RATIONALE-302

2L ESCC

RATIONALE-302 Trial Design

Phase 3

Global

Study Identifier:
BGB-A317-302, NCT03430843

Primary Endpoints: OS in all randomized patients (ITT)
Key Secondary Endpoints: OS in patients with PD-L1 TAP ≥10%[b], ORR, PFS, DoR, HRQoL, safety

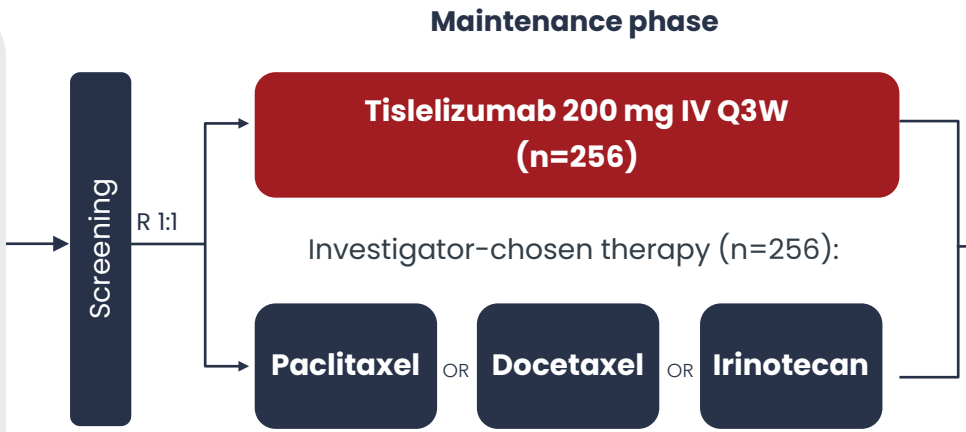
Key eligibility criteria

- Pathologically confirmed ESCC
- Progression during or after 1L therapy for advanced ESCC[a]
- ≥18 years of age
- ECOG PS ≤1

Stratification Factors

- Region (Asia [excluding Japan] vs Japan vs Europe/North America)
- ECOG PS (0 vs 1)
- Chemotherapy option (paclitaxel vs docetaxel vs irinotecan)

Treatment



Follow-up

Safety and survival

[a]First line therapy could not include PD-L1-based treatments; [b]PD-L1 expression centrally assessed with the Ventana SP263 assay with TAP score.
1L=1st line, 2L=2nd line, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, ESCC=esophageal squamous cell carcinoma, HRQoL=health-related quality of life, IV=intravenous, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, Q3W=every 3 weeks, R=randomized, TAP=tumor area positivity.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03430843 Accessed October 9, 2025; 2. Shen L et al. *J Clin Oncol*. 2022;40:3065–3076.

Baseline Demographics and Disease Characteristics

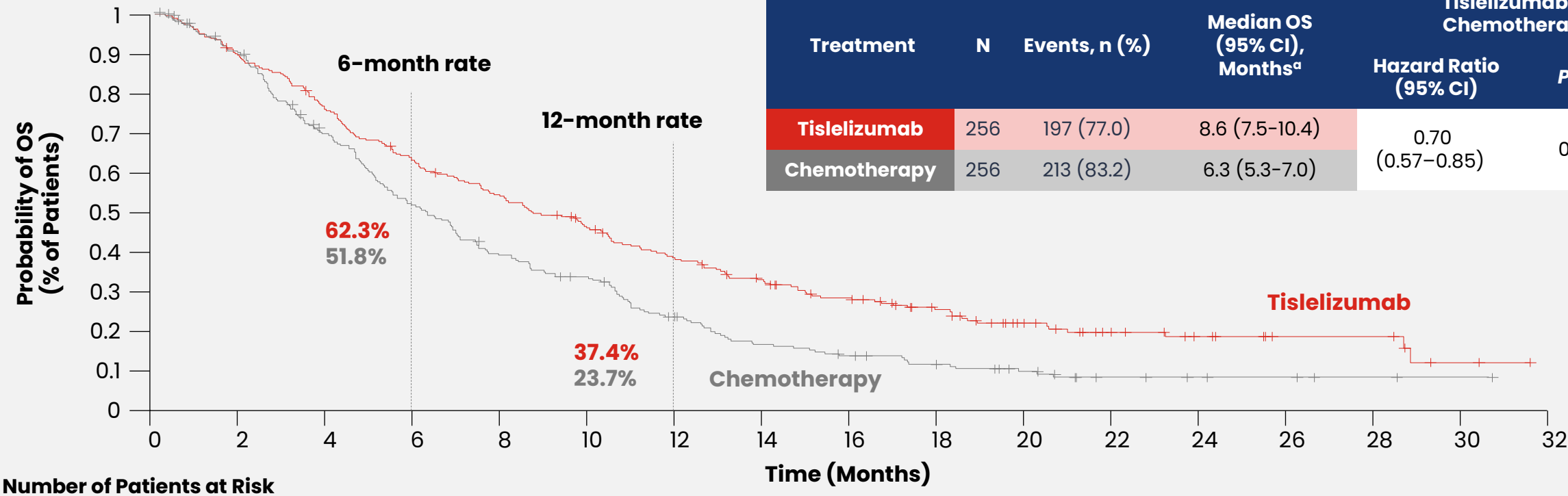
	Tislelizumab (n=256)	Chemotherapy (n=256)
Median age (range), years	62 (40–86)	63 (35–81)
Male, n (%)	217 (84.8)	215 (84.0)
Region, n (%)		
Asia[a]	201 (78.5)	203 (79.3)
Europe/North America	55 (21.5)	53 (20.7)
Race, n (%)		
Asian	201 (78.5)	207 (80.9)
White/Caucasian	53 (20.7)	44 (17.2)
Black/African American	0	2 (0.8)
Other[b]	2 (0.8)	3 (1.2)
ECOG PS, n (%)		
0	66 (25.8)	60 (23.4)
1	190 (74.2)	196 (76.6)
PD-L1 status, n (%)		
TAP score ≥ 10%	89 (34.8)	68 (26.6)
TAP score < 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)

