

RATIONALE-304: The association of tumor mutational burden (TMB) with clinical outcomes of tislelizumab (TIS) + chemotherapy (chemo) versus chemo alone as first-line treatment for advanced non-squamous non-small cell lung cancer (nsq-NSCLC)

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Abstract:

Background

In the primary analysis of RATIONALE-304 (NCT03663205), TIS + platinum-based chemo significantly improved clinical outcomes over chemo alone in treatment-naïve advanced nsq-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 TMB (tTMB and bTMB, respectively).

Methods

Patients with nsq-NSCLC were randomized 2:1 to TIS + platinum + pemetrexed or platinum + pemetrexed. 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 TIS to chemo 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 TIS + chemo as first-line therapy for advanced nsq-NSCLC.

Table. Association of TMB with PFS benefit of TIS + chemo vs chemo

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; TIS, tislelizumab; TMB, tumor mutational burden; tTMB, tissue tumor mutational burden