original reports

Phase III Trial of Avelumab Maintenance After First-Line Induction Chemotherapy Versus Continuation of Chemotherapy in Patients With Gastric Cancers: Results From JAVELIN Gastric 100

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abstract

PURPOSE The role of maintenance therapy for gastric (GC) or gastroesophageal junction cancer (GEJC) is unclear. We investigated avelumab (anti–programmed death ligand-1 [PD-L1]) maintenance after first-line induction chemotherapy for GC/GEJC.

PATIENTS AND METHODS JAVELIN Gastric 100 was a global, open-label, phase III trial. Eligible patients had untreated, unresectable, human epidermal growth factor receptor 2–negative, locally advanced or metastatic GC or GEJC. Patients without progressive disease after 12 weeks of first-line chemotherapy with oxaliplatin plus a fluoropyrimidine were randomly assigned 1:1 to avelumab 10 mg/kg every 2 weeks or continued chemotherapy, stratified by region (Asia *v* non-Asia). The primary end point was overall survival (OS) after induction chemotherapy in all randomly assigned patients or the PD-L1–positive randomly assigned population (≥ 1% of tumor cells; 73-10 assay).

RESULTS A total of 805 patients received induction; 499 were randomly assigned to avelumab (n = 249) or continued chemotherapy (n = 250). Median OS was 10.4 months (95% CI, 9.1 to 12.0 months) versus 10.9 months (95% CI, 9.6 to 12.4 months) and 24-month OS rate was 22.1% versus 15.5% with avelumab versus chemotherapy, respectively (hazard ratio [HR], 0.91; 95% CI, 0.74 to 1.11; $P = .1779$). In the PD-L1–positive population (n = 54), the HR for OS was 1.13 (95% CI, 0.57 to 2.23; $P = .6352$). In an exploratory analysis of the PD-L1–positive population, defined as combined positive score ≥ 1 (22C3 assay; n = 137), median OS was 14.9 months (95% CI, 8.7 to 17.3 months) with avelumab versus 11.6 months (95% CI, 8.4 to 12.6 months) with chemotherapy (unstratified HR, 0.72; 95% CI, 0.49 to 1.05). With avelumab and chemotherapy, treatment-related adverse events (TRAEs) occurred in 149 (61.3%) and 184 (77.3%) patients, including grade ≥ 3 TRAEs in 31 (12.8%) and 78 (32.8%) patients, respectively.

CONCLUSION JAVELIN Gastric 100 did not demonstrate superior OS with avelumab maintenance versus continued chemotherapy in patients with advanced GC or GEJC overall or in a prespecified PD-L1–positive population.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The prognosis for patients with advanced gastric cancer (GC) remains poor.[1] International guidelines recommend platinum plus a fluoropyrimidine doublet or triplet chemotherapy regimens for first-line treatment of unresectable advanced or metastatic human epidermal growth factor receptor 2 (HER2)–negative GC or gastroesophageal junction cancer (GEJC)[2-4]; however, durations of progression-free survival (PFS; median, approximately 6 months) and overall survival (OS; median, 9-18 months) are short.[5-9] Although maintenance therapy improves PFS and OS in several tumors,[10-13] its role in GC/GEJC has not been established.[14-16] Recently, anti–programmed death-1 (PD-1) immune checkpoint inhibitors nivolumab and pembrolizumab were approved for patients with previously treated advanced GC or GEJC in different regions.[17-21]

CONTEXT

Key Objective

We performed a phase III trial to determine if administering avelumab maintenance therapy after induction chemotherapy would improve outcomes versus continued chemotherapy in patients with advanced gastric cancers.

Knowledge Generated

JAVELIN Gastric 100 did not demonstrate superior overall survival (primary end point) with avelumab maintenance versus continued chemotherapy in all randomly assigned patients or in a predefined programmed death ligand-1–positive population. However, avelumab maintenance had a milder adverse event profile than continued chemotherapy and showed evidence of clinical activity, including prolonged duration of response and potentially increased benefit in some subgroups.

Relevance

To our knowledge, this is the first phase III trial of switch maintenance treatment with an immune checkpoint inhibitor in patients with advanced gastric cancers, and its results are informative for design of future trials. Additional studies are needed to identify patients with gastric cancers who can derive greater benefit from checkpoint inhibitor therapy than standard chemotherapy.

Avelumab is an anti–programmed death ligand-1 (PD-L1) antibody that has shown antitumor activity and a tolerable safety profile in patients with various solid tumors.[22-27] In a phase Ib cohort, avelumab switch maintenance therapy exhibited encouraging activity in patients with advanced GC or GEJC without disease progression after first-line chemotherapy,[28] supporting further investigation. We report the primary analysis of the phase III JAVELIN Gastric 100 trial of avelumab switch maintenance therapy after first-line induction chemotherapy compared with continuation of first-line chemotherapy for advanced HER2-negative GC/GEJC.

PATIENTS AND METHODS

Patients

Eligible patients for induction chemotherapy had histologically confirmed, unresectable, locally advanced or metastatic adenocarcinoma of the stomach or GEJ, had not received chemotherapy for locally advanced or metastatic disease, and had measurable disease per RECIST (version 1.1). Other key inclusion criteria were age $\geq$ 18 years, Eastern Cooperative Oncology Group performance status of 0 or 1, and recently obtained ($\leq$ 6 months) tumor specimen. Key exclusion criteria included HER2-positive tumor, prior immune checkpoint inhibitor therapy, and untreated or symptomatic brain metastasis. Full eligibility criteria are provided in the Protocol (online only).

The trial was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written informed consent before enrollment. The trial Protocol and all amendments were approved by the institutional review board or ethics committee at each participating center.

Study Design and Treatment

JAVELIN Gastric 100 (ClinicalTrials.gov identifier: NCT02625610) was an open-label, multicenter, randomized phase III trial. All patients received first-line induction therapy for up to 12 weeks with one of three regimens: oxaliplatin 85 mg/m^2 intravenously (IV) and leucovorin 200 mg/m^2 (or equivalent levoleucovorin dose) in accordance with label instructions and local guidelines, followed by fluorouracil (FU) 2,600 mg/m^2 by continuous infusion over 24 hours on day 1, every 2 weeks; oxaliplatin 85 mg/m^2 IV and leucovorin 400 mg/m^2 (or equivalent levoleucovorin dose), followed by FU 400 mg/m^2 IV on day 1 and FU 2,400 mg/m^2 by continuous infusion over 46 to 48 hours on days 1 to 2, every 2 weeks; or oxaliplatin 130 mg/m^2 IV on day 1 and capecitabine 1,000 mg/m^2 orally twice daily for 2 weeks, followed by a 1-week rest period, every 3 weeks. Patients without progressive disease (PD) per RECIST (version 1.1) after induction chemotherapy, confirmed by an independent radiologist, were randomly assigned 1:1 to either switch maintenance therapy with avelumab 10 mg/kg IV every 2 weeks or continuation of the same chemotherapy. Random assignment was stratified by region (Asia *v* non-Asia). All patients received best supportive care (BSC). In the chemotherapy arm, patients unable to tolerate further combination chemotherapy could receive capecitabine, FU plus leucovorin, or oxaliplatin alone. Patients considered ineligible for further chemotherapy received BSC only. Patients received antihistamine/acetaminophen pretreatment before the first four avelumab infusions. Avelumab dose reductions were not permitted; changes in infusion rate and dose delays were permitted.

Dose modifications of chemotherapy were permitted in accordance with labeling instructions and local guidelines. All randomly assigned patients continued assigned treatment until PD, unacceptable toxicity, withdrawal of consent, or any other criterion for withdrawal occurred.

End Points and Assessments

The primary end point was OS (time from random assignment to death resulting from any cause). OS was assessed in all randomly assigned patients and in randomly assigned patients with PD-L1–positive tumors. For the primary analysis, as prespecified in the statistical analysis plan, PD-L1 status was assessed centrally at baseline using the PD-L1 immunohistochemical (IHC) 73-10 performance evaluation–only assay (Agilent Technologies/Dako, Carpinteria, CA), and PD-L1–positive status was defined as PD-L1 protein expression in ≥ 1% of tumor cells. Secondary end points included PFS (time from random assignment to first documentation of PD per RECIST [version 1.1] according to investigator assessment or death resulting from any cause, whichever occurred first), best overall response (best response among all tumor assessments from baseline [at random assignment, after induction chemotherapy] per RECIST [version 1.1]), duration of response (time from first documentation of objective response in the maintenance phase until PD per RECIST [version 1.1] or death), and safety. Tumors were assessed radiologically at baseline, every 6 weeks for the first 12 months, and every 12 weeks thereafter. In a post hoc exploratory subset analysis, PD-L1 expression in both tumor and immune cells (lymphocytes and macrophages) was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies/Dako) according to the manufacturer's instructions, with PD-L1–positive status defined as combined positive score (CPS) ≥ 1.[29] Microsatellite instability (MSI) status (exploratory analysis) was assessed using the Idylla MSI assay (Biocartis, Mechelen, Belgium). Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Immune-related AEs were identified using a prespecified list of preferred terms followed by comprehensive medical review.

