

RATIONALE-304: Baseline Tumor Genomic Alterations According to Programmed Death-Ligand 1 Subgroups in Non-Squamous Non-Small Cell Lung Cancer Treated With First-Line Tislelizumab Plus Chemotherapy vs Chemotherapy Alone

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CONCLUSIONS

- In non-squamous non-small cell lung cancer (NSCLC), distinct genomic profiles were observed between programmed death-ligand 1 (PD-L1) tumor cell (TC) expression categories, while tumor mutational burden (TMB) was similar across expression levels
- Tumors with PD-L1 $\geq 50\%$ were enriched for *KRAS*, *PBRM1*, and *EMSY* alterations, while *FOXA1* alterations were enriched in tumors with PD-L1 $< 50\%$ and *ARID1A*, *STK11*, *EPCAM*, *GRIN2A*, and *IRF4* were enriched in PD-L1 $< 1\%$ tumors. Higher prevalence of NRF2 and PIK3 signaling pathway alterations was observed in tumors with PD-L1 TC expression $< 1\%$
- Alterations in the NRF2 signaling pathway were associated with reduced progression-free survival (PFS) and overall survival (OS) benefit in the tislelizumab plus chemotherapy arm vs the chemotherapy arm
- The identification of specific genomic signatures in different PD-L1 subgroups may help optimize patient selection and treatment strategies with tislelizumab plus chemotherapy in advanced first-line non-squamous NSCLC
- Further validation in independent NSCLC datasets with larger sample sizes is required

INTRODUCTION

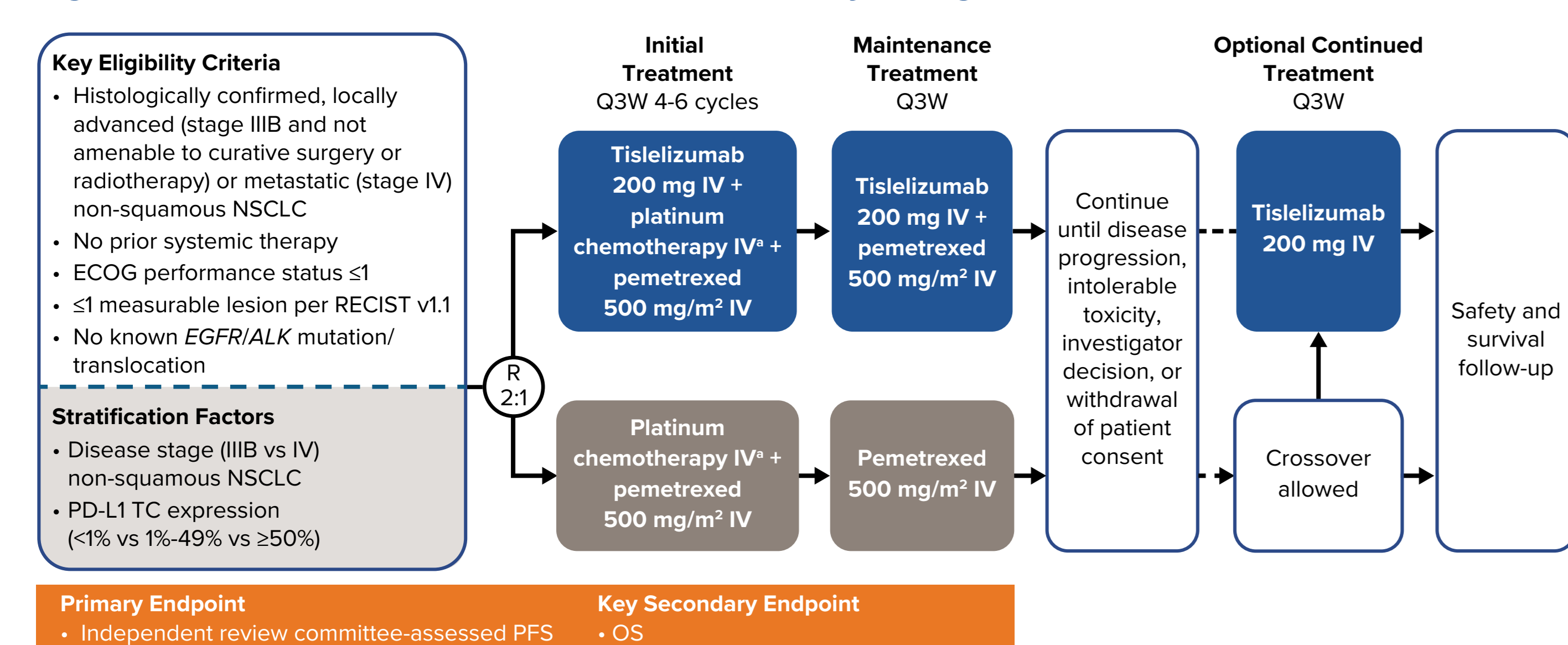
- PD-L1 serves as a valuable predictive biomarker for immunotherapy response, but its clinical utility varies. While higher PD-L1 TC expression generally correlates with improved outcomes, comprehensive models combining PD-L1 TC expression with additional genomic features may improve prediction accuracy^{1,2}
- In the phase 3 RATIONALE-304 trial (final analysis data cutoff: October 26, 2020; median follow-up 16.1 months), patients with advanced non-squamous NSCLC treated with tislelizumab plus chemotherapy experienced significant survival benefits vs those treated with chemotherapy alone, with the greatest benefit in patients whose tumors expressed PD-L1 in $\geq 50\%$ of TCs^{3,4}
- Previous retrospective analysis showed no significant association between TMB and PD-L1 expression, and TMB did not significantly differentiate treatment-specific PFS benefit⁵
- This post-hoc analysis of RATIONALE-304 (data cutoff: April 26, 2023) evaluated baseline genomic profiles of tumors with varying PD-L1 TC expression levels ($< 1\%$ vs $1\% - 49\%$ vs $\geq 50\%$) to identify potential genomic features associated with response to tislelizumab plus chemotherapy

