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TISLELIZUMAB + CHEMOTHERAPY VS PLACEBO + CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED ESOPHAGEAL SQUAMOUS CELL CARCINOMA: RATIONALE-306 SUBGROUP ANALYSIS

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DECLARATION OF INTERESTS

Prof Eric Van Cutsem has participated in advisory boards for AbbVie, Agenus, ALX, Amgen, Arcus Biosciences, Astellas, AstraZeneca, Bayer, BeOne Medicines, Bexon Clinical, BioNtech, Boehringer Ingelheim, Bristol Myers Squibb, Canfour, Daiichi Sankyo, Debiopharm, Elmedix, Eisai, Galapagos, GSK, Hookipa Pharma, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Servier, Simcere, Takeda, Taiho Pharmaceutical, and Terumo.

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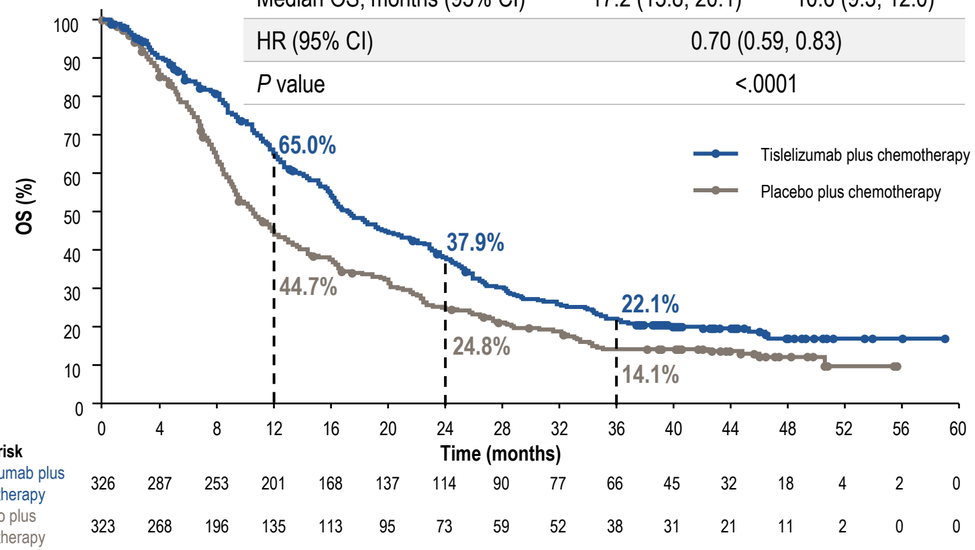
INTRODUCTION

- After a minimum 3-year follow-up of RATIONALE-306 (NCT03783442), tislelizumab plus chemotherapy demonstrated clinically meaningful and sustained improvement in OS compared with placebo plus chemotherapy[1]
- Tislelizumab in combination with platinum-based chemotherapy has received regulatory approvals for first-line treatment of advanced/metastatic ESCC – from the EMA for patients with tumor PD-L1 TAP score ≥5% and from the US FDA for patients with tumor PD-L1 expression ≥1[2,3]
- Here, we report a post-hoc subgroup analysis of patients with locally advanced ESCC (13.6%; n=88/649) and those with both locally advanced ESCC and tumor PD-L1 TAP score ≥5% (51.1%; n=45/88)
  - Patients with non-metastatic disease and deemed unfit for surgery or definitive chemoradiation were retrospectively selected and included in this analysis

OS in All Patients[1]

	Tislelizumab Plus Chemotherapy (n=326)	Placebo Plus Chemotherapy (n=323)
Events	250	264
Median OS, months (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.0)
HR (95% CI)	0.70 (0.59, 0.83)	
P value	<.0001	



Data cutoff: November 24, 2023.

1. Yoon HH, et al. *J Clin Oncol* 2024;42(Suppl 16):4032. 2. European Medicines Agency. Tevimbra 100 mg concentrate for solution for infusion. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/tevimbra-epar-product-information_en.pdf. Accessed: May 26, 2025. 3. US Food and Drug Administration. TEVIMBRA™ (tislelizumab-jsgr) injection, for intravenous use. Prescribing information. 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761417s000lbl.pdf. Accessed: May 26, 2025.

Abbreviations: CI, confidence interval; EMA, European Medicines Agency; ESCC, esophageal squamous cell carcinoma; FDA, Food and Drug Administration; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; US, United States.

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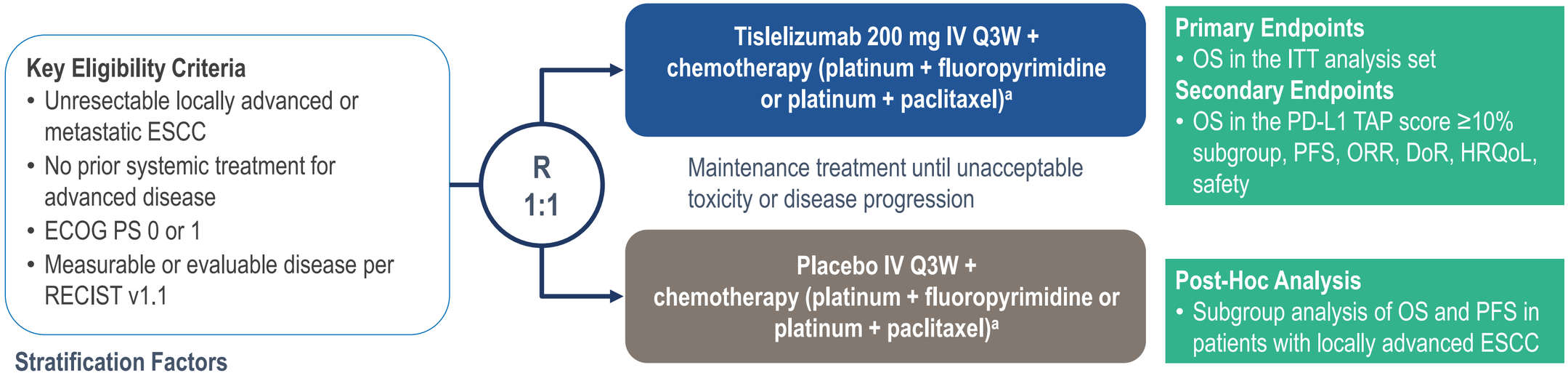
METHODS