Statistical Analysis

The original primary objective was to show superior OS or PFS of avelumab maintenance over continuation of first-line chemotherapy in all randomly assigned patients. In June 2018 (before interim analysis and availability of patient data), based on results from the phase Ib study of avelumab in GC and GEJC, which showed longer OS in the PD-L1–positive population,[28] the primary objective was amended to show the superiority of avelumab maintenance over continuation of first-line chemotherapy in prolonging OS in all randomly assigned patients or in the randomly assigned PD-L1–positive population, enabling formal statistical analysis of OS in both populations. PFS became a secondary objective. The number of patients enrolled in the induction phase was driven by the observed induction failure rate to allow approximately 466 patients to be randomly assigned. For OS in all randomly assigned patients, assuming median OS of 10.5 and 15.0 months in the chemotherapy and avelumab arms, respectively, corresponding to a hazard ratio (HR) of 0.70, and with a dropout rate of 5%, 356 events (deaths) were required to achieve 90% power in a log-rank test with one-sided α of 2%. This calculation included an interim efficacy analysis, performed after 75% of OS events had occurred. Interim and primary analyses used a sequential α-spending function approach per Lan and DeMets with an O'Brien and Fleming boundary function. For analysis of OS in the PD-L1–positive population, a median OS of 10.5 and 19.3 months was assumed in the chemotherapy and avelumab arms, respectively, corresponding to an HR of 0.54. The primary end point was considered positive if null hypothesis testing for OS in either the overall or PD-L1–positive population was rejected. An imbalanced type I error allocation was used for the two primary hypotheses to control the error rate at 2.5% (one sided), with 2% and 0.5% (one sided) allocated to the overall and PD-L1–positive populations, respectively. Calculations were performed using EAST (version 6.4; Cytel, Cambridge, MA) and R software (R Foundation, Vienna, Austria). Dual primary hypothesis testing of OS was analyzed with a closed testing procedure using weighted Bonferroni tests. If the OS comparison in one population was significant, the α value would be recycled for the OS comparison in the other population. OS and PFS were estimated using the Kaplan-Meier method. Objective response rates (ORRs; proportion with a confirmed best overall response of complete response [CR] or partial response [PR]) by treatment group were compared using the Cochran-Mantel-Haenszel test, accounting for stratification, with a one-sided α level of 0.025; two-sided 95% CIs were calculated using the Clopper-Pearson method. Safety was assessed in all patients who received ≥ one dose of randomly assigned treatment in the maintenance phase.

RESULTS

Patients and Treatment

Between December 31, 2015, and November 29, 2017, 805 patients enrolled at 178 sites in 17 countries (Appendix Table A1, online only) entered the 12-week induction phase (Fig 1). Subsequently, 499 patients with disease control were randomly assigned to avelumab maintenance (n = 249) or continued chemotherapy (n = 250), including 30 and 24 patients, respectively, with PD-L1–positive tumors based on a prespecified definition (expression in ≥ 1% of tumor cells; 73-10 assay). In the chemotherapy arm, seven patients (2.8%) were considered unsuitable for further chemotherapy and received BSC only. Baseline characteristics were similar between arms (Table 1). At data cutoff on September 13, 2019, 18 (7.2%) and five (2.0%) patients were still receiving study treatment in the avelumab

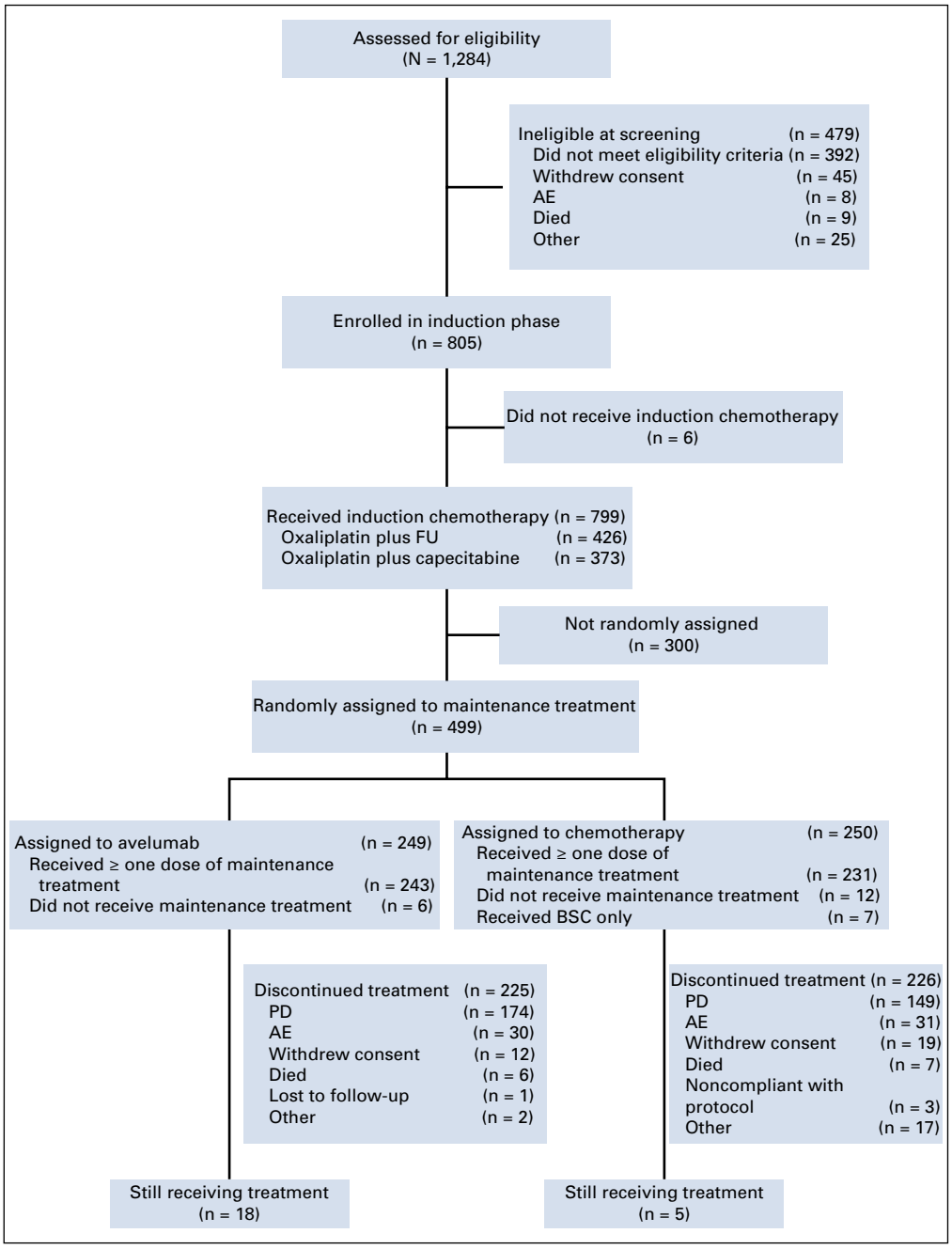


FIG 1. CONSORT diagram. AE, adverse event; BSC, best supportive care; FU, fluorouracil; PD, progressive disease.

and chemotherapy arms, respectively (Appendix Table A2, online only). Median duration of treatment in the maintenance phase was 3.2 months (range, 0.5-34.1 months) in the avelumab arm and 2.8 months (range, 0.5-28.3 months) in the chemotherapy arm, and median follow-up for OS was 24.1 and 24.0 months, respectively (minimum, 18 months in both arms). In the avelumab and chemotherapy arms, subsequent immunotherapy was received by 2.4% and 8.4% of patients, respectively, and subsequent chemotherapy was received by 51.4% and 49.2% of patients, respectively.