METHODS

Study Design

- RATIONALE-304 (NCT03663205) was an open-label, randomized, phase 3 trial conducted in China (Figure 1)

Figure 1. Overview of the RATIONALE-304 Study Design



*Platinum chemotherapy: cisplatin 75 mg/m² administered as an IV infusion over 2 hours Q3W or carboplatin AUC 5 administered as an IV infusion over 15 minutes Q3W. Abbreviations: ALK, anaplastic lymphoma kinase; AUC 5, area under the curve 5; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; IV, intravenously; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Biomarker Analysis

- PD-L1 TC expression was assessed centrally using baseline tumor tissue samples stained with the VENTANA PD-L1 (SP263) Assay (Roche)
- Genomic profiling and TMB analyses were performed on baseline tumor tissue samples using the OncoScreen Plus 520 panel
- Differences in genomic alterations across PD-L1 subgroups were analyzed using Chi-square tests or Fisher exact tests (when expected patient counts were < 5)
- Survival analyses used univariate Cox models to estimate hazard ratios (HRs) comparing mutation vs wild-type status (reference) for each pathway
- Treatment-by-biomarker interactions were assessed using Cox models with interaction terms between mutation status and treatment, using Wald and likelihood ratio tests to detect differential treatment effects
- Statistical significance: $P < .05$; adjusted P -values reported for multiple testing corrections

RESULTS

Patient Disposition and Baseline Characteristics

- As of April 26, 2023 (median study follow-up: 23.4 months), a total of 334 patients (intent-to-treat [ITT] population) were randomized to receive tislelizumab plus chemotherapy ($n=223$) or chemotherapy alone ($n=111$); 159 (47.6%) constituted the biomarker-evaluable population (BEP) for both PD-L1 TC expression and genomic alterations
- The BEP included 57 patients with PD-L1 TC expression $< 1\%$, 45 patients with $1\% - 49\%$, and 57 patients with $\geq 50\%$
- Baseline demographics were generally balanced between PD-L1 subgroups and consistent with the ITT population³ (Table 1)

