Tislelizumab + Chemotherapy vs Placebo + Chemotherapy in Patients With Locally Advanced Esophageal Squamous Cell Carcinoma: RATIONALE-306 Subgroup Analysis

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Filip Van Herpe,[1*] Eric Van Cutsem,[2] Jianming Xu,[3] Eric Raymond,[4] Richard Hubner,[5] Harry H. Yoon,[6] Ken Kato,[7] Lucjan Wyrywicz,[8] David Tougeron,[9] Sook Ryun Park,[10] Paula Jimenez-Fonseca,[11] Takashi Kojima,[12] Ryu Ishihara,[13] Antonio Avallone,[14] Roberto Pazo-Cid,[15] Sheng Xu,[16] Sebastian Yan,[17] Jingwen Shi,[18] Xuan Kong,[19] Florian Lordick[20]

[1]Universitair Ziekenhuis Leuven, Leuven, Belgium; [2]Division of Digestive Oncology, University Hospitals Gasthuisberg, Leuven, and KU Leuven, Leuven, Belgium; [3]Department of Medical Oncology, Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; [4]Department of Medical Oncology, Paris Saint-Joseph Hospital, Paris, France; [5]Department of Medical Oncology, The Christie NHS Foundation Trust Manchester, and Division of Cancer Sciences, University of Manchester, Manchester, UK; [6]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [7]Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [8]Department of Oncology and Radiotherapy, Maria Sklodowska-Curie National Cancer Research Institute, Warsaw, Poland; [9]Department of Hepato-Gastroenterology, CHU de Poitiers, Poitiers, France; [10]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [11]Department of Medical Oncology, Central University Hospital of Asturias, ISPA, Oviedo, Spain; [12]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan; [13]Department of Gastroenterology, Osaka International Cancer Institute, Osaka, Japan; [14]Department of Medical Oncology, National Cancer Institute IRCCS-G. Pascale Foundation, Naples, Italy; [15]Department of Medical Oncology, Hospital Universitario Miguel Servet, Zaragoza, Spain; [16]Global Bridges at BeOne Medicines, Ltd, Shanghai, China; [17]Clinical Development, BeOne Medicines, Ltd, Shanghai, China; [18]Clinical Biomarker, BeOne Medicines, Ltd, Beijing, China; [19]Clinical Development, BeOne Medicines, Ltd, Shanghai, China; [20]Department of Medicine II (Oncology, Gastroenterology, Hepatology, Pulmonology, and Infectious Diseases), Leipzig University Medical Center and University Cancer Center Leipzig (UCCL), Leipzig, Germany

CONCLUSIONS

- In this subgroup analysis of participants 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 participants 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

INTRODUCTION

- After a minimum 3-year follow-up of RATIONALE-306 (NCT03783442), tislelizumab plus chemotherapy demonstrated clinically meaningful and sustained improvement in overall survival (OS) compared with placebo plus chemotherapy (HR, 0.70; 95% CI: 0.59, 0.83) in advanced esophageal squamous cell carcinoma (ESCC)[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 programmed death-ligand 1 (PD-L1) Tumor Area Positivity (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 participants 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)

METHODS

Trial Design

- This post hoc subgroup analysis included retrospectively selected participants with locally advanced ESCC with non-metastatic disease and deemed unfit for surgery or definitive chemoradiation from the randomized, double-blind, global phase 3 RATIONALE-306 study
- Efficacy outcomes (OS, progression-free survival [PFS], objective response rate) and safety were analyzed

RESULTS

Baseline Characteristics

- At data cutoff (August 22, 2024), of 649 participants randomized, 88 had locally advanced ESCC
- Participants with locally advanced ESCC had a minimum of 45 months of follow-up
- Baseline characteristics are shown in **Table 1**

