Randomized, Phase 3 Study of Second-Line Tislelizumab vs Chemotherapy in Advanced or Metastatic Esophageal Squamous Cell Carcinoma (ESCC, RATIONALE 302) in the Overall Population and Europe/North America Subgroup

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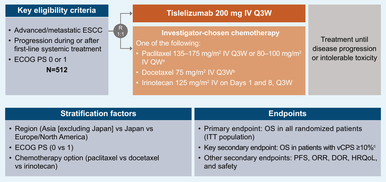
Background

- Advanced or metastatic esophageal squamous cell carcinoma (ESCC) has an estimated 5-year survival rate of 5%[1]
- Single-agent chemotherapy is recommended when ESCC progresses after first-line therapy but is associated with limited survival and poor tolerability[2–6]
- Second-line use of anti-PD-1/L1 monoclonal antibodies has improved overall survival (OS) vs chemotherapy[3–5]
- Tislelizumab has high affinity and specificity for PD-1 and was designed to minimize binding to FcγR on macrophages to limit antibody-dependent phagocytosis[7]
- We report data from the overall and European Union/North America (EU/NA) populations in the RATIONALE 302 study (NCT03430843) that evaluated the efficacy and safety of second-line tislelizumab in patients with advanced or metastatic ESCC[8]

Methods

Figure 1. Study design



ClinicalTrials.gov: NCT03430843
Assessment of tumor-response status was performed approximately every 6 weeks (± 7 days) for the first 6 months every 9 weeks (± 7 days) thereafter.
[a]For Japan: paclitaxel 100 mg/m² IV in cycles consisting of weekly dosing for 6 weeks, followed by one week of rest; [b]For Japan: docetaxel 70 mg/m² IV Q3W; [c]PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay.
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intent-to-treat; IV, intravenously; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QW, once weekly; Q3W, every three weeks; vCPS, visually-estimated combined positive score.

- 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)

Results

- The data cut-off date for the final analysis was Dec 1, 2020
- A total of 512 patients were randomized to receive tislelizumab or chemotherapy; in the EU/NA subgroup 55 patients received tislelizumab and 53 patients received chemotherapy (**Table 1**)
- Baseline characteristics in the overall population were generally balanced:
  - Median age of patients in the tislelizumab arm was 62 years vs 63 years in the chemotherapy arm
  - For both treatment arms, patients were predominately male, and a higher proportion of patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 and metastatic disease at baseline
- Baseline characteristics in the EU/NA subgroup were similar to the overall population, except for numerical variations in median age, gender, ECOG PS and prior surgery for ESCC

Conclusions

- **In the overall population, tislelizumab demonstrated statistically significant and clinically meaningful improvement in OS vs chemotherapy in patients with advanced or metastatic ESCC whose tumor progressed during or after first-line treatment**
- **The OS benefit of tislelizumab over chemotherapy in the overall population was consistently observed in patients from the EU/NA subgroup**
- **Tislelizumab showed a higher and more durable antitumor response in the overall population compared with chemotherapy**
  - **Antitumor response in the EU/NA subgroup was consistent with the overall population**
- **Tislelizumab demonstrated a tolerable safety profile compared with chemotherapy in the overall population**
  - **Safety profile of tislelizumab in the EU/NA subgroup was consistent with the overall population**
- **Tislelizumab represents a potential new second-line treatment option for patients with advanced or metastatic ESCC globally**

Table 1. Demographics and baseline patient characteristics

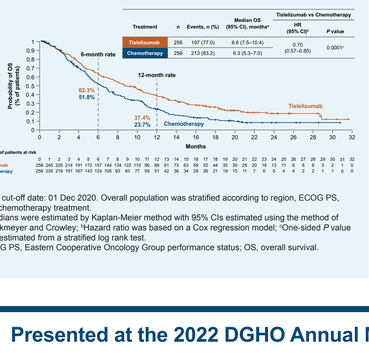
Characteristic		Overall population		EU/NA subgroup	
		Tislelizumab (n=256)	Chemotherapy (n=256)	Tislelizumab (n=55)	Chemotherapy (n=53)
Median age (range), years		62 (40–86)	63 (35–81)	65 (41–86)	65 (35–80)
Male, n (%)		217 (84.8)	215 (84.0)	37 (67.3)	36 (67.9)
Region, n (%)	Asia	201 (78.5)	203 (79.3)	0.0	0.0
	Europe/North America	55 (21.5)	53 (20.7)	55 (100)	53 (100)
Race, n (%)	Asian	201 (78.5)	207 (80.9)	0.0	4 (7.5)
	White/Caucasian	53 (20.7)	44 (17.2)	53 (96.4)	44 (83.0)
	Black/African American	0.0	2 (0.8)	0.0	2 (3.8)
	Other[a]	2 (0.8)	3 (1.2)	2 (3.6)	3 (5.7)
ECOG PS, n (%)	0	66 (25.8)	60 (23.4)	23 (41.8)	18 (34.0)
	1	190 (74.2)	196 (76.6)	32 (58.2)	35 (66.0)
PD-L1 status[b], n (%)	vCPS ≥10%	89 (34.8)	68 (26.6)	22 (40.0)	10 (18.9)
	vCPS <10%	116 (45.3)	140 (54.7)	27 (49.1)	37 (69.8)
	Unknown	51 (19.9)	48 (18.8)	6 (10.9)	6 (11.3)
Disease status at baseline, n (%)	Locally advanced	5 (2.0)	20 (7.8)	2 (3.6)	6 (11.3)
	Metastatic	251 (98.0)	236 (92.2)	53 (96.4)	47 (88.7)
Prior therapies, n (%)	Surgery	94 (36.7)	99 (38.7)	9 (16.4)	10 (18.9)
	Radiotherapy	169 (66.0)	163 (63.7)	34 (61.8)	34 (64.2)
	Platinum-based chemotherapy	249 (97.3)	252 (98.4)	54 (98.2)	53 (100.0)

Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG PS, and chemotherapy treatment.
[a]Including categories of 'not reported', 'unknown', and 'other'; [b]PD-L1 expression centrally assessed by immunohistochemistry with the Ventana SP263 assay.
ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; NA, North America; PD-L1, programmed death ligand 1; vCPS, visually-estimated combined positive score.

Overall Survival

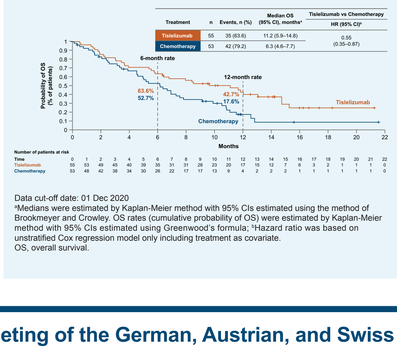
- Tislelizumab significantly improved OS compared with chemotherapy in all randomized patients:
  - A 30% reduction in the risk of death (hazard ratio [HR], 0.70, 95% confidence interval [CI], 0.57-0.85, *P* = 0.0001), with a 2.3-month improvement in median OS in all randomized patients was observed (**Figure 2**)
- Benefit in OS was consistently observed in the EU/NA subgroup (**Figure 3**)
  - Tislelizumab was associated with a 45% reduction in the risk of death (HR, 0.55, 95% CI, 0.35-0.87) compared with chemotherapy
  - Median OS was 11.2 months with tislelizumab, which was 4.9 months longer than chemotherapy

Figure 2. OS: overall population



Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG PS, and chemotherapy treatment.
[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley; [b]Hazard ratio was based on a Cox regression model; [c]One-sided *P* value was estimated from a stratified log rank test.
ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival.

Figure 3. OS: EU/NA subgroup

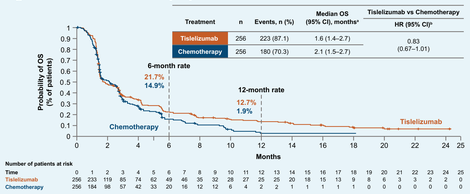


Data cut-off date: 01 Dec 2020
[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. OS rates (cumulative probability of OS) were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula; [b]Hazard ratio was based on unstratified Cox regression model only including treatment as covariate.
OS, overall survival.

Progression-free survival (PFS)

- The PFS Kaplan-Meier curves for the overall population began to separate approximately 3 months after randomization in favor of tislelizumab
  - Tislelizumab was associated with 17% reduction in the risk of disease progression compared with chemotherapy (**Figure 4**)
- In the EU/NA subgroup, there was no meaningful difference in PFS between the two arms (HR, 0.97, 95% CI, 0.64–1.47)

Figure 4. PFS: overall population



Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG PS, and chemotherapy treatment.
[a]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley; [b]Hazard ratio was based on a Cox regression model.
ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival.

Response rate and duration

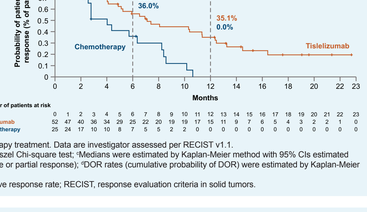
- In the overall population, tislelizumab was associated with a greater objective response rate (ORR; 20.3% vs 9.8%; odds ratio, 2.4; 95% CI, 1.4-4.0) and a more durable tumor response (median duration of response [DOR], 7.1 months vs 4.0 months) than chemotherapy (**Figures 5A and 5B**)
- Tislelizumab was associated with a greater ORR and median DOR than chemotherapy in the EU/NA population as well (**Figures 6A and 6B**)
  - The ORR was 20.0% vs 11.3% (odds ratio, 2; 95% CI, 0.7-5.8) for tislelizumab vs chemotherapy
  - Median DOR was 5.1 months vs 2.1 months for tislelizumab vs chemotherapy

