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Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/oesophageal adenocarcinoma (CheckMate 649): a multicentre, randomised, open-label, phase 3 trial

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YJ, KS, MM, and JA contributed to the concept and design of the study in collaboration with Bristol Myers Squibb. All authors gathered the data. VP, DC, M Lei, HX, and M Li analysed the data and all authors interpreted the data. All authors participated in developing or revising the manuscript, and provided final approval to submit the manuscript for publication.

Data sharing

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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Summary

Background—First-line chemotherapy for advanced/metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric/gastroesophageal junction (GEJ) adenocarcinoma results in median overall survival (OS) <1 year. The phase 3 CheckMate 649 study evaluated first-line programmed death (PD)-1 inhibitor-based therapies in gastric/GEJ/oesophageal adenocarcinoma; we report first results for nivolumab-plus-chemotherapy versus chemotherapy.

Methods—We enrolled adults with previously untreated, unresectable, non-HER2-positive gastric/GEJ/oesophageal adenocarcinoma, regardless of PD-ligand (L)1 expression. Patients were randomised to nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks)-plus-chemotherapy (XELOX every 3 weeks or FOLFOX every 2 weeks), nivolumab-plus-ipilimumab, or chemotherapy. Primary endpoints for nivolumab-plus-chemotherapy versus chemotherapy were OS or progression-free survival (PFS) by blinded independent central review, in PD-L1 combined positive score (CPS) ≥5 patients. Safety was assessed in all patients who received at least one dose of the assigned treatment.

Findings—From March 2017 through April 2019, we concurrently randomised 1581 patients to treatment (nivolumab-plus-chemotherapy, 789; chemotherapy, 792). The median follow-up for OS was: nivolumab-plus-chemotherapy, 13·1 months (IQR, 6·7–19·1) and chemotherapy, 11·1 months (5·8–16·1). Nivolumab-plus-chemotherapy resulted in significant improvements in OS (hazard ratio [HR] 0·71 [98·4% CI 0·59–0·86]; p<0·0001) and PFS (HR 0·68 [98% CI 0·56–0·81]; p<0·0001) versus chemotherapy in PD-L1 CPS ≥5 patients (minimum follow-up, 12·1 months). Additional results showed significant improvement in OS, along with PFS benefit, in PD-L1 CPS ≥1 and all-randomised patients. Among all-treated patients, 462 (59%, nivolumab-plus-chemotherapy) and 341 (44%, chemotherapy) patients had grade 3–4 treatment-related adverse events. No new safety signals were identified.

Interpretation—Nivolumab is the first PD-1 inhibitor to demonstrate superior OS, along with PFS benefit, and an acceptable safety profile, in combination with chemotherapy versus chemotherapy alone in previously untreated patients with advanced gastric/GEJ/oesophageal adenocarcinoma. Nivolumab-plus-chemotherapy represents a potential standard first-line treatment for these patients.

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Introduction

Gastric cancer, including gastroesophageal junction (GEJ) cancer, is the fourth leading cause of cancer-related deaths worldwide.[1] Adenocarcinoma is the most common (>90%)

histological type of gastric and GEJ cancer[2] and accounts for approximately 65% and 40% of oesophageal cancer in North America and Europe, respectively.[3]

Fluoropyrimidine plus platinum-based chemotherapy, the standard first-line treatment for unresectable advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric and GEJ adenocarcinoma, results in poor survival (median overall survival [OS] less than 1 year).[4–11] Gastric/GEJ and oesophageal adenocarcinomas share similarities in their molecular profiles[12,13] and have comparable clinical outcomes with systemic chemotherapy in an advanced setting.[14,15] Although several targeted agents have been evaluated as first-line treatment for HER2-negative gastric and GEJ adenocarcinoma, none has significantly prolonged survival relative to chemotherapy.[8–11,16]

