RATIONALE-306

1L ESCC

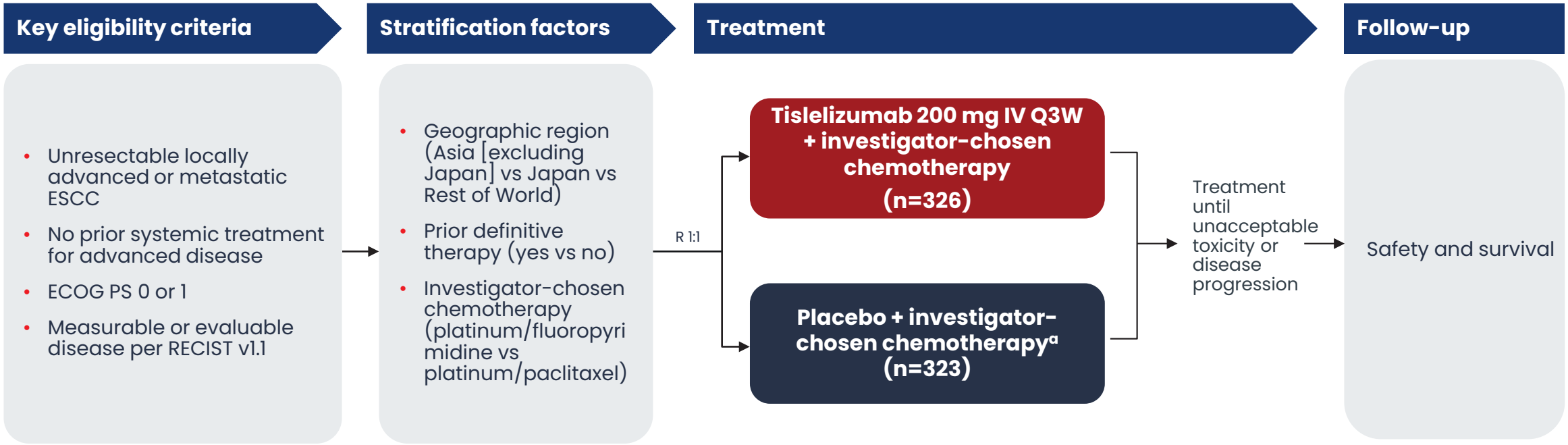
RATIONALE-306 Trial Design

Phase 3

Global

Study Identifier:
BGB-A317-306, NCT03783442

Primary Endpoints: OS (ITT population)
Key Secondary Endpoints: PFS, ORR, and DoR by investigator, OS in the PD-L1 score ≥10% subgroup[e], HRQoL, safety



[a]Investigator-chosen chemotherapy: Option A: Platinum + fluoropyrimidine cisplatin or oxaliplatin[b] + fluoropyrimidine[c]. Option B: Platinum + paclitaxel cisplatin or oxaliplatin[b]+ paclitaxel[d]; [b]Cisplatin 60-80 mg/m^2 IV or oxaliplatin 130 mg/m^2 IV Q3W (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site or investigator preference or standard practice. Platinum therapy may be stopped after six cycles, per site or investigator preference or standard practice. If platinum treatment is stopped, the non-platinum agent may continue at the regular schedule; [c]5-fluorouracil 750-800 mg/m^2 IV on Days 1-5 Q3W or capecitabine 1000 mg/m^2 orally BID on Days 1-14; [d]Paclitaxel 175 mg/m^2 IV Q3W; [e]PD-L1 expression was determined centrally by PD-L1 score (defined as the total percentage of the tumor area [tumor and any desmoplastic stroma] covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated) using the VENTANA PD-L1 (SP263) assay.
1L=1st line, BID=twice daily, DB=double-blind, 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=intention-to-treat, IV=intravenous, ORR=overall response rate, OS=overall survival, PD-L1=programmed death-ligand 1, PFS=progression-free survival, Q3W=every 3 weeks, R=randomized, RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1
Xu J et al. *Lancet Oncol*. 2023; 24(5):483-495. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03783442. Accessed October 9, 2025.