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG PS, and chemotherapy treatment. [a]There were 50 patients from Japan: 25 patients in the tislelizumab arm and 25 patients in the chemotherapy arm; [b]Including categories of 'not reported', 'unknown', and 'other.'
2L=2nd line, ECOG PS=Eastern Cooperative Oncology Group performance score, ESCC=esophageal squamous cell carcinoma, PD-L1=programmed death-ligand 1, TAP=tumor area positivity.
Shen L et al. *J Clin Oncol.* 2022;40:3065-3076.

Primary Endpoint: Overall Survival (ITT Population)

Tislelizumab demonstrated a 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

Treatment	N	Events, n (%)	Median OS (95% CI), Months[a]	Tislelizumab vs Chemotherapy	
				Hazard Ratio (95% CI)	*P*-Value
Tislelizumab	256	197 (77.0)	8.6 (7.5-10.4)	0.70 (0.57–0.85)	0.0001[b]
Chemotherapy	256	213 (83.2)	6.3 (5.3-7.0)		



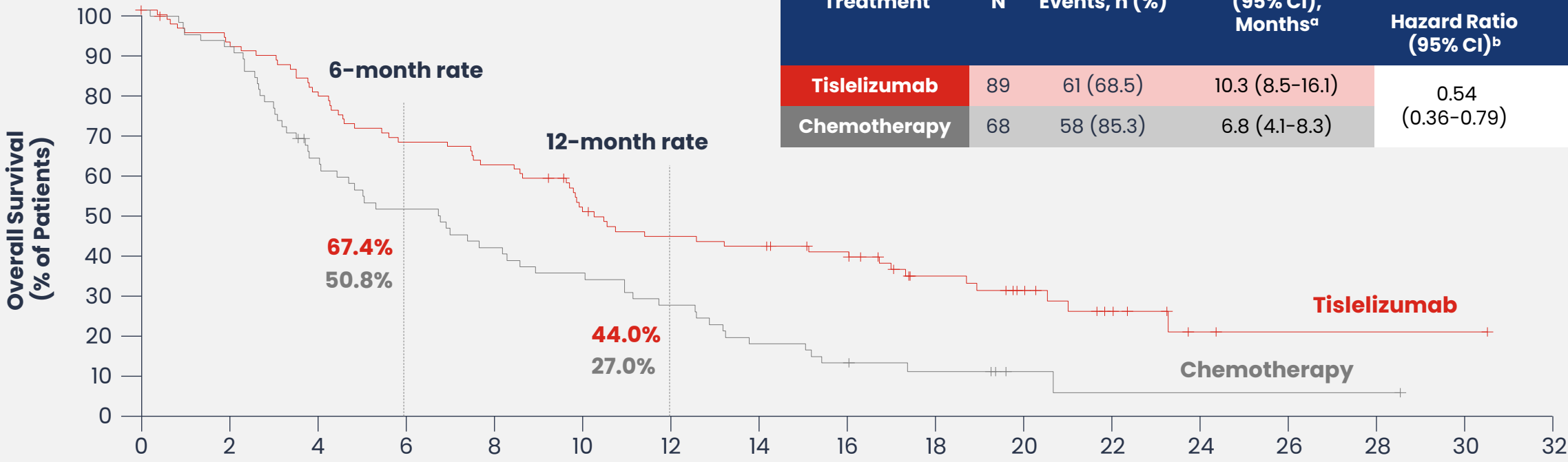
Number of Patients at Risk

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Tislelizumab	256	245	226	214	191	172	157	144	134	122	110	96	88	81	73	63	59	52	44	35	30	25	20	18	13	11	8	8	8	3	2	1	0
Chemotherapy	256	235	219	191	167	143	124	105	93	83	77	59	51	42	36	34	29	26	21	19	15	11	7	6	5	4	4	2	2	1	1	0	0

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment.
