Association of Tumor Mutational Burden (TMB) and Clinical Outcomes With Tislelizumab Versus Chemotherapy in Esophageal Squamous Cell Carcinoma (ESCC) From RATIONALE-302

Abstract Presentation No: CT077 presented at AACR 2023, Orlando, Florida

Lin Shen*,[1] Yongqian Shu,[2] Kuaile Zhao,[3] Taroh Satoh,[4] Zhendong Chen,[5] Eric Van Cutsem,[6] Guohua Yu,[7] Jun Wu,[8] Chih-Hung Hsu,[9] Sung Bae Kim,[10] Wenting Du,[11] Yang Shi,[12] Ruiqi Huang,[13] Qiao Li,[14] Jingwen Shi,[12] Yun Zhang,[12] Hongwei Wang[1,15] Kato Ken[16]

[1]Digestive Tumor Medical, Beijing Cancer Hospital, Beijing, China; [2]Cancer Center, Jiangsu Province Hospital, Nanjing, China; [3]Fudan University Cancer Hospital, Shanghai, China; [4]Osaka University Hospital, Suita, Japan; [5]The Second Hospital of Anhui Medical University, Hefei, China; [6]University Hospitals Gasthuisberg, Leuven, and University of Leuven, Leuven, Belgium; [7]Weifang People's Hospital, Shandong, China; [8]The First People's Hospital of Changzhou, Changzhou, China; [9]National Taiwan University Hospital, Taipei, Taiwan, Republic of China; [10]Asan Medical Center, Seoul, Korea; [11]Clinical Biomarkers, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [12]Clinical Biomarkers, BeiGene (Beijing) Co., Ltd., Beijing, China; [13]Statistics, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [14]Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [15]BeiGene, Ltd., Cambridge, MA, United States; [16]National Cancer Center Hospital, Tokyo, Japan. *Corresponding author. [1]Presenting author.

Conclusions

In RATIONALE-302, tislelizumab demonstrated a survival benefit vs investigator-chosen chemotherapy (ICC) as a second-line (2L) treatment in patients with advanced ESCC.[5] In this post-hoc analysis, we found that higher TMB cutoff had a trend for positive association with response and improved survival with tislelizumab vs ICC.

TMB status may play a role in predicting clinical outcomes in patients with advanced ESCC treated with tislelizumab vs ICC, especially when the appropriate TMB cutoff for the relevant drug and indication is chosen. These findings need further validation.

Background

Patients with advanced or metastatic ESCC have a poor prognosis but programmed cell death protein 1 (PD-1) inhibitors as 2L therapy can provide a clinical benefit.[1] TMB is a predictive biomarker of response to immune checkpoint blockade in multiple cancers.[2]

Tislelizumab is a humanized immunoglobulin G4 monoclonal antibody with high affinity and binding specificity for PD-1.[3,4] RATIONALE-302 is a global phase 3 study of tislelizumab vs ICC as 2L treatment for advanced unresectable/metastatic ESCC (NCT03430843).[5]

Primary results from RATIONALE-302 demonstrated a significant improvement in overall survival (OS) with tislelizumab compared with ICC alone (median OS, 8.6 vs 6.3 months, respectively; hazard ratio [HR]=0.70, *P*=0.0001) as 2L treatment in patients with advanced ESCC.[5]

Here, we investigated TMB in ESCC by retrospectively analyzing its potential association with clinical efficacy outcomes from RATIONALE-302.

Methods

RATIONALE-302 Study Design

- Study design has been previously described[5] and is summarized in **Figure 1**

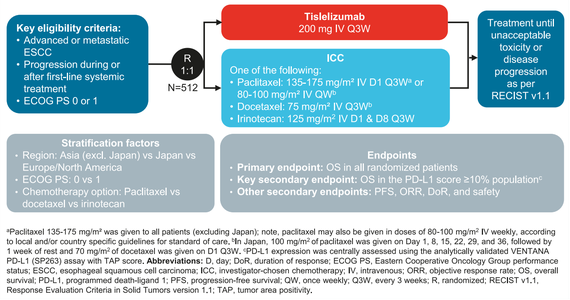
Genomic Profiling

- Genomic profiling was assessed in tumor tissues collected at baseline using the BurningRock OncoScreen Plus 520 next-generation sequencing panel[6]
- TMB was calculated as the number of non-synonymous mutations (single nucleotide variants and indels) per million bases[6]
- TMB cutoffs of 8, 10, and 12 mutations per megabase (Mut/Mb) were used to define TMB-high (TMB-H) and TMB-low (TMB-L) subgroups[6]

Statistical Analysis

- Wilcoxon rank-sum test was used to compare TMB values between non-responders and responders by each treatment arm
- Objective response rate (ORR) and 95% confidence interval (CI) were calculated using the binomial exact method
- Median progression-free survival (PFS) and OS were calculated using the Kaplan-Meier method
- Cox models, including treatment and TMB status as main effects, were applied to assess the effect of TMB on survival outcomes. Eastern Cooperative Oncology Group performance status (ECOG PS) and ICC option were stratification factors in the model. HR and 95% CI for OS and PFS in TMB subgroups were estimated

