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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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 vs. 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 1.06). 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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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
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. 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, 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 ≥ 18 years, Eastern Cooperative Oncology Group performance status of 0 or 1, and recently obtained (< 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/m² intravenously (IV) and leucovorin 200 mg/m² (or equivalent levoleucovorin dose) in accordance with label instructions and local guidelines, followed by fluorouracil (FU) 2,600 mg/m² by continuous infusion over 24 hours on day 1, every 2 weeks; oxaliplatin 85 mg/m² IV and leucovorin 400 mg/m² (or equivalent levoleucovorin dose), followed by FU 400 mg/m² IV on day 1 and FU 2,400 mg/m² by continuous infusion over 46 to 48 hours on days 1 to 2, every 2 weeks; or oxaliplatin 130 mg/m² IV and leucovorin 400 mg/m² (or equivalent levoleucovorin dose), followed by FU 400 mg/m² IV on day 1 and FU 2,400 mg/m² by continuous infusion over 46 to 48 hours on days 1 to 2, every 2 weeks; or oxaliplatin 130 mg/m² IV on day 1 and capecitabine 1,000 mg/m² 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 continued 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 \( \geq 1\% \) 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) \( \geq 1\). 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 \( \alpha \) of 2%. This calculation included an interim efficacy analysis, performed after 75% of OS events had occurred. Interim and primary analyses used a sequential \( \alpha \)-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 \( \alpha \) 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 \( \alpha \) level of 0.025; two-sided 95% CIs were calculated using the Clopper-Pearson method. Safety was assessed in all patients who received \( \geq \) 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 \( \geq 1\% \) 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
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

FIG 1. CONSORT diagram. AE, adverse event; BSC, best supportive care; FU, fluorouracil; PD, progressive disease.
## TABLE 1. Baseline Demographic and Clinical Characteristics

| Characteristic                                      | 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)*** |                |                        |
| 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)*** |                  |                        |
| 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***             |                    |                        |
| CR                                                 | 6 (2.4)            | 4 (1.6)                |
| PR                                                 | 117 (47.0)         | 127 (50.8)             |
| SDα                                                | 119 (47.8)         | 115 (46.0)             |
| PDα                                                | 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.

*Re-baseline is after induction chemotherapy and before random assignment.

*Exploratory analysis.

*Based on investigator assessment per RECIST (version 1.1).

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

*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.
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 9.7 months (95% CI, 7.0 to 12.5 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; 54 [12.3%] of 438 evaluable patients), median PFS was 4.3 months (95% CI, 2.9 to 6.8 months) in the avelumab arm and 5.1 months (95% CI, 4.0 to 7.0 months) in the chemotherapy arm (HR, 1.06; 95% CI, 0.76 to 1.49; 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, 4.0 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, the overall response rate (ORR) in patients who had achieved PD-L1–positive tumors, defined as CPS ≥1, was 31.5% (95% CI, 25.7% to 37.4%) 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.

### 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.

| Subgroup, No. | Median OS, months | HR (95% CI) |
|---------------|------------------|-------------|
| Overall | All patients (249 v 250) | 10.4 v 10.9 | 0.90 (0.74 to 1.11) |
| Age, years | < 65 (144 v 140) | 10.0 v 10.5 | 0.95 (0.73 to 1.25) |
| | ≥ 65 (106 v 110) | 11.3 v 11.1 | 0.84 (0.62 to 1.15) |
| Sex | Male (164 v 167) | 11.3 v 10.7 | 0.83 (0.64 to 1.07) |
| | Female (85 v 83) | 9.2 v 11.6 | 1.06 (0.76 to 1.49) |
| Region | Asia (57 v 57) | 10.8 v 11.9 | 0.90 (0.59 to 1.36) |
| | Non-Asia (192 v 193) | 10.2 v 10.9 | 0.91 (0.72 to 1.15) |
| Site of primary tumor | Stomach (174 v 181) | 9.7 v 11.1 | 0.95 (0.74 to 1.20) |
| | GEJ (76 v 69) | 11.8 v 10.9 | 0.62 (0.50 to 1.29) |
| Induction chemotherapy regimen | Oxaliplatin plus FU (139 v 132) | 9.6 v 9.9 | 0.91 (0.70 to 1.20) |
| | Oxaliplatin plus capecitabine (110 v 118) | 11.6 v 12.0 | 0.88 (0.65 to 1.19) |
| Overall response at random assignment (re-baseline) | CR or PR (106 v 106) | 14.2 v 13.0 | 0.89 (0.65 to 1.22) |
| | SD (137 v 137) | 9.7 v 9.6 | 0.85 (0.65 to 1.10) |
| Microsatellite status | Stable (209 v 210) | 10.6 v 10.9 | 0.91 (0.73 to 1.12) |
| | Unstable (MSI-high; 8 v 5) | NR v 8.0 | 0.27 (0.06 to 1.25) |
| Prior gastrectomy | Yes (69 v 66) | 14.2 v 14.6 | 0.90 (0.59 to 1.36) |
| | No (180 v 184) | 9.8 v 9.9 | 0.92 (0.73 to 1.16) |
| No. of metastatic sites at random assignment (re-baseline) | 0 (31 v 29) | 16.3 v 10.7 | 0.52 (0.28 to 0.98) |
| | 1 (43 v 55) | 11.5 v 12.6 | 0.79 (0.48 to 1.29) |
| | 2 (59 v 57) | 9.8 v 11.1 | 1.18 (0.77 to 1.80) |
| | ≥ 3 (116 v 109) | 9.4 v 9.8 | 0.94 (0.70 to 1.25) |