Table 1. Baseline Characteristics

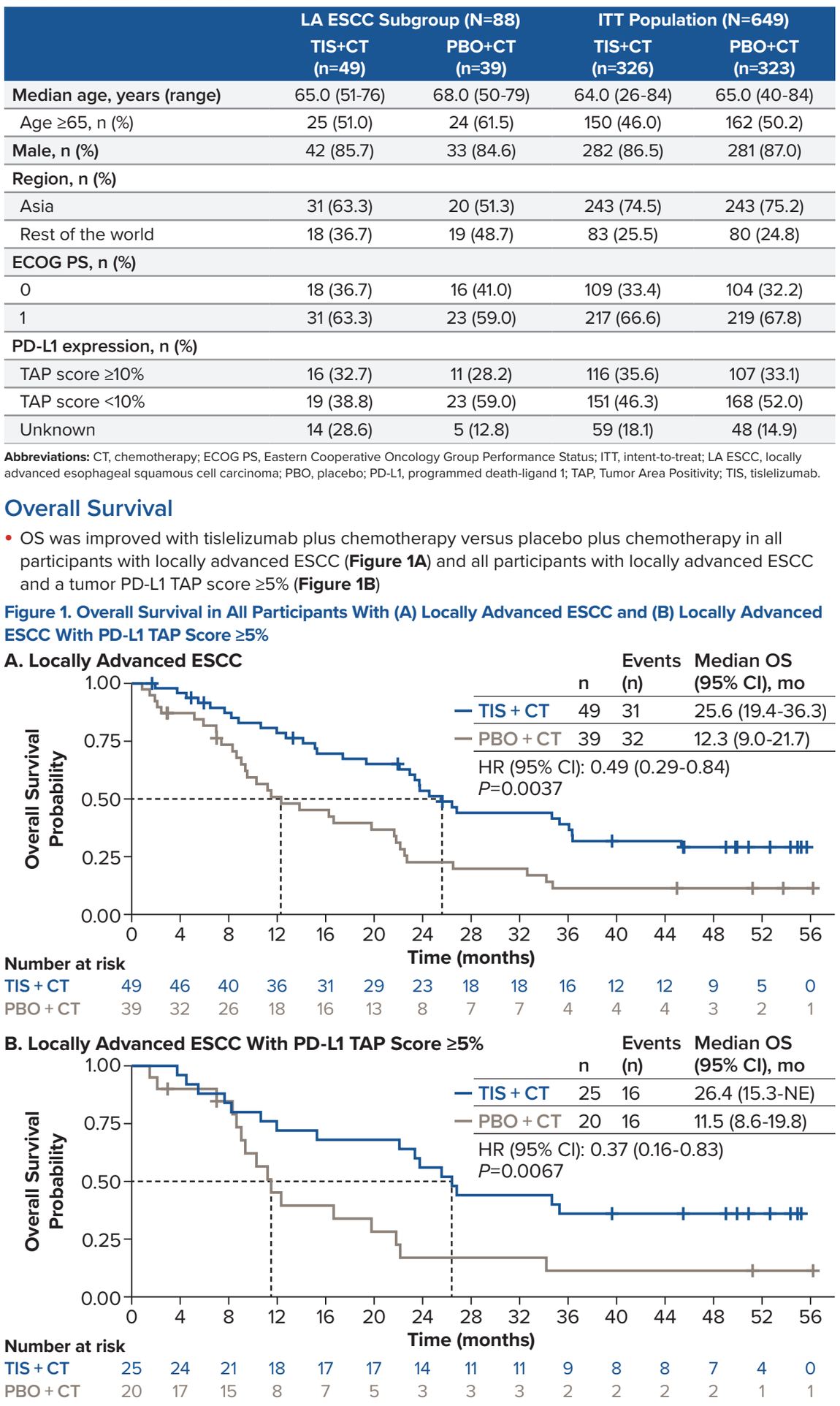
	LA ESCC Subgroup (N=88)		ITT Population (N=649)	
	TIS+CT (n=49)	PBO+CT (n=39)	TIS+CT (n=326)	PBO+CT (n=323)
Median age, years (range)	65.0 (51-76)	68.0 (50-79)	64.0 (26-84)	65.0 (40-84)
Age ≥65, n (%)	25 (51.0)	24 (61.5)	150 (46.0)	162 (50.2)
Male, n (%)	42 (85.7)	33 (84.6)	282 (86.5)	281 (87.0)
Region, 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 PS, 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: CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intent-to-treat; LA ESCC, locally advanced esophageal squamous cell carcinoma; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab.

