First-line pembrolizumab plus chemotherapy versus chemotherapy in advanced esophageal cancer: longer-term efficacy, safety, and quality-of-life results from the phase 3 KEYNOTE-590 study

J.-P. Metges[1]; K. Kato[2]; J.-M. Sun[3]; M. A. Shah[4]; P. Enzinger[5]; A. Adenis[6]; T. Doi[7]; T. Kojima[7]; Z. Li[8]; S.-B. Kim[9]; B. C. Cho[10]; W. Mansoor[11]; S.-H. Li[12]; P. Sunpaweravong[13]; M. A. Maqueda[14]; G. L. Buchschacher Jr[15]; W. Jimin[16]; S. Shah[16]; P. Bhagia[16]; L. Shen[17]

[1]CHU Brest, Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [4]Weill Cornell Medicine, New York, NY, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Institut de Recherche en Cancérologie de Montpellier (IRCM), Inserm, Université Montpellier, ICM, Montpellier, France; [7]National Cancer Center Hospital East, Kashiwa, Japan; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [10]Severance Hospital, Yonsei University Health System, Seoul, South Korea; [11]Christie Hospital NHS Trust, Manchester, United Kingdom; [12]Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [13]Prince of Songkla University Hospital, Songkhla, Thailand; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA, USA; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]Peking University Cancer Hospital and Institute, Beijing, China

Background

- The global phase 3 KEYNOTE-590 study (NCT03189719) was designed to evaluate pembrolizumab + chemotherapy versus chemotherapy as first-line therapy for locally advanced/unresectable or metastatic adenocarcinoma or esophageal squamous cell carcinoma (ESCC) or Siewert type 1 gastroesophageal junction (GEJ) adenocarcinoma[1]
  - Compared with placebo + chemotherapy, pembrolizumab + chemotherapy provided a statistically significant and clinically meaningful improvement in overall survival (OS; hazard ratio [HR], 0.73; 95% CI, 0.62-0.86; *P* < 0.0001), progression-free survival (PFS; HR, 0.65; 95% CI, 0.55-0.76; *P* < 0.0001), and objective response rate (ORR; percentage difference, 15.8; *P* < 0.0001) in all randomly assigned patients

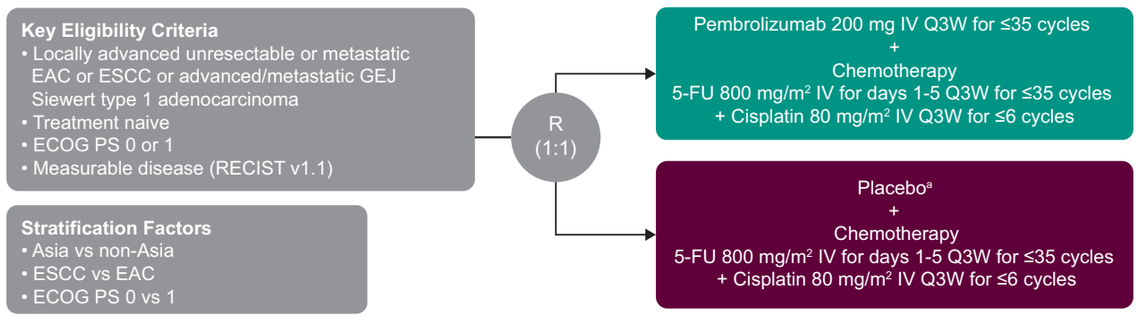
Objective

- To evaluate results from KEYNOTE-590 after an additional 12 months of follow-up

Methods

Study design

Figure 1. KEYNOTE-590 study design



Dual primary end points
- OS in all patients, patients with ESCC PD-L1 CPS ≥10, ESCC, and PD-L1 CPS ≥10 tumors
- PFS (RECIST v1.1, per investigator) in all patients, patients with ESCC, and PD-L1 CPS ≥10 tumors