Efficacy

OS was not significantly different in the avelumab and chemotherapy arms (Fig 2). In all randomly assigned patients, median OS (measured from random assignment [ie, after 12 weeks of induction chemotherapy]) was 10.4 months (95% CI, 9.1 to 12.0 months) in the avelumab arm and 10.9 months (95% CI, 9.6 to 12.4 months) in the chemotherapy arm (HR, 0.91; 95% CI, 0.74 to 1.11; one-sided $P = .1779$); 24-month OS rates were 22.1% (95% CI, 16.8 to 28.0) versus 15.5% (95% CI, 10.8 to 20.9), respectively. In the prespecified PD-L1–positive population

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	No. (%)	
	Avelumab (n = 249)	Chemotherapy (n = 250)
Median age, years	62.0	61.0
Sex		
Male	164 (65.9)	167 (66.8)
Female	85 (34.1)	83 (33.2)
Region		
North America	34 (13.7)	23 (9.2)
Europe	110 (44.2)	123 (49.2)
Asia	57 (22.9)	57 (22.8)
Rest of world	48 (19.3)	47 (18.8)
ECOG PS score at screening		
0	102 (41.0)	108 (43.2)
1	147 (59.0)	142 (56.8)
Site of primary tumor		
Stomach	174 (69.9)	181 (72.4)
GEJ	75 (30.1)	69 (27.6)
Prior gastrectomy	69 (27.7)	66 (26.4)
No. of metastatic sites at random assignment (re-baseline[a])		
0	31 (12.4)	29 (11.6)
1	43 (17.3)	55 (22.0)
2	59 (23.7)	57 (22.8)
≥ 3	116 (46.6)	109 (43.6)
Microsatellite status		
Unstable (MSI high)	8 (3.2)	5 (2.0)
Stable	209 (83.9)	210 (84.0)
Unknown	32 (12.9)	35 (14.0)
PD-L1 status (expression on ≥ 1% of tumor cells; 73-10 assay)		
Positive	30 (12.0)	24 (9.6)
Negative	194 (77.9)	190 (76.0)
Not evaluable or unavailable	25 (10.0)	36 (14.4)
PD-L1 status (combined positive score ≥ 1; 22C3 assay)[b]		
Positive	74 (29.7)	63 (25.2)
Negative	40 (16.1)	36 (14.4)
Not evaluable or unavailable	135 (54.2)	151 (60.4)
Objective response at re-baseline[ac]		
CR	6 (2.4)	4 (1.6)
PR	117 (47.0)	127 (50.8)
SD[d]	119 (47.8)	115 (46.0)
PD[e]	6 (2.4)	3 (1.2)
Not evaluable	1 (0.4)	1 (0.4)

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; MSI, microsatellite instability; PD, progressive disease; PD-L1, programmed death ligand-1; PR, partial response; SD, stable disease.

[a]Re-baseline is after induction chemotherapy and before random assignment.

[b]Exploratory analysis.

[c]Based on investigator assessment per RECIST (version 1.1).

[d]Includes one patient with non-CR/non-PD who had no target lesion per investigator.

[e]Eight of nine patients with PD by investigator assessment had no PD by independent review; one patient (avelumab arm) with PD by both investigator and independent review was randomly assigned (Protocol deviation).

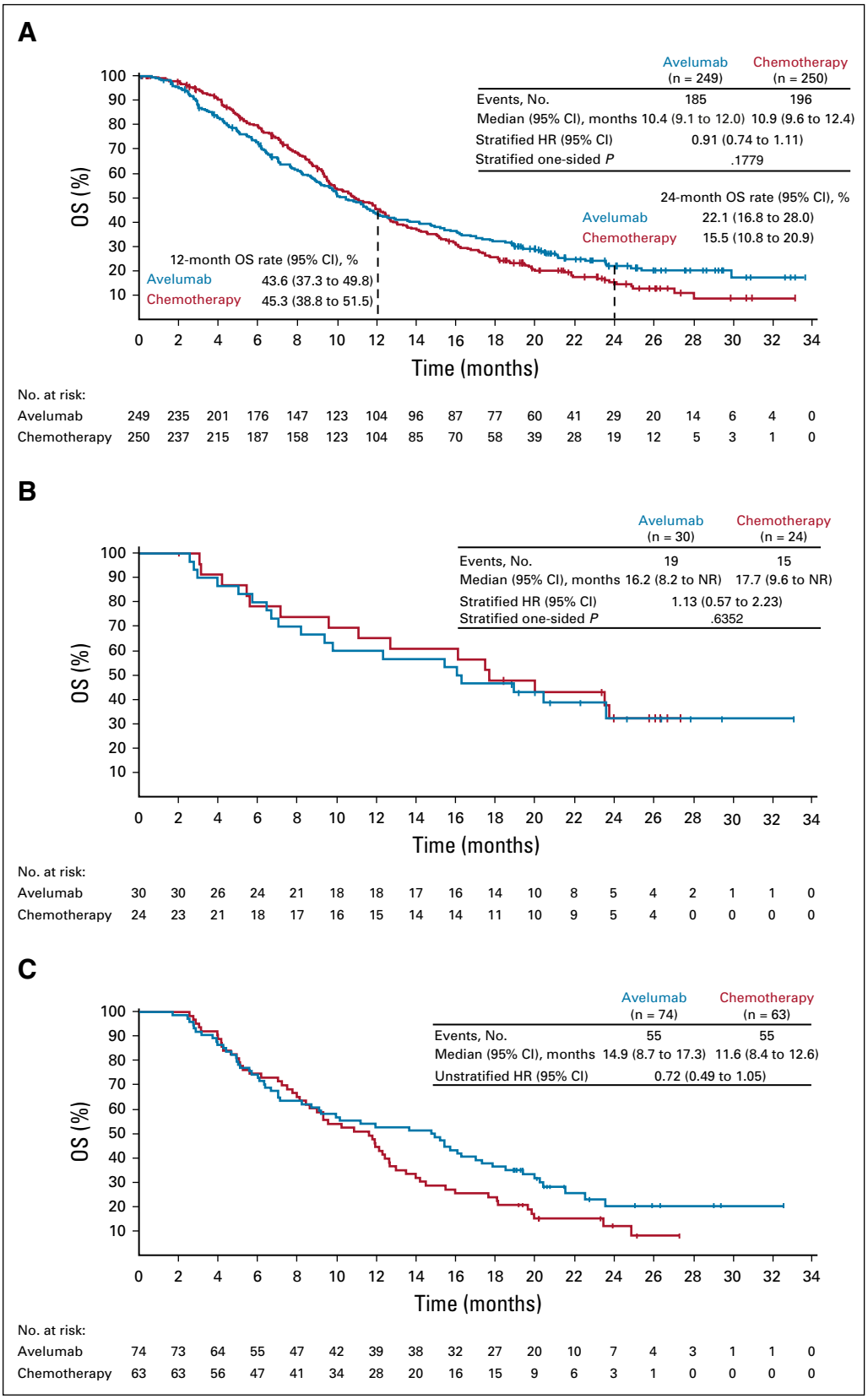


FIG 2. Overall survival (OS; measured from random assignment after 12 weeks of induction chemotherapy) in (A) all randomly assigned patients, (B) prespecified programmed death ligand-1 (PD-L1)–positive population (tumor cell PD-L1 expression, ≥ 1% cutoff; 73-10 assay), and (C) exploratory subset of patients with PD-L1–positive tumors based on combined positive score (≥ 1 cutoff; 22C3 assay). HR, hazard ratio; NR, not reached.