The programmed death (PD)-1 inhibitor nivolumab provided superior OS versus placebo in heavily pretreated advanced or recurrent gastric or GEJ cancer in the phase 3 ATTRACTION-2 study.[17] Chemotherapy, in addition to its direct cytotoxic properties, may contribute to antitumour immune response elicited by nivolumab through induction of immunogenic cell death.[18–20] PD-ligand (L)1 expression on tumour cells and tumour-associated immune cells (combined positive score [CPS]) has shown better enrichment for efficacy of checkpoint inhibitors than tumour cell PD-L1 expression in advanced gastric/GEJ/oesophageal adenocarcinoma.[21–23]

The phase 3 CheckMate 649 study evaluated PD-1 inhibitor-based therapies in previously untreated advanced gastric/GEJ/oesophageal adenocarcinoma; here we report results from the nivolumab plus chemotherapy versus chemotherapy groups.

Methods

Study design and participants

We conducted a multicentre, randomised, open-label, phase 3 study at 175 sites in 29 countries. Eligible patients were 18 years of age or older, with previously untreated, unresectable advanced or metastatic gastric, GEJ, or oesophageal adenocarcinoma, regardless of PD-L1 expression. Other key inclusion criteria were measurable (at least one lesion) or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; Eastern Cooperative Oncology Group performance status of 0 or 1; adequate organ function; and availability to provide a fresh or archival tumour sample to evaluate PD-L1. Patients with prior adjuvant or neoadjuvant chemotherapy, radiotherapy, and/or chemoradiotherapy (administered at least 6 months before randomisation) were allowed. Patients with known HER2-positive status; untreated central nervous system metastases peripheral neuropathy (> grade 1); active, known, or suspected autoimmune disease; positive test result for hepatitis B or hepatitis C virus; and known history of positive test for human immunodeficiency virus or known acquired immunodeficiency syndrome were excluded.

During enrolment, the primary population was amended to patients whose tumours expressed PD-L1 CPS ≥5 based on results from the gastroesophageal cohort of CheckMate 032 and other published studies suggesting that PD-L1 CPS may be better associated with

anti–PD-1 therapy efficacy than tumour cell PD-L1 expression.[21–23] Patients continued to be enrolled regardless of PD-L1 expression.

The trial was conducted according to Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the trial protocol (appendix protocol). The protocol was approved by the institutional review boards or independent ethics committees at each site. All patients provided written informed consent per Declaration of Helsinki principles. An independent data monitoring committee monitored safety and efficacy data.

Randomisation and masking

Patients were randomly assigned to nivolumab plus chemotherapy (XELOX [capecitabine and oxaliplatin] or FOLFOX [fluorouracil, leucovorin, and oxaliplatin]) or nivolumab plus ipilimumab versus chemotherapy alone at a 1:1:1 ratio after the nivolumab plus chemotherapy group was added and later at a ratio of 1:1 after enrolment in the nivolumab plus ipilimumab group was closed. We report results from patients concurrently randomised to nivolumab plus chemotherapy versus chemotherapy; results for nivolumab plus ipilimumab versus chemotherapy remain blinded and will be reported later.

Randomisation was performed using interactive (voice/web) response technology (block size 6) and stratified according to tumour cell PD-L1 status (≥1% *vs* <1% or indeterminate), region (Asia *vs* United States and Canada *vs* rest of world), Eastern Cooperative Oncology Group performance status (0 *vs* 1), and type of chemotherapy (XELOX *vs* FOLFOX). After informed consent was obtained, the patient was enrolled and assigned to treatment, and a treatment allocation list was generated by the sponsor. The web registration system was implemented by a third party, which ensured that the assignment sequence was concealed until the treatment allocation was completed. The study was open label so investigators were not blinded to treatment allocation.

Procedures

Patients were administered nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks) plus investigator's choice of chemotherapy (XELOX [capecitabine 1000 mg/m^2 twice daily, days 1–14 and oxaliplatin 130 mg/m^2, day 1, every 3 weeks] or FOLFOX [leucovorin 400 mg/m^2, day 1, fluorouracil 400 mg/m^2, day 1 and 1200 mg/m^2, days 1–2, and oxaliplatin 85 mg/m^2, day 1, every 2 weeks]) or chemotherapy alone. All treatments were administered intravenously except for capecitabine, which was administered orally. Treatment continued until documented disease progression, unacceptable toxicity, withdrawal of consent, or study end. Nivolumab was given for a maximum of 2 years. Chemotherapy was given per local standards. Patients were permitted to continue treatment beyond initial disease progression (per RECIST version 1.1) in the nivolumab plus chemotherapy group, based on investigator judgment.