Overall Survival

- OS was improved with tislelizumab plus chemotherapy versus placebo plus chemotherapy in all participants with locally advanced ESCC (**Figure 1A**) and all participants with locally advanced ESCC and a tumor PD-L1 TAP score ≥5% (**Figure 1B**)

Figure 1. Overall Survival in All Participants With (A) Locally Advanced ESCC and (B) Locally Advanced ESCC With PD-L1 TAP Score ≥5%

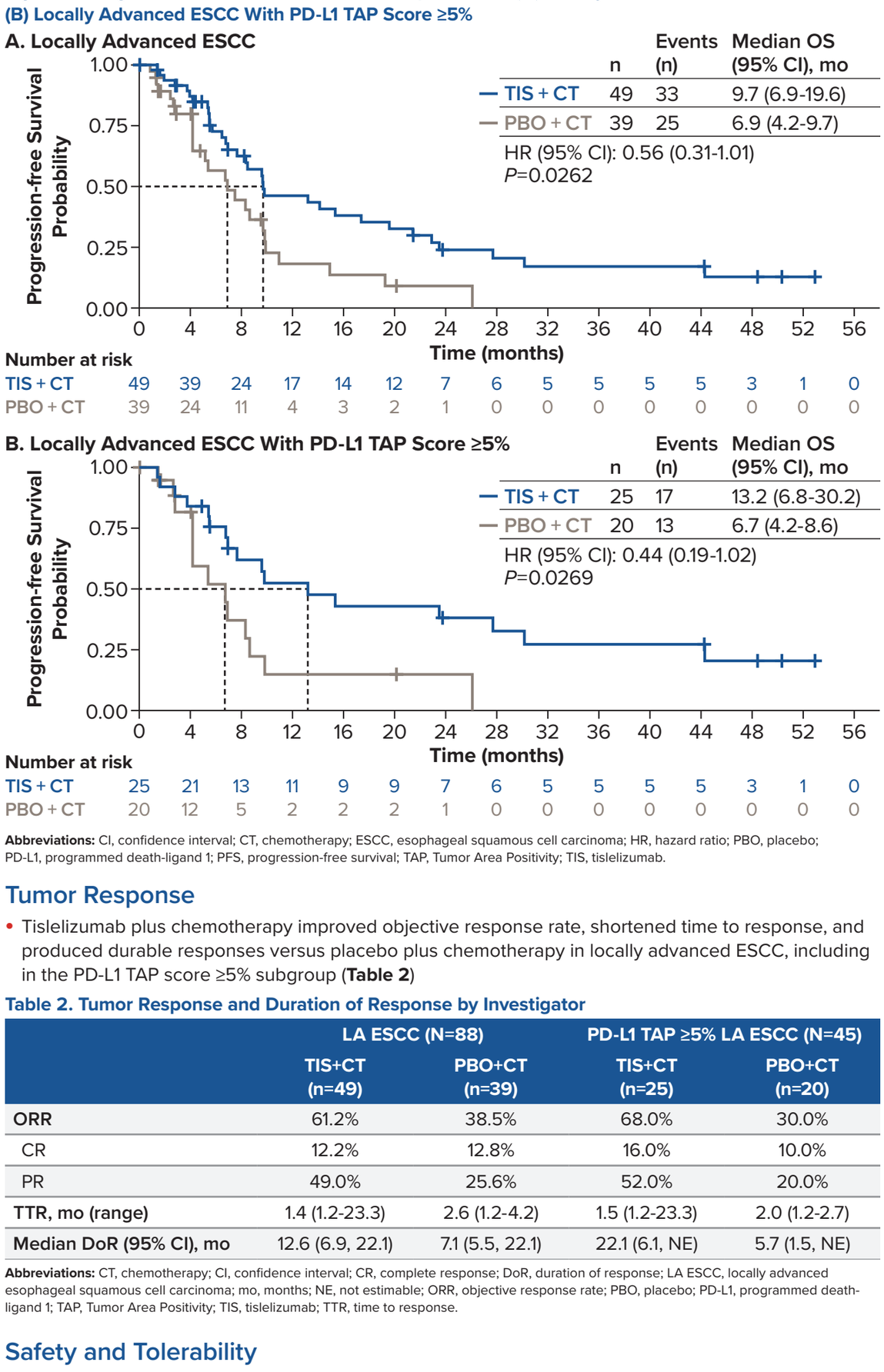


Abbreviations: CI, confidence interval; CT, chemotherapy; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, Tumor Area Positivity; TIS, tislelizumab.