[a]Median OS and 95% CI were calculated using a generalized Brookmeyer and Crowley method, and the cumulative probability of OS at 6 and 12 months was calculated (with two-sided 95% CI) using Greenwood's formula; [b]One-sided *P*-value was estimated from a log-rank test stratified by ECOG PS and chemotherapy option. HR was based on a Cox regression model including treatment as a covariate and ECOG PS and chemotherapy option as strata.
2L=2nd line, CI=confidence interval, ECOG=Eastern Cooperative Oncology Group, ESCC=esophageal squamous cell carcinoma, ITT=intent-to-treat, OS=overall survival.
Shen L et al. *J Clin Oncol.* 2022;40:3065-3076.

Overall Survival in Patients With PD-L1 TAP ≥ 10%

Treatment	N	Events, n (%)	Median OS (95% CI), Months[a]	Tislelizumab vs Chemotherapy	
				Hazard Ratio (95% CI)[b]	*P*-Value
Tislelizumab	89	61 (68.5)	10.3 (8.5-16.1)	0.54 (0.36-0.79)	0.0006*
Chemotherapy	68	58 (85.3)	6.8 (4.1-8.3)		



Number of Patients at Risk

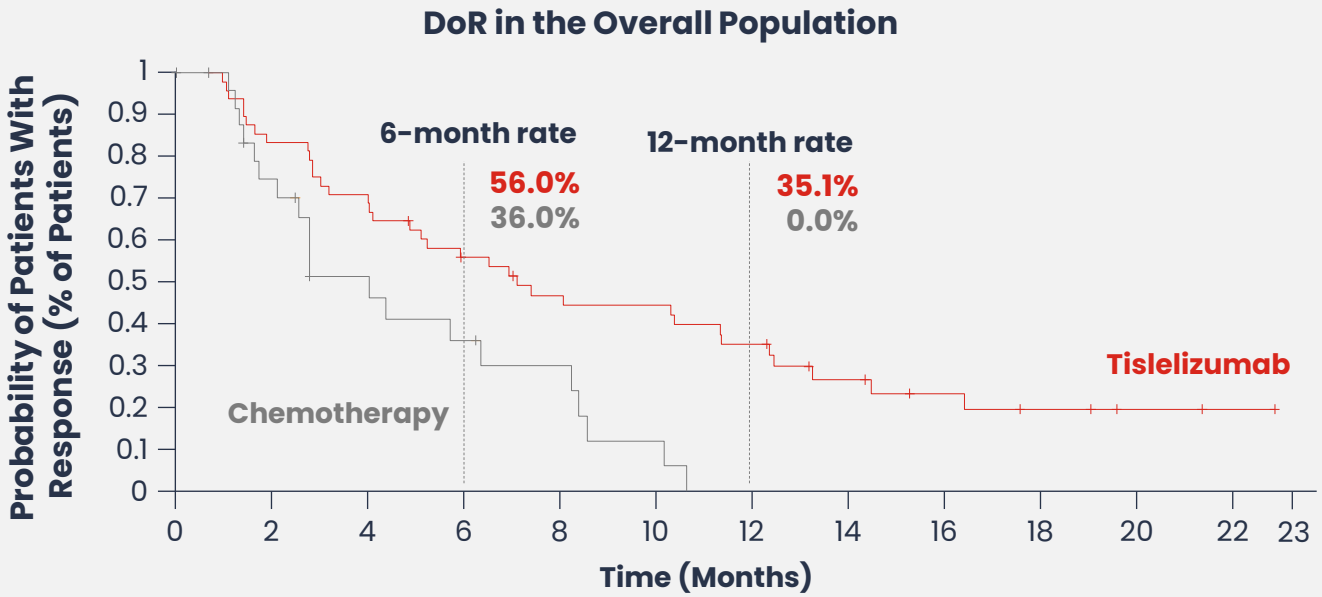
Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Tislelizumab	89	85	82	79	71	63	60	59	55	52	43	37	36	35	34	32	30	25	19	17	14	11	8	6	2	1	1	1	1	1	1	0	0
Chemotherapy	68	63	60	51	40	35	32	29	26	22	22	19	17	14	11	11	8	6	5	5	2	1	1	1	1	1	1	1	1	0	0	0	0