Baseline Demographics and Disease Characteristics

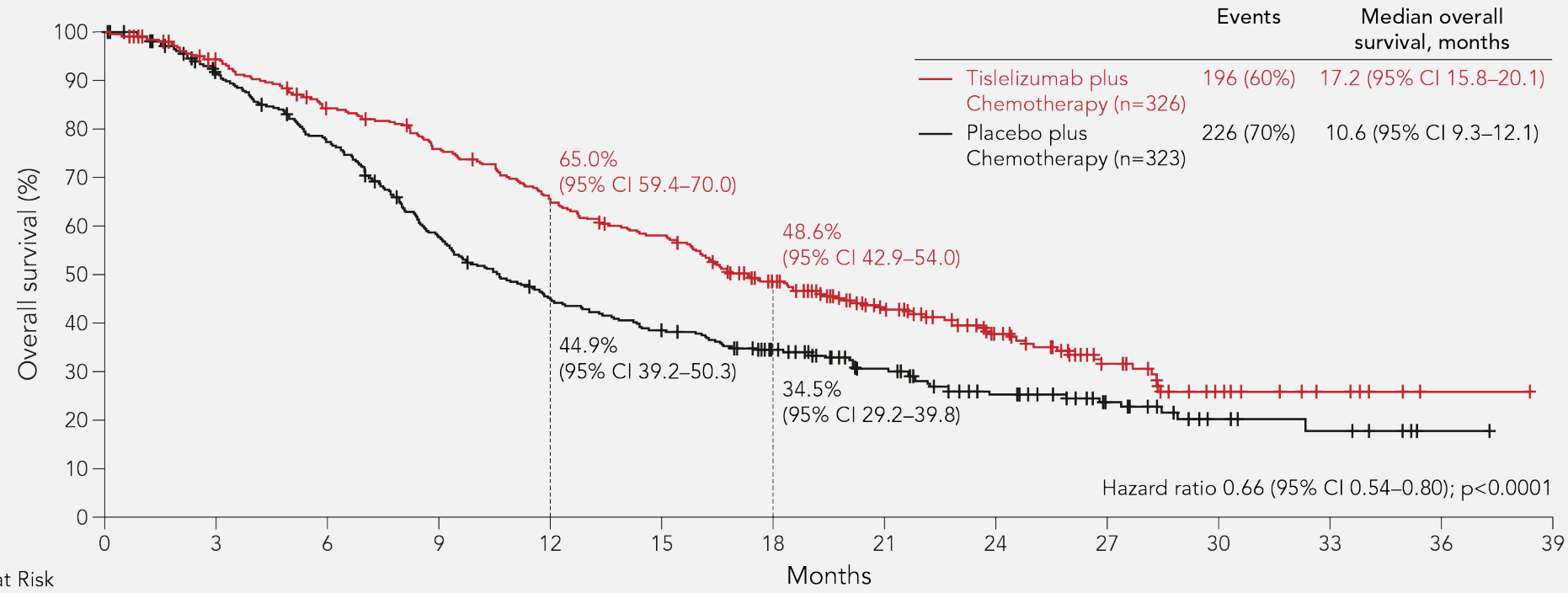
	Tislelizumab + Chemotherapy (n=326)	Placebo + Chemotherapy (n=323)
Median age (IQR), years	64.0 (59.0-68.0)	65.0 (58.0-70.0)
Male, n (%)	282 (87)	281 (87)
Region, n (%)		
Asia[a]	243 (75)	243 (75)
Europe	79 (24)	77 (24)
North America	1 (<1)	1 (<1)
Oceania	3 (1)	2 (1)
Race, n (%)		
Asian	243 (75)	243 (75)
White	79 (24)	76 (24)
ECOG PS, n (%)		
0	109 (33)	104 (32)
1	217 (67)	219 (68)

	Tislelizumab + Chemotherapy (n=326)	Placebo + Chemotherapy (n=323)
Histologic type, n (%)		
Squamous cell carcinoma	325 (>99)	323 (100)
Other[b]	1 (<1)	0
Disease status at baseline, n (%)		
Metastatic	279 (86)	282 (87)
Locally advanced	47 (14)	41 (13)
Prior definitive therapy, n (%)		
Definitive surgery[c]	107 (33)	107 (33)
Definitive RT[d]	40 (12)	40 (12)
Definitive surgery & RT[e]	4 (1)	6 (2)
No definitive therapy	183 (56)	182 (56)
PD-L1 expression[f], n (%)		
TAP score ≥ 10%	116 (36)	107 (33)
TAP score < 10%	151 (46)	168 (52)
Unknown[g]	59 (18)	48 (15)

