Concordance Among Three Programmed Death-Ligand 1 Scoring Methods and Their Association With Clinical Outcomes of Tislelizumab Monotherapy in Esophageal Squamous Cell Carcinoma

Abstract no. 390 presented at ASCO GI, Moscone West, San Francisco, California, January 18-20, 2024

Yongqian Shu,[1] Jufeng Wang,[2] Zhendong Chen,[3] Sung-Bae Kim,[4] Chen-Yuan Lin,[5] Ken Kato,*[6] Eric Van Cutsem,[7] Wenting Du,[8] Jingwen Shi,[9] Tianyu Xia,[10] Ruiqi Huang,[11] Qiao Li,[12] Yun Zhang,[9] Zhirong Shen,[9] Lin Shen†[13]

[1]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [2]Henan Cancer Hospital, Zhengzhou, Henan, China; [3]The Second Hospital of Anhui Medical University, Hefei, China; [4]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [5]China Medical University Hospital, Taichung, Taiwan; [6]National Cancer Center Hospital, Tokyo, Japan; [7]University Hospitals Gasthuisberg Leuven and University of Leuven, Leuven, Belgium; [8]Clinical Biomarker, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [9]Clinical Biomarker, BeiGene (Beijing) Co., Ltd., Beijing, China; [10]Statistics, BeiGene (Beijing) Co., Ltd., Beijing, China; [11]Statistics, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [12]Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [13]Peking University Cancer Hospital & Institute, Beijing, China. *Presenting author; †Corresponding author

Conclusions

Tumor area positivity (TAP) score at a cutoff of 10% and combined positive score (CPS) at a cutoff of 10 based on SP263 staining exhibited substantial concordance in esophageal squamous cell carcinomas (ESCCs) of patients enrolled in the RATIONALE-302 trial.[1] TAP score showed less concordance with tumor cell (TC) score than CPS.

Overall survival (OS) subgroup analysis showed comparable treatment effect in patients with ESCC treated with tislelizumab (TIS) by TAP score at a cutoff of 10%, CPS at a cutoff of 10, and TC score at a cutoff of 1%.

These results indicate that the less time-consuming, visually estimated TAP score and CPS may be interchangeable for the clinical measurement of programmed death-ligand 1 (PD-L1) expression in patients with ESCC.

Background

Multiple scoring methods and cutoffs have been developed to evaluate PD-L1 expression status for both TCs and immune cells (ICs) in patients with ESCC, and PD-L1 expression level has been associated with the degree of response to anti-programmed cell death protein 1 (PD-1)/PD-L1 therapy.[2]

The TAP score is determined by visually estimating the proportion of total tumor area covered by TCs and tumor-associated ICs with immunohistochemical staining positive for PD-L1.[3] This score was developed as a combined score of PD-L1-positive TCs and tumor-associated ICs to evaluate PD-L1 expression based on simple, visual-based methodology to address the limitations of a cell-counting approach.

In patients with ESCC treated with TIS in combination with chemotherapy, similar OS has been demonstrated for PD-L1 subgroups defined by different scoring methods.[4] The investigation presented in this poster was conducted to confirm this conclusion in patients treated with TIS monotherapy.

Here, we retrospectively investigated the concordance between three PD-L1 scoring methods and their association with clinical outcomes in RATIONALE-302, a phase 3 study of the anti-PD-1 antibody TIS versus investigator-chosen chemotherapy (ICC) as second-line treatment for advanced unresectable/metastatic ESCC (NCT03430843).[1]

Methods

- The open-label, phase 3 RATIONALE-302 study enrolled patients with advanced or metastatic ESCC with tumor progression during or after first-line systemic treatment
- These patients were randomly assigned (1:1) to receive intravenous TIS 200 mg every 3 weeks or ICC of paclitaxel, docetaxel, or irinotecan
- Patients enrolled in RATIONALE-302 with evaluable PD-L1 expression by TAP score (based on visual estimation of positive TCs and tumor-associated ICs) using the VENTANA PD-L1 (SP263) assay were categorized using a cutoff of 10%
- Stained slides from these patients were rescored post hoc using both CPS (based on counting positive TCs and tumor-associated ICs) at a cutoff of 10 and TC score (based on counting positive TCs only) at a cutoff of 1%, which are the thresholds currently used in ESCC patients treated with anti-PD-(L)1 therapy[5-7]
- The concordance at these thresholds between the three scoring methods was investigated. Clinical benefit (OS and objective response rate [ORR]) for PD-L1 subgroups was assessed

Results

Patients

- At data cutoff (December 1, 2020), 256 patients were enrolled in each treatment arm (TIS and ICC), with baseline characteristics balanced across arms