Benefit for Avelumab | Benefit for Chemotherapy
---|---
0.1 | 1.0 | 5.0
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% vs 15.5%) and longer durations of response (probability of ongoing response at 24 months, 51.0% vs 13.5%) compared with chemotherapy.
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 $\geq 1$ (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 $\geq 3$ TRAEs (12.8% vs 32.8%), permanent discontinuations because of TRAEs (10.3% vs 27.3%), and reductions in treatment-related gastrointestinal AEs, hematologic AEs, and neuropathy. The safety profile of avelumab was consistent with previous avelumab mono-therapy 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 $\geq 1$ (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 $\geq 1$). 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 $\geq 1$ (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 $\geq 10$); 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 $\geq 10$ 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–high tumors based on a pre-specified definition (12.4% with $\geq 1$% 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.

**FIG 5.** Treatment-related adverse events (TRAEs) that occurred at any grade in $\geq 10$% or grade $\geq 3$ in $\geq 1$% of patients in either arm during the maintenance phase (after random assignment). GGT, $\gamma$-glutamyltransferase; PPE, palmar-plantar erythrodysesthesia syndrome.
of third-line avelumab versus chemotherapy (JAVELIN Gastric 300; 26.8%) 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). 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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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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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.
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(continued on following page)
| Country                   | Site                                                                 | Principal Investigator  |
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|                           | 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 Hospital 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 | Irina Rozhkova          |
|                           | Kaluga Region                                                        |                         |
|                           | 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 Battle      |
|                           | Hospital Universitario 12 de Octubre                                 | Carlos Martin           |
|                           | Hospital Clinic de Barcelona                                        | Joan Maurel             |
|                           | Hospital Universitario Virgen                                       | Maria Miron             |
|                           | Corporació Sanitaria Parc Taulí                                      | Carles Pericay          |
|                           | Hospital General Universitario Eliche                                | Javier Plazas           |
|                           | Hospital General Universitario Gregorio Maranon                      | Garcia Alfonso Pilar    |
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|                           | 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                                  | Busypamas Chewaskulyong|
|                           | Siriraj Hospital                                                     | Vichien Srimuninimit    |
|                           | Chula Clinical Research Centre                                       | Suebpong Tanasanvimon   |
| Turkey                    | Necmettin Erbakan University Tip Fakültesi                           | Mehmet Artac            |
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|                           | İnönü University Medical Faculty                                     | Hakan Harputluoglu      |
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|                           | Hacettepe University                                                 | Suayb Yalcin            |
|                           | Acibadem Adana Hospital                                              | Sinan Yavuz             |

(continued on following page)
| Country           | Site                                      | Principal Investigator |
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|                   | 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                          | 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                        | Avelumab (n = 249) | Chemotherapy (n = 250) |
|------------------------------------------|--------------------|------------------------|
| **Confirmed best overall response**     |                    |                        |
| CR                                       | 8 (3.2)            | 5 (2.0)*               |
| PR                                       | 25 (10.0)          | 31 (12.4)              |
| SDb                                      | 92 (36.9)          | 117 (46.8)             |
| Non-CR/non-PD*                           | 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           |
| **Disease control rate, %**              |                    |                        |
| 95% CI                                   | 54.2               | 65.6                   |
| 95% CI                                   | 47.8 to 60.5       | 59.4 to 71.5           |
| **Patients with objective response, No.**|                    |                        |
|                                          | 33                 | 36                     |
| **Median duration of response, months**  |                    |                        |
| 95% CI                                   | Not reached        | 5.9                    |
|                                          | 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.

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

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).

Common OR adjusted by stratification factor (Asia v non-Asia).
### TABLE A4. Overview of Safety Findings During Maintenance Phase (After Random Assignment)

| AE                                                   | 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)*                   |
| 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.

*aTRAEs 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%).

*bAs a result of cerebrovascular accident.

*cIdentified 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).