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

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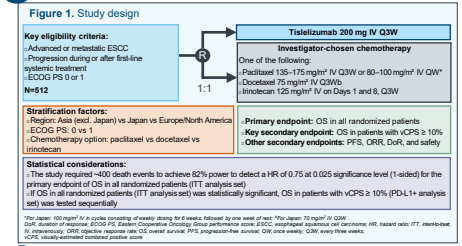
Introduction

- 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

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, intention-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

Table 1. Patient baseline characteristics in all randomized patients

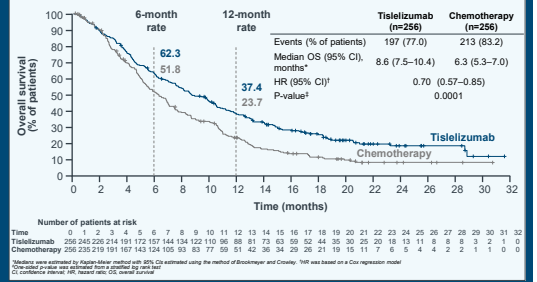
Characteristic	Tislelizumab (n=256)	Chemotherapy (n=256)
Median age (range), years	62.0 (40–86)	63.0 (35–81)
Male, n (%)	217 (84.8)	215 (84.0)
Region, n (%)		
Asia	201 (78.5)	203 (79.3)
Europe/North America	55 (21.5)	53 (20.7)
ECOG PS, n (%)		
0	66 (25.8)	60 (23.4)
1	190 (74.2)	196 (76.6)
PD-L1 status, 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)

"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

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 treatment
- 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)

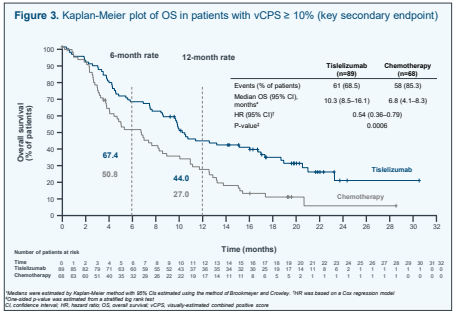


Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. †HR was based on a Cox regression model
‡One-sided p-value was estimated from a stratified log rank test
CI, confidence interval; HR, hazard ratio; OS, overall survival

Overall survival

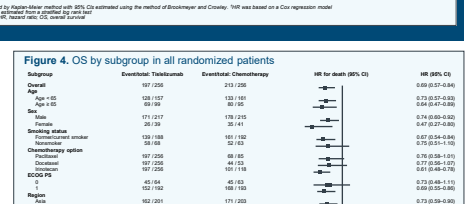
- Tislelizumab significantly improved OS compared to chemotherapy in all randomized patients, as well as in patients with vCPS ≥ 10%:
  - A 30% reduction in the risk of death (HR 0.70, 95% confidence interval [CI]: 0.57–0.85, p=0.0001), with a 2.3 month improvement in median OS in all randomized patients 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

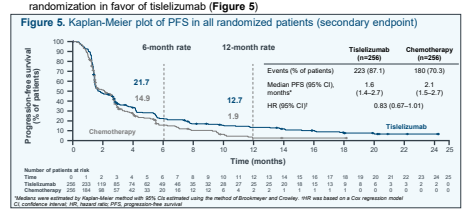


HR was based on an unstratified Cox regression model including treatment as covariate
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; PD-L1, programmed death ligand 1; vCPS, visually-estimated combined positive score

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**)

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

	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)

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**)

Table 3. Summary of AEs

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)

Death events due to disease progression were excluded
AEs were graded according to 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

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

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)

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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