Study Design: Randomized, Double-Blind, Global Phase 3 Study



Stratification Factors

- Geographic region (Asia [excluding Japan] vs Japan vs rest of world)
- Prior definitive therapy (yes vs no)
- Investigator-chosen chemotherapy (platinum + fluoropyrimidine vs platinum + paclitaxel)

[a]The platinum agent may be cisplatin 60-80 mg/m^2 on day 1 or oxaliplatin 130 mg/m^2 on day 1 (except in China, Taiwan, Japan, and countries where oxaliplatin substitution is not permitted) according to site or investigator preference, or standard practice as determined prior to randomization. The fluoropyrimidine may be 5-fluorouracil 750-800 mg/m^2 on days 1-5 or capecitabine 1000 mg/m^2 on days 1-14, twice a day. Paclitaxel was administered at a dose of 175 mg/m^2 on day 1.

Abbreviations: DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HRQoL, health-related quality of life; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, once every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumours; TAP, Tumor Area Positivity.

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RESULTS: BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

- The baseline demographic and disease characteristics in the locally advanced ESCC subgroup were consistent with that of the ITT population

	Locally Advanced ESCC Subgroup (N=88)		ITT Population (N=649)	
	Tislelizumab Plus Chemotherapy (n=49)	Placebo Plus Chemotherapy (n=39)	Tislelizumab Plus Chemotherapy (n=326)	Placebo Plus Chemotherapy (n=323)
Median age, years (range)	65.0 (51-76)	68.0 (50-79)	64.0 (26-84)	65.0 (40-84)
Age ≥65, n (%)	25 (51.0)	24 (61.5)	150 (46.0)	162 (50.2)
Male, n (%)	42 (85.7)	33 (84.6)	282 (86.5)	281 (87.0)
Region, n (%)				
Asia	31 (63.3)	20 (51.3)	243 (74.5)	243 (75.2)
Rest of the world	18 (36.7)	19 (48.7)	83 (25.5)	80 (24.8)
ECOG performance status, n (%)				
0	18 (36.7)	16 (41.0)	109 (33.4)	104 (32.2)
1	31 (63.3)	23 (59.0)	217 (66.6)	219 (67.8)
PD-L1 expression, n (%)				
TAP score ≥10%	16 (32.7)	11 (28.2)	116 (35.6)	107 (33.1)
TAP score <10%	19 (38.8)	23 (59.0)	151 (46.3)	168 (52.0)
Unknown	14 (28.6)	5 (12.8)	59 (18.1)	48 (14.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

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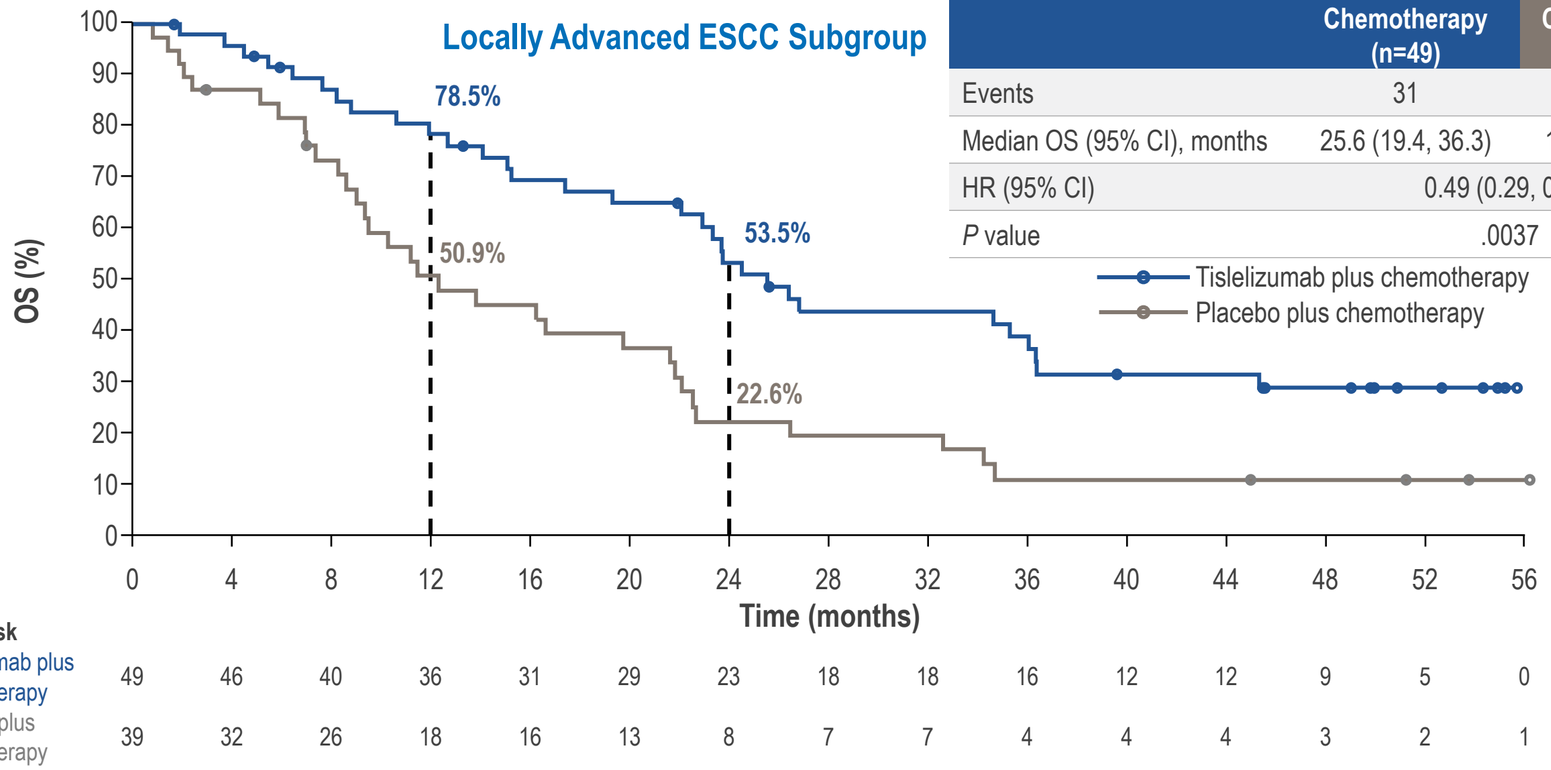
RESULTS: OS IN THE LOCALLY ADVANCED ESCC SUBGROUP