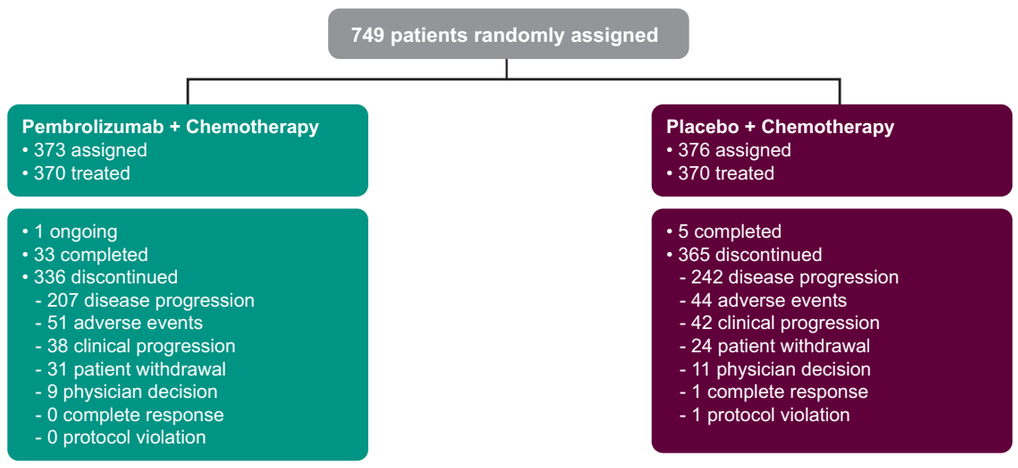
Secondary end points
- ORR (RECIST v1.1, per investigator)
- Change from baseline to week 18 in HRQoL using the EORTC QLQ-C30 and EORTC QLQ-OES 18 dysphagia, reflux, and pain scales

5-FU, 5-fluorouracil; CPS, combined positive score; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-OES 18, EORTC Quality of Life Questionnaire Oesophageal Cancer Module 18; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; HRQoL, health-related quality of life; IV, intravenously; Q3W, every 3 weeks; R, randomization.

[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision.

Results

Figure 2. Disposition of study treatment



- Median time from randomization to data cutoff was 34.8 months (range, 25.4-45.9) for pembrolizumab + chemotherapy and 34.8 months (range, 25.2-46.6) for placebo + chemotherapy
  - Database cutoff date: July 9, 2021

Figure 3. Kaplan-Meier estimates of overall survival in (A) all patients and patients with (B) ESCC + PD-L1 CPS ≥10, (C) ESCC, and (D) PD-L1 CPS ≥10