PD-L1 Expression

- Of 512 patients enrolled, 364 had evaluable TAP scores (TIS, n=180; ICC, n=184), of whom 355 had evaluable post-hoc CPS and TC scores (TIS, n=175; ICC, n=180)
- Based on cutoffs of TAP 10%, CPS 10, and TC 1%, PD-L1 status of 30.0%, 32.0%, and 39.4% of patients in the intention-to-treat analysis set were determined as positive, respectively

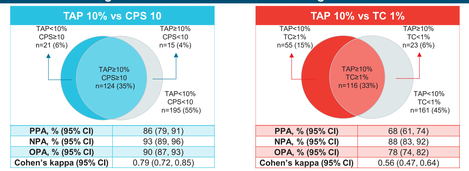
Concordance Between Scoring Methods

- TAP score and CPS showed a high concordance in terms of overall percentage agreement (OPA: 90%) and Cohen's kappa (0.79), while TAP and TC scores had a lower concordance (OPA: 78%; Cohen's kappa: 0.56), an expected outcome based on the different components of these two scoring methods (**Figure 1**)

Clinical Benefit in PD-L1 Subgroups

- Regardless of the PD-L1 scoring method used, similar clinical benefit (OS and ORR) was observed across all subgroups with a PD-L1 expression score above the cutoff, below the cutoff, as well as missing PD-L1 status (**Tables 1 & 2, Figures 2-4**)

Figure 1. Concordance Between Scoring Methods[a]



	TAP 10% vs CPS 10	TAP 10% vs TC 1%
PPA, % (95% CI)	86 (79, 91)	68 (61, 74)
NPA, % (95% CI)	93 (89, 96)	88 (83, 92)
OPA, % (95% CI)	90 (87, 93)	78 (74, 82)
Cohen's kappa (95% CI)	0.79 (0.72, 0.85)	0.56 (0.47, 0.64)

[a]In the PD-L1-evaluable set, defined as all patients with tumors evaluable for scoring using the TAP, CPS, and TC methods.
Abbreviations: CI, confidence interval; CPS, combined positive score; NPA, negative percentage agreement; OPA, overall percentage agreement; PD-L1, programmed death-ligand 1; PPA, positive percentage agreement; TAP, tumor area positivity; TC, tumor cell.

Table 1. ORR Benefit in PD-L1 Subgroups by Scoring Method[a]

PD-L1 Status		ORR,[b] % (95% CI)[c]		Odds Ratio[c] (95% CI)	*P*-Value
		Tislelizumab	ICC		
TAP Score	≥10%	26.3 (17.0, 37.3)	11.3 (4.7, 21.9)	2.80 (1.10, 7.09)	0.0268
	<10%	16.0 (9.4, 24.7)	9.0 (4.6, 15.6)	1.92 (0.85, 4.36)	0.1140
	Missing[e]	19.7 (11.5, 30.5)	9.7 (4.0, 19.0)	2.28 (0.87, 5.98)	0.0880
CPS	≥10	23.8 (14.9, 34.6)	9.2 (3.5, 19.0)	3.06 (1.14, 8.20)	0.0218
	<10	17.9 (10.8, 27.1)	10.4 (5.5, 17.5)	1.87 (0.84, 4.14)	0.1197
	Missing[e]	19.8 (11.7, 30.1)	9.2 (3.8, 18.1)	2.43 (0.94, 6.28)	0.0627
TC Score	≥1%	21.3 (13.5, 30.9)	9.1 (3.7, 17.8)	2.70 (1.08, 6.79)	0.0302
	<1%	19.8 (11.7, 30.1)	10.7 (5.5, 18.3)	2.06 (0.90, 4.72)	0.0851
	Missing[e]	19.8 (11.7, 30.1)	9.2 (3.8, 18.1)	2.43 (0.94, 6.28)	0.0627

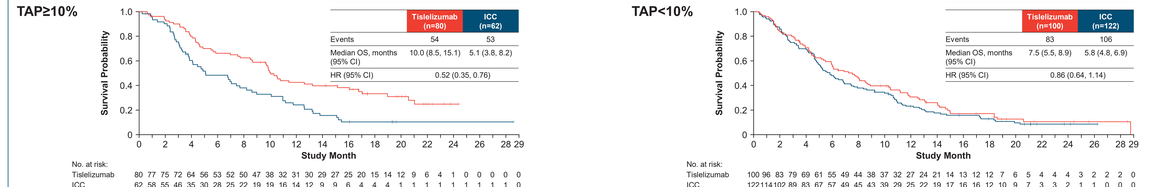
[a]In the ITT analysis set, which included all randomized patients; [b]ORR was unconfirmed and defined as the proportion of patients with a PR or CR assessed by investigator per RECIST version 1.1; [c]Two-sided 95% CI was calculated using the Clopper-Pearson method; [d]Objective response rate and odds ratios between arms were calculated using the unstratified Cochran-Mantel-Haenszel Chi-square test; [e]Missing refers to patients without sample collection, with non-evaluable samples, or with scored unqualified samples reclassified after database lock.
Abbreviations: CI, confidence interval; CPS, combined positive score; CR, complete response; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; TAP, tumor area positivity; TC, tumor cell.