- OS was improved with tislelizumab plus chemotherapy vs placebo plus chemotherapy in all patients with locally advanced ESCC



	Tislelizumab Plus Chemotherapy (n=49)	Placebo Plus Chemotherapy (n=39)
Events	31	32
Median OS (95% CI), months	25.6 (19.4, 36.3)	12.3 (9.0, 21.7)
HR (95% CI)	0.49 (0.29, 0.84)	
P value	.0037	

Data cutoff: August 22, 2024. **Abbreviations:** CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; OS, overall survival.

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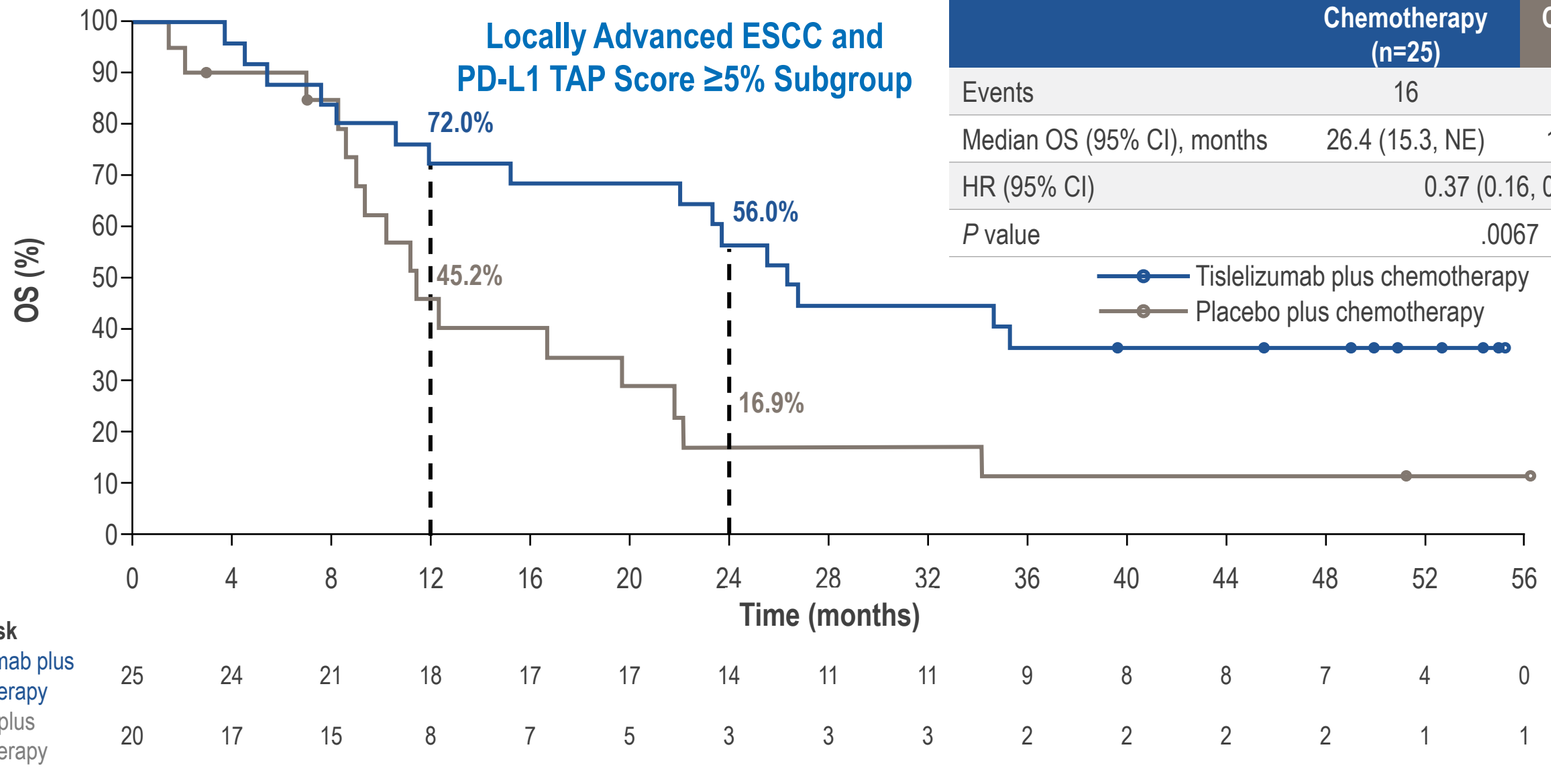
RESULTS: OS IN THE LOCALLY ADVANCED ESCC AND PD-L1 TAP SCORE ≥5% SUBGROUP

