RATIONALE-307: Updated biomarker analysis of Phase 3 study of tislelizumab plus chemo vs chemo alone for 1L advanced sq-NSCLC

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Introduction

In the RATIONALE-307 trial (NCT03594747), tislelizumab plus platinum-based chemotherapy significantly improved clinical outcomes vs chemotherapy alone in treatment-naïve advanced squamous non-small cell lung cancer (sq-NSCLC). Previously, we showed superior clinical efficacy of tislelizumab plus chemotherapy vs chemotherapy alone regardless of PD-L1 expression (J Clin Oncol 38:2020[suppl; Abstr 9554]) and blood tumor mutational burden (Ann Oncol 2020;31[4]:S754–S840). Here we report the updated biomarker analysis of PD-L1 expression, tissue tumor mutational burden (tTMB) and gene expression profiling (GEP) in baseline tumor samples.

Methods

Biomarkers were assessed in 360 patients randomized in RATIONALE-307. The association of the above-mentioned biomarkers and progression-free survival (PFS) between and within the two treatment groups was assessed using a stratified Cox proportional hazards model. P-values < 0.05 were considered statistically significant without multiplicity adjustment.

Results

A total of 263 (73%) randomized patients had evaluable tTMB and 275 (76%) had evaluable GEP. Baseline characteristics were similar to that of the overall study population. PFS benefits of tislelizumab plus chemotherapy vs chemotherapy alone were not associated with tTMB status (**Table**). Significant treatment-specific differences in PFS were observed in patients with high expression levels of interferon-related genes, including *PSMB9*, *HERC6*, *OAS2* (Interaction P-value: 0.029, 0.037, 0.025, respectively), etc., and an 18-gene tumor inflammation signature (TIS) (Interaction P-value: 0.001).

High TIS score was associated with significantly longer PFS in the tislelizumab plus chemotherapy group, but not in the chemotherapy alone group. The association of TIS score and PFS was independent from PD-L1 and tTMB status. Additional analysis on GEP signatures and genomic alterations, including their association with TIS, PD-L1 expression and clinical efficacy, will be presented.

Conclusions

This exploratory analysis of RATIONALE-307 is the first Phase 3 trial indicating a strong association between TIS score and clinical benefit of PD-1 blockade plus chemotherapy vs chemotherapy alone in sq-NSCLC. These data support TIS score as a potential predictive biomarker for PD-1 inhibitor response, regardless of PD-L1 and tTMB status.

Table: Association of biomarkers with PFS in tislelizumab plus chemotherapy vs chemotherapy alone treatment groups.

Biomarkers*	N	mPFS, Mo (95% CI) Tislelizumab + chemo vs chemo alone	PFS HR (95% CI)	Interaction P-value
PD-L1 positive	213	7.62 (6.74–11.01) vs 4.96 (4.14–5.59)	0.41 (0.28–0.60)	0.143
PD-L1 negative	136	7.56 (5.68–9.69) vs 5.45 (4.21–6.97)	0.64 (0.40–1.02)	
tTMB-high	131	9.69 (7.59–NR) vs 5.42 (4.17–5.78)	0.44 (0.27–0.72)	0.463
tTMB-low	132	6.90 (5.55–7.69) vs 5.39 (3.71–5.88)	0.57 (0.36–0.91)	
TIS-high†	138	9.79 (65.75–NR) vs 4.17 (4.04–5.55)	0.26 (0.16–0.43)	0.001
TIS-low†	137	6.9 (5.49–7.59) vs 5.78 (4.30–7.43)	0.84 (0.53–1.35)	

*PD-L1 positive: TC ≥ 1%; PD-L1 negative: TC < 1%; tTMB-high: ≥ 10 mutations/Mb; tTMB-low: < 10 mutations/Mb; TIS-high: ≥ median score; TIS-low: < median score.
†18-gene TIS included: *TIGIT, CD27, CD8A, PDCD1LG2, LAG3, CD274, CXCR6, CMKLR1, NKG7, CCL5, PSMB10, IDO1, CXCL9, HLA-DQA1, CD276, STAT1, HLA-DRB1, HLA-E*.

Abbreviations: CI, confidence interval; HR, hazard ratio; Mb, megabase; Mo, month; mPFS, median progression-free survival; NR, not reached; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cells; TIS, tumor inflammation signature; tTMB, tissue tumor mutational burden.