

KRAS and STK11 Mutations in Non-Small Cell Lung Cancer in a Resource-Limited Real-World Cohort

Cassio Murilo Hidalgo-Filho¹, Ibere Cauduro Soares¹, Ana Julia Freitas², Felipe Lazar Neto¹, Gabriel Berlingieri Polho², Victor Rocha Pinheiro¹, Leticia de Mello Graziano¹, Juliana Mandarano de Mattos¹, Victoria Jatobá Pimentel¹, Maristela Cesar Freire¹, Amanda Acioli de Almeida Robatto¹, Cristiane Santos de Almeida Robatto¹, Cristiane Santos de Mesquita¹, Fernanda Frozoni Antonacio¹, Fernanda Kaori Fujiki¹, Francesco Bermejo Sansone¹, Marcelo Malandrino Felizola¹, Renata Villar Ponte¹, Teresa Yae Takagaki¹, Luiz Guilherme Cernaglia Aureliano De Lima¹, Alberto Jorge Monteiro Dela Veja¹, Leticia L. Lauricella¹, Monteiro Dela Veja¹, Leticia L. Lauricella¹, Pedro Henrique Xavier Nabuco de Araujo¹, Ricardo M. Terra¹, Evandro Sobroza de Mello¹, Milena Perez Mak¹, Gilberto de Castro Junior¹

¹Instituto do Cancer do Estado de Sao Paulo ICESP, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR. ²Hospital Sirio-Libanês, Sao Paulo, SP, BR.

INTRODUCTION

- The prognostic impact of *KRAS* and *STK11* mutations in NSCLC has been defined in immunotherapy-treated populations.
- STK11* mutations have been associated with resistance to immune immune checkpoint inhibitors and worse survival outcomes.
- However, this data comes from patients usually treated with immune immune checkpoint inhibitors.

We aimed to characterize the pattern of *KRAS* and *STK11* mutations in an immunotherapy-naïve Brazilian cohort.

METHODS

1 Study population

- Patients with NSCLC diagnosed between 2019–2023 at Instituto do Instituto do Cancer do Estado de Sao Paulo.
- Retrospective analysis of NGS tests performed.
- All patients with unavailable *KRAS* status were excluded from analysis.

- Cohort was entirely immunotherapy-naïve.

N = 691 tests screened · evaluable patients

2 Variant curation

- Only pathogenic and likely pathogenic tumors were included in the in the analysis.
- Molecular profiling was done via Agilent panel.
- STK11* status not available for all patients.

ACMG curation · only pathogenic or likely pathogenic included for *KRAS/STK11*

3 Outcomes analysis

- Survival analyses performed using the log-rank tests.
- PFS and ORR among treated patients.
- Only patients with available *STK11* status were considered for the *STK11* outcomes.

Metastatic cohort · by *KRAS* and *STK11*

Figure 1. Flow chart of patients included in the final analysis of the study.

691 NGS tests (ICD-10 C34) January 2019 – March 2023

Exclusions (n = 156)

- 46 duplicate tests
- 59 no longitudinal clinical follow-up
- 11 without confirmed NSCLC diagnosis
- 40 missing *KRAS* status

Final cohort (N = 535) unique patients

RESULTS

Figure 2. Distribution of *KRAS* mutation subtypes (N = 535 patients).