Tumours were assessed using computed tomography or magnetic resonance imaging per RECIST version 1.1, by blinded independent central review (BICR) at baseline, every 6 weeks from the start of cycle 1 for 48 weeks, and every 12 weeks thereafter until disease progression.

PD-L1 immunohistochemistry was performed at two central laboratories using the Dako PD-L1 immunohistochemistry 28–8 pharmDx assay (Dako, an Agilent Technologies company, Santa Clara, CA, USA), which has been analytically validated in gastric/GEJ/oesophageal adenocarcinoma, according to the manufacturer's instructions with the Dako Autostainer Link-48 system. Tumour cell PD-L1 expression was defined as the percentage of viable tumour cells with partial or complete membrane staining in at least 100 viable tumour cells. CPS was generated by rescoring PD-L1 stained slides using the CPS algorithm, defined as the number of PD-L1–positive tumour cells (partial or complete membrane staining), lymphocytes, and macrophages (membrane staining and/or intracellular staining) divided by the total number of viable tumour cells multiplied by 100.

Treatment-related adverse events (TRAEs) included events reported between first dose and 30 days after last dose of study therapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and Medical Dictionary for Regulatory Activities, version 23.0, per investigator assessment. Treatment-relatedness in the nivolumab plus chemotherapy group refers to nivolumab, at least one chemotherapy component, or both. Patients were allowed to discontinue individual treatment components and continue on other components in a combination regimen (appendix protocol). TRAEs leading to discontinuation due to any treatment component were recorded in a cumulative manner throughout the duration of treatment and used to calculate the proportion of patients who discontinued treatment due to TRAEs.

Outcomes

Dual primary endpoints for the nivolumab plus chemotherapy versus chemotherapy groups were OS (time from randomisation to death) or progression-free survival (PFS; time from randomisation to the date of first documented tumour progression or death) by BICR per RECIST version 1.1, evaluated in patients with PD-L1 CPS ≥5. Hierarchically tested secondary endpoints were OS in patients with PD-L1 CPS ≥1 and all randomised patients. Additional secondary endpoints that were not formally tested included BICR-assessed PFS and objective response rate at different PD-L1 CPS cutoffs and in all randomised patients. Key prespecified exploratory endpoints included BICR-assessed duration of response; landmark survival rates; biomarkers potentially predictive of efficacy; health-related quality of life (HRQoL); and safety and tolerability.

All randomised patients included all enrolled patients who were randomised concurrently to either nivolumab plus chemotherapy or chemotherapy. Patients with PD-L1 CPS ≥5 included all randomised patients whose tumours expressed PD-L1 CPS ≥5. Objective response was evaluated in all randomised patients who had at least one target/measurable lesion at baseline. Safety analysis was conducted in all treated patients, which included all randomised patients who received at least one dose of study treatment during the trial. Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) analysis was performed for patients with PD-L1 CPS ≥5 and all randomised patients who had an assessment at baseline (day 1, assessment prior to administration of treatment on day of first dose) and at least one subsequent assessment while on treatment. Additional details about HRQoL are in the appendix (p 3). Time to symptom deterioration (TTSD) analysis was conducted in patients

with PD-L1 CPS ≥5 and all randomised patients with intent to treat. Biomarker analysis was conducted in all randomised patients with available biomarker data (eg, PD-L1 expression by tumour cell PD-L1 expression and other assays).