- OS was improved with tislelizumab plus chemotherapy vs placebo plus chemotherapy in all patients with locally advanced ESCC and a tumor PD-L1 TAP score ≥5%



	Tislelizumab Plus Chemotherapy (n=25)	Placebo Plus Chemotherapy (n=20)
Events	16	16
Median OS (95% CI), months	26.4 (15.3, NE)	11.5 (8.6, 19.8)
HR (95% CI)	0.37 (0.16, 0.83)	
P value	.0067	

Data cutoff: August 22, 2024. **Abbreviations:** CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

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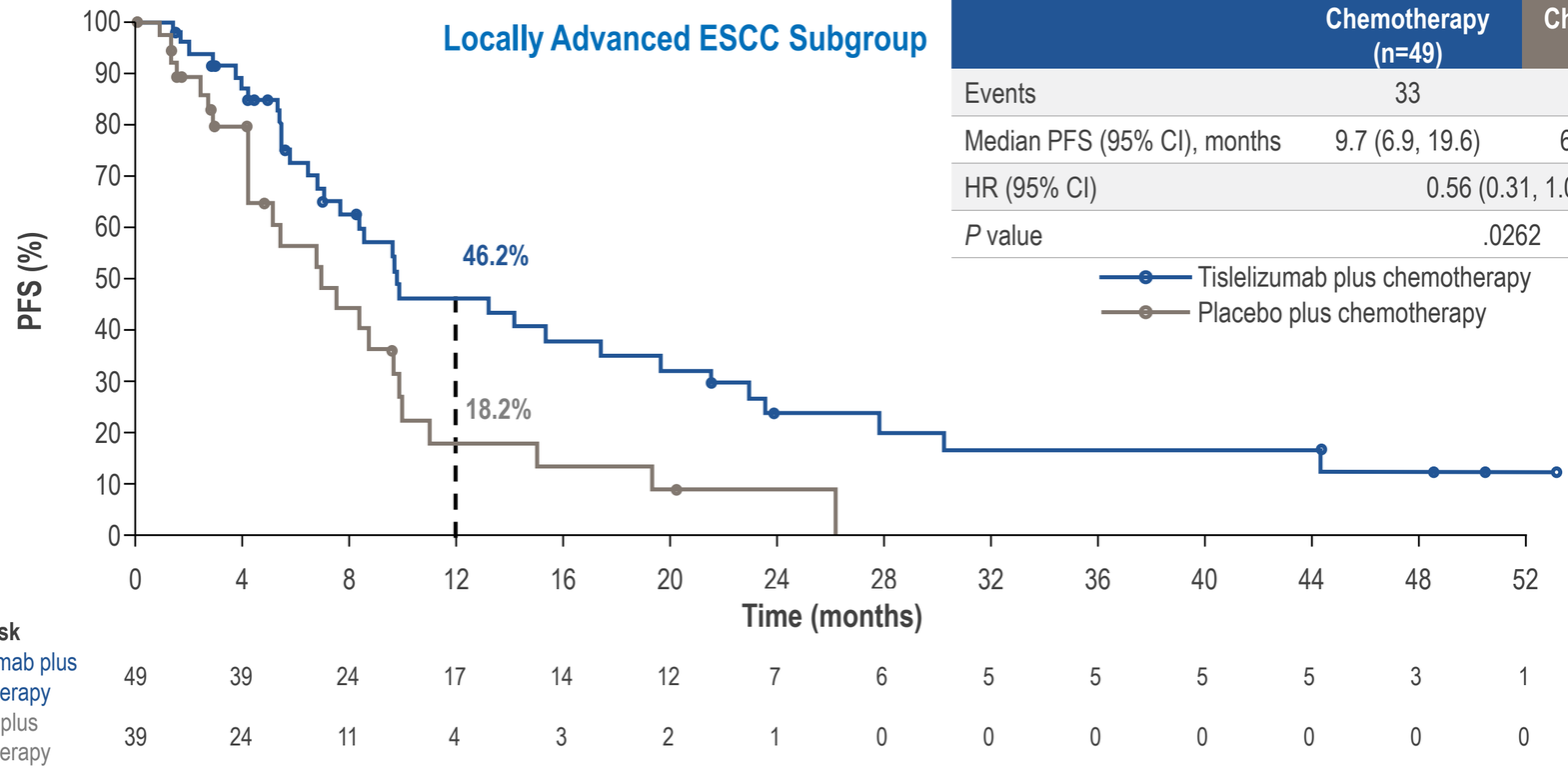
RESULTS: PFS BY INVESTIGATOR IN THE LOCALLY ADVANCED ESCC SUBGROUP

- PFS was prolonged with tislelizumab plus chemotherapy vs placebo plus chemotherapy in patients with locally advanced ESCC



	Tislelizumab Plus Chemotherapy (n=49)	Placebo Plus Chemotherapy (n=39)
Events	33	25
Median PFS (95% CI), months	9.7 (6.9, 19.6)	6.9 (4.2, 9.7)
HR (95% CI)	0.56 (0.31, 1.01)	
P value	.0262	

Tislelizumab plus chemotherapy
Placebo plus chemotherapy

Data cutoff: August 22, 2024. **Abbreviations:** CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; PFS, progression-free survival.