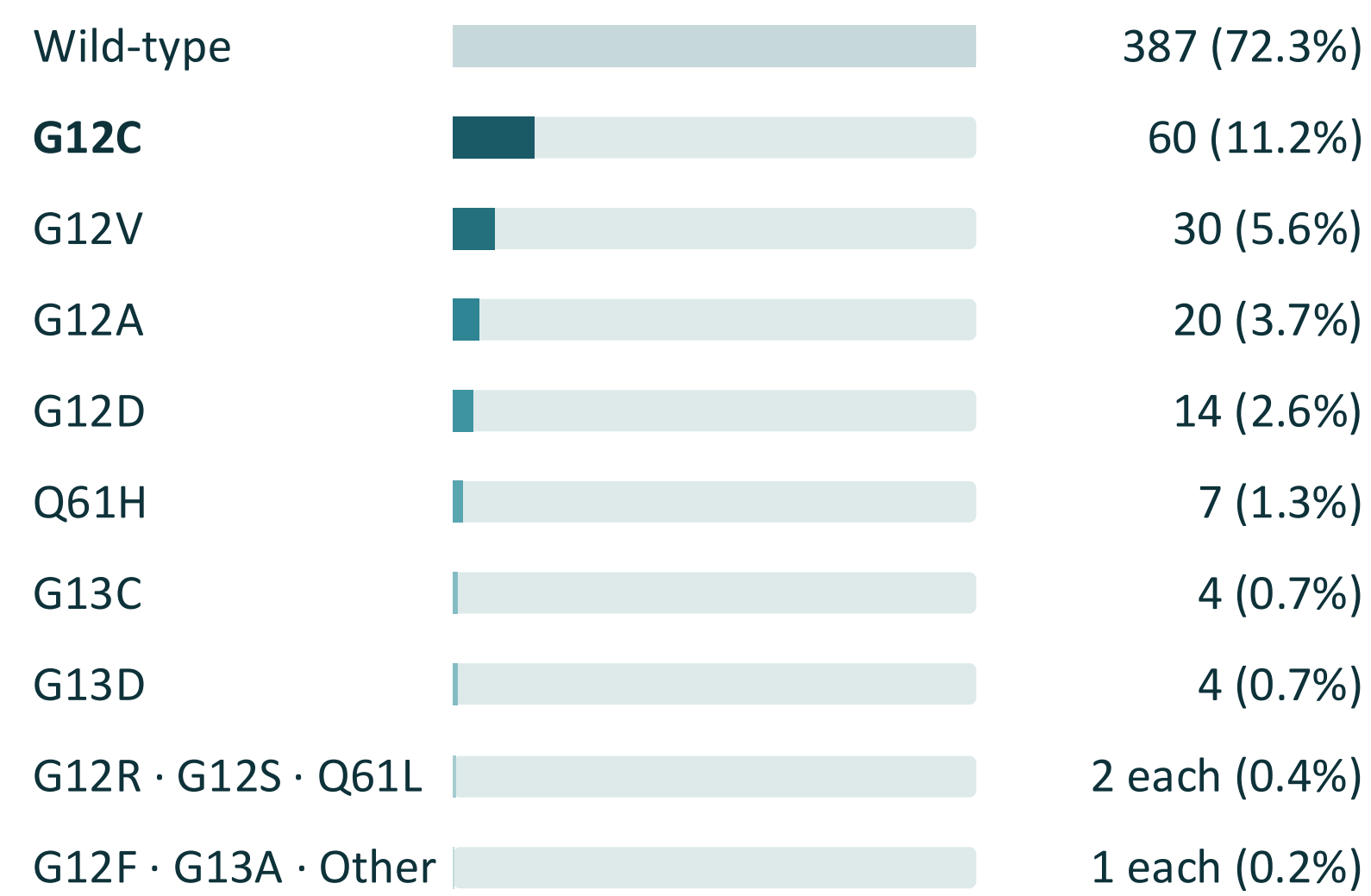


Figure 4. *STK11* variant curation according to ACMG classification.

