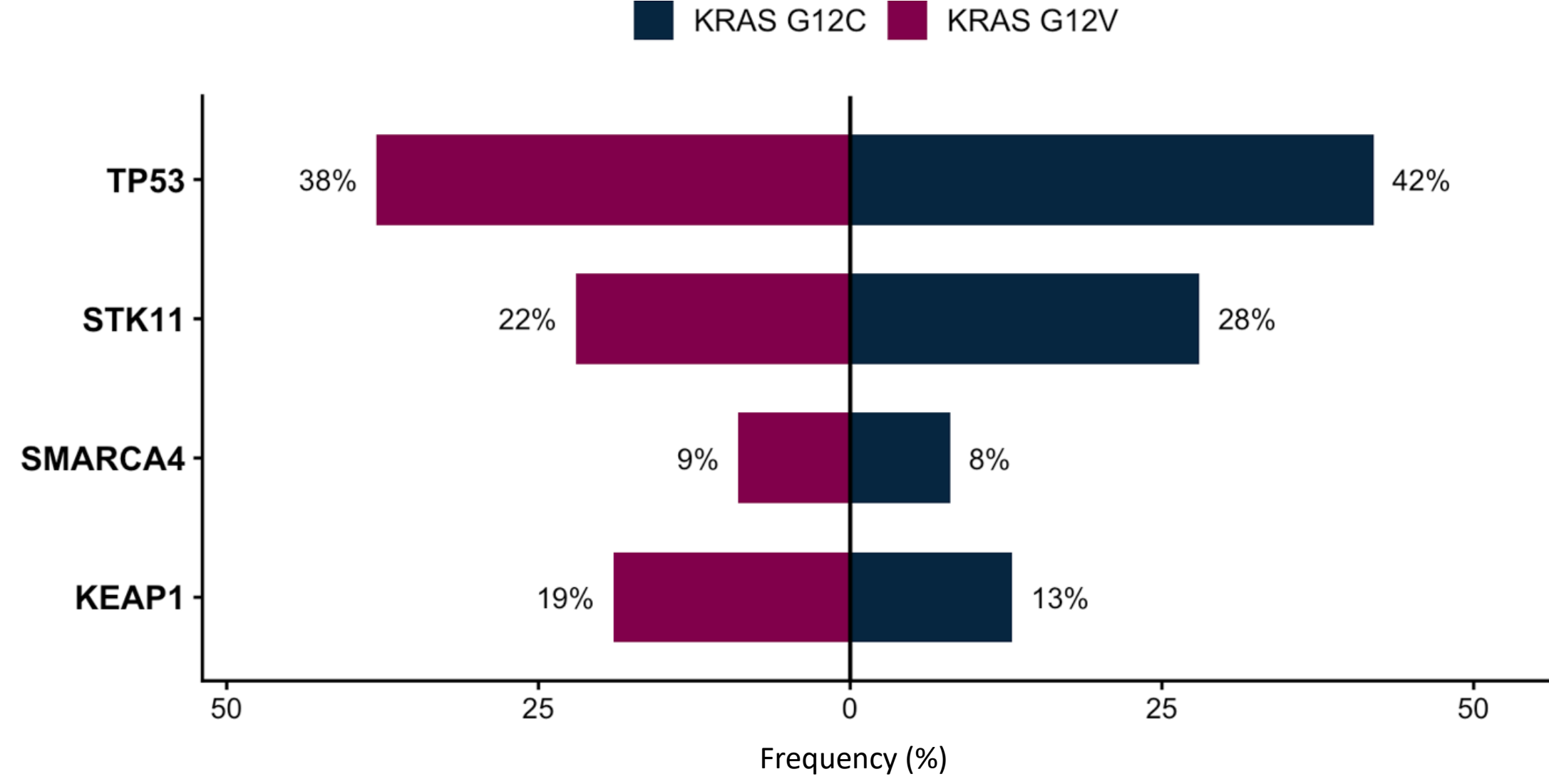


Figure 3: Co-alterations observed in KRAS^{G12V} and KRAS^{G12C} NSCLC in DFCI cohort