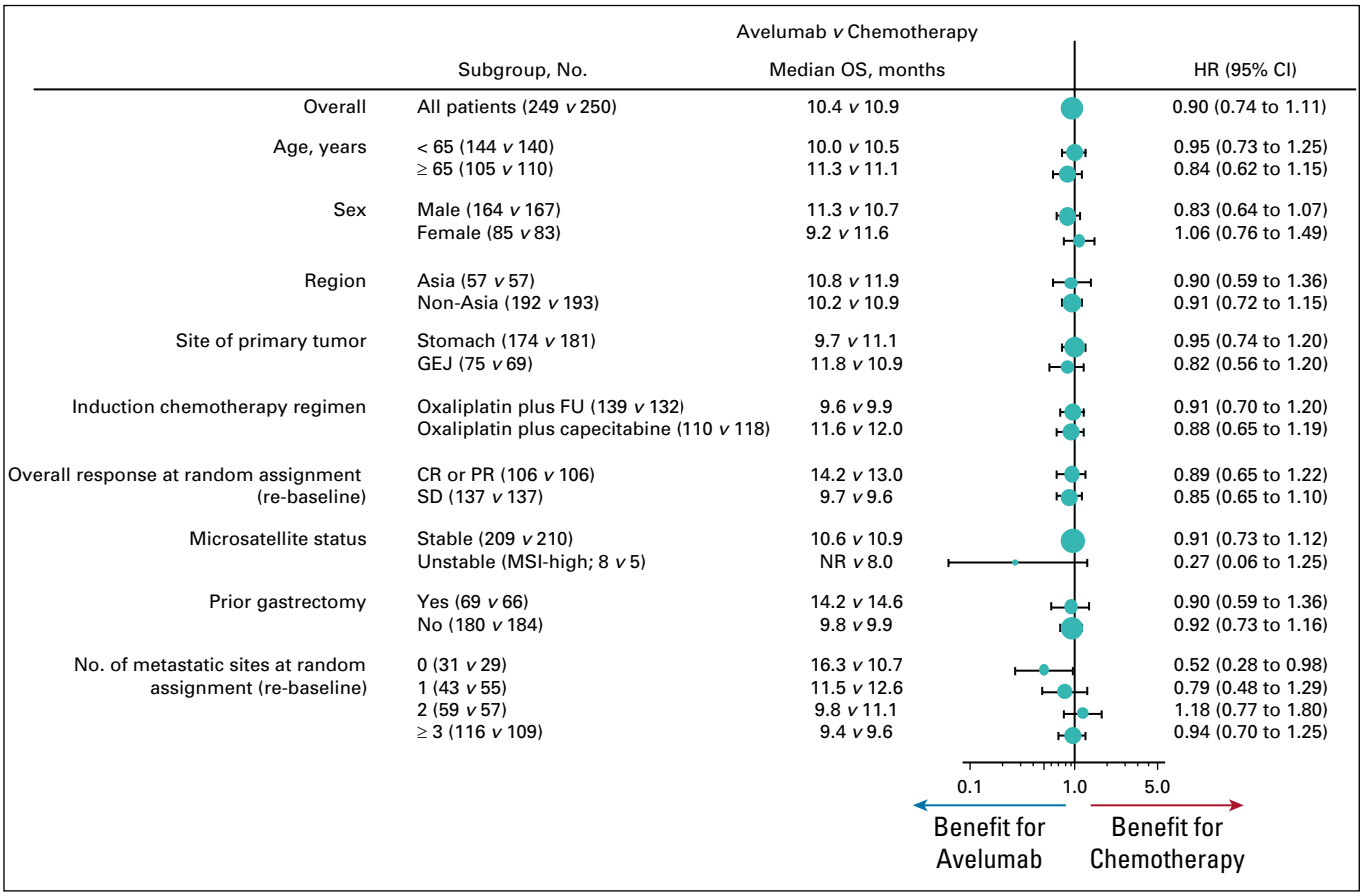


FIG 3. Overall survival (OS; measured from random assignment after 12 weeks of induction chemotherapy [ie, re-baseline]) in subgroups. Hazard ratios (HRs) were calculated for a univariable unstratified model. In the microsatellite instability (MSI)–high subgroup, 12-month OS rate was 75.0% (95% CI, 31.5 to 93.1) in the avelumab arm and 40.0% (95% CI, 5.2 to 75.3) in the chemotherapy arm. CR, complete response; FU, fluorouracil; GEJ, gastroesophageal junction; NR, not reached; PR, partial response; SD, stable disease.

(≥ 1% of tumor cells; 73-10 assay; 54 [12.3%] of 438 evaluable patients), median OS was 16.2 months (95% CI, 8.2 months to not reached [NR]) in the avelumab arm and 17.7 months (95% CI, 9.6 months to NR) in the chemotherapy arm (HR, 1.13; 95% CI, 0.57 to 2.23; one-sided $P = .6352$). OS trends were similar in most Protocol-specified subgroups (Fig 3), including Asian patients (n = 114; HR, 0.90; 95% CI, 0.59 to 1.36; Appendix Fig A1A, online only); however, an OS difference was seen in two prespecified populations: patients with no metastatic sites after induction chemotherapy (n = 114; HR, 0.52; 95% CI, 0.28 to 0.98) and the small subset with MSI-high tumors (n = 13; HR, 0.27; 95% CI, 0.06 to 1.25). In an exploratory analysis performed in the subset of evaluable patients with PD-L1–positive tumors, defined as CPS ≥ 1 using the 22C3 assay (137 [64.3%] of 213 evaluable patients), median OS was 14.9 months (95% CI, 8.7 to 17.3 months) with avelumab and 11.6 months (95% CI, 8.4 to 12.6 months) with chemotherapy (unstratified HR, 0.72; 95% CI, 0.49 to 1.05; Fig 2C). In the subset with PD-L1–high tumors based on the 22C3 assay (CPS ≥ 10; n = 43), no evidence of avelumab benefit was seen (Appendix Fig A1B).

In all randomly assigned patients, median PFS (after random assignment) was 3.2 months (95% CI, 2.8 to 4.1 months) in the avelumab arm and 4.4 months (95% CI, 4.0 to 5.5 months) in the chemotherapy arm (HR, 1.04; 95% CI, 0.85 to 1.28; Appendix Fig A2A, online only). In the prespecified PD-L1–positive population (≥ 1% of tumor cells; 73-10 assay), median PFS was 4.1 months (95% CI, 1.6 to 16.0 months) in the avelumab arm and 9.7 months (95% CI, 2.8 to 12.5 months) in the chemotherapy arm (HR, 1.04; 95% CI, 0.53 to 2.02; Appendix Fig A2B). In the exploratory subset with PD-L1–positive tumors, defined as CPS ≥ 1 (22C3 assay), median PFS was 4.3 months (95% CI, 2.9 to 6.8 months) in the avelumab arm and 5.1 months (95% CI, 4.2 to 7.0 months) in the chemotherapy arm (unstratified HR, 0.87; 95% CI, 0.60 to 1.27; Appendix Fig A2C).

The ORR, representing additional or deepening tumor responses after random assignment in patients who had achieved PR or stable disease with induction chemotherapy, was 13.3% (95% CI, 9.3 to 18.1) in the avelumab arm and 14.4% (95% CI, 10.3 to 19.4) in the chemotherapy arm (Appendix Table A3, online only). At random

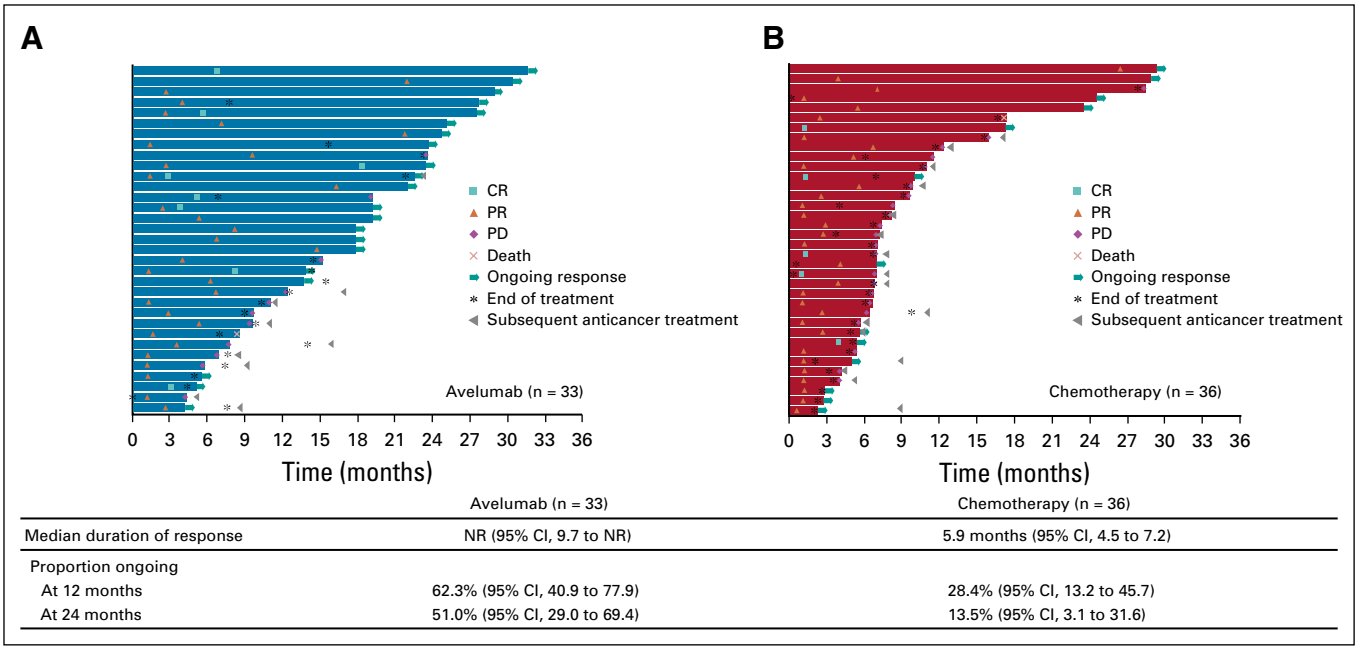
assignment, 10 patients had CR after induction chemotherapy and were not included in the numerator for ORR because these patients no longer had tumors to monitor, except for one patient in the chemotherapy arm misclassified as having CR during the maintenance phase. Within this subgroup, three patients in the avelumab arm and two patients in the chemotherapy arm maintained no evidence of disease at time of data cutoff. Median time to response was 16.1 weeks (range, 5.6-96.4 weeks) with avelumab versus 6.4 weeks (range, 3.3-116.0 weeks) with chemotherapy. Median duration of response achieved after random assignment was not reached (95% CI, 9.7 months to not estimable) with avelumab versus 5.9 months (95% CI, 4.5 to 7.2 months) with chemotherapy (Fig 4). The probability of ongoing response at 12 months with avelumab versus chemotherapy was 62.3% (95% CI, 40.9 to 77.9) versus 28.4% (95% CI, 13.2 to 45.7), and at 24 months, it was 51.0% (95% CI, 29.0 to 69.4) versus 13.5% (95% CI, 3.1 to 31.6), respectively.