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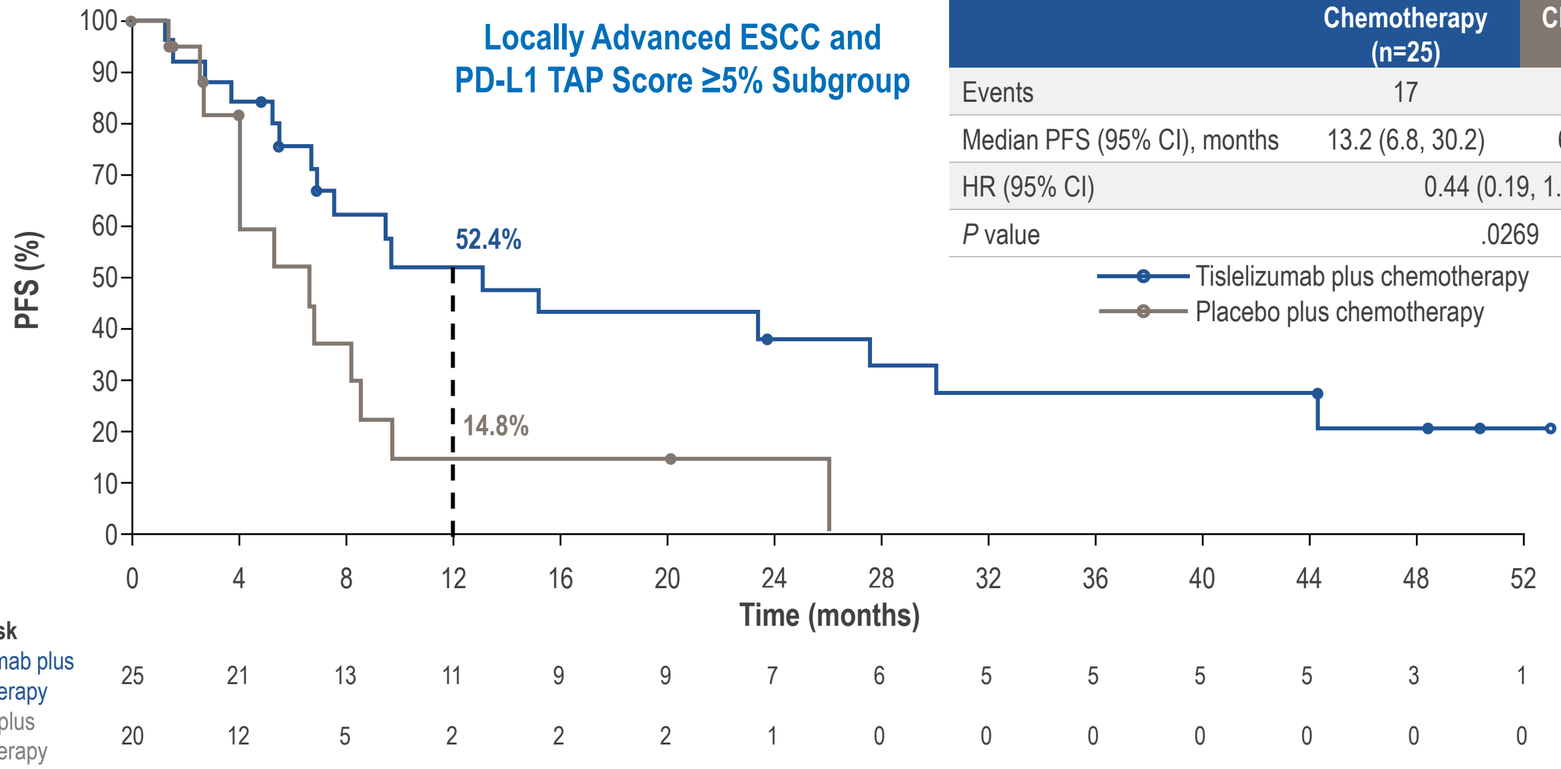
RESULTS: PFS BY INVESTIGATOR IN THE LOCALLY ADVANCED ESCC AND PD-L1 TAP SCORE ≥5% SUBGROUP

- PFS was prolonged with tislelizumab plus chemotherapy vs placebo plus chemotherapy in patients with locally advanced ESCC and a tumor PD-L1 TAP score ≥5%



	Tislelizumab Plus Chemotherapy (n=25)	Placebo Plus Chemotherapy (n=20)
Events	17	13
Median PFS (95% CI), months	13.2 (6.8, 30.2)	6.7 (4.2, 8.6)
HR (95% CI)	0.44 (0.19, 1.02)	
P value	.0269	

Tislelizumab plus chemotherapy
Placebo plus chemotherapy

Data cutoff: August 22, 2024. **Abbreviations:** CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, Tumor Area Positivity.

