



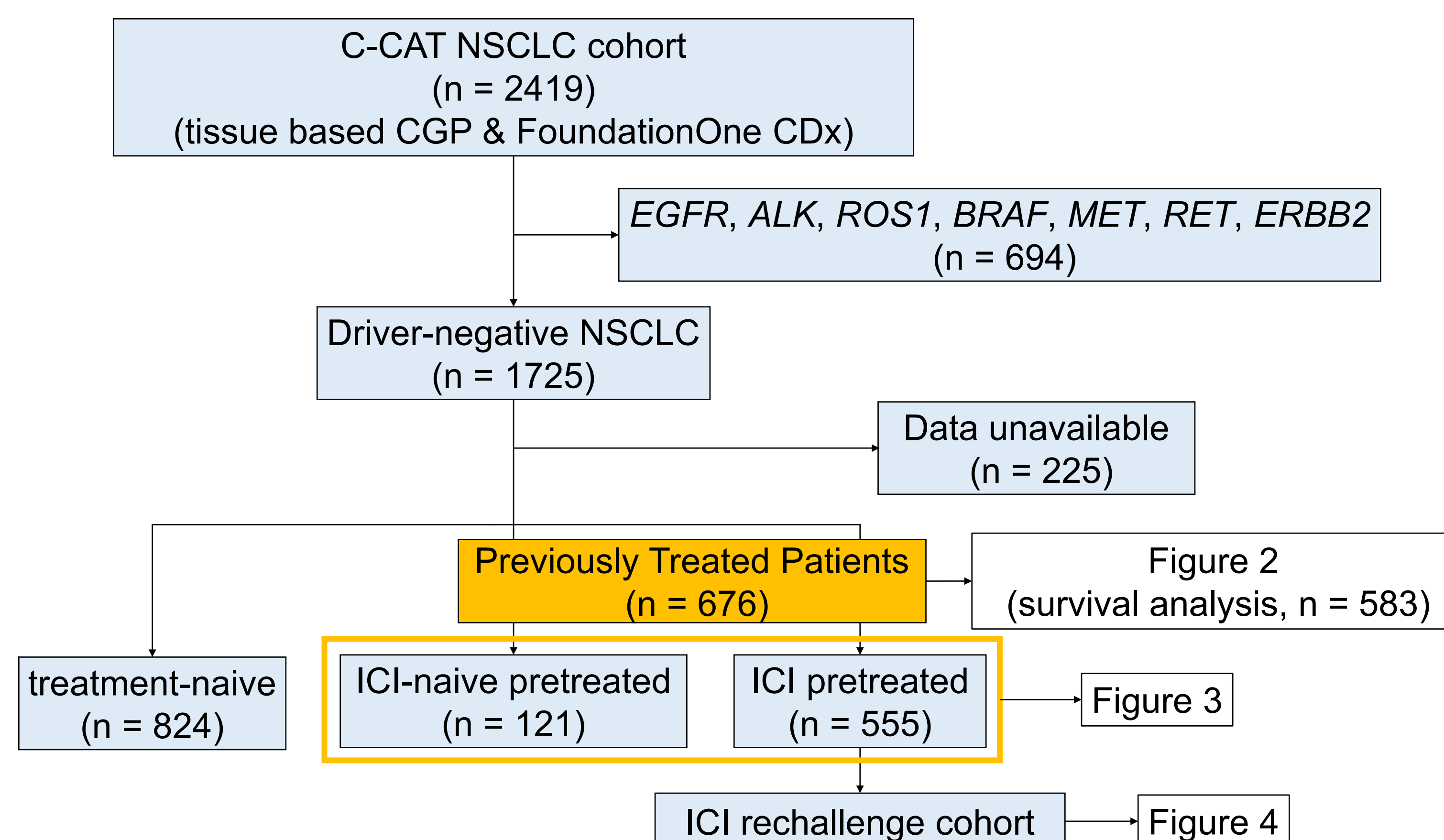
P1.267: *STK11/KEAP1* Mutations Define a Favorable Subset for ICI Rechallenge in TMB-High NSCLC

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Background and Purpose

- Tumour mutational burden (TMB) is an established predictive biomarker for immune checkpoint inhibitors (ICIs), but its clinical utility has been evaluated primarily in treatment-naïve tumours.¹⁻³
- Anticancer therapies, including ICIs, can reshape tumour clonal architecture and the immune microenvironment,⁴⁻⁶ whereas the clinical significance of post-treatment TMB remains unknown.
- We aimed to evaluate the clinical significance of post-treatment TMB and identify genomic determinants associated with the efficacy of ICI rechallenge in previously treated NSCLC.