Data cut-off date: December 1, 2020.
[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. *One-sided *P*-value was estimated from a stratified log rank test.
2L=2nd line, CI=confidence interval, ECOG=Eastern Cooperative Oncology Group, ESCC=esophageal squamous cell carcinoma, OS=overall survival, PD-L1=programmed death ligand 1, TAP=tumor area positivity.
Shen L et al. *J Clin Oncol.* 2022;40:3065-3076.

ORR and DoR

Tislelizumab showed a higher and more durable antitumor response in the overall population compared with chemotherapy

Response	Tislelizumab (n=256)	Chemotherapy (n=256)
ORR, n (%)	52 (20.3)	25 (9.8)
95% CI[a]	15.6-25.8	6.4-14.1
Odds Ratio for ORR, (95% CI)	2.39 (1.42-4.01)	
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[b]	1 (0.4)	3 (1.2)
Not assessable[c]	19 (7.4)	60 (23.4)
DoR		
Median (95% CI), months	7.1 (4.1-11.3)	4.0 (2.1-8.2)
HR (95% CI)[d]	0.42 (0.23-0.75)	
Pts with ongoing response, n (%)	10 (19.2)	0 (0.0)



Number of Patients at Risk

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Tislelizumab	52	47	40	36	34	29	25	22	20	19	19	17	15	11	9	7	6	5	4	3	2	2	1	0
Chemotherapy	25	24	17	10	10	8	7	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0

Data cut-off date: December 1, 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment. Data are investigator assessed per RECIST v1.1.
[a]ORR and DoR results were based on unconfirmed tumor responses; [b]Not evaluable on the basis of RECIST v1.1; [c]Patients with no postbaseline tumor assessment by data cutoff, including those who discontinued study for any reason or died without having any postbaseline tumor assessment; [d]HR was based on a Cox regression model including treatment as a covariate and Eastern Cooperative Oncology Group performance status and chemotherapy option as strata.
2L=2nd line, CI=confidence interval, DoR=duration of response, ECOG=Eastern Cooperative Oncology Group, ESCC=esophageal squamous cell carcinoma, ORR=overall response rate, pts=patients, RECIST=response evaluation criteria in solid tumors.
Shen L et al. *J Clin Oncol*. 2022;40:3065-3076.

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

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

	PD-L1 Status	ORR,[b] % (95% CI)[c]		Odds Ratio[d] (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

Data cut-off: December 1, 2020.
[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 v1.1; [c]Two-sided 95% CI was calculated using the Clopper-Pearson method; [d]ORR 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 nonevaluable samples, or with scored unqualified samples reclassified after database lock.
2L=2nd line, CI=confidence interval, CPS=combined positive score, CR=complete response, ESCC=esophageal squamous cell carcinoma, 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.
Shu Y et al. Poster Presentation at ASCO-GI 2024; Poster 390.

