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

Shun Lu*,[1] Meili Sun,[2] Yunpeng Liu,[3] Yanping Hu,[4] Yanyan Xie,[5] Zhehai Wang,[6] Dong Wang,[7] Zhenzhou Yang,[7] Liang Liang,[8] Yi Huo,[8] Yun Zhang,[8] Ruiqi Huang,[8] Yang Shi,[8] Wanyu He,[9] Zhirong Shen,[8] Yan Yu[10]

[1]Medical Oncology, Shanghai Chest Hospital, Jiao Tong University, Shanghai, China; [2]Jinan Central Hospital Affiliated to Shandong University, Shandong, China; [3]The First Hospital of China Medical University, Shenyang, China; [4]Hubei Cancer Hospital, Wuhan, China; [5]West China Hospital, Sichuan University, Chengdu, China; [6]Shandong Cancer Hospital, Department of Internal Medicine-Oncology, Jinan, China; [7]Daping Hospital, Third Military Medical University, Chongqing, China; [8]Department of Clinical Biomarkers, BeiGene (Beijing) Co., Ltd., Beijing, China; [9]Department of Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [10]Affiliated Tumor Hospital of Harbin Medical University, Harbin, China. *Presenting and corresponding author

Conclusions

- Baseline TMB demonstrated **a trend for association** with PFS benefit in patients receiving tislelizumab plus chemotherapy vs chemotherapy alone
- **Further assessment in prospective research** is needed to validate the clinical utility of TMB in patients with nsq-NSCLC treated with PD-(L)1 inhibitors in combination with chemotherapy

Background

- Lung cancer is the leading cause of cancer death globally, with approximately 2.2 million new lung cancer cases and 1.8 million deaths in 2020,[1] indicating high unmet medical need
- Tislelizumab is an anti-programmed cell death protein 1 (anti-PD-1) antibody engineered to minimize binding to Fcγ receptors on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapies[2,3]
- Primary results from the RATIONALE-304 (NCT03663205) trial showed that tislelizumab plus platinum-based chemotherapy significantly improved progression-free survival (PFS) over chemotherapy alone in treatment-naïve advanced nonsquamous non-small cell lung cancer (nsq-NSCLC) (hazard ratio [HR]=0.645, *P*=0.0044, median PFS: 9.7 vs 7.6 months, respectively)[4]
- Tumor mutational burden (TMB) is a biomarker of interest due to its association with response to immunotherapy treatment in NSCLC[5,6]
- Here we report a post-hoc, retrospective biomarker analysis of baseline tissue and blood TMB (tTMB and bTMB, respectively)
- **Scan QR code to view the primary publication of RATIONALE-304:**

Methods

- Patients with nsq-NSCLC were randomized 2:1 to tislelizumab plus platinum plus pemetrexed or platinum plus pemetrexed, as previously described.[4] The primary endpoint was PFS determined by independent review committee
- TMB scores were evaluated in baseline tumor and blood samples by OncoScreen Plus®. Baseline programmed death-ligand 1 (PD-L1) status was tested by VENTANA SP263 Assay. The Spearman's rank correlation was assessed among tTMB, bTMB, and PD-L1
- PFS of tislelizumab plus chemotherapy vs chemotherapy alone was compared within subgroups defined by TMB status using a Cox proportional hazard model with disease stage and PD-L1 expression as stratification factors. The interaction between treatment type and TMB status was analyzed. Interaction *P* values <0.05 were considered statistically significant without multiplicity adjustment

Results

- Across 325 patients who were treated, and did not have an *epidermal growth factor receptor (EGFR)* sensitizing mutation, 177 (54.5%) had evaluable tTMB, and 107 (32.9%) had evaluable bTMB
- Demographics and baseline characteristics were generally balanced across arms in the overall population, tTMB, and bTMB biomarker-evaluable populations (BEPs), aside from age distribution, sex, and smoking status (**Table 1**)
- The PFS benefit of tislelizumab plus chemotherapy vs chemotherapy alone was observed in both the tTMB BEP (HR [95% CI]=0.76 [0.47, 1.25]) and bTMB BEP (0.48 [0.26, 0.87])