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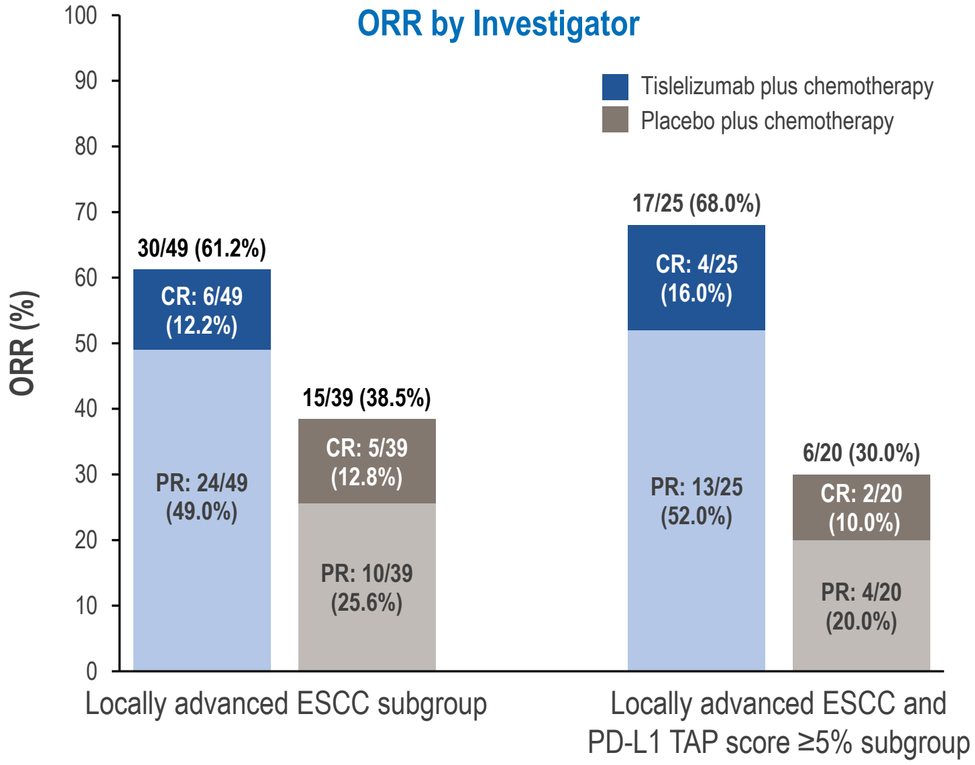
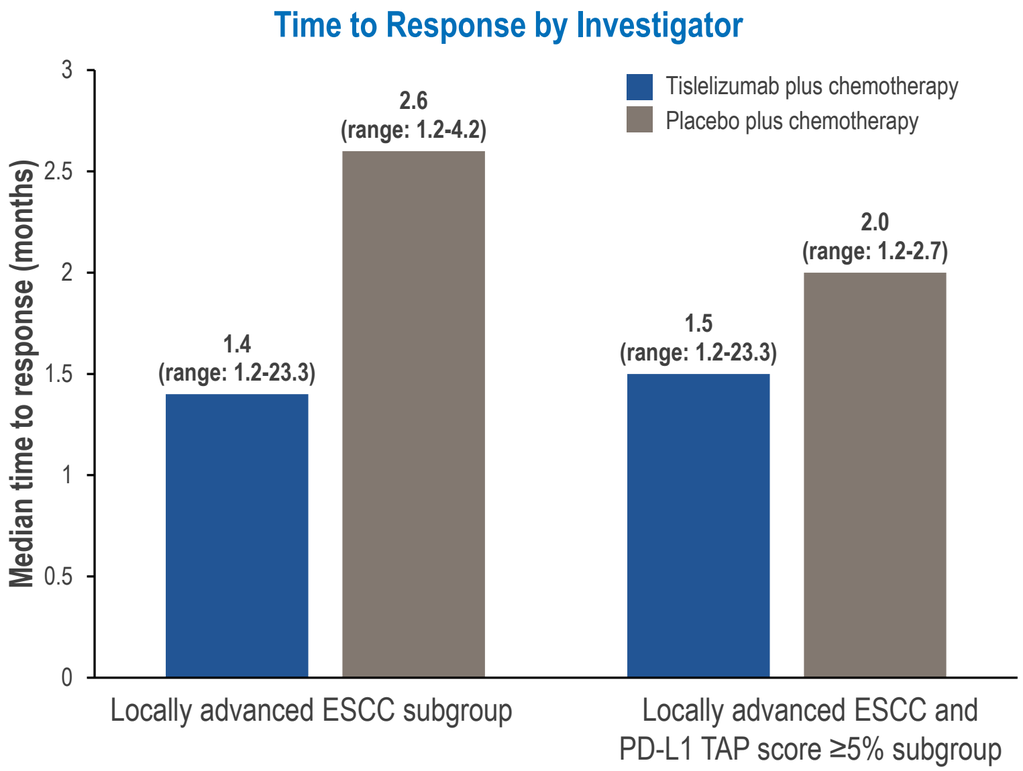
RESULTS: TUMOR RESPONSE BY INVESTIGATOR

- Tislelizumab plus chemotherapy improved ORR and shortened time to response vs placebo plus chemotherapy in locally advanced ESCC, including in the PD-L1 TAP score ≥5% subgroup





Data cutoff: August 22, 2024. **Abbreviations:** CR, complete response; ESCC, esophageal squamous cell carcinoma; ORR, objective response rate; PD-L1, programmed death-ligand 1; PR, partial response; TAP, Tumor Area Positivity.

