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RATIONALE 302: Randomized, Phase 3 study of tislelizumab vs chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma

Lin Shen,[1] Ken Kato,[2] Sung-Bae Kim,[3] Jaffer Ajani,[4] Kuaile Zhao,[5] Zhiyong He,[6] Xinmin Yu,[7] Yonqian Shu,[8] Qi Luo,[9] Jufeng Wang,[10] Zhendong Chen,[11] Zuoxing Niu,[12] Jong-Mu Sun,[13] Chen-Yuan Lin,[14] Hiroki Hara,[15] Roberto Pazo-Cid,[16] Christophe Borg,[17] Liyun Li,[18] Aiyang Tao,[18] Eric Van Cutsem[19]

[1]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [4]University of Texas MD Anderson Cancer Center, Houston, Texas; [5]Fudan Cancer Hospital, Shanghai, China; [6]Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fujian, China; [7]Zhejiang Cancer Hospital, Hangzhou, China; [8]Jiangsu Province Hospital, Jiangsu, China; [9]The First Affiliated Hospital of Xiamen University, Fujian, China; [10]The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [11]2nd Hospital of Anhui Medical University, Anhui, China; [12]Department of Medical Oncology, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Jinan, China; [13]Samsung Medical Center, Seoul, South Korea; [14]China Medical University Hospital, and China Medical University, Taichung, Taiwan; [15]Saitama Cancer Center, Saitama, Japan; [16]Hospital Universitario Miguel Servet, Zaragoza, Spain; BeiGene Ltd, Beijing, China; [17]Medical Oncology Department, University Hospital of Besançon, Besançon, France; [18]BeiGene Ltd, Zhongguancun Life Science Park, Beijing, China; [19]University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium

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Introduction

- Advanced or metastatic esophageal squamous cell carcinoma (ESCC) has a poor prognosis, with an estimated 5-year survival rate of ~5%[1]
- Tislelizumab is an anti-programmed cell death protein 1 (PD-1) monoclonal antibody with high affinity and specificity for PD-1, engineered to minimize binding to FcγR on macrophages to limit antibody-dependent phagocytosis, a mechanism of T-cell clearance and a potential mechanism of resistance to anti-PD-1 therapy[2]
- Tislelizumab monotherapy has demonstrated antitumor activity in patients with solid tumors, including ESCC[3–5]
- Here, we report the primary results of a global Phase 3 study (NCT03430843) that investigated the effect of second-line tislelizumab compared with chemotherapy on overall survival (OS) in adult patients with advanced or metastatic ESCC

Methods

Key eligibility criteria:
- Advanced or metastatic ESCC
- Progression during or after first-line systemic treatment
- ECOG PS 0 or 1

N=512

R → 1:1

Tislelizumab 200 mg IV Q3W

Investigator-chosen chemotherapy
One of the following:
- Paclitaxel 135–175 mg/m² IV Q3W or 80–100 mg/m² IV QW*
- Docetaxel 75 mg/m² IV Q3Wb
- Irinotecan 125 mg/m² IV on Days 1 and 8, Q3W

Stratification factors:
- Region: Asia (excl. Japan) vs Japan vs Europe/North America
- ECOG PS: 0 vs 1
- Chemotherapy option: paclitaxel vs docetaxel vs irinotecan

- **Primary endpoint:** OS in all randomized patients
- **Key secondary endpoint:** OS in patients with vCPS ≥ 10%
- **Other secondary endpoints:** PFS, ORR, DoR, and safety

Statistical considerations:
- The study required ~400 death events to achieve 82% power to detect a HR of 0.75 at 0.025 significance level (1-sided) for the primary endpoint of OS in all randomized patients (ITT analysis set)
- If OS in all randomized patients (ITT analysis set) was statistically significant, OS in patients with vCPS ≥ 10% (PD-L1+ analysis set) was tested sequentially

Figure 1. Study design

For Japan: 100 mg/m² IV in cycles consisting of weekly dosing for 6 weeks, followed by one week of rest; †For Japan: 70 mg/m² IV Q3W
DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; ITT, intent-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, once weekly, Q3W, every three weeks; vCPS, visually-estimated combined positive score

Results

- 512 patients were randomized (256 to tislelizumab and 256 to chemotherapy) from 132 sites in 11 countries/regions in Asia, Europe, and North America. Treatment was received by 255 patients (99.6%) for tislelizumab and 240 patients (93.8%) for chemotherapy
- At the data cut-off of final analysis (Dec 1, 2020):
  - Median (range) follow-up in months was 8.5 (0.2–31.7) for tislelizumab and 5.8 (0–30.8) for chemotherapy
  - 16 patients (6.3%) remained on treatment with tislelizumab vs 1 patient (0.4%) with chemotherapy