Safety

During the maintenance phase, AEs of any causality occurred in 223 (91.8%) of 243 avelumab-treated patients and in 214 (89.9%) of 238 patients treated in the chemotherapy arm, including grade ≥ 3 AEs in 132 (54.3%) and 128 patients (53.8%), respectively (Appendix Table A4, online only). In the avelumab and chemotherapy arms, treatment-related AEs (TRAEs) of any grade occurred in 149 (61.3%) versus 184 patients (77.3%), including grade ≥ 3 TRAEs in 31 (12.8%) and 78 patients (32.8%), respectively. The most common grade ≥ 3 TRAEs in the avelumab arm were increased amylase, increased lipase, asthenia, colitis, decreased appetite, hypertension, and pneumonitis (n = 2 each [0.8%]), and in the chemotherapy arm, they were neutropenia (n = 19 [8.0%]), decreased neutrophil count (n = 10 [4.2%]), and peripheral sensory neuropathy (n = 8 [3.4%]; Fig 5). In the avelumab and chemotherapy arms, serious TRAEs occurred in 19 (7.8%) versus 23 (9.7%) patients, and TRAEs led to permanent discontinuation in 25 (10.3%) versus 65 (27.3%) patients, respectively. A TRAE led to death in one patient in the chemotherapy arm (cerebrovascular event). In the avelumab arm, 32 patients (13.2%) had an immune-related AE, including grade ≥ 3 events in eight patients (3.3%). The most frequent immune-related AEs of any grade (≥ 2.0%) were hypothyroidism (n = 7 [2.9%]), pneumonitis (n = 6 [2.5%]), and rash (n = 5 [2.1%]).

DISCUSSION

The JAVELIN Gastric 100 trial did not meet its primary objective of demonstrating superior OS with switch maintenance avelumab versus continued chemotherapy in patients with advanced GC of GEJC who had disease control after first-line induction chemotherapy, either in the overall or prespecified PD-L1–positive population (≥ 1% of tumor cells; 73-10 assay). Nonsignificant trends toward a higher 24-month OS rate (22.1% *v* 15.5%) and longer durations of response (probability of ongoing response at 24 months, 51.0% *v* 13.5%) compared with chemotherapy



	Avelumab (n = 33)	Chemotherapy (n = 36)
Median duration of response	NR (95% CI, 9.7 to NR)	5.9 months (95% CI, 4.5 to 7.2)
Proportion ongoing		
At 12 months	62.3% (95% CI, 40.9 to 77.9)	28.4% (95% CI, 13.2 to 45.7)
At 24 months	51.0% (95% CI, 29.0 to 69.4)	13.5% (95% CI, 3.1 to 31.6)

FIG 4. Time to and duration of response (investigator assessed per RECIST [version 1.1]) during the maintenance phase (after random assignment) in (A) avelumab and (B) chemotherapy arms. Responses were based on subsequent change after random assignment (during maintenance) in patients who had achieved partial response (PR) or stable disease (SD) after induction chemotherapy. Excludes 10 patients with complete response (CR) during induction chemotherapy. NR, not reached; PD, progressive disease.

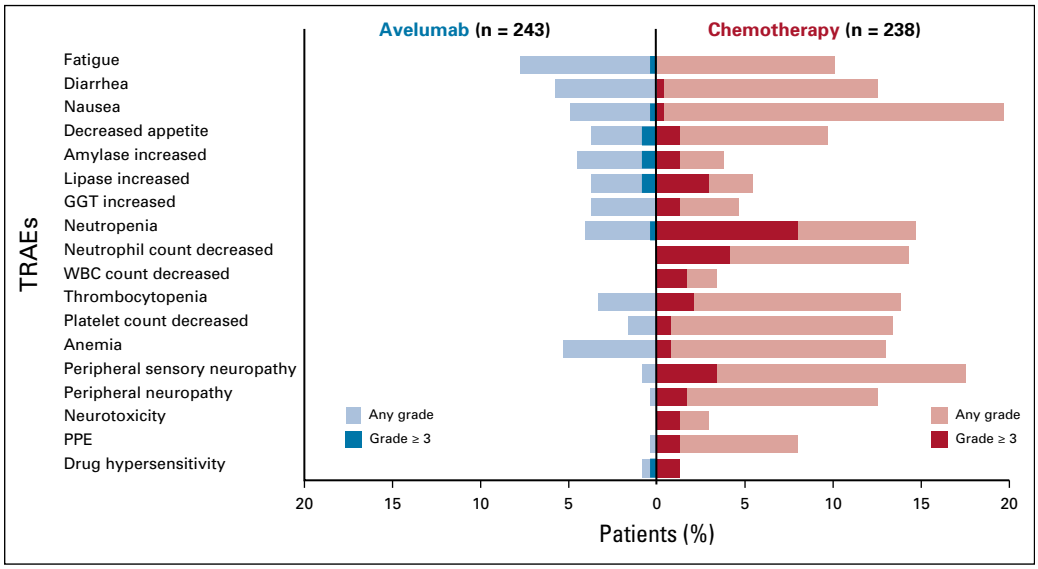


FIG 5. Treatment-related adverse events (TRAEs) that occurred at any grade in ≥ 10% or grade ≥ 3 in ≥ 1% of patients in either arm during the maintenance phase (after random assignment). GGT, γ-glutamyltransferase; PPE, palmar-plantar erythrodysesthesia syndrome.

were observed. On the basis of exploratory subset analyses, OS differences with avelumab versus chemotherapy were seen in subgroups with no metastatic sites at random assignment; in a small subset of patients with MSI-high tumors, although the 95% CI for the HR (0.06 to 1.25) overlaps with 1; and in patients with PD-L1–positive tumors, defined as CPS ≥ 1 (22C3 assay), accounting for PD-L1 protein expression in tumor cells, lymphocytes, and macrophages, and thus representing possible areas for further evaluation. Avelumab showed favorable safety versus continued chemotherapy, including lower rates of grade ≥ 3 TRAEs (12.8% *v* 32.8%), permanent discontinuations because of TRAEs (10.3% *v* 27.3%), and reductions in treatment-related gastrointestinal AEs, hematologic AEs, and neuropathy. The safety profile of avelumab was consistent with previous avelumab monotherapy studies.[22-26,28,30]

Anti–PD-1 antibodies are approved for later-line treatment of GC and GEJC, but to our knowledge, no phase III has shown statistical superiority compared with chemotherapy in any line.[4,14,31] In the analysis of OS in all randomly assigned patients, the Kaplan-Meier curve was lower in the avelumab versus chemotherapy arm at initial time points, but the curves crossed at approximately 12 months, and the OS curve was higher for avelumab at later time points. In the phase III KEYNOTE-062 trial, which compared first-line pembrolizumab monotherapy versus chemotherapy in patients with PD-L1–positive GC or GEJC, defined as CPS ≥ 1 (22C3 assay), OS curves had a generally similar shape to those in JAVELIN Gastric 100, although the initial detrimental effect on OS with pembrolizumab versus chemotherapy was more marked, likely reflecting differences in study design and population enrichment between trials.[31] Specifically, in JAVELIN Gastric 100, avelumab maintenance was administered only to patients who had disease control after first-line induction chemotherapy (ie, chemotherapy-sensitive patients), whereas in KEYNOTE-062, first-line pembrolizumab was administered to patients with PD-L1–positive tumors (CPS ≥ 1). In addition, in JAVELIN Gastric 100, OS was measured from random assignment after 12 weeks of induction chemotherapy, whereas in KEYNOTE-062, OS was measured from enrollment. In an exploratory hypothesis-generating analysis of patients with PD-L1–positive tumors, defined as CPS ≥ 1 (22C3 assay), in JAVELIN Gastric 100, OS was similar in the avelumab and chemotherapy arms until 12 months, when the curves diverged, suggesting that this subgroup may have excluded those who had worse outcomes with avelumab during initial treatment. In KEYNOTE-062, OS differences for pembrolizumab versus chemotherapy were increased in patients with PD-L1–high tumors (CPS ≥ 10); this was not seen in our study, suggesting that high PD-L1 may not predict increased benefit in patients with disease control after chemotherapy. However, few patients had tumors with CPS ≥ 10 in JAVELIN Gastric 100 (n = 43), limiting interpretation.