Figure 1. RATIONALE-302 Study Design



[a]Paclitaxel 135-175 mg/m² was given to all patients (excluding Japan); note, paclitaxel may also be given in doses of 80-100 mg/m² IV weekly, according to local and/or country specific guidelines for standard of care, [b]In Japan, 100 mg/m² of paclitaxel was given on Day 1, 8, 15, 22, 29, and 36, followed by 1 week of rest and 70 mg/m² of docetaxel was given on D1 Q3W, [c]PD-L1 expression was centrally assessed using the analytically validated VENTANA PD-L1 (SP263) assay with TAP score, **Abbreviations:** D, day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; ICC, investigator-chosen chemotherapy; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TAP, tumor area positivity.

Results

Baseline Characteristics and Clinical Efficacy Results

- Among 512 patients in the intent-to-treat (ITT) population, 209 had tumor samples evaluable for TMB (tislelizumab, n=105; ICC, n=104)
- Baseline characteristics and clinical efficacy were comparable between the ITT population and TMB biomarker-evaluable population (BEP) (**Table 1**)

Table 1. Baseline Characteristics and Clinical Efficacy

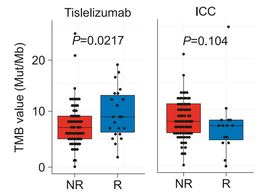
	ITT (N=512)		TMB BEP (N=209)	
	Tislelizumab (n=256)	ICC (n=256)	Tislelizumab (n=105)	ICC (n=104)
Mean (SD) age, years	61.5 (8.4)	61.6 (8.0)	60.9 (8.1)	62.3 (8.2)
Sex, male	217 (84.8)	215 (84.0)	88 (83.8)	89 (85.6)
ECOG PS 1	190 (74.2)	196 (76.6)	75 (71.4)	83 (79.8)
Region				
Asia[a]	201 (78.5)	203 (79.3)	75 (71.4)	79 (76.0)
EU/US	55 (21.5)	53 (20.7)	30 (28.6)	25 (24.0)
ICC option				
Paclitaxel	NA	85 (33.2)	NA	44 (42.3)
Docetaxel	NA	53 (20.7)	NA	16 (15.4)
Irinotecan	NA	118 (46.1)	NA	44 (42.3)
PD-L1 status, n (% in PD-L1-evaluable patients[b])				
PD-L1 ≥10%	80 (44.4)	62 (33.7)	45 (48.9)	35 (37.6)
PD-L1 <10%	100 (55.6)	122 (66.3)	47 (51.1)	58 (62.4)
Efficacy outcomes				
ORR, % (95% CI)	20.3 (15.6, 25.8)	9.8 (6.4, 14.1)	21.0 (13.6, 30.0)	14.4 (8.3, 22.7)
mPFS, mo (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)	1.5 (1.4, 2.7)	2.6 (1.5, 2.8)
PFS HR (95% CI)	0.83 (0.67, 1.01)		0.88 (0.64, 1.21)	
mOS, mo (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)	8.0 (5.2, 11.6)	6.8 (4.6, 7.6)
OS HR (95% CI)	0.70 (0.57, 0.85)		0.68 (0.50, 0.92)	

Data are n (%), unless otherwise stated.
[a]Including Japan. [b]71.1% of the ITT population were PD-L1-evaluable while 88.5% of the TMB BEP were PD-L1 evaluable.
Abbreviations: BEP, biomarker-evaluable population; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, Europe; HR, hazard ratio; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; m, median; mo, months; NA, not available; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SD, standard deviation; TMB, tumor mutational burden; US, United States.

Association of TMB Status With Response to Tislelizumab

- In the TMB BEP (N=209), the median TMB was 7.24 Mut/Mb (range: 0 to 25.85). TMB was comparable between the two treatment arms
- Responders to tislelizumab had higher TMB values than non-responders (median TMB 9.31 vs 7.24 Mut/Mb, respectively; *P*=0.0217). No correlation between higher TMB and ICC was observed (median TMB 7.24 in responders vs 8.27 in non-responders; *P*=0.104) (**Figure 2**)
- Patients in the TMB-H subgroup had a trend of higher ORR compared with those in the TMB-L subgroup by cutoffs 8, 10, and 12 Mut/Mb when treated with tislelizumab (**Table 2**)
- In the TMB-H subgroups, increased TMB cutoffs were associated with numerically higher ORR in patients treated with tislelizumab and numerically lower ORR in patients treated with ICC (**Table 2**)

Figure 2. Response by TMB Status



Abbreviations: ICC, investigator-chosen chemotherapy; Mut/Mb, mutations per megabase; NR, non-responders; R, responders; TMB, tumor mutational burden.