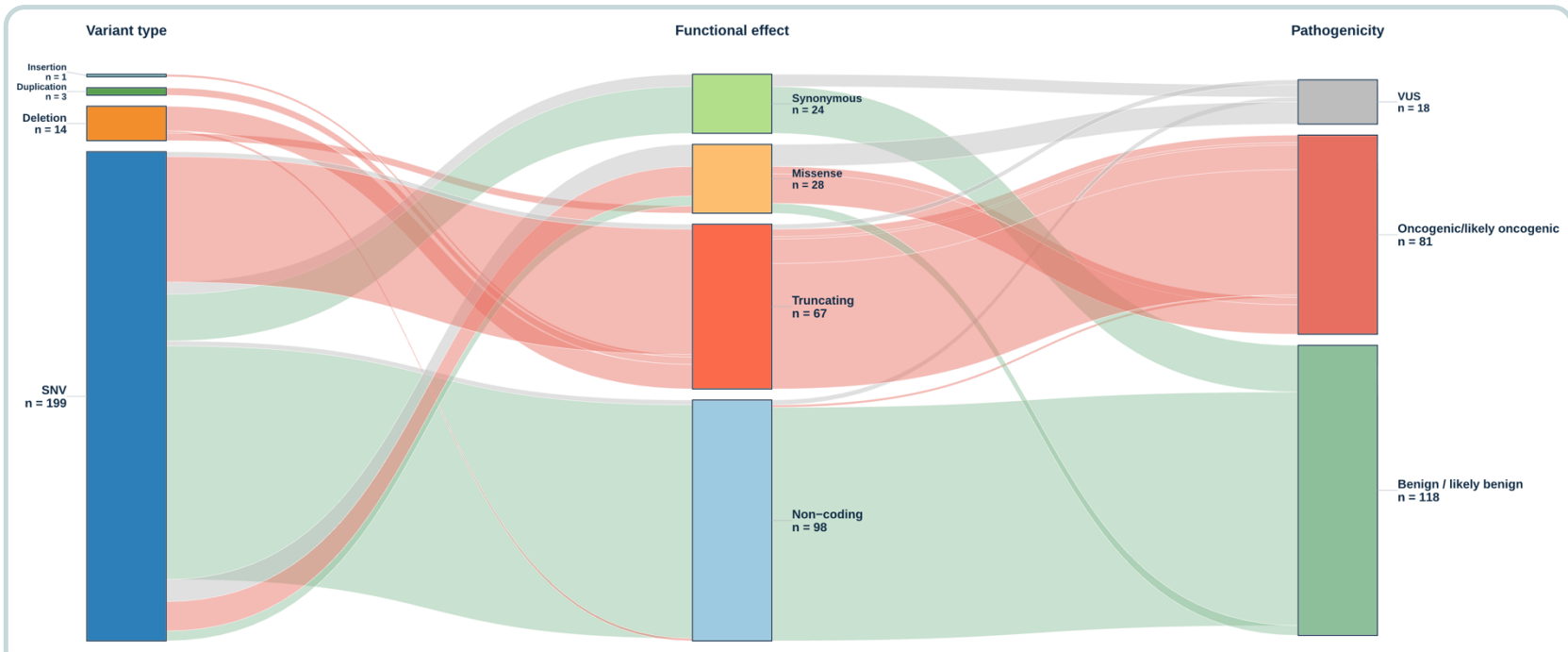


Figure 5. Response rates among *KRAS* and *STK11* subgroups.