Data cutoff: February 28, 2022
Data are median (IQR) or n (%). [a]Including 33 patients from Japan per group; [b]One patient had neuroendocrine tumour histology; [c]Definitive surgery included surgery with or without adjuvant or neoadjuvant treatment; four patients in the tislelizumab arm and six in the placebo arm who had received both definitive surgery and radiotherapy were included in this category; [d]Definitive radiotherapy included radiotherapy with or without chemotherapy; four patients in the tislelizumab arm and six in the placebo arm who had received both definitive surgery and radiotherapy were included in this category; [e]Patients who received previous definitive surgery and radiotherapy were included in the previous definitive therapy subgroup for all subgroup analyses; [f]PD-L1 expression by combined positive score and tumor cell score is provided in the appendix of the publication; [g]Unknown refers to patients without sample collection, with nonevaluable samples, or with scored unqualified samples (patients with scored unqualified samples were identified and reclassified as unknown after database lock
ECOG PS=Eastern Cooperative Oncology Group performance status, IQR=interquartile range, PD-L1=programmed death-ligand 1, RT=radiotherapy, TAP=tumor area positivity.
Xu J et al. *Lancet Oncol*. 2023;24(5):483-495.

Primary Endpoint: Overall Survival (ITT Population)

At the prespecified interim analysis, the primary endpoint was met, with a statistically significant and clinically meaningful improvement in OS



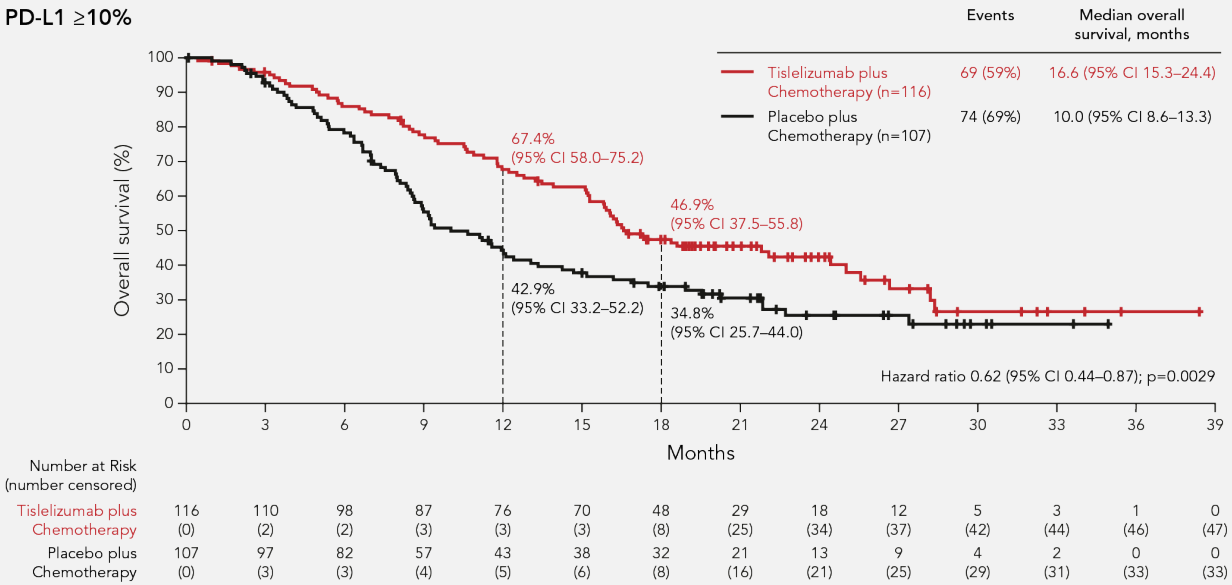
Number at Risk (number censored)	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Tislelizumab plus Chemotherapy	326 (0)	300 (8)	264 (12)	236 (14)	201 (15)	178 (17)	136 (30)	90 (62)	58 (85)	34 (101)	14 (116)	6 (124)	1 (129)	0 (130)
Placebo plus Chemotherapy	323 (0)	285 (11)	239 (13)	176 (16)	135 (18)	115 (19)	91 (31)	63 (50)	40 (63)	25 (76)	11 (87)	7 (90)	1 (96)	0 (97)

Data cutoff: February 28, 2022.
CI=confidence interval, HR=hazard ratio, OS=overall survival.
Xu J et al. *Lancet Oncol*. 2023; 24(5):483-495.