Patients and Methods



- Primary cohort: C-CAT (nationwide Japanese clinico-genomic database)
- External validation: MSK-CHORD
- Mechanistic analyses: GSE243013 (post-ICI single-cell RNA-seq)
- TMB-high was defined as ≥ 10 mutations/Mb, and TMB-low as < 10 mutations/Mb
- Patients without survival data were excluded from overall survival analyses

Results

Table1. Patient characteristics

Characteristics	ICI-naïve pretreated (n=121)	ICI pretreated (n=555)
Age		
Median (IQR)	65.0 (58.0-73.0)	67.0 (59.0-72.0)
Sex		
Male	76 (62.8%)	400 (72.1%)
Female	45 (37.2%)	155 (27.9%)
Tumour histology		
Adenocarcinoma	97 (80.2%)	452 (81.4%)
Squamous cell carcinoma	24 (19.8%)	103 (18.6%)
Smoking status		
Current/former	90 (74.4%)	457 (82.3%)
Never	30 (24.8%)	90 (16.2%)
TMB (mut/Mb)		
Median (IQR)	6.0 (3.0-12.0)	7.0 (4.0-13.0)
TMB category		
TMB-High (≥ 10 mut/Mb)	44 (36.4%)	216 (38.9%)

Figure 1. TMB by Prior Treatment Status