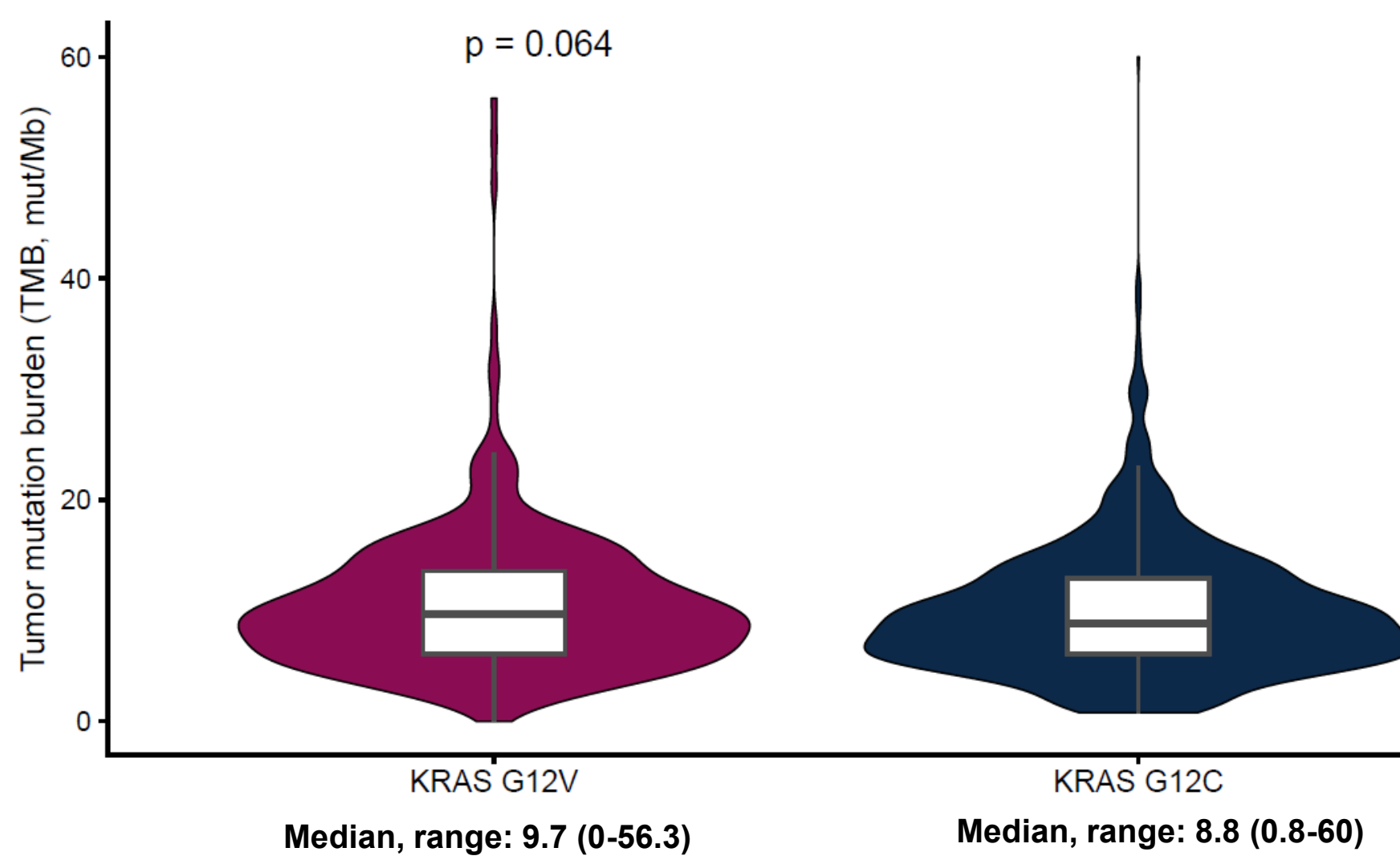


Figure 4: Tumor mutation burden (TMB) in KRAS^{G12V} and KRAS^{G12C} NSCLC

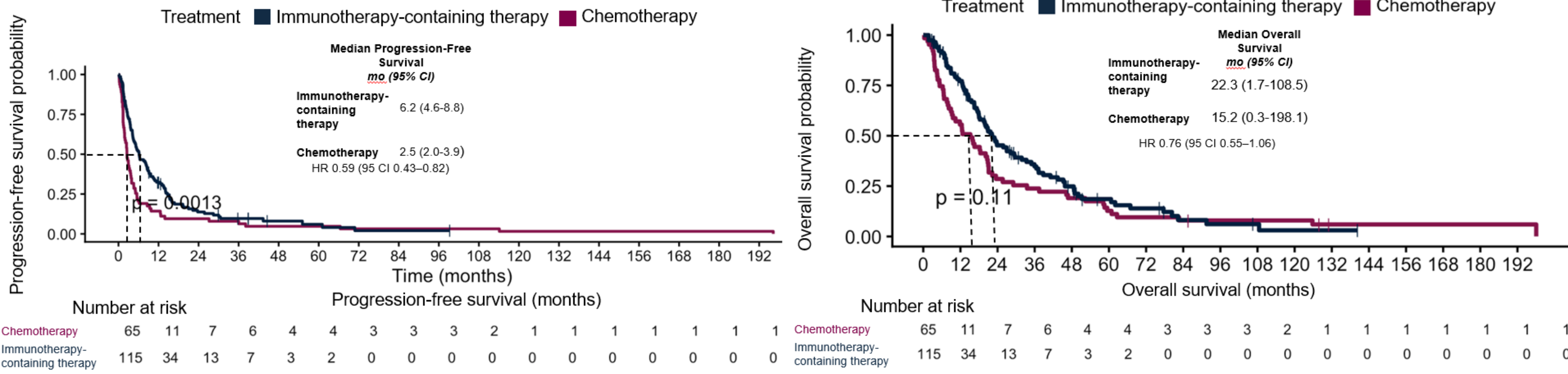


Figure 5: Progression-free survival and overall survival of first-line treatment in advanced KRAS^{G12V} NSCLC (DFCI cohort).