Figure 5. ORR and DOR: overall population

A

	Tislelizumab (n=256)	Chemotherapy (n=256)
ORR, n	52	25
% (95% CI)[a]	20.3 (15.6–25.8)	9.8 (6.4–14.1)
Odds ratio for ORR, (95% CI)[b]	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)
DOR[c]		
Median (95% CI), months	7.1 (4.1–11.3)	4.0 (2.1–8.2)
Patients with ongoing response, n (%)	10 (19.2)	0 (0.0)

B



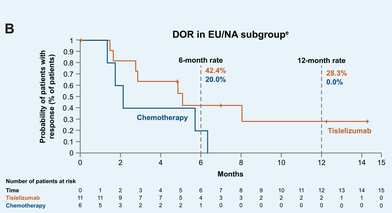
Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG PS, and chemotherapy treatment. Data are investigator assessed per RECIST v1.1.
[a]Two-sided 95% CI was calculated using Clopper-Pearson method; [b]Calculated using the Cochran-Mantel-Haenszel Chi-square test; [c]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); [d]DOR rates (cumulative probability of DOR) were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors.

Figure 6. ORR and DOR: EU/NA subgroup

A

	Tislelizumab (n=55)	Chemotherapy (n=53)
ORR, n	11	6
% (95% CI)[a]	20.0 (10.4–33.0)	11.3 (4.3–23.0)
Odds ratio for ORR, (95% CI)[b]	2.0 (0.7–5.8)	
ORR difference, % (95% CI)	8.7 (-4.9–22.3)	
Best overall response, n (%)		
Complete response	2 (3.6)	0 (0.0)
Partial response	9 (16.4)	6 (11.3)
Stable disease	17 (30.9)	20 (37.7)
Progressive disease	23 (41.8)	16 (30.2)
Not evaluable[c]	4 (7.3)	11 (20.8)
DOR[d]		
Median (95% CI), months	5.1 (1.6–NE)	2.1 (1.3–6.3)
Patients with ongoing response, n (%)	4 (36.4)	0 (0.0)

B



Data cut-off date: 01 Dec 2020. Data are investigator assessed per RECIST v1.1 criteria.
[a]Two-sided 95% CI was calculated using Clopper-Pearson method; [b]Calculated using the Cochran-Mantel-Haenszel Chi-square test; [c]Including those with no post-baseline assessment or an unevaluable post-baseline assessment; [d]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); [e]DOR rates (cumulative probability of DOR) were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula.
DOR, duration of response; NE, not evaluable; ORR, objective response rate; RECIST, response evaluation criteria in solid tumors.

Safety

- Overall, tislelizumab showed a favourable and manageable safety profile compared with chemotherapy in both the overall population and the EU/NA subgroup (**Table 2**)
  - There was a lower incidence of Grade 3–5 adverse events (AEs), serious AEs, and AEs that lead to treatment discontinuation with tislelizumab vs chemotherapy
  - Treatment-emergent AEs that lead to death were low in both arms
  - The most common treatment-related AEs had lower incidence in the tislelizumab vs the chemotherapy arm
- The safety profile of tislelizumab was generally similar between the overall population and the EU/NA subgroup

Table 2. Summary of Adverse Events

Characteristic	Overall population		EU/NA subgroup	
	Tislelizumab (n=255)	Chemotherapy (n=240)	Tislelizumab (n=54)	Chemotherapy (n=49)
Patients with >1 TEAE	244 (95.7)	236 (98.3)	52 (96.3)	47 (95.9)
Grade 3–5	118 (46.3)	163 (67.9)	30 (55.6)	35 (71.4)
Serious AEs	105 (41.2)	105 (43.8)	21 (38.9)	23 (46.9)
Leading to death[a]	14 (5.5)	14 (5.8)	3 (5.6)	5 (10.2)
Leading to treatment discontinuation	49 (19.2)	64 (26.7)	8 (14.8)	15 (30.6)
Most common (incidence ≥20%) TRAEs				
Anemia	28 (11.0)	83 (34.6)	2 (3.7)	13 (26.5)
Decreased appetite	16 (6.3)	75 (31.3)	5 (9.3)	12 (24.5)
Diarrhea	14 (5.5)	66 (27.5)	7 (13.0)	16 (32.7)
Nausea	7 (2.7)	66 (27.5)	3 (5.6)	12 (24.5)
White blood cell count decreased	5 (2.0)	98 (40.8)	0	2 (4.1)
Neutrophil count decreased	3 (1.2)	94 (39.2)	0	5 (10.2)

Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment; [a]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); TRAEs include TEAEs that were considered by the investigator to be related to study drug or TEAEs with a missing causality.
AE, adverse event; ECOG, Eastern Cooperative Oncology Group; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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Disclosures

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