

STK11 and KEAP1 co-mutations show context-dependent effects in RAS-activated, KRAS wild-type NSCLC

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01 Background

RAS-activated, KRAS wild-type (RASa/KRASwt) NSCLC is a molecular subset characterised by MAPK pathway activation through alternative oncogenic drivers.

In **KRAS-mutant** NSCLC, co-mutations in **STK11** and **KEAP1** have been consistently associated with resistance to immune checkpoint inhibitors (ICI) and inferior outcomes.

Whether these effects extend to RASa/KRASwt tumours **remains unknown**.

02 Methods

Retrospective analysis of patients with metastatic non-squamous NSCLC treated with ICI at **Dana-Farber Cancer Institute** and **Memorial Sloan Kettering** .

RAS-ACTIVATED DEFINITION

NF1, NF2, BRAF, RAF1, MAP2K1/2, MAP3K1, MAPK1, PTPN11, SOS1, HRAS, NRAS, RIT1, RASA1 or **GNAS** , excluding KRAS-mutant and EGFR/ALK-driven tumours.

Co-occurring **STK11, KEAP1** and **SMARCA4** alterations by targeted NGS. Endpoints: PFS, OS, ORR. Kaplan–Meier with log-rank tests; hazard ratios from Cox models.

03 Cohort

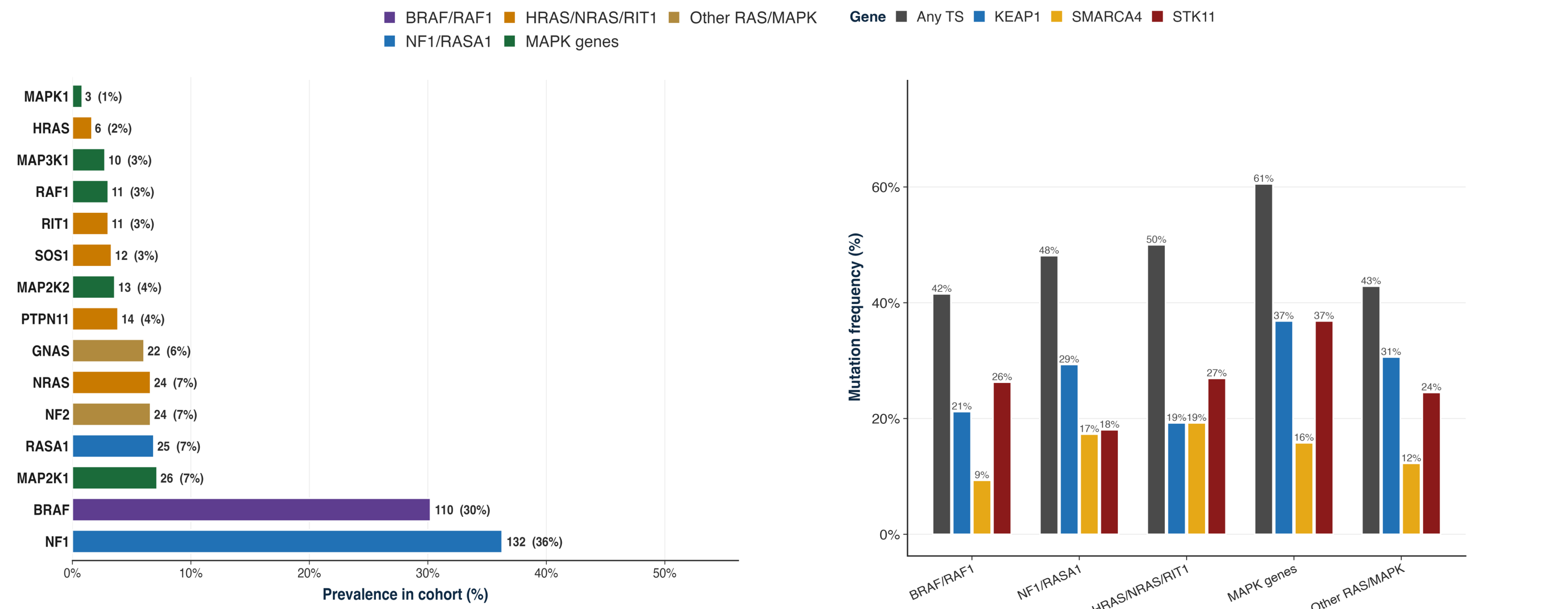
Patients screened	2,406
KRAS-WT · EGFR/ALK-negative · non-squamous	992
RAS–MAPK altered — analysis cohort	364

Co-mutated tumours were enriched for smoking history (**95% vs 84%** , p<0.001) whereas triple-WT tumors more frequently had PD-L1 TPS ≥50% (41% vs 23%; P<0.001), with otherwise similar clinical characteristics.