Statistical analysis

For the dual primary endpoints, two-sided significance levels of 0·03 and 0·02 (type I error) were allocated to OS and PFS, respectively. Upon superiority of OS in patients with PD-L1 CPS ≥5, it was hierarchically tested in patients with PD-L1 CPS ≥1 with a fraction of alpha (50% α transmitted=0·015), followed by all randomised patients (100% α transmitted=0·015). The study was designed to conduct the final PFS and interim OS analyses at 12-month minimum follow-up and final OS analysis at 24-month minimum follow-up. Lan and DeMets α-spending functions were employed to determine the significance level for the interim analysis of OS.

With an assumed PD-L1 CPS ≥5 prevalence of 35%, based on limited available data,[21–23] it was estimated that the primary population would consist of 554 patients. For OS, the hazard ratio (HR) was modelled as a two-piece HR, a delayed effect for the first 6 months followed by a constant HR of 0·65 thereafter, providing an average HR of 0·74. At final analysis, it was expected that 466 events would provide approximately 85% power. The HR for PFS was modelled as a two-piece HR with a delayed effect for the first 3 or 6 months followed by a constant HR of 0·56. At 12-month minimum follow-up, the expected numbers of PFS events were estimated to be 497 for a 3-month delay with approximately 99% power and 506 for a 6-month delay with approximately 60% power.

All patients with PD-L1 CPS ≥5 concurrently randomised to the nivolumab plus chemotherapy or chemotherapy groups were included in the primary OS and PFS analyses. For OS and PFS, the stratified log-rank test was used to compare the treatment groups and the stratified Cox proportional hazards regression model was used to estimate the HR. The proportional hazards assumption was tested using a Cox model with treatment and treatment by time interaction at prespecified significance level of 0·1. For time-to-event endpoints, the median was estimated using the Kaplan-Meier method, and the corresponding two-sided 95% confidence intervals (CIs) were calculated using the log-log transformation method. A post-hoc exploratory analysis was performed to assess a potential treatment effect by baseline characteristics on OS using Cox proportional hazards model with treatment, subgroup, and treatment by subgroup interaction as terms. P values for interaction are provided and there were no adjustments for multiplicity. A prespecified analysis evaluated the treatment effect by biomarker (PD-L1 CPS, tumour cell PD-L1, and microsatellite instability [MSI]) on OS and PFS in all randomised patients using Cox models fitted with the biomarker as categorical variable, the treatment, and the interaction between the biomarker and treatment. The significance level for interaction was predefined at 0·2.

Stratification factors as recorded in interactive (voice/web) response system were used for stratified analyses. The proportion of patients who survived at a given timepoint was derived from the Kaplan-Meier method with corresponding two-sided 95% CIs calculated based on the Greenwood formula for variance derivation based on log-log transformation. The proportion of patients with an objective response and corresponding two-sided 95% CIs

were calculated using the Clopper-Pearson method. For subgroup analyses of OS, PFS, and objective response, unstratified HRs and corresponding 95% CIs for nivolumab plus chemotherapy relative to chemotherapy were calculated using a Cox proportional-hazards regression model with treatment as the covariate. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Role of the funding source

The study was sponsored and conducted by Bristol Myers Squibb, in collaboration with Ono Pharmaceutical Co., Ltd. The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the clinical study report. All authors had access to all study data, participated in developing or reviewing the manuscript, and provided final approval to submit the manuscript for publication.

Results

From March 2017 through April 2019, 2687 patients were assessed for eligibility at 175 sites in 29 countries. Of these, 1581 patients were concurrently randomised to receive nivolumab plus chemotherapy (789 patients) or chemotherapy (792 patients); 1549 patients received one or more doses of the assigned treatment (nivolumab plus chemotherapy, 782 patients; chemotherapy, 767 patients; figure 1).

The median follow-up for OS (time from concurrent randomisation of the last patient to last known date alive or death) was 13·1 months (IQR, 6·7–19·1) in the nivolumab plus chemotherapy group and 11·1 months (5·8–16·1) in the chemotherapy group. A total of 698 and 728 patients discontinued treatment with nivolumab plus chemotherapy and chemotherapy, respectively; the most common reason for treatment discontinuation in both groups was disease progression (515 patients [66%] and 528 patients [69%], respectively; figure 1).