Table 2. Response by TMB Status

TMB Cutoff (Mut/Mb)	TMB Status	Prevalence	Tislelizumab Arm ORR		ICC Arm ORR	
			n/N	% (95% CI)	n/N	% (95% CI)
8	TMB-L	51.2%	9/56	16.1 (7.6, 28.3)	10/51	19.6 (9.8, 33.1)
	TMB-H	48.8%	13/49	26.5 (14.9, 41.1)	5/53	9.4 (3.1, 20.7)
10	TMB-L	72.2%	13/78	16.7 (9.2, 26.8)	13/73	17.8 (9.8, 28.5)
	TMB-H	27.8%	9/27	33.3 (16.5, 54.0)	2/31	6.5 (0.8, 21.4)
12	TMB-L	83.2%	14/86	16.3 (9.2, 25.8)	14/88	15.9 (9.0, 25.2)
	TMB-H	16.7%	8/19	42.1 (20.3, 66.5)	1/16	6.3 (0.2, 30.2)

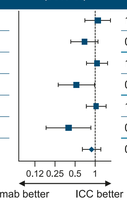
Abbreviations: H, high TMB≥cutoff; ICC, investigator-chosen chemotherapy; L, low TMB<cutoff; Mut/Mb, mutations per megabase; n, number of responders; N, total number of patients; ORR, objective response rate; TMB, tumor mutational burden.

Association of TMB Status With Survival

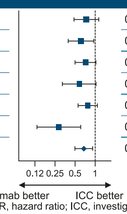
- There was a trend towards greater survival benefit with tislelizumab vs ICC observed in TMB-H subgroups compared with TMB-L subgroups (**Figure 3**)
- The predictive effect of TMB on survival outcomes was numerically higher but not significant at the cutoffs of 8 and 10 Mut/Mb (interaction *P*-value=0.1631 and 0.0537 for PFS, 0.5565 and 0.5374 for OS, respectively) (**Figure 3**)
- TMB-H with cutoff 12 Mut/Mb was correlated with a substantial OS and PFS benefit for tislelizumab vs ICC (interaction *P*-value=0.0267 for PFS, 0.0175 for OS) (**Figure 3**)

Figure 3. Forest Plots of PFS and OS by TMB Status

TMB Cutoff (Mut/Mb)	TMB Status	Tislelizumab Event/Total	ICC Event/Total	PFS HR (95% CI)	Interaction *P*-value
8	TMB-L	48/56	38/51	1.09 (0.70, 1.70)	0.1631
	TMB-H	44/49	40/53	0.69 (0.43, 1.10)	
10	TMB-L	69/78	55/73	1.06 (0.73, 1.53)	0.0537
	TMB-H	23/27	23/31	0.52 (0.28, 0.97)	
12	TMB-L	76/86	65/88	1.03 (0.73, 1.46)	0.0267
	TMB-H	16/19	13/16	0.40 (0.18, 0.86)	
All		92/105	78/104	0.88 (0.64, 1.21)	



TMB Cutoff (Mut/Mb)	TMB Status	Tislelizumab Event/Total	ICC Event/Total	OS HR (95% CI)	Interaction *P*-value
8	TMB-L	43/56	44/51	0.74 (0.48, 1.14)	0.5565
	TMB-H	36/49	48/53	0.62 (0.40, 0.96)	
10	TMB-L	59/78	64/73	0.72 (0.50, 1.03)	0.5374
	TMB-H	20/27	28/31	0.58 (0.32, 1.04)	
12	TMB-L	66/86	76/88	0.78 (0.55, 1.09)	0.0175
	TMB-H	13/19	16/16	0.28 (0.13, 0.61)	
All		79/105	92/104	0.68 (0.50, 0.92)	



Abbreviations: CI, confidence interval; H, high TMB≥cutoff; HR, hazard ratio; ICC, investigator-chosen chemotherapy; L, low TMB<cutoff; Mut/Mb, mutations per megabase; OS, overall survival; PFS, progression-free survival; TMB, tumor mutational burden.

References

1. Zhu X, et al. *BMC Cancer.* 2021;21(1):1195.
2. Klempner SJ, et al. *Oncologist.* 2020;25(1):e147-e159.
3. Zhang T, et al. *Cancer Immunol Immunother.* 2018;67(7):1079-1090.
4. Qin S, et al. *Future Oncol.* 2019;15(16):1811-1822.
5. Shen L, et al. *J Clin Oncol.* 2022;40(26):3065-3076.
6. Tang Y, et al. *Transl Lung Cancer Res.* 2020;9(1):71-81.

Acknowledgments

This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Victoria Dagwell, MSc, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd. Editorial support was provided by Elizabeth Hermans, PhD, of BeiGene, Ltd.

Disclosures

Disclosure information will be available online with the abstract details.

***Author contact details: linshenpku@163.com (Lin Shen)**