Characteristic	Tislelizumab (n=256)	Chemotherapy (n=256)
Median age (range), years	62.0 (40–86)	63.0 (35–81)
Male, n (%)	217 (84.8)	215 (84.0)
Region, n (%)		
Asia	201 (78.5)	203 (79.3)
Europe/North America	55 (21.5)	53 (20.7)
ECOG PS, n (%)		
0	66 (25.8)	60 (23.4)
1	190 (74.2)	196 (76.6)
PD-L1 status, n (%)		
vCPS ≥ 10%	89 (34.8)	68 (26.6)
vCPS < 10%	116 (45.3)	140 (54.7)
Unknown	51 (19.9)	48 (18.8)
Disease status at baseline, n (%)		
Locally advanced	5 (2.0)	20 (7.8)
Metastatic	251 (98.0)	236 (92.2)
Prior therapies, n (%)		
Surgery	94 (36.7)	99 (38.7)
Radiotherapy	169 (66.0)	163 (63.7)
Platinum-based chemotherapy	249 (97.3)	252 (98.4)

Table 1. Patient baseline characteristics in all randomized patients

Including categories of 'not reported', 'unknown', and 'other'
ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; vCPS, visually-estimated combined positive score

Overall survival

- Tislelizumab significantly improved OS compared with chemotherapy in all randomized patients, as well as in patients with vCPS ≥ 10%:
  - A 30% reduction in the risk of death (HR 0.70, 95% confidence interval [CI]: 0.57–0.85, p=0.0001), with a 2.3 month improvement in median OS in all randomized patients was observed (**Figure 2**)
  - A 46% reduction in the risk of death (HR 0.54, 95% CI: 0.36–0.79, p=0.0006), with a 3.5 month improvement in median OS in patients with PD-L1 vCPS ≥ 10% was observed (**Figure 3**)
- Survival benefit was consistently observed across pre-defined subgroups, including PD-L1 expression status, race and region (**Figure 4**)

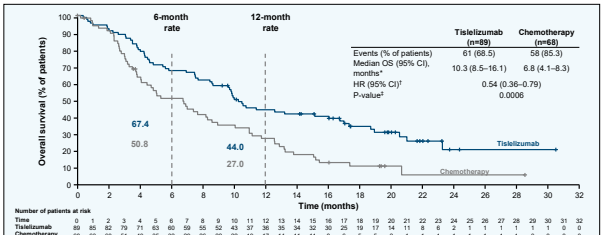

Figure 3. Kaplan-Meier plot of OS in patients with vCPS ≥ 10% (key secondary endpoint)

**Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. †HR was based on a Cox regression model*
‡One-sided p-value was estimated from a stratified log rank test
CI, confidence interval; HR, hazard ratio; OS, overall survival; vCPS, visually-estimated combined positive score

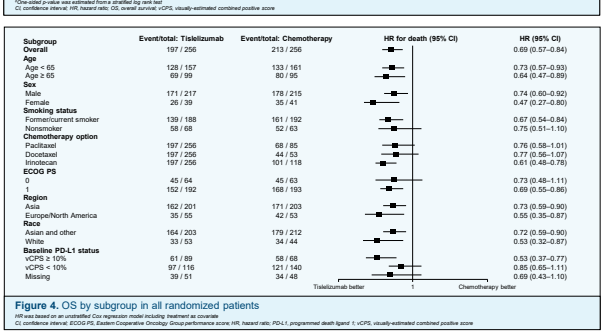

Figure 4. OS by subgroup in all randomized patients

HR was based on an unstratified Cox regression model including treatment as covariate
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; PD-L1, programmed death ligand 1; vCPS, visually-estimated combined positive score

Conclusions

- Tislelizumab demonstrated a statistically significant and clinically meaningful improvement in OS vs chemotherapy in advanced or metastatic ESCC patients whose tumor progressed during or after first line therapy
- Survival benefit was observed across pre-defined subgroups, including PD-L1 expression status, race and region
- Tislelizumab resulted in higher and more durable antitumor response than chemotherapy
- Tislelizumab showed a favorable safety profile compared with chemotherapy, with no new safety signals identified
- Tislelizumab represents a potential new second-line treatment option for patients with advanced or metastatic ESCC

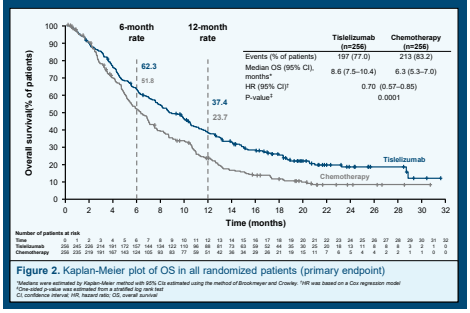

Figure 2. Kaplan-Meier plot of OS in all randomized patients (primary endpoint)

**Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. †HR was based on a Cox regression model*
‡One-sided p-value was estimated from a stratified log rank test
CI, confidence interval; HR, hazard ratio; OS, overall survival

Progression-free survival

- The PFS Kaplan-Meier curves began to separate approximately 3 months after randomization in favor of tislelizumab (**Figure 5**)

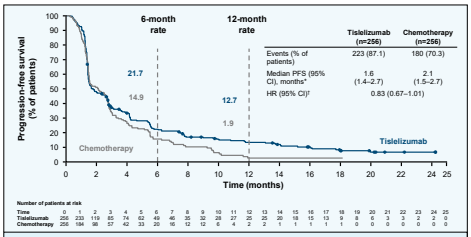

Figure 5. Kaplan-Meier plot of PFS in all randomized patients (secondary endpoint)

**Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. †HR was based on a Cox regression model*
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Response rate and duration

- Tislelizumab was associated with a greater ORR (20.3% vs 9.8%; odds ratio 2.4, 95% CI 1.4–4.0) and a more durable tumor response (median DoR: 7.1 months vs 4.0 months) than chemotherapy (**Table 2**)

	Tislelizumab (n=256)	Chemotherapy (n=256)
ORR		
n	52	25
% (95% CI)*	20.3 (15.6–25.8)	9.8 (6.4–14.1)
Odds ratio (95% CI)†	2.4 (1.4–4.0)	
Best overall response, n (%)		
Complete response	5 (2.0)	1 (0.4)
Partial response	47 (18.4)	24 (9.4)
Stable disease	68 (26.6)	82 (32.0)
Progressive disease	116 (45.3)	86 (33.6)
Not evaluable‡	20 (7.8)	63 (24.6)
Median DoR (95% CI), months§	7.1 (4.1–11.3)	4.0 (2.1–8.2)
Patients with ongoing response, n/N (%)	10/52 (19.2)	0/25 (0)

Table 2. Summary of antitumor activity per RECIST v1.1 (investigator-assessed) in all randomized patients (secondary endpoint)

**Two-sided 95% CI was calculated using Clopper-Pearson method. †Calculated using the Cochran-Mantel-Haenszel Chi-square test. ‡Including those with no post-baseline assessment or an unevaluable post-baseline assessment. §Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. DoR analysis included patients with objective response (complete or partial response)*
CI, confidence interval; DoR, duration of response; ORR, overall response rate

Safety

- Tislelizumab showed a favorable safety profile compared with chemotherapy, with no new safety signals identified (**Tables 3 and 4**)

Event, n (%)	Tislelizumab (n=255)	Chemotherapy (n=240)
Patients with at least one TEAE / TRAE	244 (95.7) / 187 (73.3)	236 (98.3) / 225 (93.8)
≥ Grade 3 TEAE / TRAE	118 (46.3) / 48 (18.8)	163 (67.9) / 134 (55.8)
Serious TEAE / TRAE	105 (41.2) / 36 (14.1)	105 (43.8) / 47 (19.6)
TEAE / TRAE leading to treatment discontinuation	49 (19.2) / 17 (6.7)	64 (26.7) / 33 (13.8)
TEAE / TRAE leading to death*	14 (5.5) / 5 (2.0)	14 (5.8) / 7 (2.9)

Table 3. Summary of AEs

**Death events due to disease progression were excluded*
All AEs are treatment-emergent and graded based on National Cancer Institute–Common Terminology Criteria for Adverse Events (version 4.03)
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Preferred term, n (%)	Tislelizumab (n=255)	Chemotherapy (n=240)
Aspartate aminotransferase increased	29 (11.4)	9 (3.8)
Anemia	28 (11.0)	83 (34.6)
Hypothyroidism	26 (10.2)	0 (0.0)
Fatigue	19 (7.5)	33 (13.8)
Decreased appetite	16 (6.3)	75 (31.3)
Diarrhea	14 (5.5)	66 (27.5)
Asthenia	12 (4.7)	28 (11.7)
Malaise	10 (3.9)	35 (14.6)
Weight decreased	8 (3.1)	25 (10.4)
Nausea	7 (2.7)	66 (27.5)
Leukopenia	7 (2.7)	30 (12.5)
White blood cell count decreased	5 (2.0)	98 (40.8)
Vomiting	4 (1.6)	43 (17.9)
Constipation	4 (1.6)	25 (10.4)
Neutrophil count decreased	3 (1.2)	94 (39.2)
Neutropenia	2 (0.8)	31 (12.9)
Alopecia	0 (0.0)	42 (17.5)

Table 4. Treatment-related AEs reported in ≥ 10% of patients*

**In either treatment group*
TRAEs included AEs that were considered by the investigator to be related to study drug or AEs with a missing causality
AE, adverse event; TRAE, treatment-related adverse event

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