Overall Survival by Centrally Assessed Baseline PD-L1 Expression Status

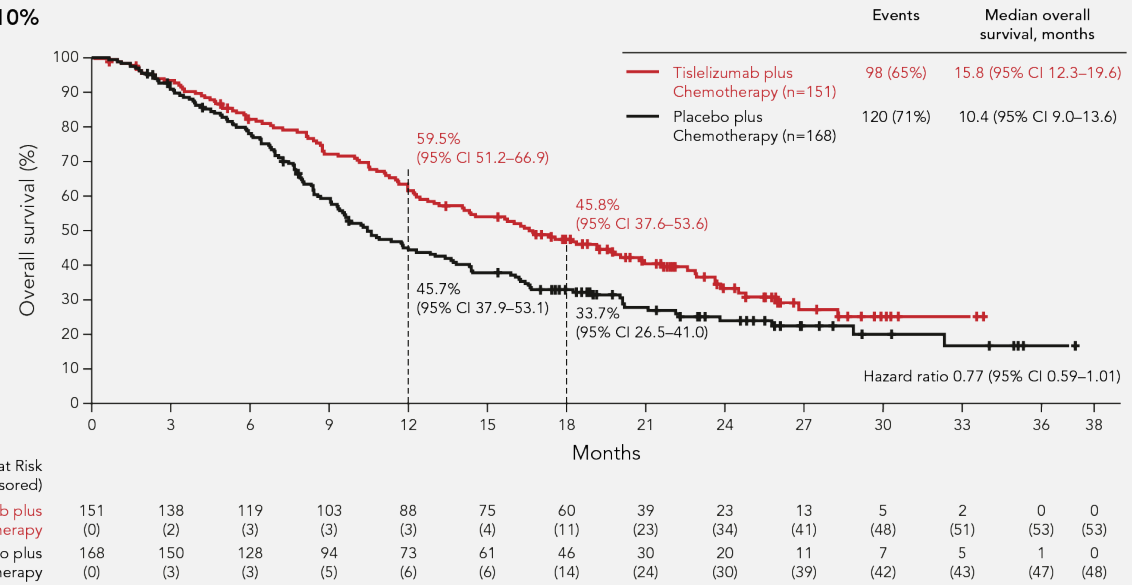
OS benefit with tislelizumab plus chemotherapy was observed regardless of baseline PD-L1 expression status

PD-L1 ≥10%



Number at Risk (number censored)														
Tislelizumab plus Chemotherapy	116 (0)	110 (2)	98 (2)	87 (3)	76 (3)	70 (3)	48 (8)	29 (25)	18 (34)	12 (37)	5 (42)	3 (44)	1 (46)	0 (47)
Placebo plus Chemotherapy	107 (0)	97 (3)	82 (3)	57 (4)	43 (5)	38 (6)	32 (8)	21 (16)	13 (21)	9 (25)	4 (29)	2 (31)	0 (33)	0 (33)