Table 2. OS Benefit in PD-L1 Subgroups by Scoring Method[a]

PD-L1 Status		TIS Event /Total	ICC Event /Total	OS HR[b] (95% CI)	OS HR[b] (95% CI)	Interaction *P*-Value
TAP Score	≥10%	54/80	53/62		0.52 (0.35, 0.76)	
	<10%	83/100	106/122		0.86 (0.64, 1.14)	0.1707
	Missing[c]	60/76	54/72		0.72 (0.49, 1.04)	
CPS	≥10	56/80	59/65		0.54 (0.37, 0.78)	
	<10	80/95	100/115		0.83 (0.62, 1.12)	0.2296
	Missing[c]	61/81	54/76		0.71 (0.49, 1.03)	
TC Score	≥1%	69/94	69/77		0.56 (0.40, 0.79)	
	<1%	67/81	90/103		0.83 (0.60, 1.14)	0.2519
	Missing[c]	61/81	54/76		0.71 (0.49, 1.03)	

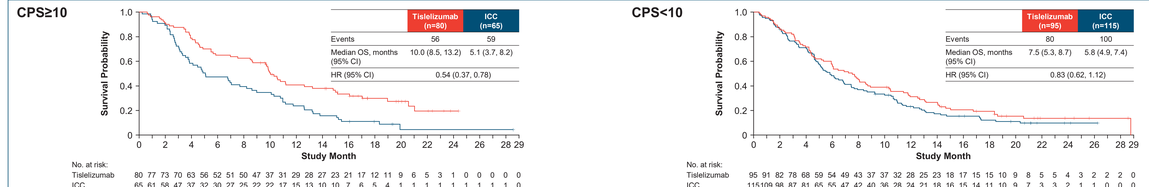
[a]In the ITT analysis set, which included all randomized patients; [b]Hazard ratio was based on the unstratified Cox regression model including treatment as a covariate; [c]Missing refers to patients without sample collection, with non-evaluable samples, or with scored unqualified samples reclassified after database lock.
Abbreviations: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; ICC, investigator-chosen chemotherapy; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumor area positivity; TC, tumor cell; TIS, tislelizumab.

Figure 2. OS Determined by TAP Score Using a Cutoff of 10%[a]



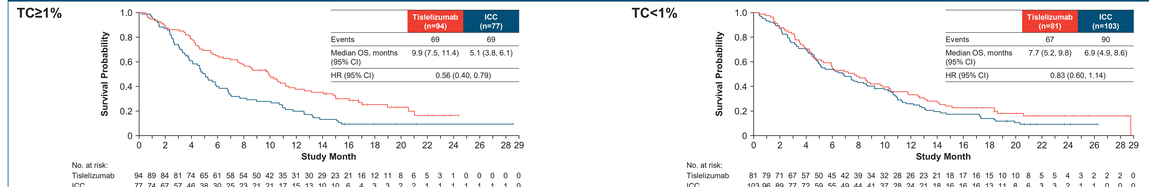
[a]In the PD-L1-evaluable set using the TAP scoring method.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator chosen chemotherapy; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

Figure 3. OS Determined by CPS Using a Cutoff of 10[a]



[a]In the PD-L1-evaluable set using the CPS scoring method.
Abbreviations: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; ICC, investigator chosen chemotherapy; OS, overall survival; PD-L1, programmed death-ligand 1.

Figure 4. OS Determined by TC Score Using a Cutoff of 1%[a]



[a]In the PD-L1-evaluable set using the TC scoring method.
Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator chosen chemotherapy; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cell.

References

1. Shen L, et al. *J Clin Oncol*. 2022;40(26):3065-3076.
2. Udall M, et al. *Diagnostic Pathol*. 2018;13(1):12.
3. Liu C, et al. *Diagnostic Pathol*. 2023;18(1):48.
4. Xu J et al. *Lancet Oncol*. 2023;24(5):483-495.
5. Vainer G, et al. *PLoS One*. 2023;18(6):e0285764.
6. Huang T-C, et al. *J Cancer Res Clin Oncol*. 2022;148(7):1803-1811.
7. Davis AA & Patel VG. *J Immunother Cancer*. 2019;7(1):278.

Acknowledgments

This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Saxony Olivier, MMed For Path, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd. Editorial support was provided by Elizabeth Hermans, PhD, of BeiGene, Ltd. The authors would like to thank Hongqian Wu (BeiGene, Ltd.) for their statistical input.

Disclosures

Ken Kato declares receipt of consulting fees from AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Janssen, Merck & Co., Merck Bio, Novartis, ONO, and Roche; payment for expert testimony from Bristol Myers Squibb and ONO; and data safety monitoring or advisory board participation for Bristol Myers Squibb, Chugai, Merck & Co., and ONO.