Baseline characteristics were balanced across the treatment groups in the primary population (PD-L1 CPS ≥5) and all randomised patients (table 1 and appendix p 4). A total of 473 (60%) of 789 patients in the nivolumab plus chemotherapy group and 482 (61%) of 792 patients in the chemotherapy group had tumours expressing PD-L1 CPS ≥5. Most patients were non-Asian (1206 [76%] of 1581) and most had gastric cancer (1110 [70%] of 1581), while 260 (16%) had GEJ cancer and 211 (13%) had oesophageal adenocarcinoma.

Both primary endpoints were met. At a minimum follow-up (time from concurrent randomisation of the last patient to data cutoff [May 27, 2020]) of 12·1 months, nivolumab plus chemotherapy demonstrated superior OS, with a 29% reduction in the risk of death compared with chemotherapy (HR 0·71 [98·4% CI 0·59–0·86]; p<0·0001) and a 3·3-month improvement in median OS (14·4 months [95% CI 13·1–16·2] *vs* 11·1 months [10·0–12·1], respectively) in patients with PD-L1 CPS ≥5 (figure 2A). The proportion of patients alive at 12 months was numerically higher with nivolumab plus chemotherapy (57% [95% CI 53–62]) than with chemotherapy (46% [95% CI 42–51]). Nivolumab plus chemotherapy also provided superior PFS in patients with PD-L1 CPS ≥5, with a 32% reduction in the risk of progression or death versus chemotherapy (HR 0·68 [98% CI 0·56–0·81]; p<0·0001) (figure

3A). Median PFS was 7·7 months (95% CI 7·0–9·2) with nivolumab plus chemotherapy versus 6·05 months (5·6–6·9) with chemotherapy. The 12-month PFS estimate was 36% (95% CI 32–41) with nivolumab plus chemotherapy versus 22% (95% CI 18–26) with chemotherapy.

In addition to the primary population, nivolumab plus chemotherapy demonstrated a significant improvement in OS in patients with PD-L1 CPS ≥1 and all randomised patients versus chemotherapy (HR 0·77 [99·3% CI 0·64–0·92]; p<0·0001 and 0·80 [0·68–0·94]; p=0·0002, respectively) (figure 2B–C). The interaction p value between treatment and time when testing the proportional hazards assumption was non-significant based on the predefined level (0·1) for all endpoints prespecified in the statistical hierarchy, supporting that the proportional assumptions were not violated (appendix p 5). While not formally tested, HRs of 0·74 (95% CI 0·65–0·85) and 0·77 (0·68–0·87) indicated that PFS benefit was also observed with nivolumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS ≥1 and all randomised patients, respectively (figure 3B–C).

The unstratified HRs for OS with nivolumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS <1 and <5 were 0·92 (95% CI 0·70–1·23) and 0·94 (0·78–1·13), respectively; unstratified HRs for PFS were 0·93 (0·69–1·26) and 0·93 (0·76–1·12), respectively (appendix p 11). Interaction analysis of OS by PD-L1 CPS cutoffs showed significant interaction by PD-L1 CPS at the cutoff of 5 (p=0·0107) but not at the cutoff of 1 (p=0·2041) (appendix p 11).

The HRs for OS favoured nivolumab plus chemotherapy over chemotherapy across multiple prespecified subgroups in patients with PD-L1 CPS ≥5 and in all randomised patients (appendix p 12 and 13). The unstratified HRs for OS with nivolumab plus chemotherapy versus chemotherapy among patients with MSI-high and microsatellite stable tumours were 0·33 (95% CI 0·12–0·87) and 0·73 (0·62–0·85), respectively, in patients with PD-L1 CPS ≥5 and 0·37 (0·16–0·87) and 0·80 (0·71–0·91), respectively, in all randomised patients. Post-hoc interaction analyses indicated no evident interaction of treatment effect on OS by the majority of the baseline demographics and disease characteristics subgroups.