PD-L1 <10%

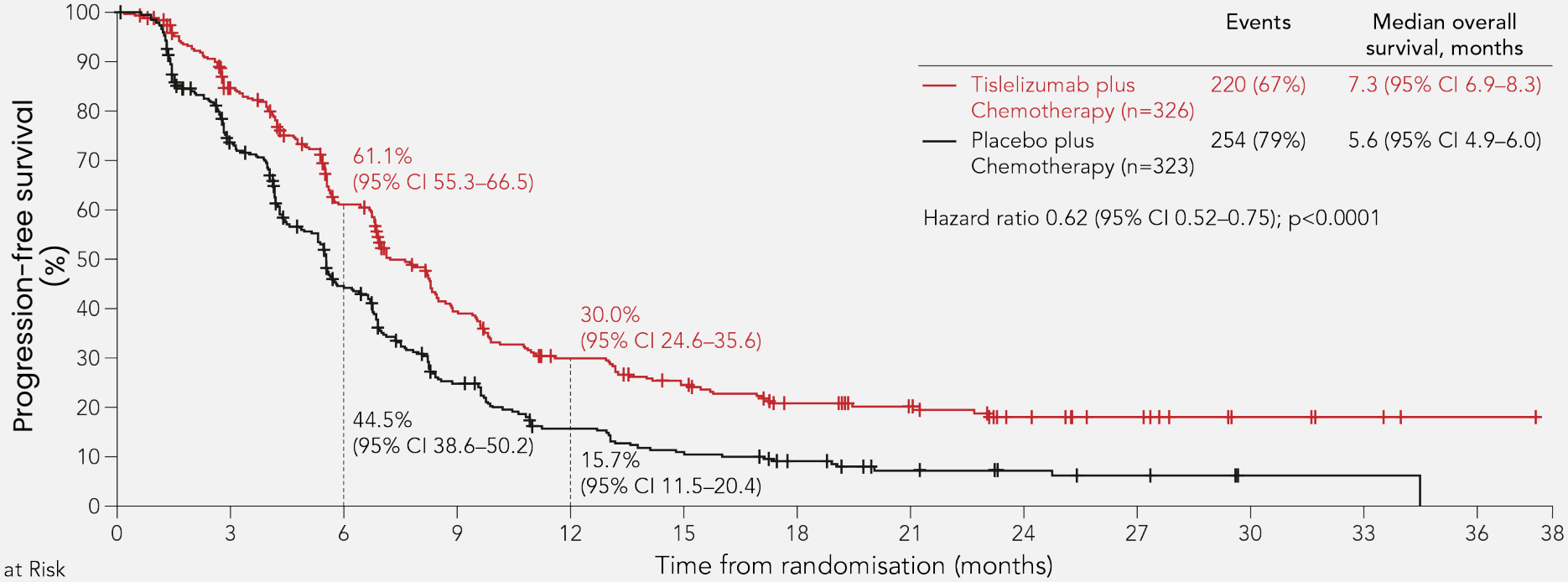


Number at Risk (number censored)														
Tislelizumab plus Chemotherapy	151 (0)	138 (2)	119 (3)	103 (3)	88 (3)	75 (4)	60 (11)	39 (23)	23 (34)	13 (41)	5 (48)	2 (51)	0 (53)	0 (53)
Placebo plus Chemotherapy	168 (0)	150 (3)	128 (3)	94 (5)	73 (6)	61 (6)	46 (14)	30 (24)	20 (30)	11 (39)	7 (42)	5 (43)	1 (47)	0 (48)

Data cutoff: February 28, 2022.
PD-L1 expression was determined centrally by PD-L1 score (defined as the total percentage of the tumor area [tumor and any desmoplastic stroma] covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated) using the VENTANA PD-L1 (SP263) assay. HR was based on Cox regression model including treatment as covariate and using the predefined strata (pooled geographic region [Asia vs Rest of World], prior definitive therapy and investigator-chosen chemotherapy option).
CI=confidence interval, HR=hazard ratio, OS=overall survival, PD-L1=programmed death-ligand 1.
Xu J et al. *Lancet Oncol*. 2023; 24(5):483-495.

PFS in All Randomized Patients (Secondary Endpoint)

PFS was significantly improved with tislelizumab plus chemotherapy



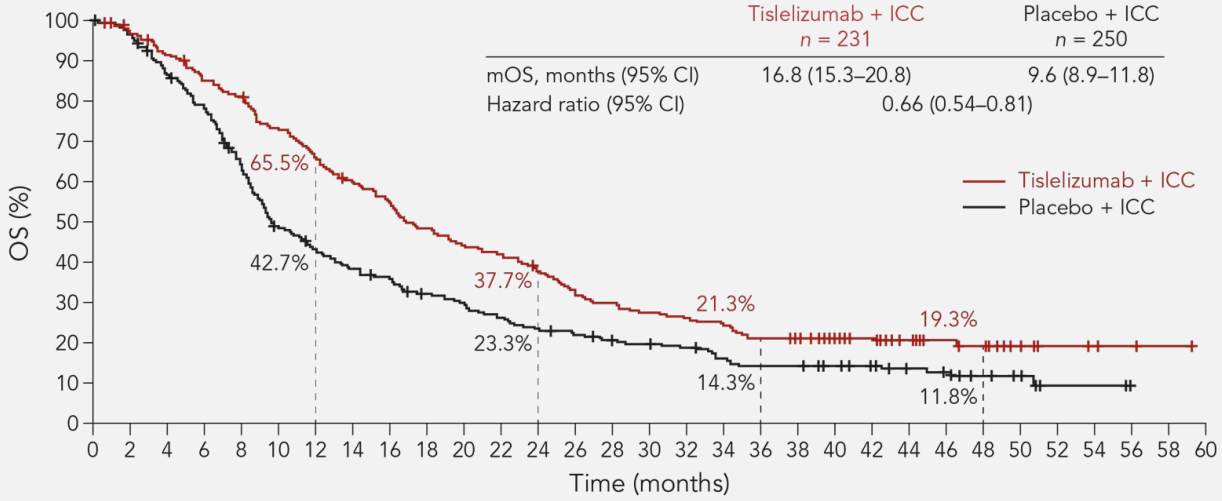
Number at Risk (number censored)														
Tislelizumab plus Chemotherapy	326 (0)	249 (29)	168 (44)	101 (54)	73 (58)	59 (61)	38 (72)	32 (77)	18 (88)	12 (94)	5 (101)	3 (103)	1 (105)	0 (106)
Placebo plus Chemotherapy	323 (0)	212 (31)	119 (43)	62 (49)	36 (53)	25 (53)	17 (57)	10 (61)	4 (64)	4 (66)	1 (69)	1 (69)	0 (69)	0 (69)

Data cutoff: February 28, 2022
CI=confidence interval, HR=hazard ratio, PFS=progression-free survival.
Xu J et al. *Lancet Oncol*. 2023;24(5):483-495.

