RATIONALE-304: The Association of Tumor Mutational Burden With Clinical Outcomes of Tislelizumab + Chemotherapy Versus Chemotherapy Alone as First-Line Treatment for Advanced Nonsquamous Non-Small Cell Lung Cancer

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Objectives: In the primary analysis of RATIONALE-304 (NCT03663205), tislelizumab + platinum-based chemotherapy significantly improved clinical outcomes over chemotherapy alone in treatment-naïve advanced nonsquamous non-small cell lung cancer (NSCLC; median progression-free survival [PFS] by IRC [9.7 vs 7.6 months, HR=0.645, *P*=0.0044]). Here we report biomarker analysis of baseline tissue and blood tumor mutational burden (tTMB and bTMB, respectively).

Methods: Patients with nonsquamous NSCLC were randomized 2:1 to tislelizumab + platinum + pemetrexed or platinum + pemetrexed. Tumor mutational burden (TMB) scores were evaluated on baseline tumor and blood samples by OncoScreen Plus®. The Spearman's rank correlation of tTMB with bTMB was assessed. PFS by independent review committee (primary endpoint) was assessed within subgroups defined by TMB status, using a Cox proportional hazard model with disease stage and programmed death-ligand 1 (PD-L1) expression as stratification factors. Interaction *P*-values <0.05 were considered statistically significant without multiplicity adjustment.

Results: Of 325 patients treated in RATIONALE-304, without an *EGFR* sensitizing mutation, 177 (54.5%) had evaluable tTMB and 107 (32.9%) had evaluable bTMB. Median tTMB and bTMB were 7.2 and 3.1 mut/Mb, respectively. There was a modest correlation between tTMB and bTMB (r=0.71, *P*<0.001). Prolonged PFS benefit of adding tislelizumab to chemotherapy was observed in patients with TMB-high status compared with TMB-low status (**Table**). Interaction analysis showed that neither tTMB nor bTMB significantly differentiated treatment-specific PFS benefit (interaction *P*-values >0.05; **Table**).

Conclusions: In this retrospective analysis, neither tTMB nor bTMB was significantly associated with PFS benefit, suggesting limited clinical utility of tTMB and bTMB in the setting of tislelizumab + chemotherapy as first-line therapy for advanced nonsquamous NSCLC.

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Table. Association of TMB With PFS Benefit of Tislelizumab + Chemotherapy Versus Chemotherapy Alone

tTMB				bTMB			
Cutoffs mut/Mb	**N**	**HR (95% CI)**	**Interaction *P*-value**	**Cutoffs mut/Mb**	**N**	**HR (95% CI)**	**Interaction *P*-value**
BEP	177	0.76 (0.46, 1.25)	NA	**BEP**	107	0.48 (0.26, 0.87)	NA
≥8 (TMB-high)	80	0.52 (0.25, 1.10)	0.208	**≥4 (TMB-high)**	47	0.30 (0.12, 0.75)	0.212
<8 (TMB-low)	97	0.98 (0.51, 1.88)		**<4 (TMB-low)**	60	0.64 (0.29, 1.39)	

BEP, biomarker evaluable population; bTMB, blood tumor mutational burden; CI, confidence interval; HR, hazard ratio; Mb, megabase; mut, mutation; NA, not applicable; PFS, progression-free survival; TMB, tumor mutational burden; tTMB, tissue tumor mutational burden.