04 Clinical characteristics

Characteristic	Overall N = 364	TS wild-type N = 194	Any TS mut. N = 170	p
Age, years (median, Q1–Q3)	67.8 (60.5–68.0; 74.0)	60.9–67.6 (75.3)	60.0–73.5 (73.5)	0.219
Sex				0.268
Female	174 (48%)	98 (51%)	76 (45%)	
Male	190 (52%)	96 (49%)	94 (55%)	
Smoking status				0.001
Ever	324 (89%)	163 (84%)	161 (95%)	
Never	40 (11%)	31 (16%)	9 (5.3%)	
ECOG PS				0.064
0–1	301 (85%)	155 (82%)	146 (89%)	
2+	52 (15%)	34 (18%)	18 (11%)	
Missing	11	5	6	
PD-L1 TPS				0.001
Negative	116 (39%)	49 (31%)	67 (48%)	
Low	87 (29%)	46 (29%)	41 (29%)	
High	97 (32%)	65 (41%)	32 (23%)	
Missing	64	34	30	
TMB				0.208
High	210 (58%)	106 (55%)	104 (61%)	
Low	154 (42%)	88 (45%)	66 (39%)	
Line of therapy				0.854
First-line	223 (61%)	118 (61%)	105 (62%)	
Later-line	141 (39%)	76 (39%)	65 (38%)	
Treatment type				0.890
Chemo-ICI	140 (39%)	74 (38%)	66 (39%)	
ICI monotherapy	222 (61%)	119 (62%)	103 (61%)	
Missing	2	1	1	
Institution				0.103
DFCI	207 (57%)	118 (61%)	89 (52%)	
MSKCC	157 (43%)	76 (39%)	81 (48%)	