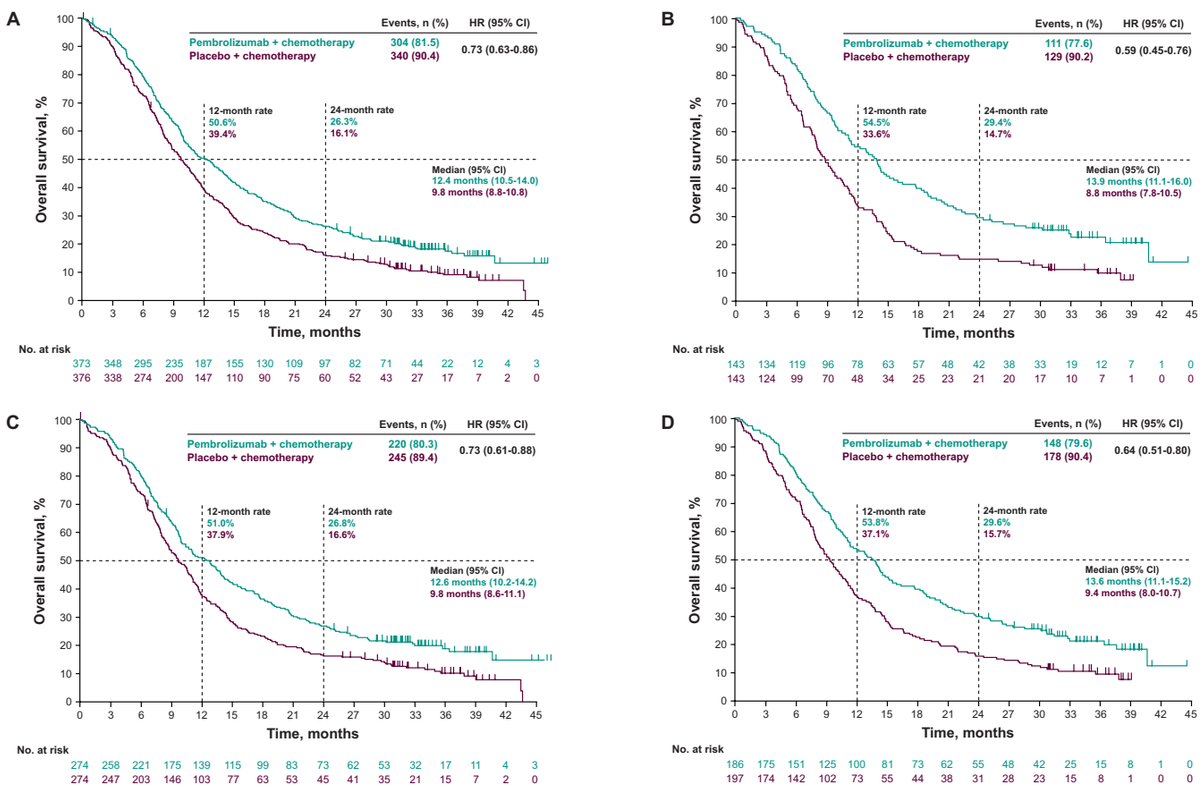


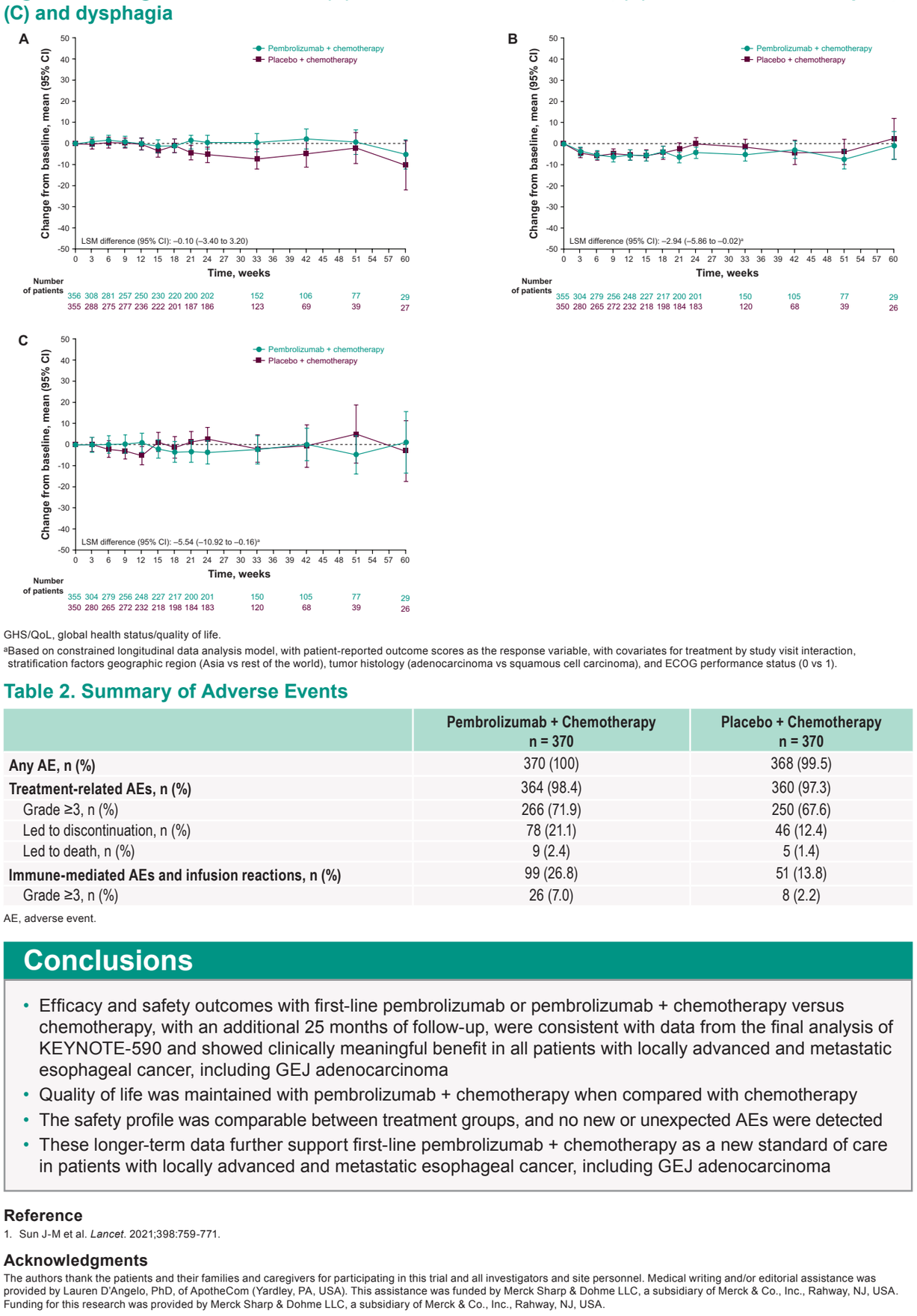
Figure 4. Kaplan-Meier estimates of progression-free survival in (A) all patients and patients with (B) ESCC and (C) PD-L1 CPS ≥10