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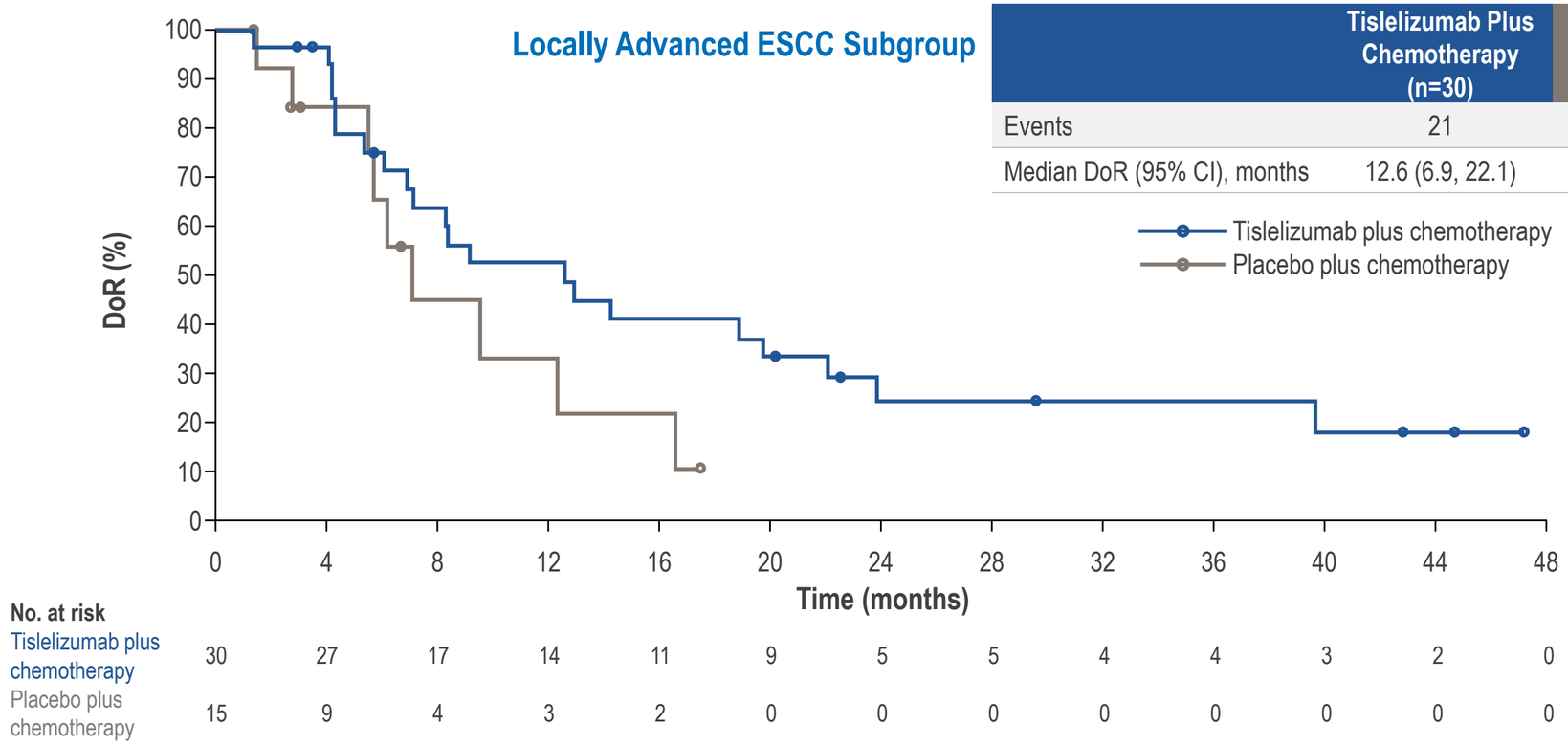
RESULTS: DOR BY INVESTIGATOR IN THE LOCALLY ADVANCED ESCC SUBGROUP

- Tislelizumab plus chemotherapy vs placebo plus chemotherapy produced durable responses in patients with locally advanced ESCC



	Tislelizumab Plus Chemotherapy (n=30)	Placebo Plus Chemotherapy (n=15)
Events	21	9
Median DoR (95% CI), months	12.6 (6.9, 22.1)	7.1 (5.5, 16.6)

Data cutoff: August 22, 2024. **Abbreviations:** CI, confidence interval; DoR, duration of response; ESCC, esophageal squamous cell carcinoma.