To our knowledge, JAVELIN Gastric 100 is the first phase III trial of switch maintenance treatment with an immune checkpoint inhibitor in GC/GEJC, and its results are informative for future trials. The low proportion of evaluable patients with PD-L1–positive tumors based on a prespecified definition (12.4% with ≥ 1% PD-L1–positive tumor cells; 73-10 assay) meant that the analysis of OS in this population was underpowered. This proportion was smaller than that in the phase Ib study of avelumab performed in a similar setting (33.3%)[28] and in a phase III trial

of third-line avelumab versus chemotherapy (JAVELIN Gastric 300; 26.8%)[32] but is comparable to proportions with ≥ 1% PD-L1–positive tumor cells in the ATTRACTION-2 (ClinicalTrials.gov identifier: NCT02267343; 13.5%; 28-8 assay) and KEYNOTE-059 studies (ClinicalTrials.gov identifier: NCT02335411; 12.5%; 22C3 assay).[17,29] However, assessment of PD-L1 expression in both tumor and immune cells via CPS may be more useful. A majority of patients had disease control with induction chemotherapy, and nearly all patients subsequently randomly assigned to the chemotherapy arm received continued chemotherapy in the maintenance phase (92.4%) rather than BSC alone, which may reflect the relative fitness of patients who achieve disease control. Of note, median duration of chemotherapy, including induction treatment, was approximately 6 months.

In conclusion, the JAVELIN Gastric 100 trial did not achieve its primary objective of OS improvement with maintenance avelumab in patients with disease control after induction chemotherapy for advanced GC/GEJC. However, results suggest potential activity in selected patient subsets and a favorable safety profile, providing guidance for future studies in this challenging disease.

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DATA SHARING STATEMENT

For all new products or new indications approved in both the European Union and the United States after January 1, 2014, Merck KGaA, Darmstadt, Germany will share patient-level and study-level data after deidentification, as well as redacted study Protocols and clinical study reports from clinical trials in patients. These data will be shared with qualified scientific and medical researchers, upon researcher's request, as necessary for conducting legitimate research. Such requests must be submitted in writing to the company's data sharing portal. More information can be found at https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html. Where Merck KGaA has a co-research, co-development or co-marketing/co-promotion agreement or where the product has been out-licensed, it is recognized that the responsibility for disclosure may be dependent on the agreement between parties. Under these circumstances, Merck KGaA will endeavor to gain agreement to share data in response to requests.

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Phase III Trial of Avelumab Maintenance After First-Line Induction Chemotherapy Versus Continuation of Chemotherapy in Patients With Gastric Cancers: Results From JAVELIN Gastric 100

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APPENDIX

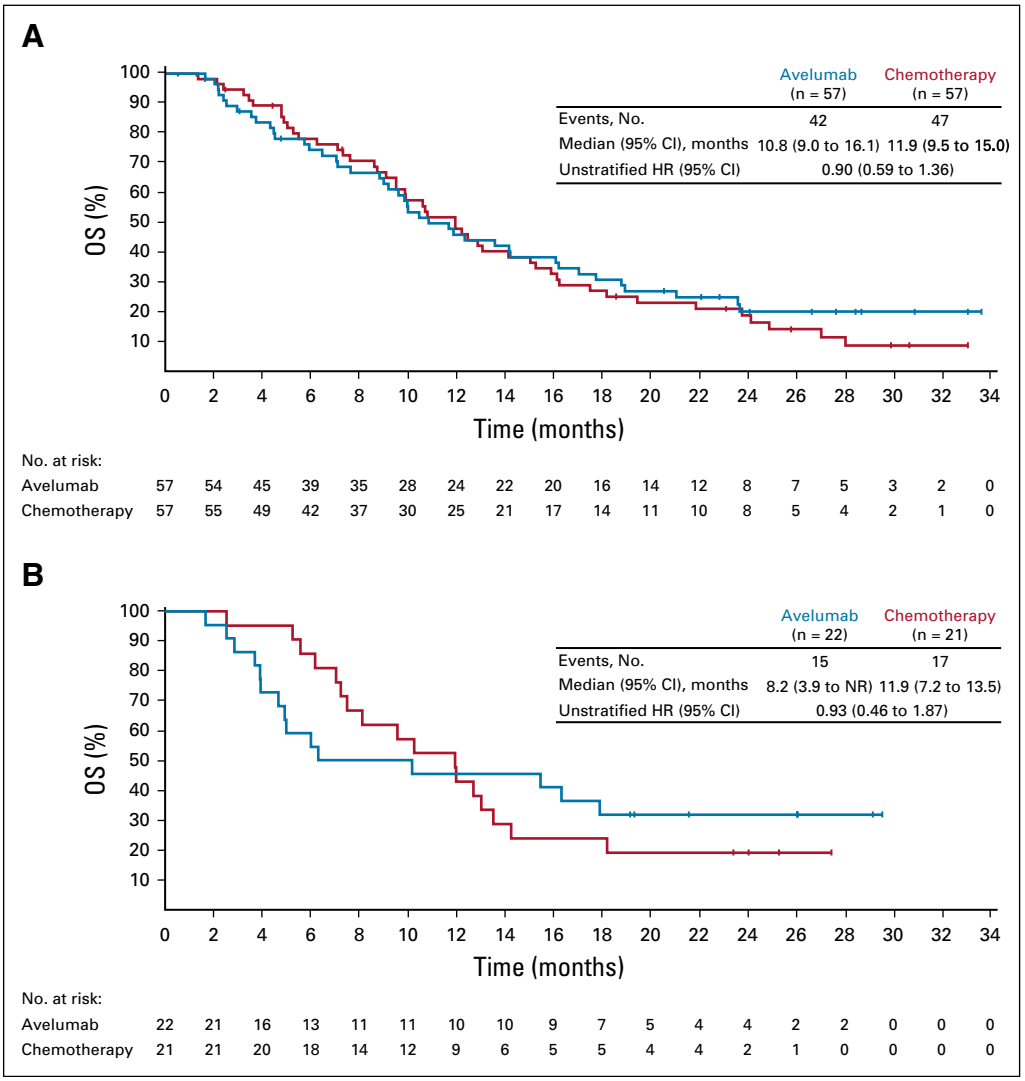

FIG A1. Overall survival (OS; measured from random assignment after 12 weeks of induction chemotherapy) in (A) Asian patients and (B) subset with programmed death ligand-1–high tumors based on the 22C3 assay (combined positive score ≥ 10; 22C3 assay). HR, hazard ratio; NR, not reached.

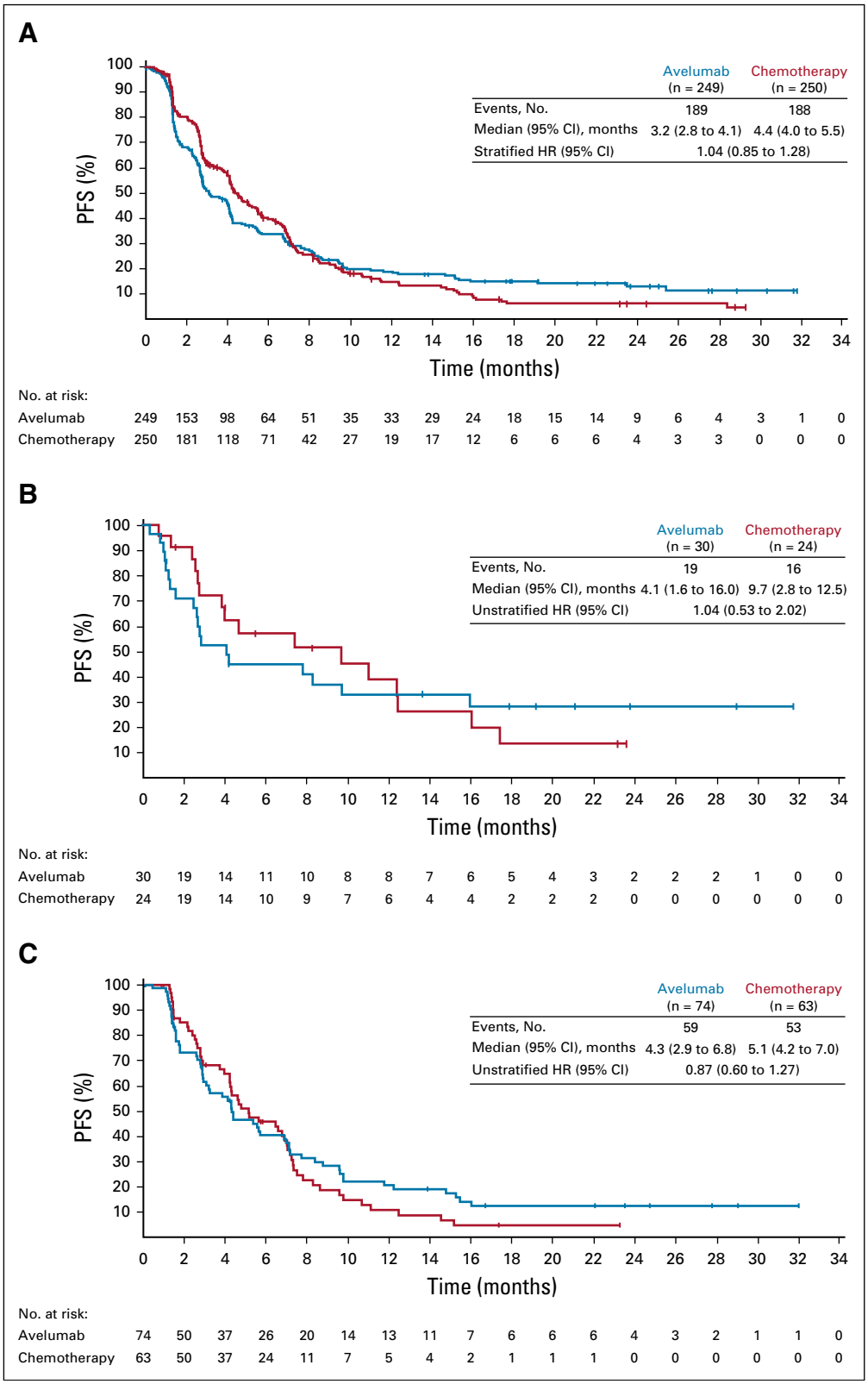

FIG A2. Progression-free survival (PFS; measured from random assignment to first documentation of progressive disease per RECIST [version 1.1] according to investigator assessment or death resulting from any cause, whichever occurred first) in (A) all randomly assigned patients, (B) prespecified programmed death ligand-1 (PD-L1)–positive population (≥ 1% of tumor cells; 73-10 assay), and (C) exploratory subset with PD-L1–positive tumors (combined positive score ≥ 1; 22C3 assay). HR, hazard ratio.