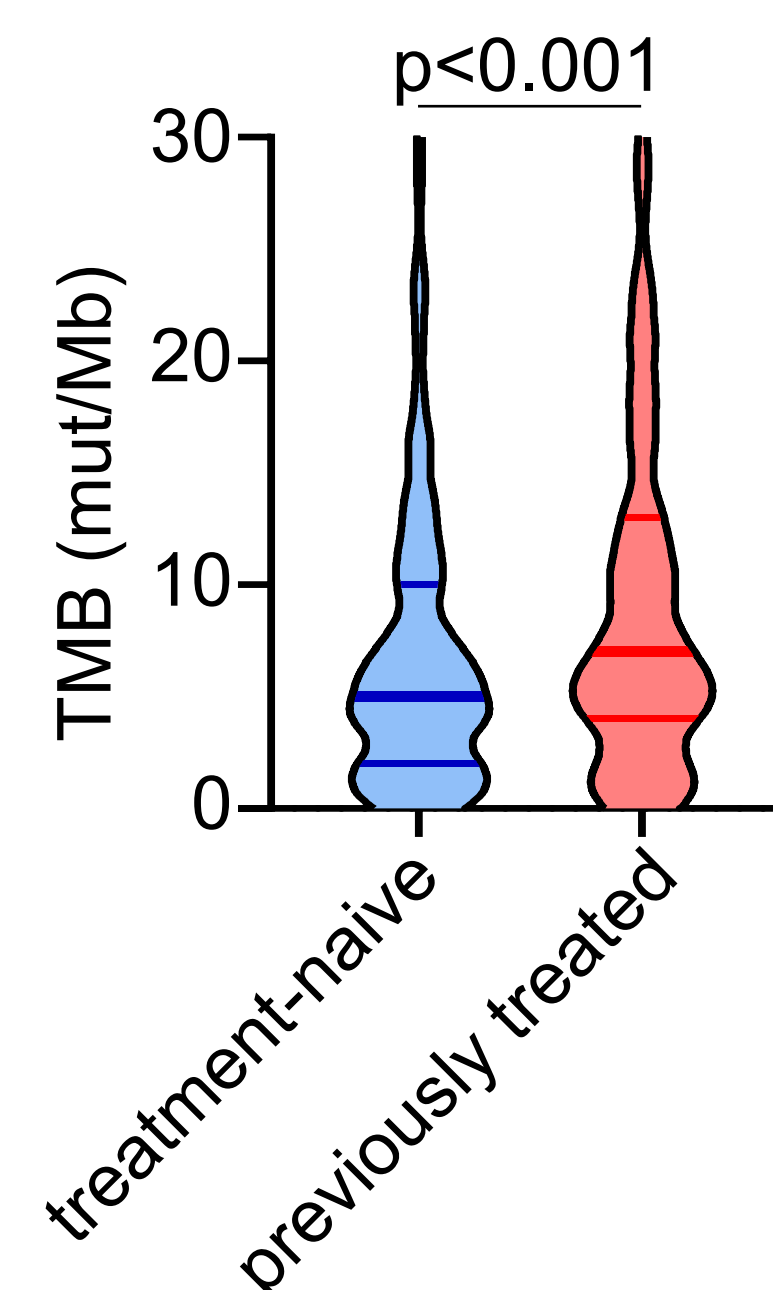


Figure 2. OS by TMB Status in Previously Treated Patients

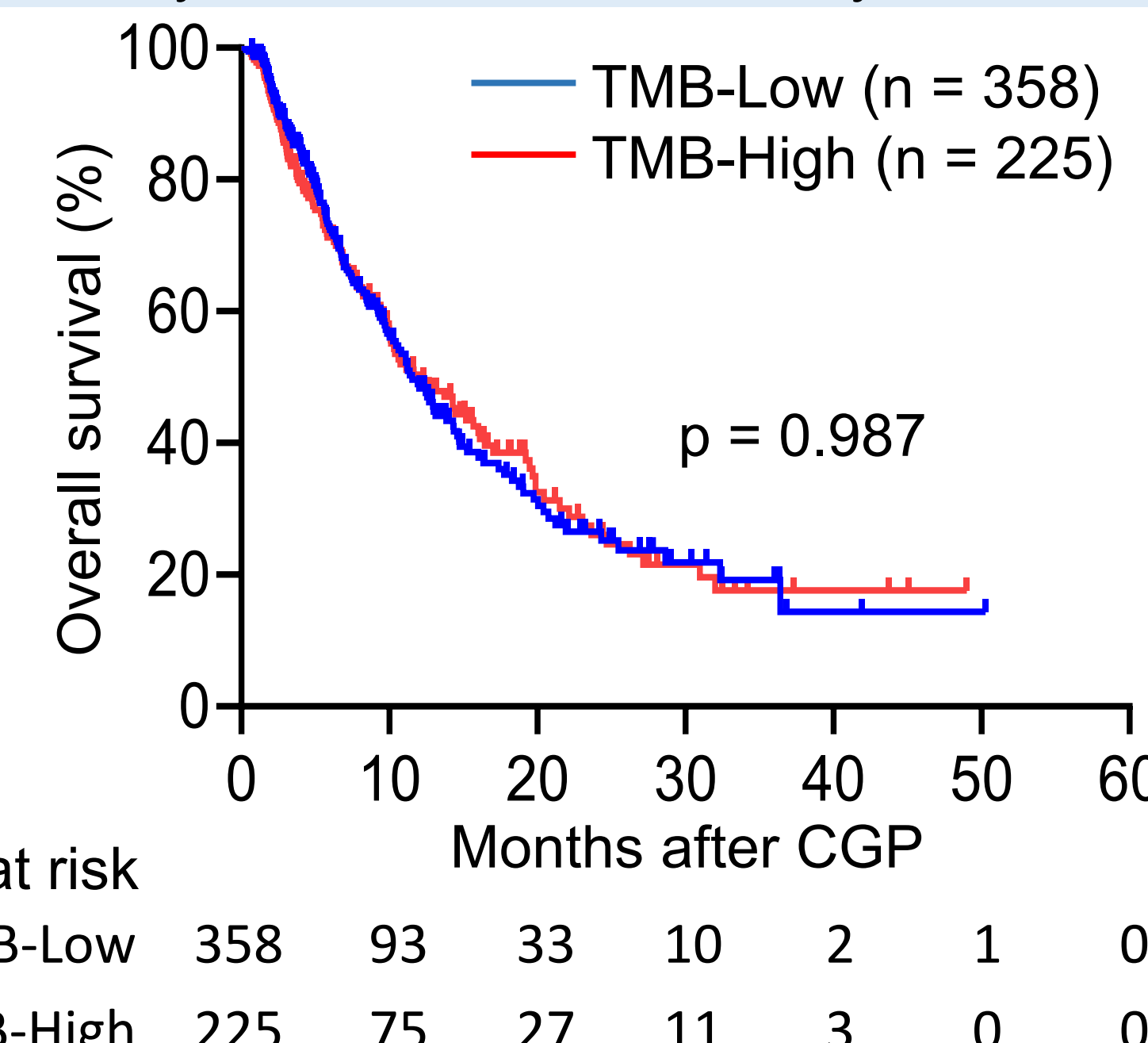


Figure 3. TMB by Prior ICI Exposure

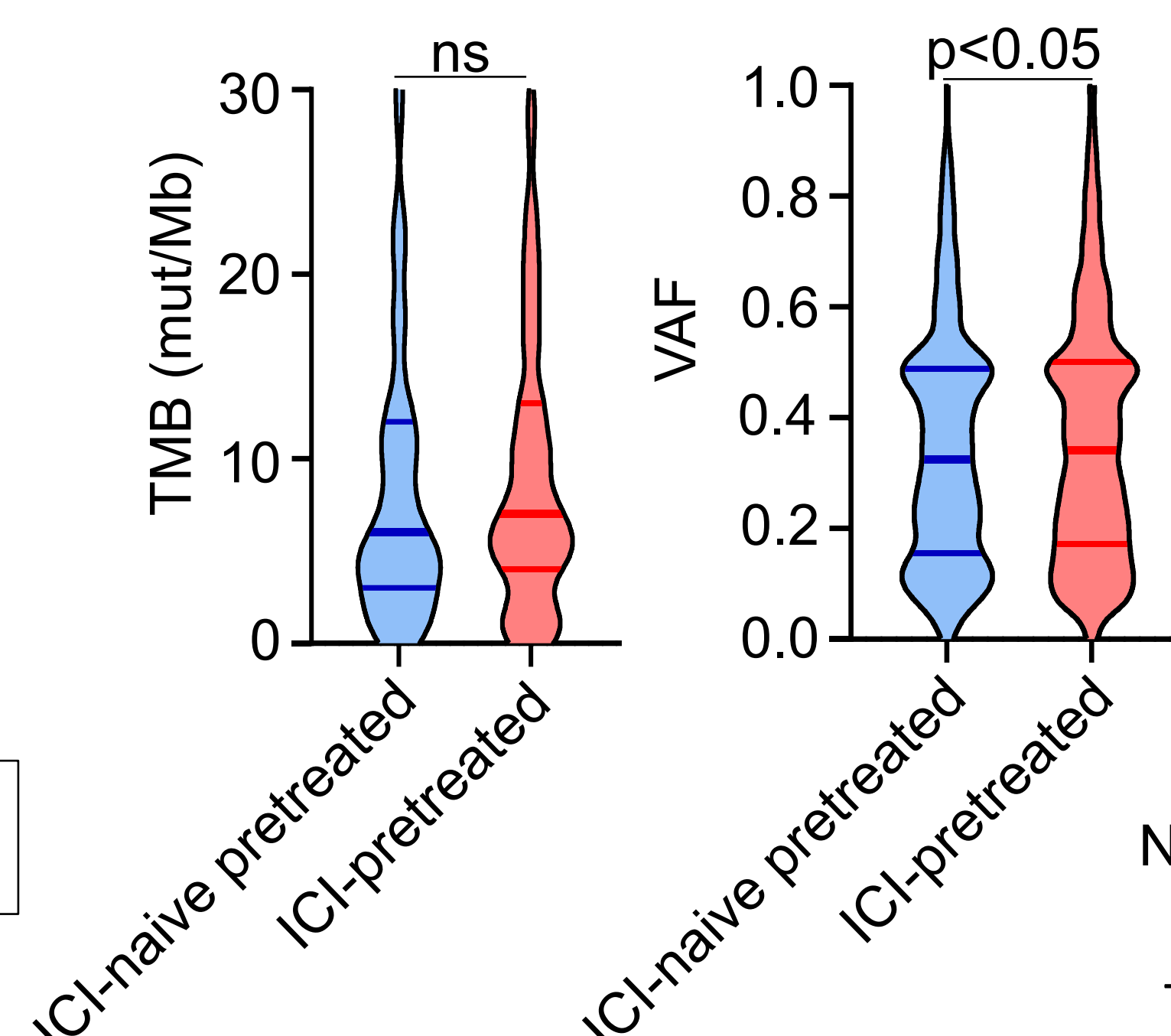
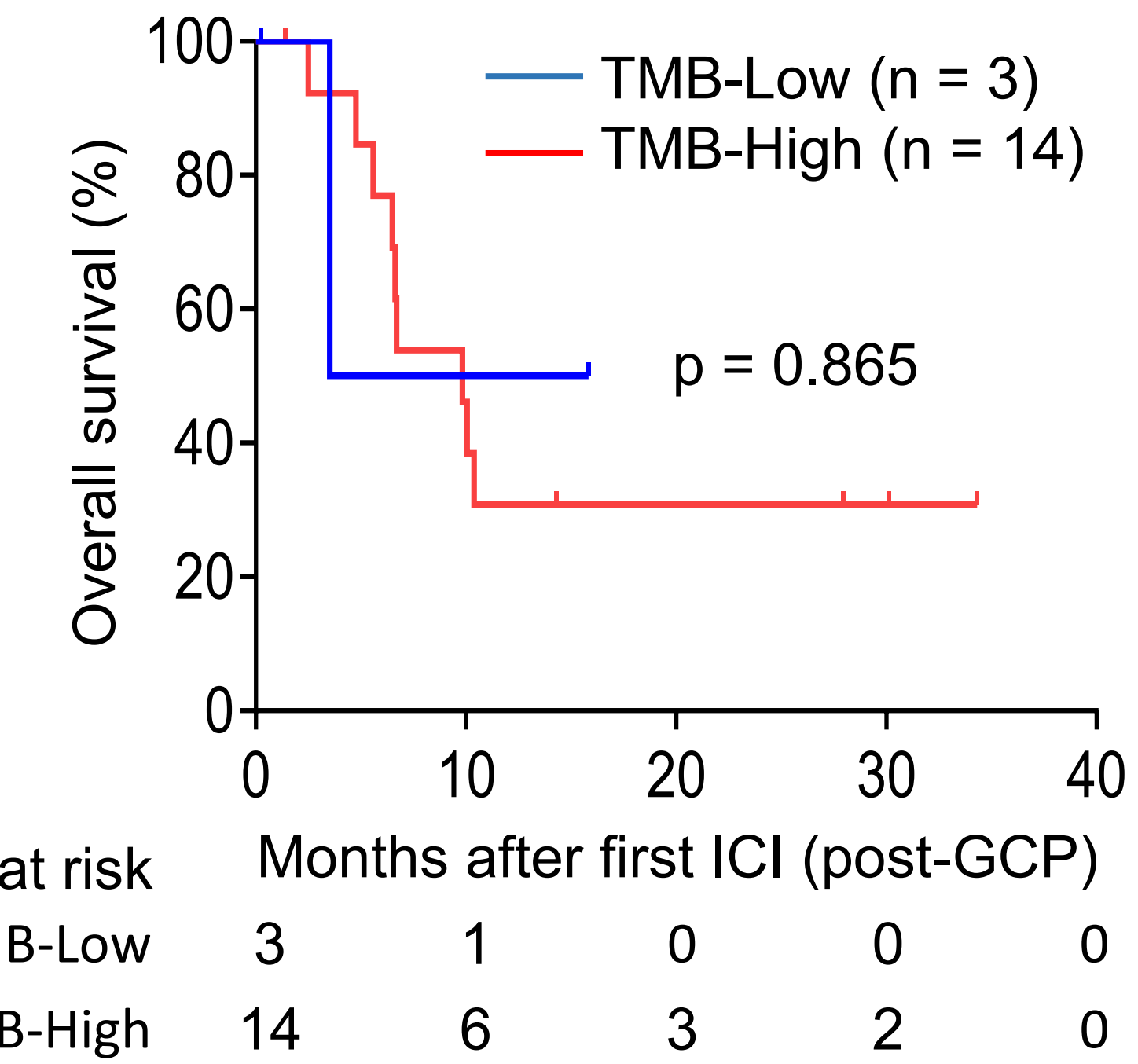
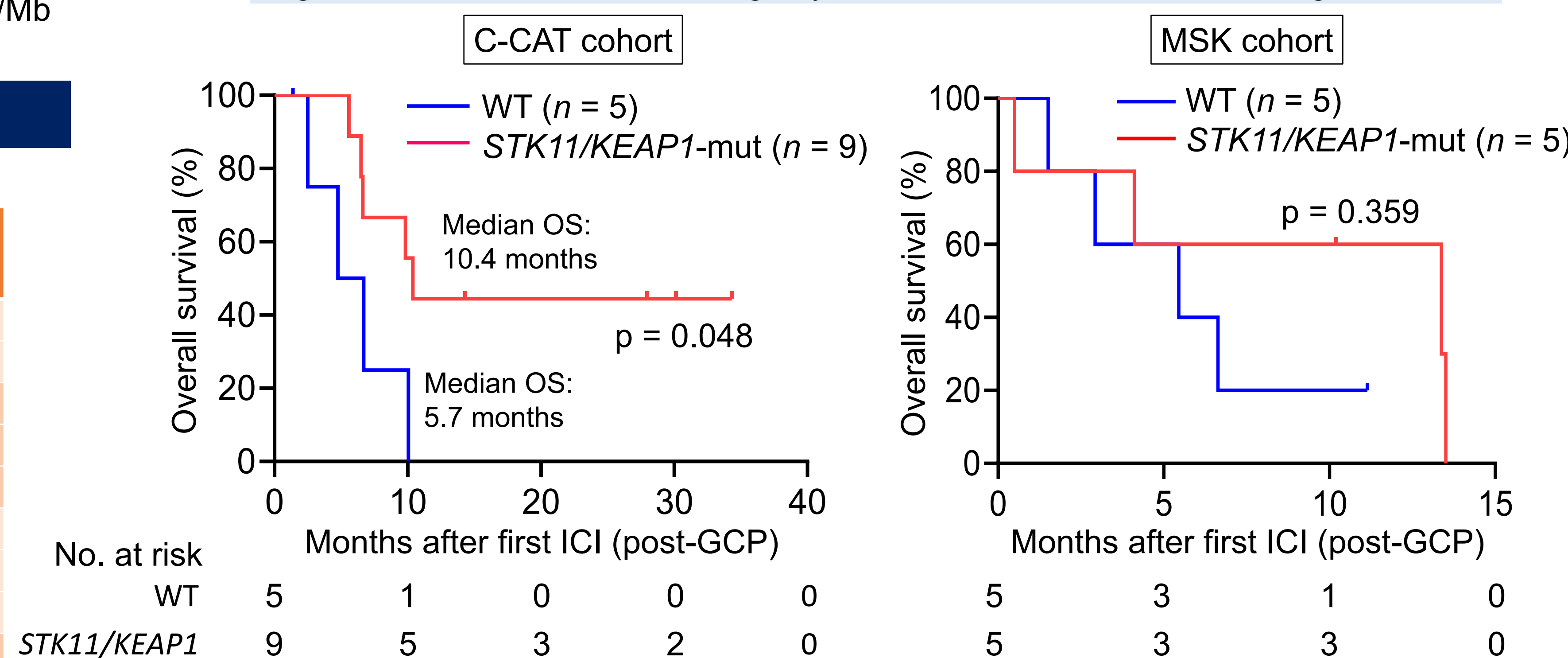