In the primary population, 226 (60% [95% CI 55–65]) of 378 patients in the nivolumab plus chemotherapy group and 177 (45% [40–50]) of 391 patients in the chemotherapy group achieved an objective response (per BICR assessment). The proportion of patients with a complete response was 12% and 7%, respectively, and median duration of response was 9·5 months (95% CI 8·0–11·4) versus 7·0 months (5·7–7·9), respectively (appendix p 6 and 15). Consistent results were observed in all randomised patients (appendix p 6 and 15). The proportion of patients with PD-L1 CPS <1 and <5 who achieved objective response was 51% (47 of 93 patients) and 55% (121 of 219 patients) in the nivolumab plus chemotherapy group and 41% (35 of 85 patients) and 46% (97 of 209 patients) in the chemotherapy group, respectively (appendix p 11).

Among all randomised patients, 297 (38%) of 789 patients in the nivolumab plus chemotherapy group and 326 (41%) of 792 patients in the chemotherapy group received at least one subsequent therapy for advanced gastric/GEJ/oesophageal adenocarcinoma. The

most common subsequent therapy in both groups was systemic anticancer therapy (268 [34%] of 789 and 311 [39%] of 792 patients, respectively); 12 (2%) and 64 (8%) patients received subsequent immunotherapy, respectively (appendix p 7).

Among all treated patients, the median (IQR) treatment duration was 6·8 months (3·7–13·3) with nivolumab plus chemotherapy and 4·9 months (2·5–8·4) with chemotherapy (appendix p 8). The most common TRAEs were nausea, diarrhoea, and peripheral neuropathy across both groups (table 2). Grade 3–4 treatment-related adverse events (TRAEs) occurred in 462 of 782 (59%) and 341 of 767 (44%) patients, respectively, and any-grade TRAEs leading to discontinuation were reported in 284 (36%) and 181 (24%) patients, respectively (table 2). Any-grade serious TRAEs were reported in 172 (22%) of 782 patients treated with nivolumab plus chemotherapy (grade 3–4, 131 patients [17%], four grade 5 events), and in 93 (12%) of 767 patients treated with chemotherapy (grade 3–4, 77 patients [10%], no grade 5 events). Sixteen deaths (2%) in the nivolumab plus chemotherapy group and four deaths (<1%) in the chemotherapy group were considered treatment related (table 2). Of the 16 deaths in the nivolumab plus chemotherapy group, four were deemed to be related to nivolumab, five to nivolumab plus chemotherapy, and seven to chemotherapy (appendix p 9). Dose delays due to any-grade TRAEs were observed in 524 of 782 (67%) and 447 of 767 (58%) patients in the nivolumab plus chemotherapy and chemotherapy groups, respectively. Modifications in chemotherapy doses were comparable across groups (appendix p 8). The majority of TRAEs with potential immunologic aetiology were grade 1 or 2; grade 3–4 events occurred in ≤5% of patients (appendix p 10).

The proportion of patients with PD-L1 CPS ≥5 and all randomised patients completing the FACT-Ga questionnaire was ≥90% at baseline and ≥80% at most subsequent assessments for which at least ten patients responded (until week 109). Baseline FACT-Ga total scores were similar between the nivolumab plus chemotherapy and chemotherapy groups for patients with PD-L1 CPS ≥5 (127·6 [standard deviation, 27·4] and 127·6 [26·4], respectively) and all randomised patients (126·6 [28·3] and 126·8 [26·8], respectively), with an improvement from baseline in FACT-Ga total score at all on-treatment assessments. In patients with PD-L1 CPS ≥5 and all randomised patients, the least squares mean difference between treatment groups favoured nivolumab plus chemotherapy versus chemotherapy (at timepoints with ≥50 patients in each group). However, this was less than the minimally important difference of 15·1 points (appendix p 16). Patients in the nivolumab plus chemotherapy group had decreased risk of symptom deterioration compared with the chemotherapy group while on treatment (patients with PD-L1 CPS ≥5, HR 0·64 [95% CI 0·49–0·83] and all randomised patients, HR 0·77 [0·63–0·95]) (appendix p 17).