Table 1. Patient Demographics and Baseline Characteristics by PD-L1 TC Expression Level

	ITT		BEP ^a	
	Tislelizumab Plus Chemotherapy (n=223)	Chemotherapy (n=111)	Tislelizumab Plus Chemotherapy (n=108)	Chemotherapy (n=51)
Median age (range), years	61 (28-76)	62 (25-75)	61 (36-74)	62 (25-75)
Sex, n (%)				
Female	55 (24.7)	32 (28.8)	21 (19.4)	14 (27.5)
Male	168 (75.3)	79 (71.2)	87 (80.6)	37 (72.5)
Disease stage, n (%)				
IIIB	40 (17.9)	21 (18.9)	24 (22.2)	11 (21.6)
IV	183 (82.1)	90 (81.1)	84 (77.8)	40 (78.4)
ECOG performance status, n (%)				
0	54 (24.2)	24 (21.6)	25 (23.1)	11 (21.6)
1	169 (75.8)	87 (78.4)	83 (76.9)	40 (78.4)
Smoking status, n (%)				
Current	32 (14.3)	13 (11.7)	17 (15.7)	5 (9.8)
Former	115 (51.6)	53 (47.7)	59 (54.6)	29 (56.9)
Never	76 (34.1)	45 (40.5)	32 (29.6)	17 (33.3)
PD-L1 subgroup, n (%)				
TC $< 1\%$	91 (40.8)	48 (43.2)	40 (37.0)	17 (33.3)
TC $\geq 1\%$ and $< 50\%$	53 (23.8)	27 (24.3)	29 (26.9)	16 (31.4)
TC $\geq 50\%$	74 (33.2)	36 (32.4)	39 (36.1)	18 (35.3)
Not evaluable	5 (2.2)	0	0	0

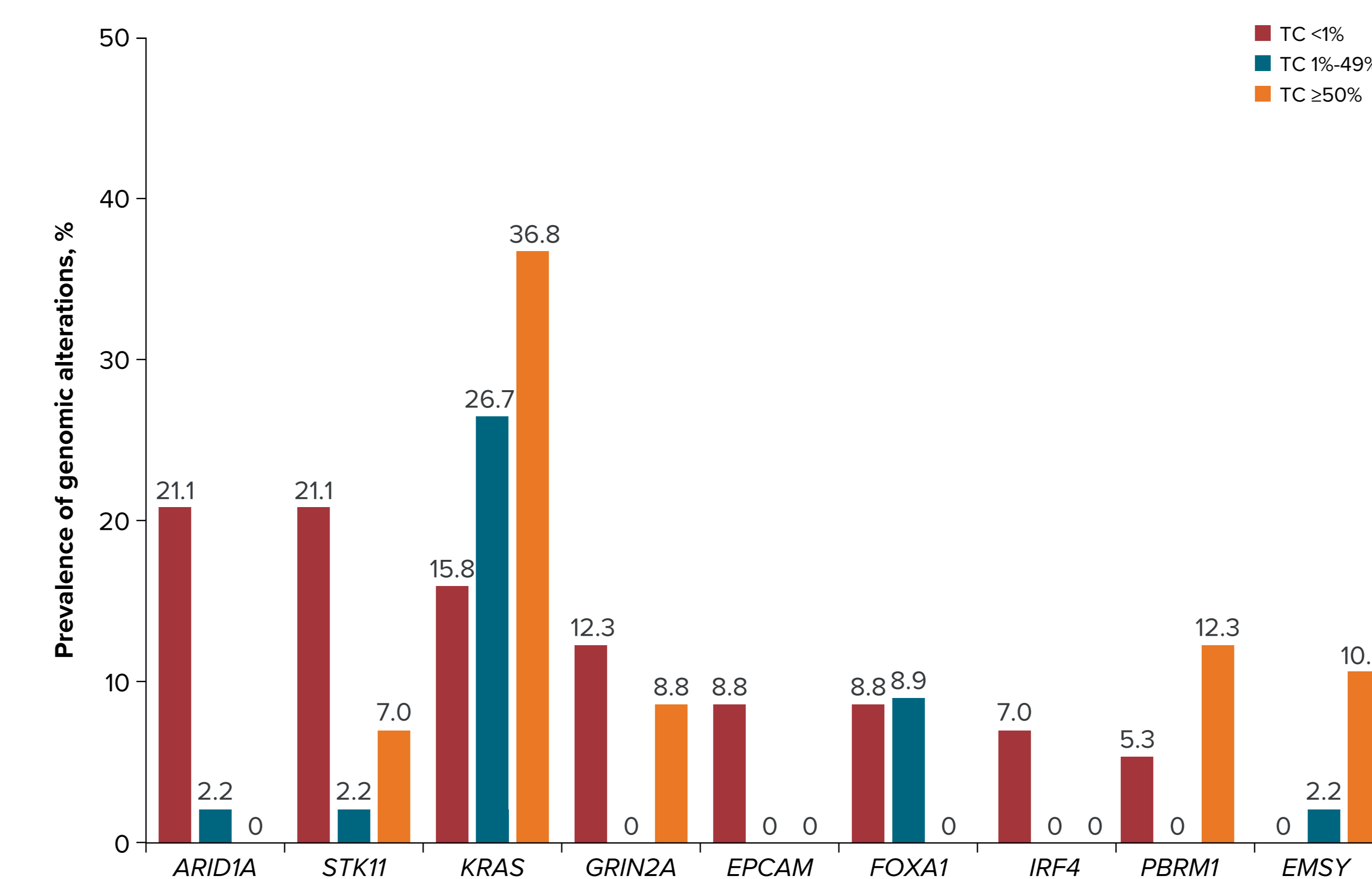
^aALK fusion and EGFR sensitizing mutations are excluded from the BEP.

