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 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **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