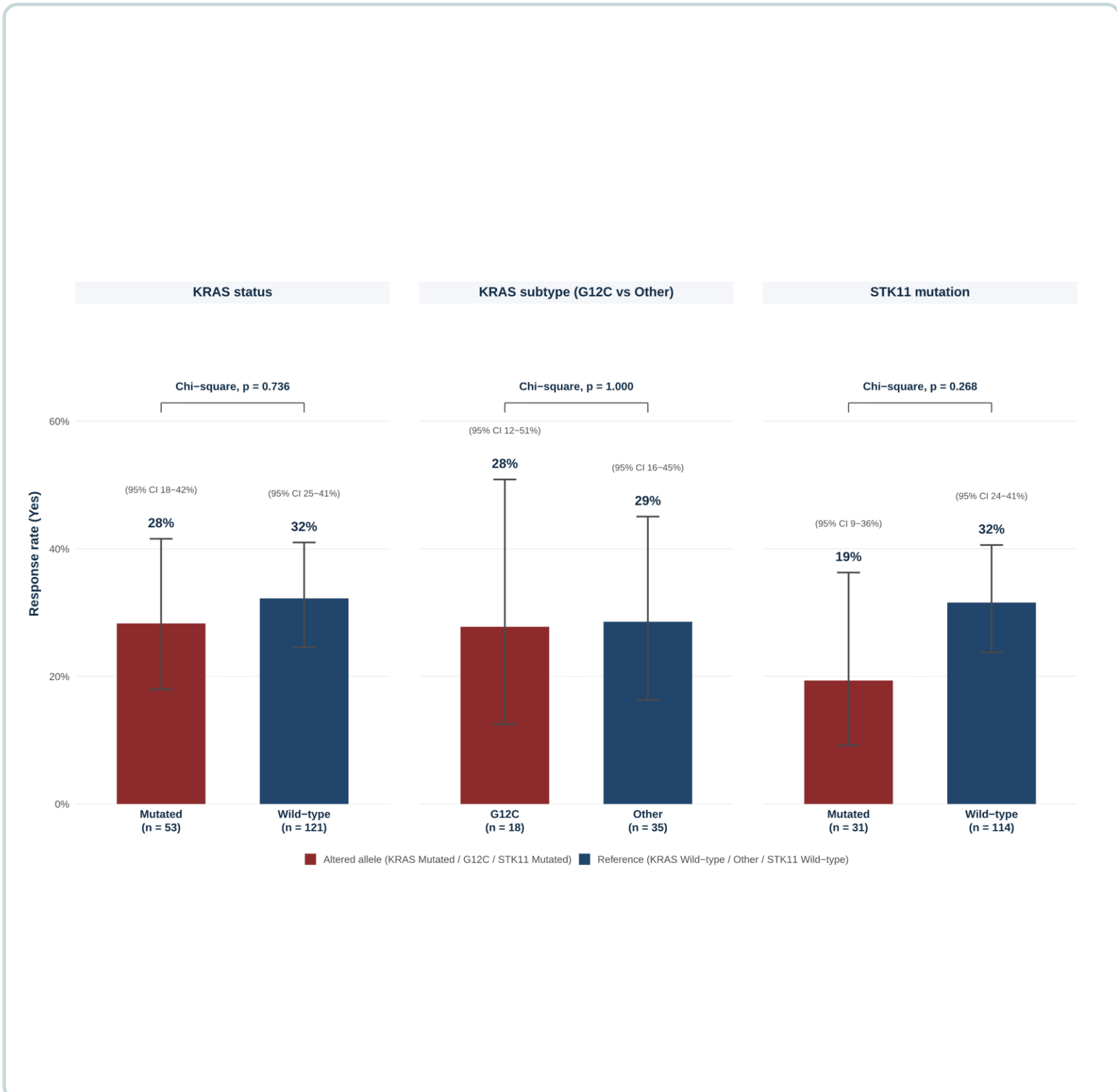


Table 1. Baseline characteristics according to *KRAS* mutation status.

Variable	Wild-type N = 387 ¹	Mutated N = 148 ¹	p-value ²	Overall N = 535 ¹
Age at diagnosis (years)	66.0 (58.9–73.0)	66.7 (60.8–72.2)	0.584	66.2
Sex			0.160	
Female	228 (59%)	97 (66%)		325 (61%)
Male	159 (41%)	51 (34%)		210 (39%)
Race			0.909	
White	230 (73%)	91 (72%)		321 (72%)
Black	82 (26%)	34 (27%)		116 (26%)
Asian	5 (1.6%)	1 (0.8%)		6 (1.4%)
Not assessed	70	22		92
Smoking status			<0.001	
Never	134 (35%)	10 (6.8%)		144 (27%)
Ever	245 (65%)	136 (93%)		381 (73%)
Not assessed	8	2		10
Histology			0.005	
Non-squamous	370 (96%)	148 (100%)		518 (97%)
Squamous	17 (4.4%)	0 (0%)		17 (3.2%)
Clinical stage			<0.001	
I	46 (12%)	22 (15%)		68 (13%)
II	21 (5.4%)	21 (14%)		42 (7.9%)
III	63 (16%)	11 (7.5%)		74 (14%)
IV	256 (66%)	93 (63%)		349 (65%)
Not assessed	1	1		2
Metastatic disease (any time)	318 (82%)	119 (80%)	0.637	437 (82%)
<i>STK11</i> variant detected	157 (49%)	60 (51%)	0.724	217 (50%)
<i>STK11</i> mutant	53 (17%)	28 (24%)	0.084	81 (19%)
ECOG performance status			0.479	
0–1	248 (64%)	95 (64%)		343 (64%)
2	66 (17%)	20 (14%)		86 (16%)
3–4	73 (19%)	33 (22%)		106 (20%)

¹Median (Q1–Q3); n (%). ²Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

Figure 3. Clinical, pathological, and genomic landscape of *KRAS*-mutated tumors.