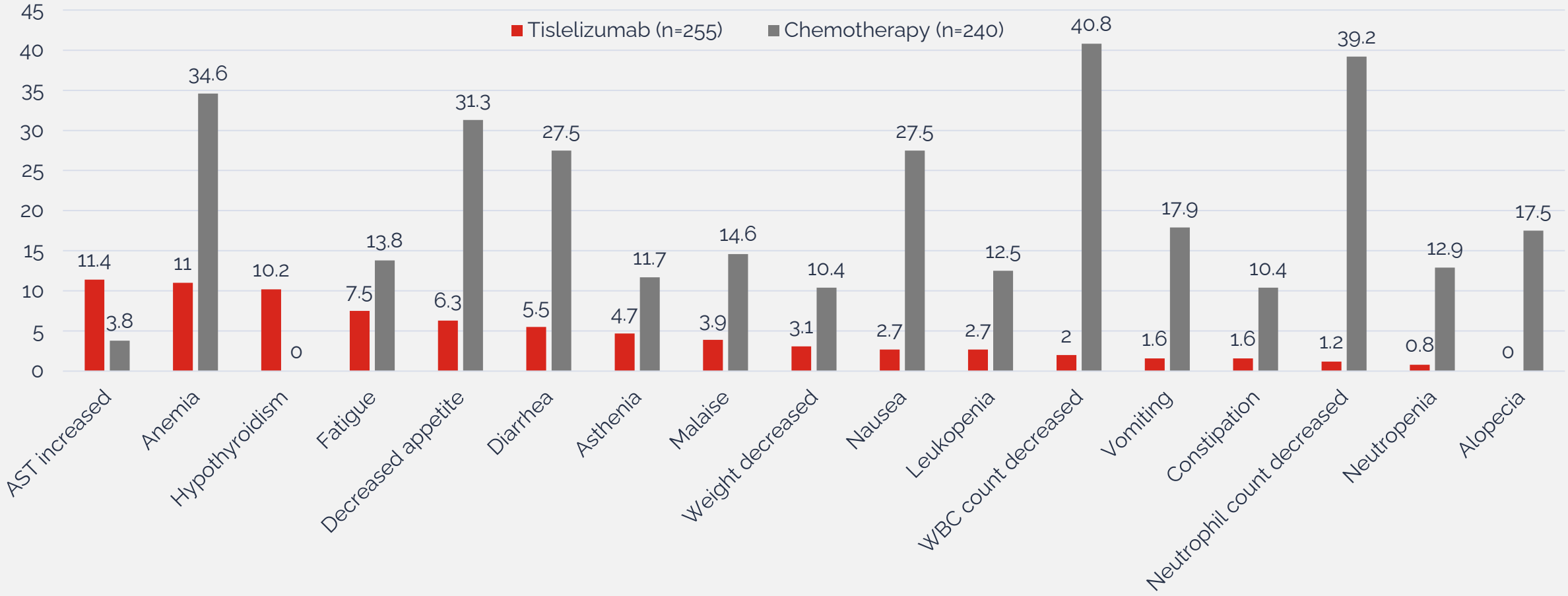
Summary of Adverse Events

- Tislelizumab treatment led to fewer Grade ≥3 TEAEs (46.3%) versus chemotherapy (67.9%)
- Tislelizumab treatment led to fewer Grade ≥3 TRAEs (18.8%) versus chemotherapy (55.8%)

	Overall Population	
	Tislelizumab (n=255)	Chemotherapy (n=240)
Patients with ≥1 TEAE, n (%)	**244 (95.7)**	**236 (98.3)**
Grade ≥3	118 (46.3)	163 (67.9)
Serious TEAEs	105 (41.2)	105 (43.8)
Leading to death[a]	35 (13.7)	28 (11.7)
Leading to treatment discontinuation	49 (19.2)	64 (26.7)
Patients with ≥1 TRAE, n (%)	187 (73.3)	225 (93.8)
Grade ≥3	48 (18.8)	134 (55.8)
Serious TRAE	36 (14.1)	47 (19.6)
Leading to death[a]	7 (2.7)	8 (3.3)
Leading to treatment discontinuation	17 (6.7)	33 (13.8)

Data cut-off date: December 1, 2020.
[a]TEAEs and TRAEs leading to death reported include those that were due to disease progression. Deaths attributed to TRAEs included one each of hemoptysis, pulmonary arterial hypertension, upper gastrointestinal hemorrhage, pneumonia, and decreased platelet count in the tislelizumab arm, and three of septic shock, and one each of pneumonia, febrile neutropenia, death, and multiple organ dysfunction syndrome in the chemotherapy arm. 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.
2L=2nd line, AE=adverse event, ECOG=Eastern Cooperative Oncology Group, ESCC=esophageal squamous cell carcinoma, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event.
Shen L et al. *J Clin Oncol.* 2022;40:3065-3076.

Treatment-Related AEs Reported in ≥10% of Patients



Data cut-off date: December 1, 2020.
TRAEs included AEs that were considered by the investigator to be related to study drug or AEs with a missing causality.
2L=2nd line, AE=adverse event, AST=aspartate aminotransferase, ESCC=esophageal squamous cell carcinoma, TRAE=treatment-related adverse event, WBC=white blood cell.
Shen L et al. *J Clin Oncol.* 2022;40:3065-3076.