RESULTS (CONT)

Distributions of Genomic Alterations and Co-Occurrence Patterns

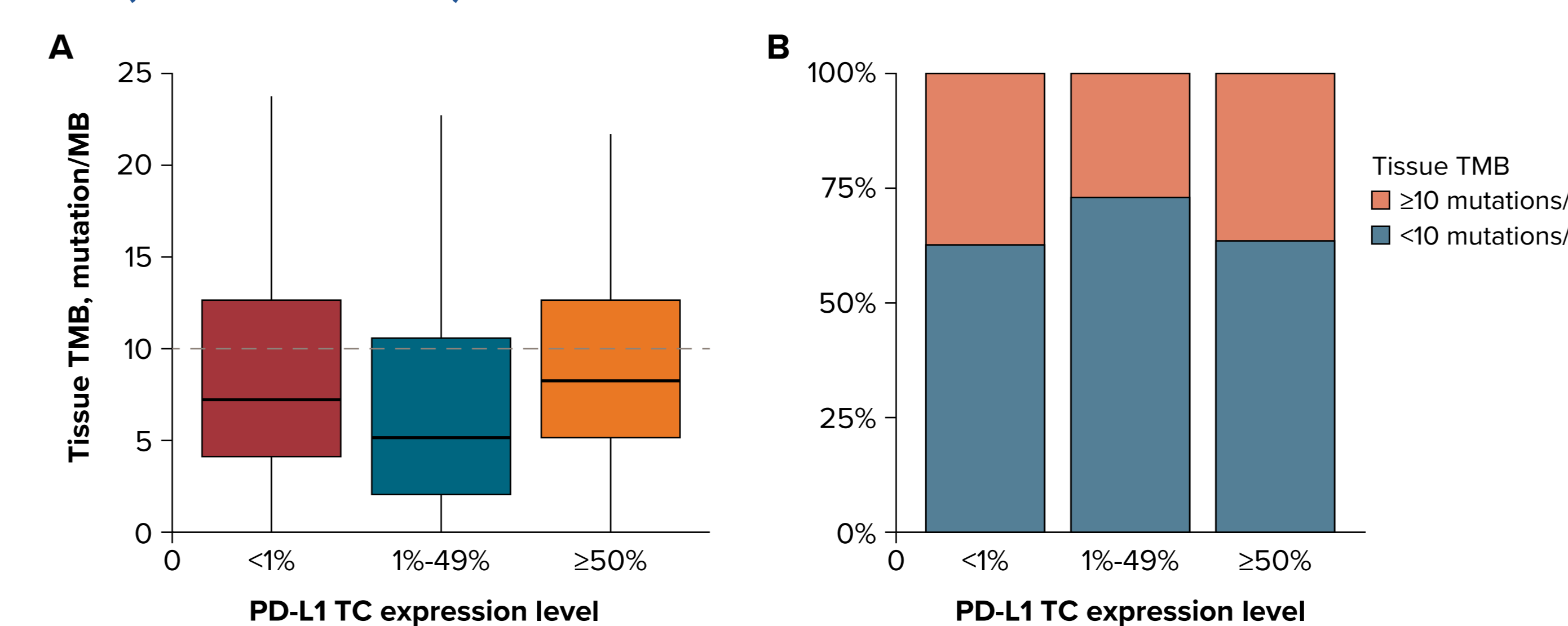
- Tumors with PD-L1 TC expression $\geq 50\%$ showed increased prevalence of alterations in *KRAS*, *PBRM1*, and *EMSY* genes compared with tumors with PD-L1 TC expression $< 50\%$ (all $P < .05$) (Figure 2)
- FOXA1* alterations were enriched in tumors with PD-L1 TC expression $< 50\%$ ($P < .05$) compared with tumors with PD-L1 TC expression $\geq 50\%$
- Tumors with PD-L1 TC expression $< 1\%$ demonstrated higher prevalence of alterations in the *ARID1A*, *STK11*, *EPCAM*, *GRIN2A*, and *IRF4* genes (all $P < .05$)