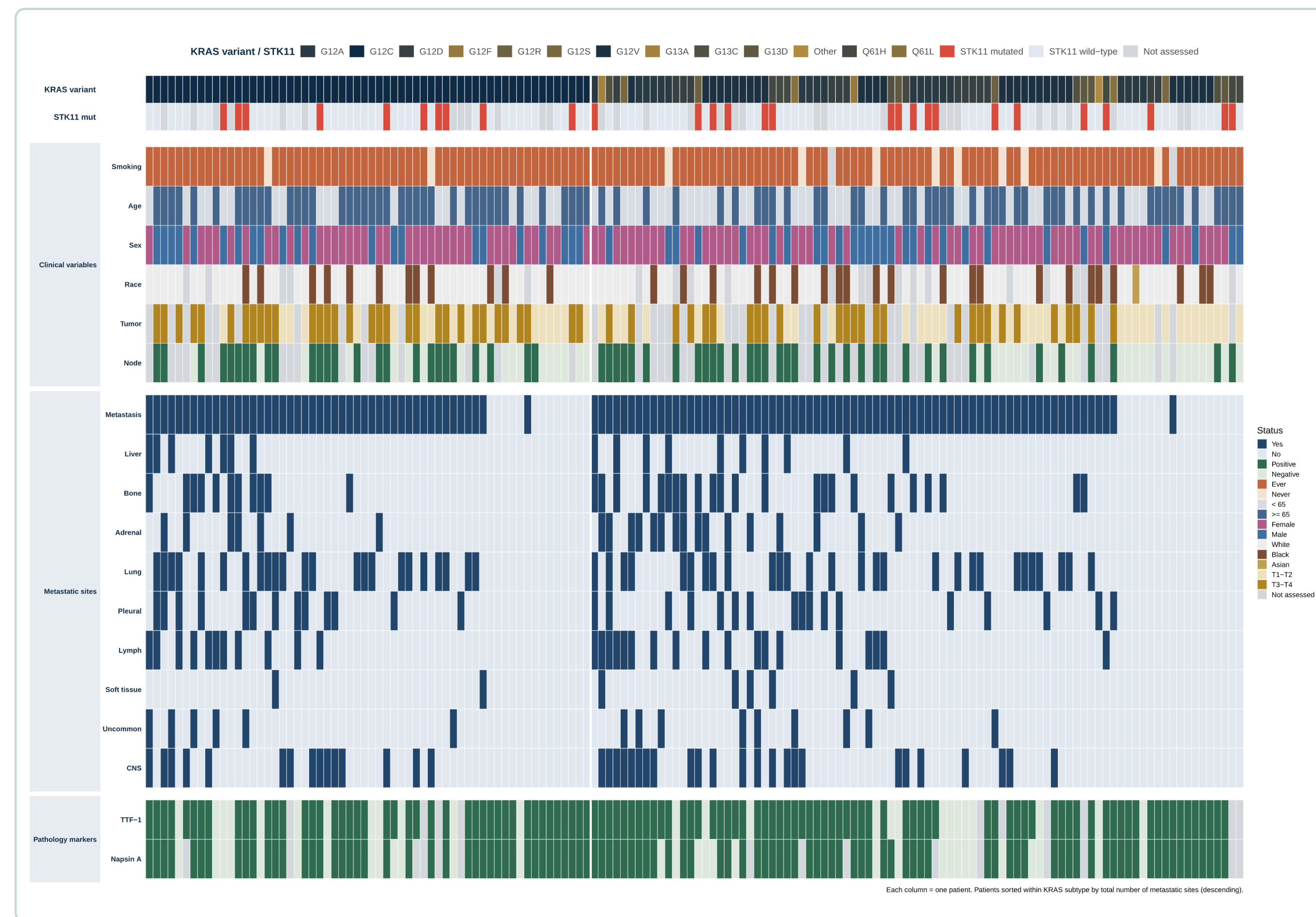
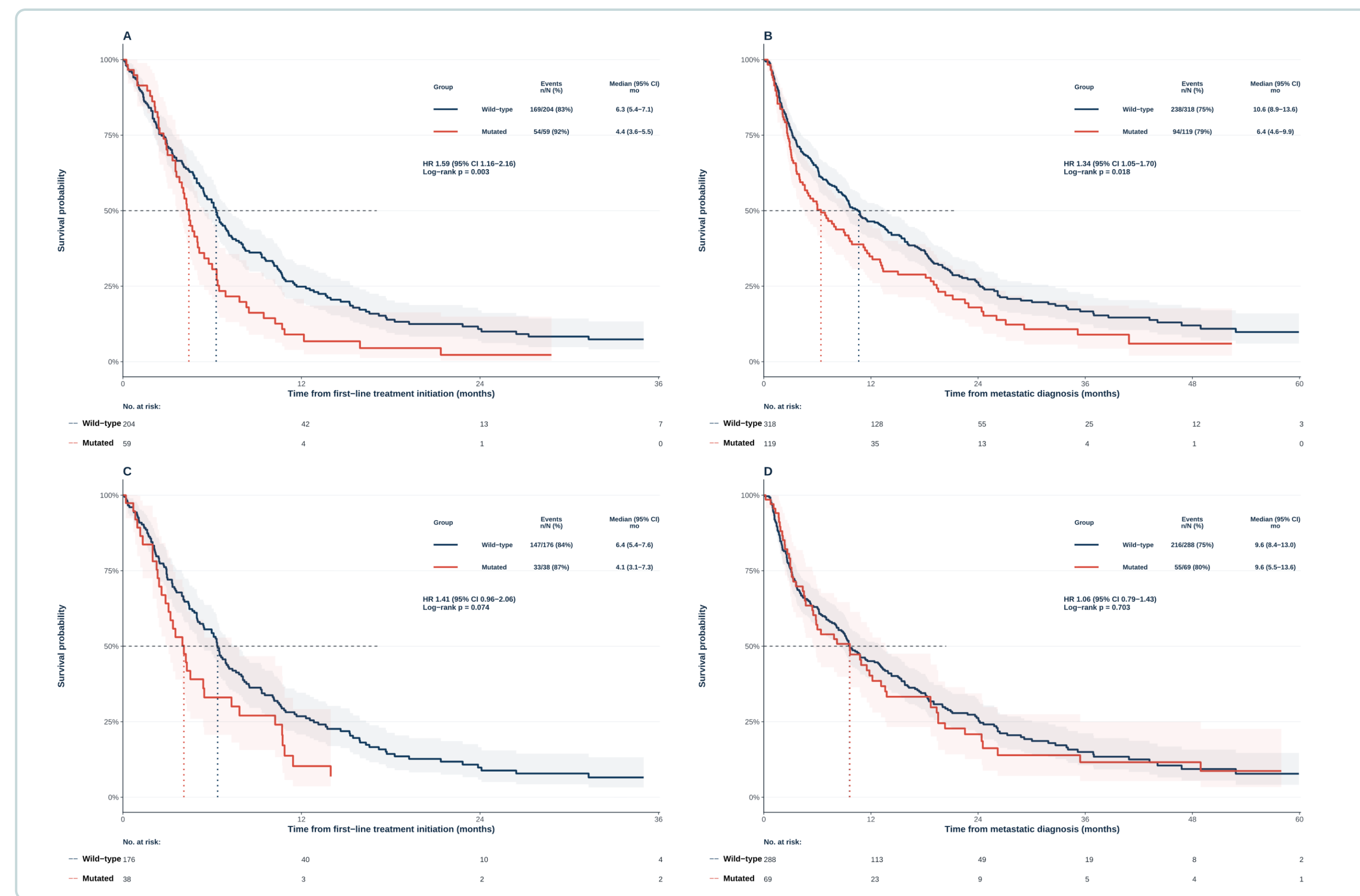


Figure 6. PFS and OS according to *KRAS* and *STK11* mutation status in the metastatic cohort. A, PFS by *KRAS*; B, OS by *KRAS*; C, PFS by *STK11*; D, OS by *STK11*.



CORRESPONDENCE

cmtrovohidalgo@usp.br

Cassio Murilo Hidalgo-Filho · ICESP / HCFMUSP

CONCLUSIONS

- In this immunotherapy-naïve Brazilian cohort, *KRAS* mutations were associated with worse PFS and OS outcomes.
- In contrast, *STK11* mutations did not associate with survival outcomes, suggesting that the impact of these mutations is highly treatment context dependent.
- In resource-limited settings, the clinical interpretation of *KRAS* and *STK11* as biomarkers must account for both access to molecular testing and the therapeutic context.