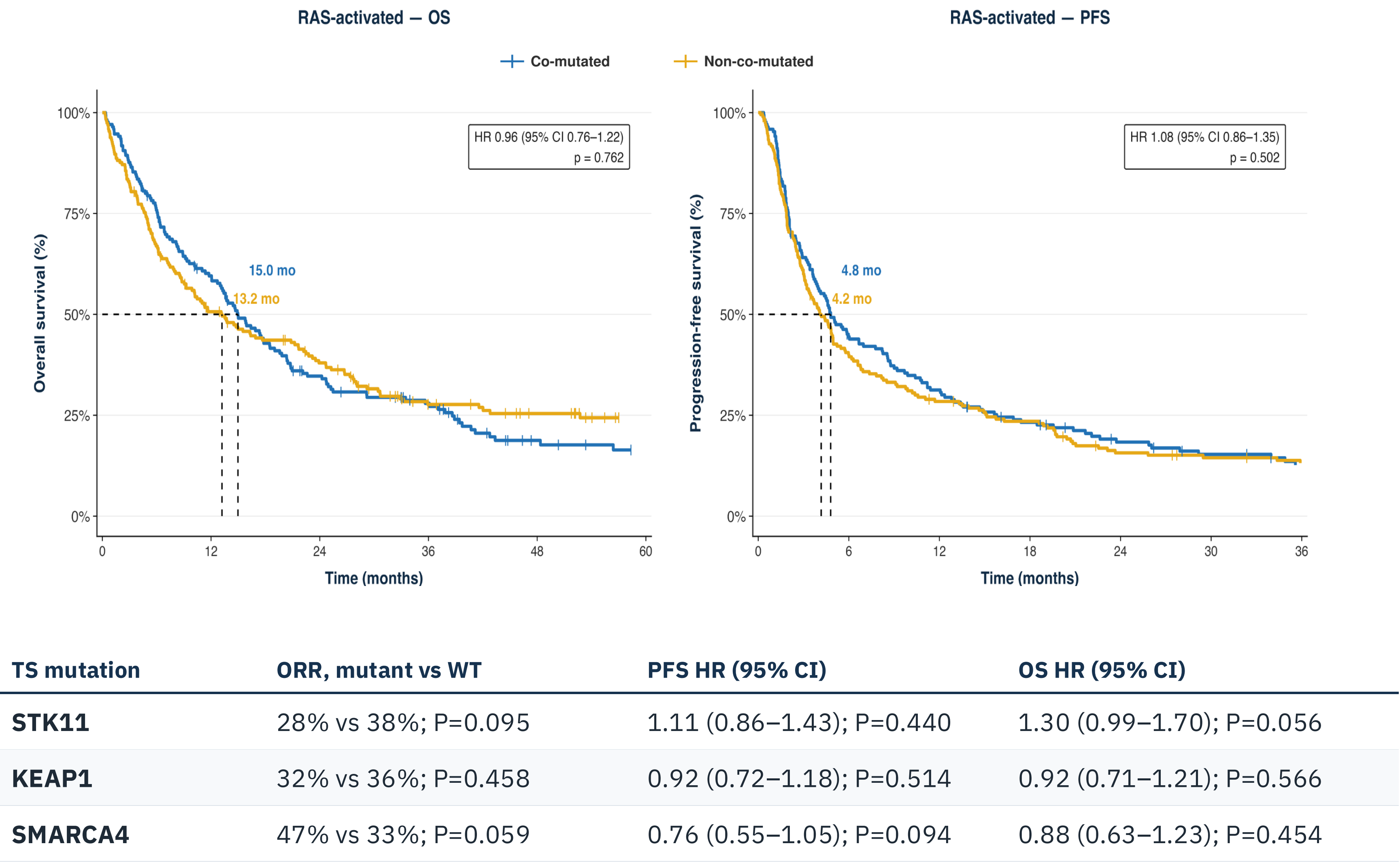
05 Genomic landscape



KEAP1 98 (27%)	STK11 88 (24%)	SMARCA4 51 (14%)	≥ 1 TS gene 170 (46%)
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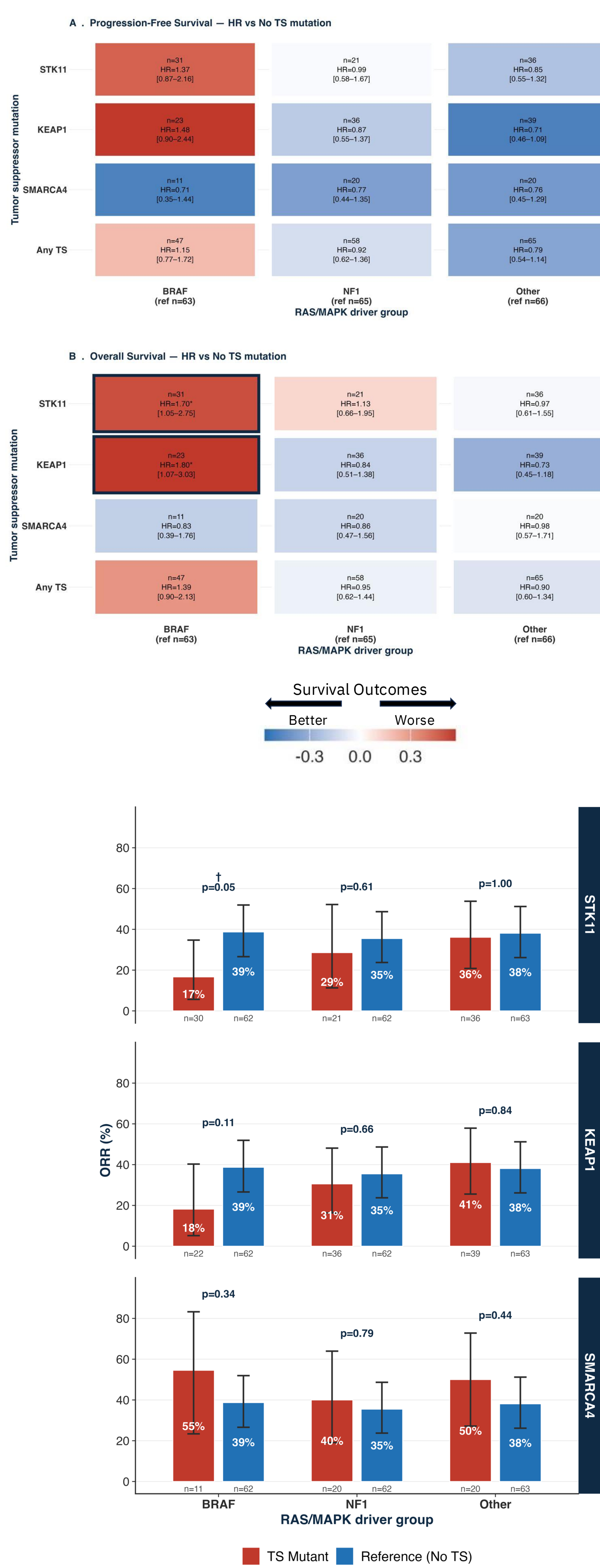
06 Primary result

No difference in OS, PFS or ORR with vs without TS co-mutation



TS mutation	ORR, mutant vs WT	PFS HR (95% CI)	OS HR (95% CI)
STK11	28% vs 38%; P=0.095	1.11 (0.86–1.43); P=0.440	1.30 (0.99–1.70); P=0.056
KEAP1	32% vs 36%; P=0.458	0.92 (0.72–1.18); P=0.514	0.92 (0.71–1.21); P=0.566
SMARCA4	47% vs 33%; P=0.059	0.76 (0.55–1.05); P=0.094	0.88 (0.63–1.23); P=0.454

07 Subgroup analysis



08 Conclusions

- In RASa/KRASwt NSCLC, **STK11, KEAP1** and **SMARCA4** co-mutations **do not appear to confer the same adverse impact** on immunotherapy outcomes as in KRAS-mutant tumours.
- This suggests **context-dependent biomarker effects** — the same co-mutations behave differently across RAS/MAPK drivers.
- Within **BRAF-mutant** tumors, STK11 and KEAP1 co-mutations were associated with worse OS, while STK11 was also associated with lower ORR, suggesting **biologically distinct subgroups** and warranting further investigation.