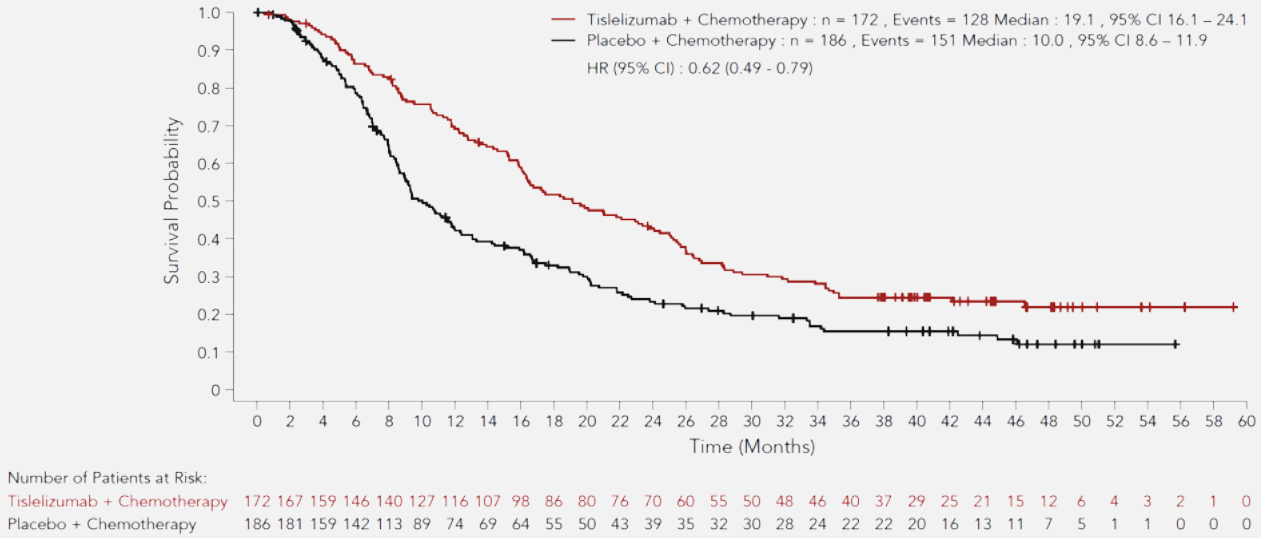
Overall Survival by PD-L1 TAP Scores ≥1% and ≥5%

OS was improved with tislelizumab plus chemotherapy in patients with PD-L1 TAP scores of ≥1% and ≥5%

Kaplan-Meier plot of OS in patients with PD-L1 TAP score ≥1%[1]



Kaplan-Meier plot of OS in patients with PD-L1 TAP score ≥5%[2]



Data cut-off: November 24, 2023.
Hazard ratio was based on a stratified Cox regression model.
CI=confidence interval, ECOG PS=Eastern Cooperative Oncology Group performance status, HR=hazard ratio, ICC=investigator-chosen chemotherapy, OS=overall survival, PD-L1=programmed death-ligand 1, TAP=tumor area positivity.
1. Xu J et al. *Adv Ther*. 2025; https://doi.org/10.1007/s12325-025-03115-9; 2. Tislelizumab Summary of Product Characteristics. 2025.