Table 1. Summary of Response

	Pembrolizumab + Chemotherapy n = 373	Placebo + Chemotherapy n = 376
ORR, n (%)	168 (45.0)	110 (29.3)
CR, n (%)	25 (6.7)	9 (2.4)
PR, n (%)	143 (38.3)	101 (26.9)
SD, n (%)	126 (33.8)	174 (46.3)
DCR (CR + PR + SD), n (%)	294 (78.8)	284 (75.5)
PD, n (%)	43 (11.5)	59 (15.7)
Not evaluable/No assessment, n (%)	36 (9.6)	33 (8.7)
DOR, median (range), months	8.3 (1.2+ to 41.7+)	6.0 (1.5+ to 34.9+)
≥24 months response duration, %	20.4	6.2

CR, complete response; DCR, disease control rate; DOR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. Change from baseline in (A) EORTC QLQ-C30 GHS/QoL, (B) EORTC QLQ-OES 18 pain, (C) and dysphagia



GHS/QoL, global health status/quality of life.

[a]Based on constrained longitudinal data analysis model, with patient-reported outcome scores as the response variable, with covariates for treatment by study visit interaction, stratification factors geographic region (Asia vs rest of the world), tumor histology (adenocarcinoma vs squamous cell carcinoma), and ECOG performance status (0 vs 1).

Table 2. Summary of Adverse Events

	Pembrolizumab + Chemotherapy n = 370	Placebo + Chemotherapy n = 370
Any AE, n (%)	370 (100)	368 (99.5)
Treatment-related AEs, n (%)	364 (98.4)	360 (97.3)
Grade ≥3, n (%)	266 (71.9)	250 (67.6)
Led to discontinuation, n (%)	78 (21.1)	46 (12.4)
Led to death, n (%)	9 (2.4)	5 (1.4)
Immune-mediated AEs and infusion reactions, n (%)	99 (26.8)	51 (13.8)
Grade ≥3, n (%)	26 (7.0)	8 (2.2)

AE, adverse event.

Conclusions

- Efficacy and safety outcomes with first-line pembrolizumab or pembrolizumab + chemotherapy versus chemotherapy, with an additional 25 months of follow-up, were consistent with data from the final analysis of KEYNOTE-590 and showed clinically meaningful benefit in all patients with locally advanced and metastatic esophageal cancer, including GEJ adenocarcinoma
- Quality of life was maintained with pembrolizumab + chemotherapy when compared with chemotherapy
- The safety profile was comparable between treatment groups, and no new or unexpected AEs were detected
- These longer-term data further support first-line pembrolizumab + chemotherapy as a new standard of care in patients with locally advanced and metastatic esophageal cancer, including GEJ adenocarcinoma

Reference

1. Sun J-M et al. *Lancet*. 2021;398:759-771.

Acknowledgments

The authors thank the patients and their families and caregivers for participating in this trial and all investigators and site personnel. Medical writing and/or editorial assistance was provided by Lauren D'Angelo, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Contact Information

Contact the author at jean-philippe.metges@chu-brest.fr for questions or comments.

https://bit.ly/3AgdsJ2

Presented at the Singapore Society of Oncology 7th Annual Scientific Meeting (Virtual); July 8-9, 2022