TABLE A1. List of JAVELIN Gastric 100 Investigators

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	Royal North Shore Hospital	Stephen Clarke
	Queen Elizabeth Hospital	Rohit Joshi
	Greenslopes Private Hospital	Warren Joubert
	Flinders Medical Centre	Chris Karapetis
	St George Hospital	Winston Liauw
	Bendigo Hospital	Say Ng
	Fiona Stanley Hospital	David Ransom
	Border Medical Oncology	Christopher Steer
	Monash Medical Centre	Andrew Strickland
	Box Hill Hospital	Rachel Wong
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	Hospital Bruno Born	Leandro Brust
	Faculdade de Medicina de São José do Rio Preto	Gustavo Colagiovanni Girotto
	Núcleo de Oncologia da Bahia	Eduardo Dias de Moraes
	Hospital de Clínicas de Porto Alegre	Sergio Jobim de Azevedo
	Centro de Estudos e Pesquisas em Hematologia e Oncologia	Daniel Iracema Gomes Cubero
	Hospital São Lucas da Pontifical Catholic University of Rio Grande do Sul	Ana Caroline Zimmer Gelatti
Canada	McGill University	Thierry Alcindor
	Cite de la Sante de Laval	Nathalie Aucoin
	Mount Sinai Hospital	Ronald Burkes
	Odette Cancer Centre	Yoo-Joung Ko
	Royal Victoria Hospital	Dawn Ng
	Queen Elizabeth II Health Science Centre, Victorial General site	Stephanie Snow
	Humber River Hospital	Jonathan Wilson

(continued on following page)

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	Hôpital de la Timone	Laetitia Dahan
	Clinique Victor Hugo	Olivier Dupuis
	Centre Antoine-Lacassagne	Eric Francois
	L'Institut de Cancérologie de l'Ouest, site Rene Gauducheau	Sandrine Hiret
	Centre Régional de Lutte Contre le Cancer Eugene Marquis	Samuel Le Sourd
	Hôpital Bretonneau	Thierry Lecomte
	Pharmacie Hôpital Morvan	Jean-Philippe Metges
	Centre Hospitalier Universitaire de Gabrielle Montpied	Denis Pezet
	Hôpital Haut-Lévêque, Groupe Hospitalier Sud	Denis Smith
	Hôpital Européen Georges-Pompidou	Julien Taieb
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	Klinikum Bogenhausen	Martin Fuchs
	Onkologischen Schwerpunktpraxis Eppendorf	Eray Goekkurt
	Leopoldina Krankenhaus Schweinfurt	Stephan Kanzler
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	Szabolcs-Szatmár-Bereg Megyei Kórházak és Egyetemi Oktatókórház	Tamas Babicz
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	Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto	Maria Di Bartolomeo
	Istituto Europeo di Oncologia	Nicola Fazio
	Ospedale San Raffaele	Luca Gianni
	S. C. Oncologica Medica, Azienda Ospedaliera S. Maria	Fausto Roila
	Ospedale degli Infermi	Emiliano Tamburini
	Azienda Socio-Sanitaria Territoriale di Cremona	Gianluca Tomasello
	Università Campus Bio-Medico di Roma	Giuseppe Tonini
	Veneto Institute Oncologico	Vittorina Zagone

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TABLE A1. List of JAVELIN Gastric 100 Investigators (continued)

Country	Site	Principal Investigator
Japan	Kumamoto University Hospital	Hideo Baba
	National Cancer Center Hospital	Narikazu Boku
	Tochigi Cancer Center	Takeshi Fujita
	Saitama Cancer Center	Hara Hiroki
	Kindai University Hospital	Hisato Kawakami
	Oita University Hospital	Satoshi Otsu
	Saitama Medical University	Shinichi Sakuramoto
	Kagoshima University Hospital	Natsugoe Shoji
	Chiba Cancer Center	Hironaka Shuichi
	Tohoku University Hospital	Shin Takahashi
	Toranomon Hospital	Toshimi Takano
	Izumi Municipal Hospital	Hiroshi Tsukuda
	Kagawa University Hospital	Akihito Tsuji
	Niigata Cancer Centre Hospital	Hiroshi Yabusaki
	Kanagawa Cancer Center	Takaki Yoshikawa
	National Cancer Center Hospital	Honma Yoshitaka
Republic of Korea	Seoul National University Hospital	Yung-Jue Bang
	Severance Hospital	Hyun Cheol Chung
	Chonnam National University Hwansun Hospital	Ik Joo Chung
	Catholic University of Korea	In-Ho Kim
	Kyungpook National University Med Center	Jong Gwang Kim
	Keimyung University Dongsan Hospital	Jin Young Kim
	Korea University Anam Hospital	Yeul Hong Kim
	Seoul National University Bundang Hospital	Keun-Wook Lee
	Inje University Haeundae Paik Hospital	Sung Sook Lee
	National Cancer Center	Young-Lee Park
	Asan Medical Center	Min-Hee Ryu
	Chungbuk National University	YaeWon Yang
Romania	Spitalul Clinic Coltea	Ciprian Aldea
	Institutul Clinic Fundeni	Adina Croitoru
	Institute of Oncology Dr Ion Chiricuţă	Alina Simona Muntean
	S. C. Oncomed	Serban Mircea Negru
	Centrul de Oncologie	Michael Schenker
	Spital Lotus	Alina Turcu
	S. C. Radiotherapy	Andrei Ungureanu

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TABLE A1. List of JAVELIN Gastric 100 Investigators (continued)

Country	Site	Principal Investigator
Russian Federation	Federal State Budgetary Institution Russian Research Center	Igor Bazin
	Budgetary Healthcare Institution of Omsk Region	Mikhail Dvorkin
	Evimed	Oleg Gladkov
	Regional Budgetary Healthcare Institution, Ivanovo	Eugeny Gotovkin
	State Budgetary Institution	Yuliya Makarova
	State Budgetary Institution Hospital of Saint Petersburg	Georgy Manikhas
	State Budgetary Institution Hopsital of Arkhangelsk	Marina Nechaeva
	Pavlov First Saint Petersburg	Sergei Orlov
	Petrov Research Institute of Oncology, St Petersburg	Artem Poltoratskiy
	Clinical Oncology Dispensary, State Budgetary Institution Hospital of Kaluga Region	Irina Rozhkova
	State Budgetary Institution Hospital of Stavropol Territory	Vladimir Vladimirov
Spain	Hospital General Universitario Gregorio Marañon	Garcia Alfonso Pilar
	Hospital Universitario Vall d'Hebron	Maria Alsina Maqueda
	Hospital Durán i Reynals	Mariona Campos
	Hospital Universitario	Antonio Cubillo Gracian
	Hospital Infanta Cristina	Ignacio Delgado
	Hospital Universitario La Paz	Jaime Feliu Batlle
	Hospital Universitario 12 de Octubre	Carlos Martin
	Hospital Clinic de Barcelona	Joan Maurel
	Hospital Universitario Virgen	Maria Miron
	Corporació Sanitària Parc Taulí	Carles Pericay
	Hospital General Universitario Elche	Javier Plazas
	Hospital General Universitario Gregorio Maranon	Garcia Alfonso Pilar
Taiwan	China Medical University Hospital	Li-Yuan Bai
	Taipei Veterans General Hospital	Yee Chao
	Linkou Chang Gung Memorial Hospital	Jen-Shi Chen
	Kaohsiung Chang Gung Hospital	Yen-Yang Chen
	Mackay Memorial Hospital	Ruey-Kuen Hsieh
	National Cheng Kung University Hospital	Chia-Jui Yen
	National Taiwan University Hospital	Kun-Huei Yeh
Thailand	Maharaj Nakorn Chiang Mai Hospital	Busyamas Chewaskulyong
	Siriraj Hospital	Vichien Srimuninnimit
	Chula Clinical Research Centre	Suebpong Tanasanvimon
Turkey	Necmettin Erbakan University Tıp Fakültesi	Mehmet Artac
	Adana Şehir Hospital	Timucin Cil
	Akdeniz University Medical Faculty	Hasan S. Coşkun
	Inönü University Medical Faculty	Hakan Harputluoglu
	Istanbul University Cerrahpaşa	Mustafa Ozguroglu
	Mersin University Medical Faculty	Emel Sezer
	Kocaeli University Medical Faculty	Kazim Uygun
	Hacettepe University	Suayib Yalcin
	Acıbadem Adana Hospital	Sinan Yavuz