Table 1. Demographics and Baseline Characteristics

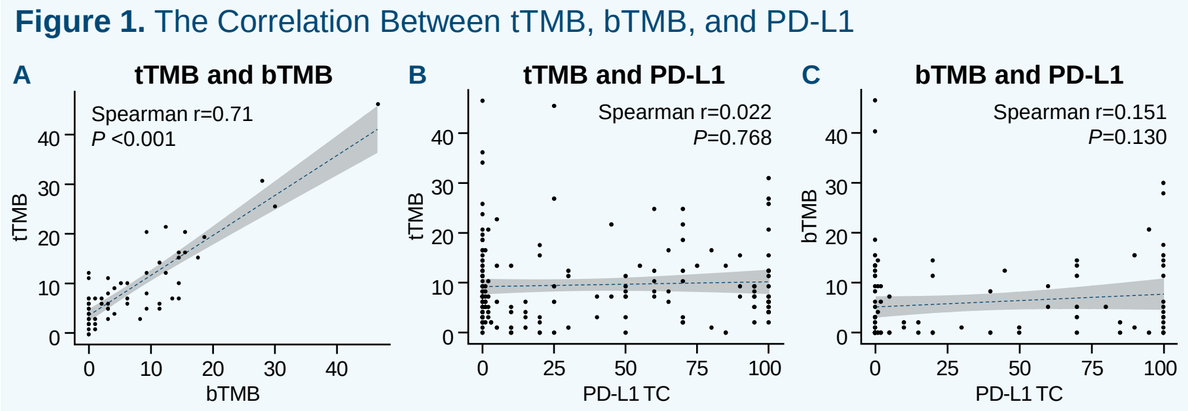
	Overall Population		tTMB BEP		bTMB BEP	
	TIS + chemo (n=217)	Chemo (n=108)	TIS + chemo (n=118)	Chemo (n=59)	TIS + chemo (n=74)	Chemo (n=33)
Age, years						
Median (IQR)	60.0 (55-65)	61.5 (55-67)	60.0 (55-66)	61.0 (55-67)	60.0 (54-65)	64.0 (60-68)
Age group, n (%)						
<65 years	159 (73.3)	71 (65.7)	81 (68.6)	41 (69.5)	55 (74.3)	18 (54.5)
≥65 years	58 (26.7)	37 (34.3)	37 (31.4)	18 (30.5)	19 (25.7)	15 (45.5)
Sex, n (%)						
Female	52 (24.0)	32 (29.6)	26 (22.0)	20 (33.9)	19 (25.7)	2 (6.1)
Male	165 (76.0)	76 (70.4)	92 (78.0)	39 (66.1)	55 (74.3)	31 (93.9)
Smoking status, n (%)						
Current/former	145 (66.8)	65 (60.2)	81 (68.6)	36 (61.0)	52 (70.3)	26 (78.8)
Never	72 (33.2)	43 (39.8)	37 (31.4)	23 (39.0)	22 (29.7)	7 (21.2)
ECOG PS, n (%)						
0	52 (24.0)	23 (21.3)	28 (23.7)	15 (25.4)	24 (32.4)	7 (21.2)
1	165 (76.0)	85 (78.7)	90 (76.3)	44 (74.6)	50 (67.6)	26 (78.8)
Disease stage, n (%)						
IIIB	40 (18.4)	21 (19.4)	26 (22.0)	14 (23.7)	15 (20.3)	7 (21.2)
IV	177 (81.6)	87 (80.6)	92 (78.0)	45 (76.3)	59 (79.7)	26 (78.8)
PD-L1 expression on tumor cells, n (%)						
TC <1%	87 (40.1)	47 (43.5)	43 (36.4)	23 (39.0)	29 (39.2)	12 (36.4)
TC 1-49%	53 (24.4)	27 (25.0)	33 (28.0)	17 (28.8)	17 (23.0)	9 (27.3)
TC ≥50%	72 (33.2)	34 (31.5)	42 (35.6)	19 (32.2)	23 (31.1)	12 (36.4)
NE	5 (2.3)	0 (0)	0 (0)	0 (0)	5 (6.8)	0 (0)

Data cutoff: January 23, 2020.
Abbreviations: BEP, biomarker-evaluable population; bTMB, blood tumor mutational burden; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; NE, not evaluable; PD-L1, programmed death-ligand 1; TC, tumor cell; TIS, tislelizumab; tTMB, tissue tumor mutational burden.

Correlation Between tTMB, bTMB, and PD-L1

- Median tTMB and bTMB were 7.2 and 3.1 mutations per megabase (mut/Mb), respectively
- There was a modest correlation between tTMB and bTMB (Spearman r=0.71, *P*<0.001) (**Figure 1A**)
- Neither tTMB nor bTMB was correlated with PD-L1 expression on tumor cells (**Figure 1B** and **Figure 1C**)