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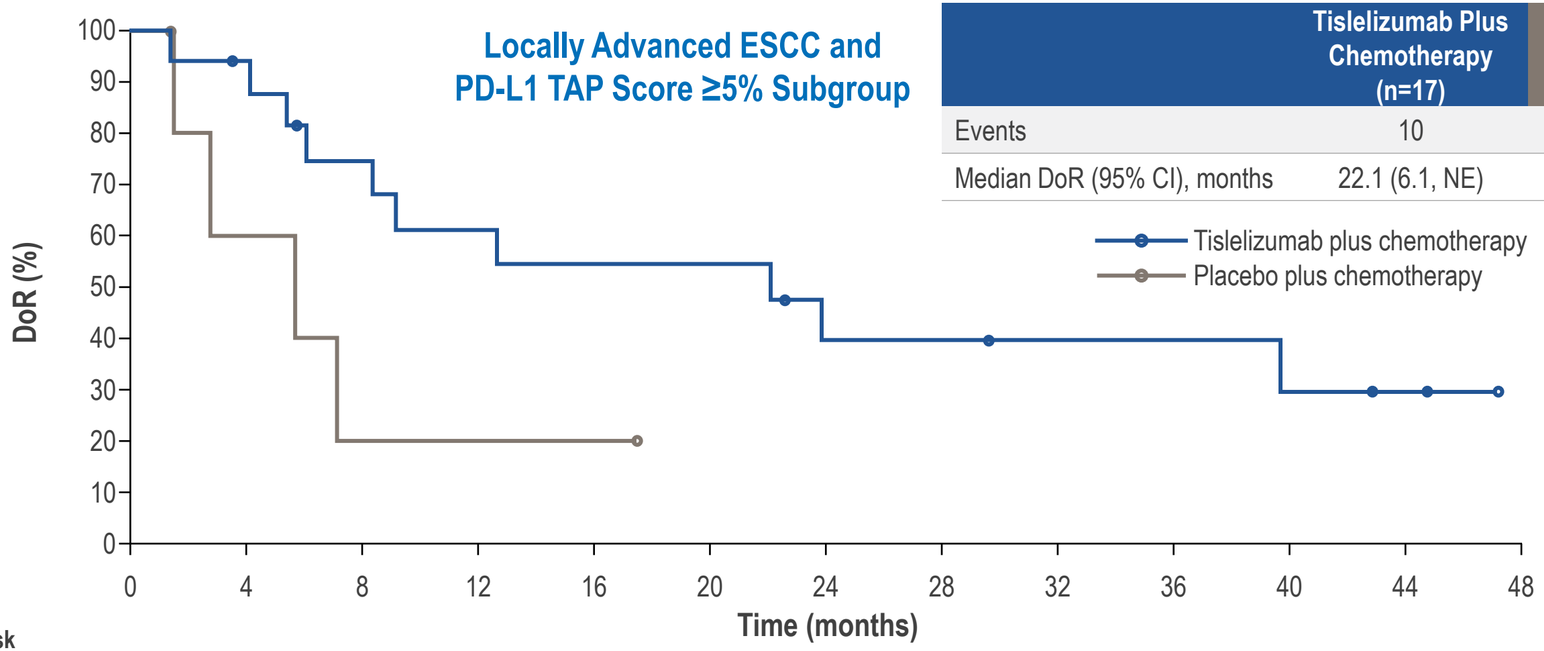
RESULTS: DOR BY INVESTIGATOR IN THE LOCALLY ADVANCED ESCC AND PD-L1 TAP SCORE ≥5% SUBGROUP

- Tislelizumab plus chemotherapy vs placebo plus chemotherapy produced durable responses in patients with locally advanced ESCC and a tumor PD-L1 TAP score ≥5%



	Tislelizumab Plus Chemotherapy (n=17)	Placebo Plus Chemotherapy (n=6)
Events	10	4
Median DoR (95% CI), months	22.1 (6.1, NE)	5.7 (1.5, NE)

Data cutoff: August 22, 2024. **Abbreviations:** CI, confidence interval; DoR, duration of response; ESCC, esophageal squamous cell carcinoma; NE, not estimable; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

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RESULTS: SAFETY/TOLERABILITY

- The safety/tolerability profile of tislelizumab plus chemotherapy in the locally advanced ESCC subgroup was consistent with that of the ITT population, with no new safety signals
- The most common grade ≥3 TRAE in the locally advanced ESCC subgroup was decreased neutrophil count in both the tislelizumab plus chemotherapy and placebo plus chemotherapy arms (26.5% and 10.3%), consistent with the ITT population (30.9% and 32.7%)

	Locally Advanced ESCC Subgroup[a] (N=88)		ITT Population[b] (N=645)	
n (%)	Tislelizumab Plus Chemotherapy (n=49)	Placebo Plus Chemotherapy (n=39)	Tislelizumab Plus Chemotherapy (n=324)	Placebo Plus Chemotherapy (n=321)
Patients with ≥1 TEAE	49 (100.0)	38 (97.4)	323 (99.7)	319 (99.4)
Grade ≥3	32 (65.3)	29 (74.4)	254 (78.4)	249 (77.6)
Serious	22 (44.9)	20 (51.3)	160 (49.4)	128 (39.9)
Leading to death	3 (6.1)	2 (5.1)	16 (4.9)	17 (5.3)
Patients with ≥1 TRAE	49 (100.0)	36 (92.3)	313 (96.6)	309 (96.3)
Grade ≥3	29 (59.2)	23 (59.0)	217 (67.0)	207 (64.5)
Serious	14 (28.6)	8 (20.5)	97 (29.9)	63 (19.6)
Leading to death, related to tislelizumab/placebo	1 (2.0)	0 (0.0)	5 (1.5)	2 (0.6)
TEAEs leading to any treatment discontinuation	20 (40.8)	14 (35.9)	104 (32.1)	71 (22.1)
TEAEs leading to discontinuation of tislelizumab/placebo	10 (20.4)	4 (10.3)	43 (13.3)	21 (6.5)
Subsequent anticancer therapy[c]	21 (42.9)	20 (51.3)	168 (51.5)	187 (57.9)
Subsequent radiation therapy[c]	9 (18.4)	12 (30.8)	66 (20.2)[a]	86 (26.6)[a]

Evaluated in the safety analysis set, except where indicated. [a]Data cutoff: August 22, 2024. [b]Data cutoff: November 24, 2023. [c]ITT analysis set.
Abbreviations: ESCC, esophageal squamous cell carcinoma; ITT, intent-to-treat; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

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CONCLUSIONS

- In this subgroup analysis of patients with locally advanced ESCC, first-line tislelizumab plus chemotherapy showed substantial and clinically meaningful improvements in efficacy, consistent with the primary and 3-year long-term follow-up analyses
  - Similar improvements in efficacy were observed in patients with locally advanced disease and a tumor PD-L1 TAP score ≥5%

- The safety profile in this subgroup was tolerable and consistent with that of the overall ITT population, with no new safety signals

- These findings further support the use of tislelizumab plus chemotherapy as a first-line treatment option for patients with locally advanced ESCC

Abbreviations: ESCC, esophageal squamous cell carcinoma; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

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THANK YOU

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