Figure 4. OS after ICI Rechallenge by TMB Status



Key finding

- TMB-high alone was not sufficient to predict benefit from ICI rechallenge.
- We therefore investigated genomic features associated with differential outcomes among TMB-high tumours.

Figure 5. OS after ICI Rechallenge by *STK11/KEAP1* Status in TMB-High Tumours

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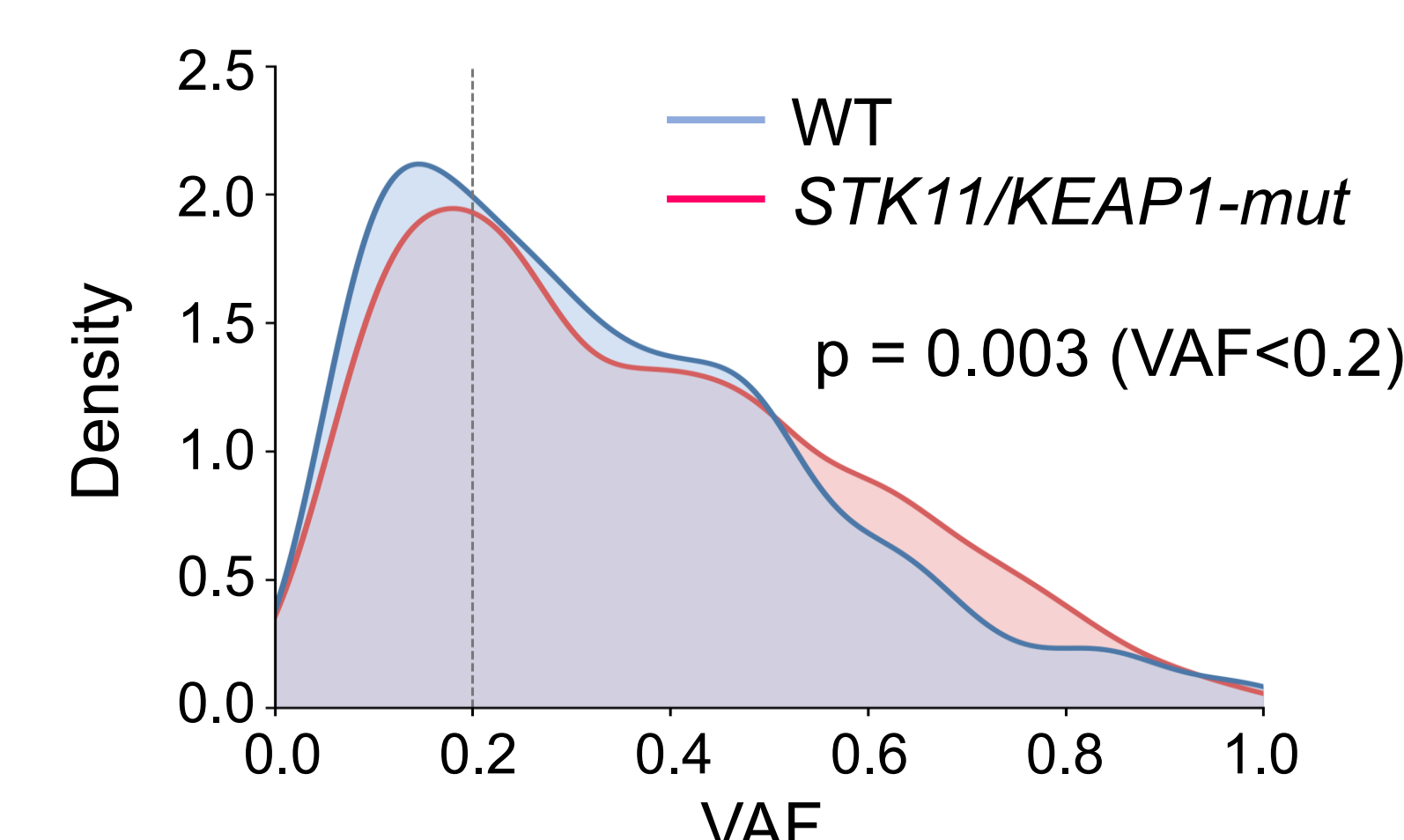
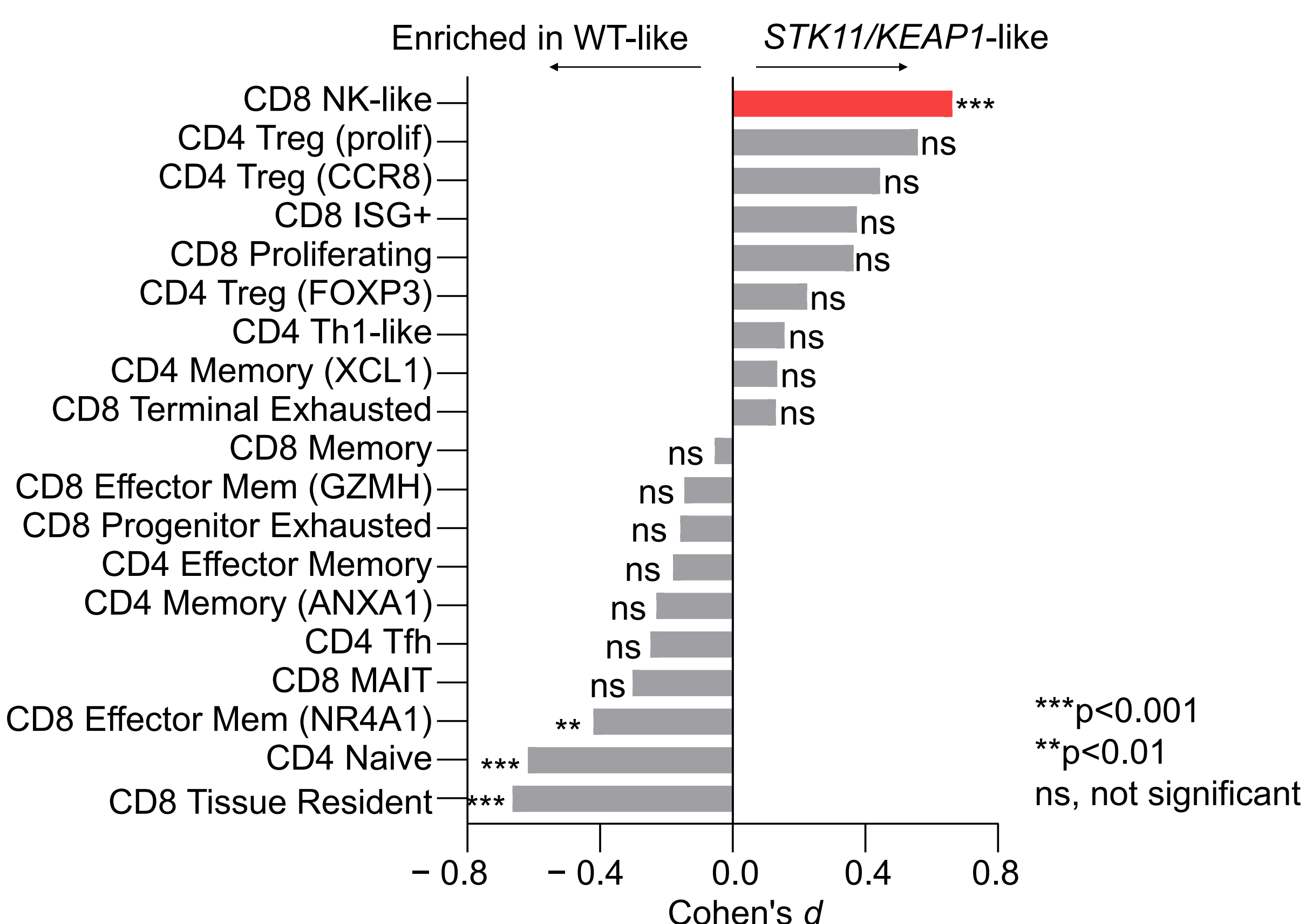
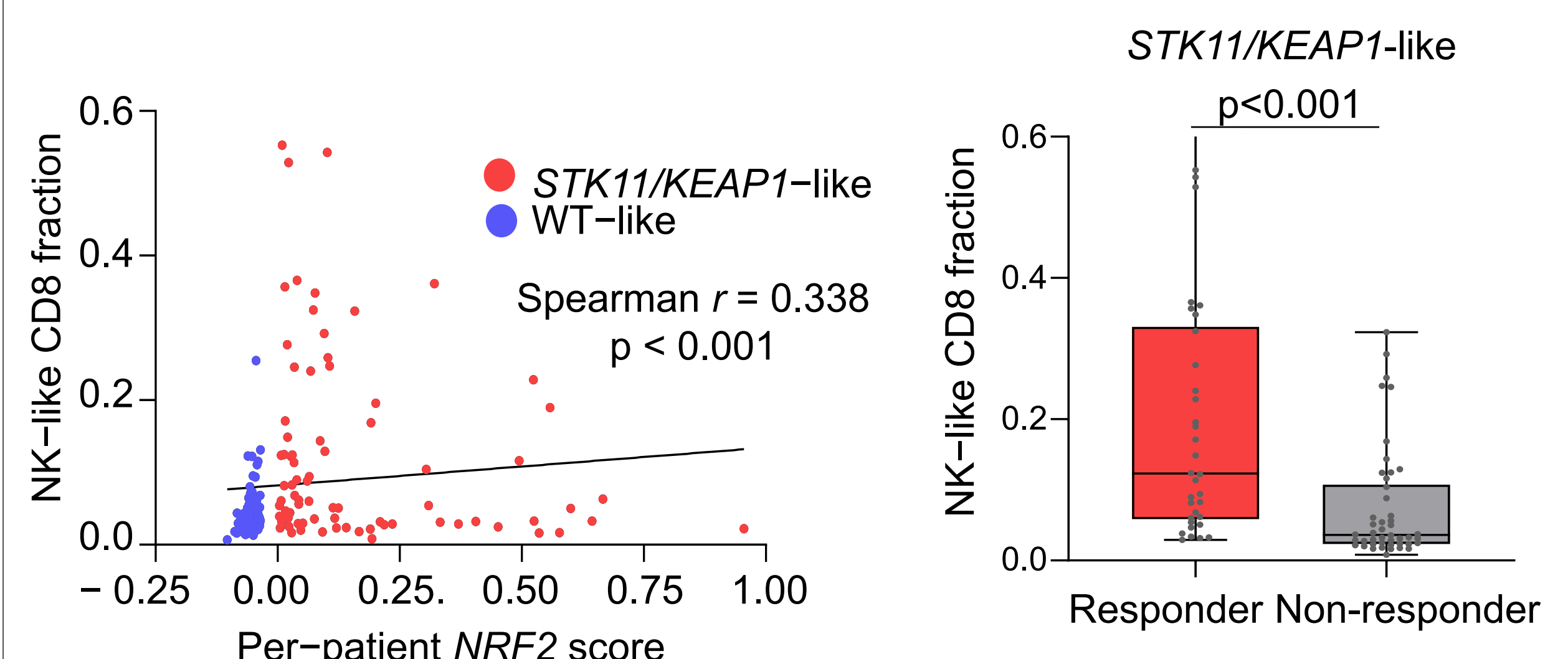
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Artificial Intelligence (AI) Use Disclosure

ChatGPT (OpenAI) was used to assist with language editing and improvement of the presentation text. All scientific analyses, data interpretation, and conclusions were performed, reviewed, and approved by the authors.

Figure 6. VAF Distribution by *STK11/KEAP1* Status in TMB-High TumoursFigure 7. Immune Cell Signatures by *STK11/KEAP1* Status (GSE243013)Figure 8. NK-like CD8⁺ T Cells, *NRF2* Activity, and Pathological Response

Discussion and Conclusion

- Distinct VAF distributions in *STK11/KEAP1*-mutant tumours suggest that differences in tumour clonal architecture may contribute to the heterogeneous efficacy of ICI rechallenge among TMB-high tumours.
- KEAP1* loss constitutively activates *NRF2* signalling and is associated with an immune-cold phenotype.⁷ Our findings suggest that ICI exposure may induce immune remodelling characterised by NK-like CD8⁺ T-cell enrichment in *STK11/KEAP1*-mutant tumours.
- Post-treatment TMB alone was insufficient to predict benefit from ICI rechallenge. Integrating tumour clonal architecture and genomic context may improve patient stratification for ICI rechallenge.