Figure 2. Prevalence of Genomic Alterations in Tumors by PD-L1 TC Expression Level (BEP)



- No difference in TMB was observed in tumors with PD-L1 TC expression $< 1\%$ vs $1\% - 49\%$ vs $\geq 50\%$ ($P = .357$) (Figure 3)

Figure 3. TMB by PD-L1 TC Expression Level (BEP). (A) Distribution of Tissue TMB Across PD-L1 TC Expression Groups. (B) Proportion of Tumors With High (≥ 10 Mutations/MB) vs Low (< 10 Mutations/MB) TMB

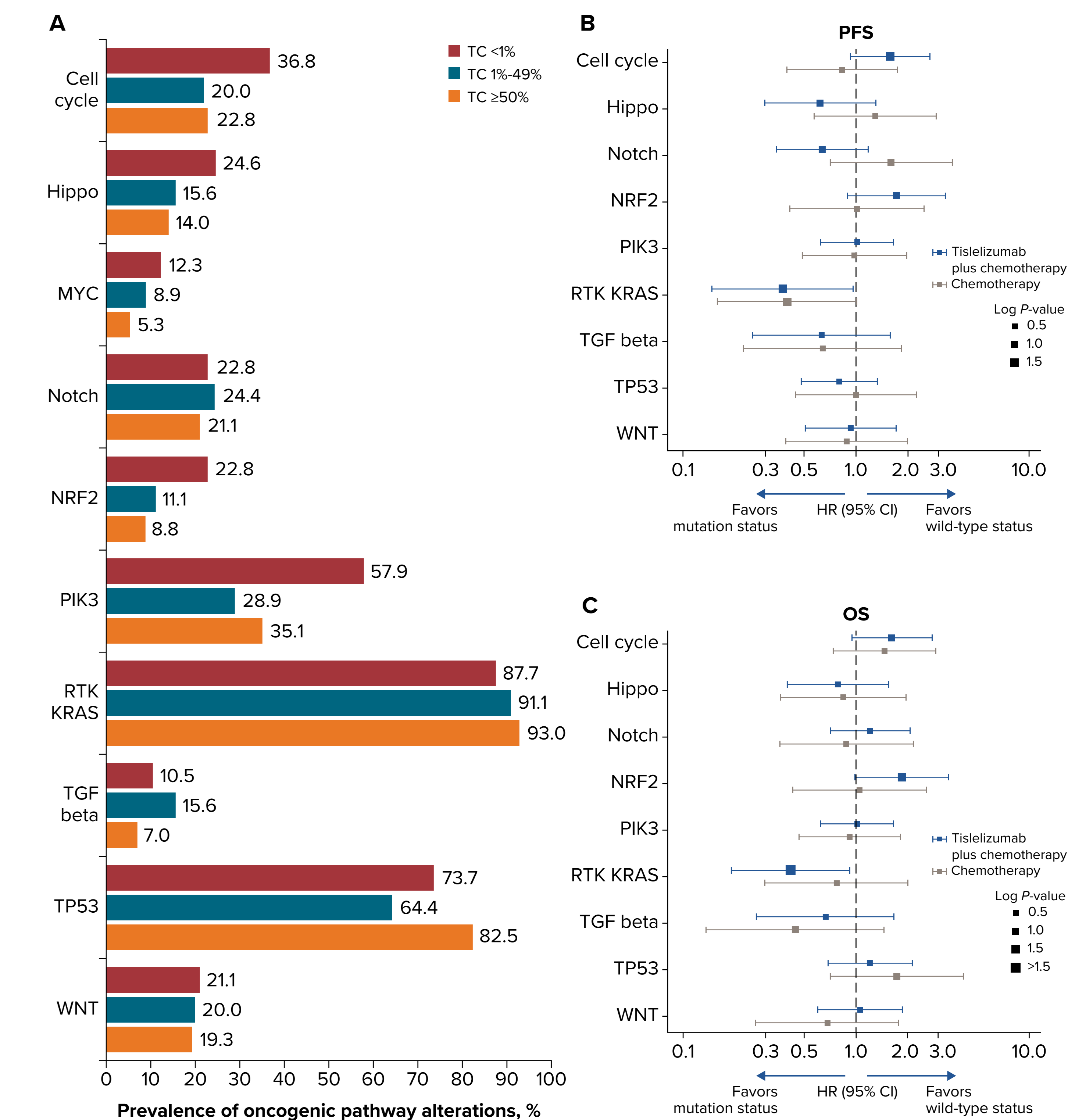


Genomic Alterations in Oncogenic Signaling Pathways and Association With Survival Outcomes

- Higher prevalence of alterations in the NRF2 ($P = .078$) and PIK3 ($P = .006$) signaling pathways was observed in tumors with PD-L1 TC expression $< 1\%$ (Figure 4A)

- Alterations in Hippo and Notch signaling pathways were associated with an improved PFS benefit, while cell cycle and NRF2 pathway alterations were associated with reduced PFS benefit among patients who received tislelizumab plus chemotherapy vs chemotherapy (Figure 4B)
- Alterations in the RTK KRAS signaling pathways were associated with enhanced OS benefit, while NRF2 signaling pathway alterations were associated with reduced OS benefit among patients who received tislelizumab plus chemotherapy vs chemotherapy (Figure 4C)

Figure 4. (A) Prevalence of Oncogenic Pathway Alterations by PD-L1 TC Expression Level and Association of Pathway Alterations With (B) PFS and (C) OS Outcomes With Tislelizumab Plus Chemotherapy vs Chemotherapy (BEP)



Abbreviations: CI, confidence interval; RTK, receptor tyrosine kinase.

REFERENCES

- Strati A, et al. *Int J Mol Sci*. 2025;26:1235.
- Tang Q, et al. *Front Immunol*. 2022;13:964442.
- Lu S, et al. *ESMO Open*. 2024;9:103728.
- Lu S, et al. *Oncol Ther*. 2025;13:1087-1104.
- Lu S, et al. *Cancer Res*. 2022;82(Suppl 12):LB512.

DISCLOSURES

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