Summary of Antitumor Activity (Investigator-Assessed)

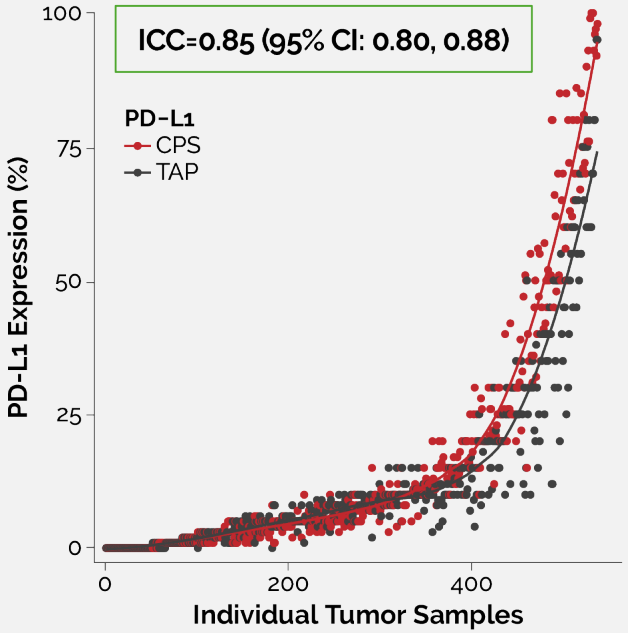
Clinically meaningful improvements in PFS, DoR, and ORR with tislelizumab plus ICC versus placebo plus ICC were maintained relative to the interim analysis

	Tislelizumab + Chemotherapy (n=326)	Placebo + Chemotherapy (n=323)
Median PFS (95% CI), months[a]	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	0.60 (0.50, 0.72)	
36-month PFS rate (95% CI), %[a]	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)
ORR (95% CI), %[a]	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
Median DoR (95% CI), months[a]	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
36-month DoR rate (95% CI), %[a,b]	17.7 (12.3, 24.0)	5.0 (1.5, 11.8)

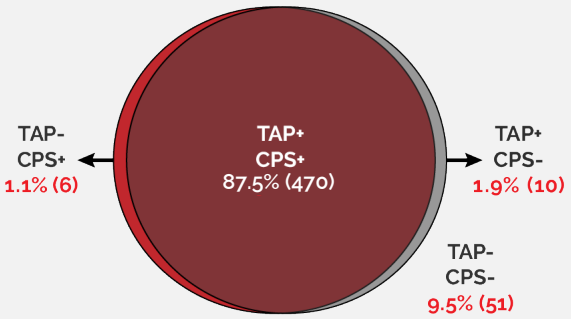
Data cut-off: November 24, 2023.
The ITT Analysis Set includes all randomized patients. [a]Per investigator. [b]TIS plus ICC: n=207; PBO plus ICC: n=137.
CI=confidence interval, DoR=duration of response, HR=hazard ratio, ICC=investigator-chosen chemotherapy, ITT=intent-to-treat, ORR=objective response rate, PBO=placebo, PFS=progression-free survival, TIS=tislelizumab.
Yoon HH et al. Poster Presentation at ASCO 2024;abstract 4032.

Concordance and Correlation Between TAP and CPS

- Good correlation was observed between TAP score and CPS, as shown by the interclass correlation coefficient (ICC=0.85 [0.80, 0.88])
- TAP score and CPS showed substantial concordance at multiple cutoffs in terms of OPA and Cohen's Kappa (OPA [95% CI]: 97% [96, 98], 85% [82, 88], 89% [87, 92] at 1%, 5%, and 10% thresholds of each score, respectively)

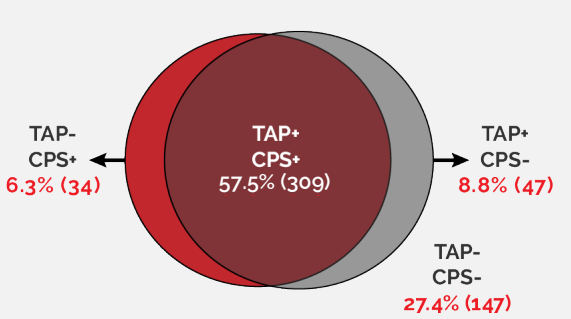


TAP Score 1% vs CPS 1



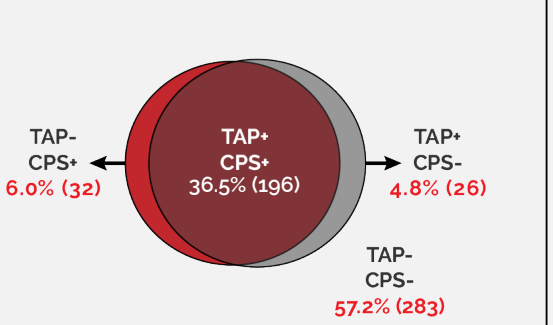
	n/N	Agreement
PPA, % (95% CI)	470/480	98 (97, 99)
NPA, % (95% CI)	51/57	89 (81, 96)
OPA, % (95% CI)	521/537	**97 (96, 98)**
Cohen's Kappa (95% CI)	0.85 (0.77, 0.92)	