Progression-Free Survival

- PFS was prolonged with tislelizumab plus chemotherapy versus placebo plus chemotherapy in both participants with locally advanced ESCC (**Figure 2A**) and all participants with locally advanced ESCC and a tumor PD-L1 TAP score ≥5% (**Figure 2B**)

Figure 2. Progression-Free Survival in All Participants With (A) Locally Advanced ESCC and (B) Locally Advanced ESCC With PD-L1 TAP Score ≥5%



Abbreviations: CI, confidence interval; CT, chemotherapy; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, Tumor Area Positivity; TIS, tislelizumab.

Tumor Response

- Tislelizumab plus chemotherapy improved objective response rate, shortened time to response, and produced durable responses versus placebo plus chemotherapy in locally advanced ESCC, including in the PD-L1 TAP score ≥5% subgroup (**Table 2**)

Table 2. Tumor Response and Duration of Response by Investigator

	LA ESCC (N=88)		PD-L1 TAP ≥5% LA ESCC (N=45)	
	TIS+CT (n=49)	PBO+CT (n=39)	TIS+CT (n=25)	PBO+CT (n=20)
ORR	61.2%	38.5%	68.0%	30.0%
CR	12.2%	12.8%	16.0%	10.0%
PR	49.0%	25.6%	52.0%	20.0%
TTR, mo (range)	1.4 (1.2-23.3)	2.6 (1.2-4.2)	1.5 (1.2-23.3)	2.0 (1.2-2.7)
Median DoR (95% CI), mo	12.6 (6.9, 22.1)	7.1 (5.5, 22.1)	22.1 (6.1, NE)	5.7 (1.5, NE)

Abbreviations: CT, chemotherapy; CI, confidence interval; CR, complete response; DoR, duration of response; LA ESCC, locally advanced esophageal squamous cell carcinoma; mo, months; NE, not estimable; ORR, objective response rate; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity; TIS, tislelizumab; TTR, time to response.

Safety and Tolerability

- The safety/tolerability profile of tislelizumab plus chemotherapy in the locally advanced ESCC subgroup was consistent with that of the intent-to-treat (ITT) population, with no new safety signals (**Table 3**)
- The most common grade ≥3 treatment-related adverse event 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%)

Table 3. Overall Safety Summary

	LA ESCC Subgroup[a] (N=88)		ITT Population[b] (N=645)	
n (%)	TIS+CT (n=49)	PBO+CT (n=39)	TIS+CT (n=324)	PBO+CT (n=321)
Participants 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)
Participants 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 TIS/PBO	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 TIS/PBO	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: CT, chemotherapy; ITT, intent-to-treat; LA ESCC, locally advanced esophageal squamous cell carcinoma; PBO, placebo; TEAE, treatment-emergent adverse event; TIS, tislelizumab; TRAE, treatment-related adverse event.

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DISCLOSURES

FVH: No conflicts declared. **EVC:** 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.

ACKNOWLEDGMENTS

The authors thank the participants and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines, Ltd (formerly BeiGene, Ltd). Medical writing was provided by Jose Casasnovas Nieves, an employee of BeOne Medicines, Ltd.

*Non-author presenting on behalf of the authors
CORRESPONDENCE: Eric Van Cutsem, Eric.VanCutsem@uzleuven.be

Presented at the 38th Belgian Week of Gastroenterology; February 11-13, 2026; Antwerp, Belgium
Data previously presented at the ESMO Gastrointestinal Cancers Congress 2025, July 2-5, 2025, Barcelona, Spain