Figure 1. The Correlation Between tTMB, bTMB, and PD-L1

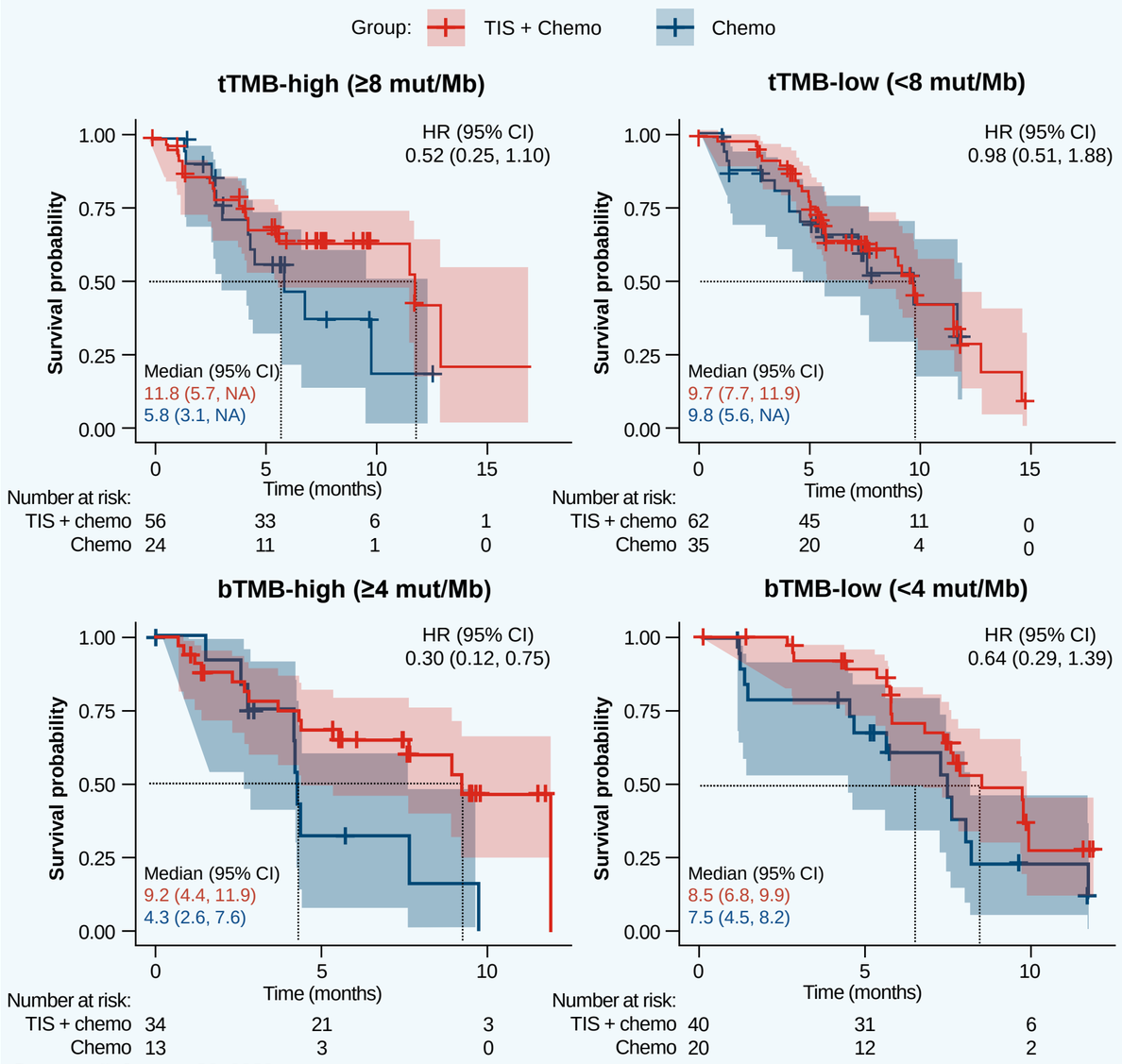


Abbreviations: bTMB, blood tumor mutational burden; PD-L1, programmed death-ligand 1; TC, tumor cell; tTMB, tissue tumor mutational burden.

Correlation of PFS With TMB Status

- The cutoffs of tTMB and bTMB were determined by the smallest integer greater than the median value of each dataset, 8 and 4 mut/Mb, respectively
- The prevalence of TMB-high was balanced between the tislelizumab plus chemotherapy arm and chemotherapy arm (tTMB: 47% vs 41%; bTMB: 46% vs 39%, respectively)
- Lower PFS HRs of tislelizumab plus chemotherapy vs chemotherapy alone were observed in patients with TMB-high status compared with TMB-low status (**Figure 2**)
- Interaction analysis showed that neither tTMB nor bTMB significantly differentiated treatment-specific PFS benefit (interaction *P* value=0.208 and 0.212, respectively)

Figure 2. PFS (IRC Assessed) by tTMB and bTMB Status



Data cutoff: January 23, 2020.
Abbreviations: bTMB, blood tumor mutational burden; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; Mb, megabase; mut, mutation; NA, not applicable; PFS, progression-free survival; tTMB, tissue tumor mutational burden.

- TMB-high subgroups showed a trend for inferior PFS in the chemotherapy arm (HR [95% CI] in tTMB: 1.75 [0.77, 3.99]; in bTMB: 2.21 [0.83, 5.89]), but not in the tislelizumab + chemotherapy arm (HR [95% CI] in tTMB: 0.93 [0.52, 1.66]; in bTMB: 1.04 [0.52, 2.12])

Limitations

- The small sample size represents a limitation of this study
- OS will be analyzed to assess the consistency and robustness of TMB as a biomarker when it is available

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***Author contact details:** shun.lu@me.com (Shun Lu)