TAP Score 5% vs CPS 5



	n/N	Agreement
PPA, % (95% CI)	309/343	90 (87, 93)
NPA, % (95% CI)	147/194	76 (70, 82)
OPA, % (95% CI)	456/537	**85 (82, 88)**
Cohen's Kappa (95% CI)	0.67 (0.60, 0.73)	

TAP Score 10% vs CPS 10



	n/N	Agreement
PPA, % (95% CI)	196/228	86 (82, 90)
NPA, % (95% CI)	283/309	92 (88, 94)
OPA, % (95% CI)	479/537	**89 (87, 92)**
Cohen's Kappa (95% CI)	0.78 (0.72, 0.83)	

Strength of Reliability (ICC)

Poor (<0.50)	Moderate (0.50-0.75)	Good (0.50-0.90)	Moderate (≥0.90)

Strength of Agreement (Kappa)

Slight (0.01-0.20)	Fair (0.21-0.40)	Moderate (0.41-0.60)	Substantial (0.61-0.80)	Almost Perfect (0.81-1.0)

CI=confidence interval, CPS=combined positive score, ESCC=esophageal squamous cell carcinoma, NPA=negative percent agreement, OPA=overall percent agreement, PD-L1=programmed death-ligand 1, PPA=positive percent agreement, TAP=Tumor Area Positivity.

Raymond E et al. Mini Oral Presentation at ESMO-GI 2024. Moehler M, et al. Mod Pathol. 2025 Sep;38(9):100793.

Safety Summary: Overall Population

- The most common Grade ≥3 TRAEs (tislelizumab plus ICC vs placebo plus ICC) were decreased neutrophil count (30.9% vs 32.7%), anemia (14.8% vs 12.8%), and decreased white blood cell count (10.8% vs 15.6%)

	Tislelizumab + Chemotherapy (n=324)	Placebo + Chemotherapy (n=321)
Patients with ≥1 TRAE, n (%)	313 (96.6)	309 (96.3)
Grade ≥3	217 (67.0)	207 (64.5)
Serious	97 (29.9)	63 (19.6)
Leading to death	6 (1.9)	4 (1.2)
Patients with ≥1 TEAE leading to any treatment discontinuation, n (%)	104 (32.1)	71 (22.1)
Patients with ≥1 TEAE leading to any dose modification, n (%)	247 (76.2)	229 (71.3)

Data cut-off: November 24, 2023.
The Safety Analysis Set includes all enrolled patients who received ≥1 dose of study drug. Adverse event grades were evaluated 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.
ICC=investigator-chosen chemotherapy, PBO=placebo, TEAE=treatment emergent adverse event, TRAE=treatment-related adverse event.
Yoon HH et al. Poster Presentation at ASCO 2024;abstract 4032.

Safety Summary: PD-L1 ≥1% Analysis

- The most common Grade ≥3 TRAEs (tislelizumab plus ICC vs placebo plus ICC) were decreased neutrophil count (30.9% vs 31.0%), anemia (12.2% vs 12.9%), and decreased white blood cell count (11.3% vs 15.7%)

	Tislelizumab + Chemotherapy (n=230)	Placebo + Chemotherapy (n=248)
Patients with ≥1 TEAE, n (%)	229 (99.6)	248 (100)
Grade ≥3	180 (78.3)	192 (77.4)
Serious	107 (46.5)	97 (39.1)
Patients with ≥1 TRAE, n (%)	223 (97.0)	240 (97.2)
Grade ≥3	154 (67.0)	160 (64.5)
Leading to death	5 (2.2)	4 (1.6)
Patients with ≥1 TEAE leading to any treatment discontinuation, n (%)	81 (35.2)	55 (22.2)
Patients with ≥1 TEAE leading to any dose modification, n (%)	173 (75.2)	178 (71.8)
Patients with ≥1 immune-mediated TEAE, n (%)	89 (38.7)	50 (20.2)

Data cut-off: February 28, 2022.
The Safety Analysis Set includes all enrolled patients who received ≥1 dose of study drug. Adverse event grades were evaluated 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.
ICC=investigator-chosen chemotherapy, PBO=placebo, TEAE=treatment emergent adverse event, TRAE=treatment-related adverse event.
Xu J et al. *Adv Ther*. 2025; https://doi.org/10.1007/s12325-025-03115-9.