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TABLE A1. List of JAVELIN Gastric 100 Investigators (continued)

Country	Site	Principal Investigator
United Kingdom	St James's University Hospital	Alan Anthoney
	Derriford Hospital	Geoffrey Cogill
	Royal Surrey County Hospital	Sebastian Cummins
	Mount Vernon Cancer Centre	Mark Harrison
	Clatterbridge Cancer Centre	Ayman Madi
	Christie National Health Service	Wasat Mansoor
	Ninewells Hospital	Russell Petty
	St Bartholomew's Hospital	David Propper
	University College Hospital	Kai-Keen Shiu
United States	University of Kansas	Raed Al-Rajabi
	St Luke's Hospital	Asim Ali
	Northwest Medical Specialties	Jorge Chaves
	Greenville Hospital System	Ki Chung
	Clinical Research Alliance	Morton Coleman
	Trio–Central Coast Medical	Robert Dichmann
	TriHealth Cancer Institute	David Draper
	Memorial West Cancer Institute	Pablo Ferraro
	Norwalk Hospital	Richard Frank
	Cancer Care Associates	Hugo Hool
	University of Florida Cancer Center Orlando	Omar Kayaleh
	Queens Hospital Center	Mary Kemeny
	Mid Ohio Oncology Hematology	Mark Knapp
	Virginia Crosson Cancer	William Lawler
	Virginia Piper Cancer Institute	Joseph Leach
	Tri-County Associates	Nagaprasad Nagajothi
	Wenatchee Valley Hospital	Lindsay Overton
	Comprehensive Blood & Cancer	Ravindranath Patel
	Thomas Jefferson University Hospital	James Posey
	Franciscan St Francis Center	Stephen Rubenstein
	University of Washington–Seattle Cancer Care Alliance	Veena Shankaran
	Oregon Health & Science University	Gina Vaccaro
	University of South Florida	Vic Velanovich
	Advanced Medical Pain Management Research Clinic	Luis Villa
	Ronald Reagan University of California Los Angeles Medical Center	Zev A. Wainberg
	Cedar Rapids Oncology Project	Deborah Wilbur
	Scott & White Hospital	Lucas Wong

TABLE A2. Patient Disposition and Reasons for Study Treatment Discontinuation During Maintenance Phase (after random assignment)

Disposition/Reason	No. (%)	
	Avelumab (n = 249)	Chemotherapy (n = 250)
Received ≥ one dose of maintenance treatment	243 (97.6)	231 (92.4)
Received ≥ one dose of oxaliplatin	NA	223 (89.2)
Received ≥ one dose of FU or capecitabine	NA	231 (92.4)
Duration of maintenance therapy, months		
Median	3.2	2.8
Range	0.5-34.1	0.5-28.3
Avelumab		NA
Median	3.2	
Range	0.5-34.1	
Oxaliplatin	NA	
Median		2.8
Range		0.5-28.3
FU or capecitabine	NA	
Median		3.2
Range		0.2-30.8
Received BSC only in maintenance phase	NA	7 (2.8)
Received no maintenance treatment	6 (2.4)	12 (4.8)
Maintenance treatment ongoing	18 (7.2)	5 (2.0)
FU or capecitabine only	NA	5 (2.0)
Oxaliplatin only	NA	0 (0.0)
Subsequent anticancer therapy[a]		
≥ One anticancer drug treatment	129 (51.8)	133 (53.2)
Chemotherapy	128 (51.4)	123 (49.2)
Immunotherapy	6 (2.4)	21 (8.4)
Reason for study treatment discontinuation[b]		
PD	174 (69.9)	149 (59.6)
AE	30 (12.0)	31 (12.4)
Withdrawal of consent	12 (4.8)	19 (7.6)
Death	6 (2.4)	7 (2.8)
Protocol noncompliance	0 (0.0)	3 (1.2)
Lost to follow-up	1 (0.4)	0 (0.0)
Other	2 (0.8)	17 (6.8)

Abbreviations: AE, adverse event; BSC, best supportive care; FU, fluorouracil; NA, not applicable; PD, progressive disease.
[a]Per study Protocol, subsequent anticancer treatment was administered after permanent discontinuation of maintenance phase treatment.
[b]For patients who received ≥ one chemotherapeutic agent, reason for discontinuing last chemotherapy is given.

TABLE A3. Best Overall Response (Investigator Assessed per RECIST [Version 1.1]) and Duration of Response

Response/Duration	No. (%)	
	Avelumab (n = 249)	Chemotherapy (n = 250)
Confirmed best overall response		
CR	8 (3.2)	5 (2.0)[a]
PR	25 (10.0)	31 (12.4)
SD[b]	92 (36.9)	117 (46.8)
Non-CR/non-PD[c]	10 (4.0)	11 (4.4)
PD	85 (34.1)	58 (23.2)
Not evaluable	29 (11.6)	28 (11.2)
ORR, %	13.3	14.4
95% CI	9.3 to 18.1	10.3 to 19.4
OR[c]	0.91	
95% CI	0.55 to 1.51	
Disease control rate, %	54.2	65.6
95% CI	47.8 to 60.5	59.4 to 71.5
Patients with objective response, No.	33	36
Duration of response, months		
Median	Not reached	5.9
95% CI	9.7 to NE	4.5 to 7.2
Proportion of responses ongoing, %		
After 12 months	62.3	28.4
95% CI	40.9 to 77.9	13.2 to 45.7
After 24 months	51.0	13.5
95% CI	29.0 to 69.4	3.1 to 31.6

NOTE. Responses were based on subsequent change after random assignment (during maintenance) in patients who had achieved partial response (PR) or stable disease (SD) after induction chemotherapy. Nine patients who had complete response (CR) are not included in the numerator for objective response rate (ORR). Duration of response was calculated in responding patients using Kaplan-Meier method.

Abbreviations: NE, not estimable; OR, odds ratio; PD, progressive disease.

[a]Includes one patient who had CR at re-baseline whose best overall response should have been classified as no evidence of disease.

[b]Minimum duration of SD was 6 weeks after random assignment; includes patients with non-CR/non-PD who had no target lesion after induction chemotherapy (avelumab, n = 10; chemotherapy, n = 11).

[c]Common OR adjusted by stratification factor (Asia *v* non-Asia).

TABLE A4. Overview of Safety Findings During Maintenance Phase (After Random Assignment)

AE	No. (%)	
	Avelumab Arm (n = 243)	Chemotherapy Arm (n = 238)
AE (related or unrelated)	223 (91.8)	214 (89.9)
Grade ≥ 3	132 (54.3)	128 (53.8)
TRAE	149 (61.3)	184 (77.3)
Grade ≥ 3	31 (12.8)	78 (32.8)
AE leading to permanent discontinuation	48 (19.8)	87 (36.6)
TRAE leading to permanent discontinuation[a]	25 (10.3)	65 (27.3)
Serious AE	89 (36.6)	75 (31.5)
Serious TRAE	19 (7.8)	23 (9.7)
AE leading to death	16 (6.6)	13 (5.5)
TRAE leading to death	0	1 (0.4)[b]
Immune-related AE	32 (13.2)	NA
Grade ≥ 3	8 (3.3)	
Infusion-related reaction[c]	48 (19.8)	17 (7.1)
Grade ≥ 3	1 (0.4)	4 (1.7)

Abbreviations: AE, adverse event; NA, not applicable; TRAE, treatment-related adverse event.

[a]TRAEs leading to discontinuation in ≥ 1% of patients were: avelumab arm, pneumonitis (1.6%); chemotherapy arm, peripheral sensory neuropathy (7.6%), peripheral neuropathy (6.7%), neutropenia (2.1%), neurotoxicity (2.1%), thrombocytopenia (1.7%), and decreased appetite (1.3%).

[b]As a result of cerebrovascular accident.

[c]Identified using expanded definition that included both a prespecified list of *Medical Dictionary for Regulatory Activities*–preferred terms (infusion-related reaction, drug hypersensitivity, anaphylactic reaction, or hypersensitivity reaction) that occurred on day of infusion or next day and prespecified signs/symptoms that occurred on day of infusion and resolved within 2 days (related or unrelated).