Discussion

CheckMate 649 met both primary endpoints and all formally tested secondary endpoints. This is the first global study to demonstrate superior OS in a randomised controlled trial with a median OS exceeding 1 year in the first-line setting for patients with non–HER2-positive gastric/GEJ/oesophageal adenocarcinoma, where treatment options are limited and no advances have been made in recent years. With over 1580 patients randomised, nivolumab plus chemotherapy provided a significant and clinically meaningful OS benefit in

patients with PD-L1 CPS ≥5 and ≥1, as well as in all randomised patients. PFS benefit was also observed in these populations, including when statistically tested in patients with PD-L1 CPS ≥5.

The proportion of patients with an objective response was numerically higher, with more complete and durable responses with nivolumab plus chemotherapy versus chemotherapy, in patients with PD-L1 CPS ≥5 and all randomised patients. The numerically higher 12-month OS and PFS estimates versus chemotherapy with sustained separation of Kaplan-Meier curves also suggest durable benefit with nivolumab plus chemotherapy in these populations.

The efficacy results demonstrate significant survival advantage with nivolumab plus chemotherapy for each endpoint prespecified by statistical hierarchical testing (PD-L1 CPS ≥5 and ≥1, and all randomised patients). The relatively large proportion of patients whose tumours express PD-L1 CPS ≥5 in the overall study population impacts the magnitude of the benefit observed in patients with PD-L1 CPS ≥1 and all randomised patients. In an exploratory analysis, the unstratified HRs for OS with nivolumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS <1 and <5 were higher than in all randomised patients. The observed HRs indicate enrichment of OS and PFS benefit with higher PD-L1 CPS cutoffs, along with a significant interaction of OS by PD-L1 CPS at the cutoff of 5 but not at the cutoff of 1. However, the higher objective response observed with nivolumab plus chemotherapy relative to chemotherapy across PD-L1 CPS cutoffs, including CPS <1 and <5, coupled with the potential for delayed treatment effect often seen with immuno-oncology therapy, suggests the magnitude of survival benefit may improve in these patients with longer follow-up.

CheckMate 649 enrolled patients regardless of PD-L1 CPS expression and to date is the most robust dataset to report CPS prevalence using a validated assay in advanced gastric, GEJ, or oesophageal adenocarcinoma. At the time of study amendment, a conservative PD-L1 CPS ≥5 prevalence of 35% was assumed based on limited available data in this disease setting.[21–23] The prevalence of PD-L1 CPS ≥5 (60% of all randomised patients) observed in this large, randomised controlled trial was numerically higher than that reported in previous studies in gastric, GEJ, or oesophageal adenocarcinoma (17–50%).[22,24,25] This variation in prevalence of PD-L1 CPS ≥5 may be attributed to several factors, including tumour heterogeneity, differences in patient population, and methodology.[26,27] Future studies are needed to explore the analytical concordance of the assays and the factors that influence the prevalence of PD-L1 CPS expression in gastric/GEJ/oesophageal adenocarcinoma.

OS consistently favoured nivolumab plus chemotherapy versus chemotherapy across multiple prespecified baseline demographics and disease characteristics in the primary population and all randomised patients. Particularly, survival benefit with nivolumab plus chemotherapy occurred regardless of MSI status, although the 3% of patients with MSI-high tumours had greater reduction in the risk of death than those with microsatellite stable tumours. Post-hoc interaction analyses confirmed that the majority of the baseline demographics and disease characteristics were not determinant of the OS benefit. While the prespecified interaction p value for tumour cell PD-L1 status was less than 0·2, the HRs for OS were less than 1 in both subgroups of patients with tumour cell PD-L1 expression

≥1% and <1%, suggesting a difference in magnitude of effect but no change in the direction of the treatment effect. Further research is needed to characterise patients with advanced gastric/GEJ/oesophageal adenocarcinoma who may derive the greatest clinical benefit from immunotherapies.

Pembrolizumab plus chemotherapy did not result in significant improvement in OS versus chemotherapy in patients with advanced or recurrent gastric/GEJ adenocarcinoma and PD-L1 CPS ≥1 (HR 0·85; p=0·05) and ≥10 (HR 0·85; p=0·16) in the smaller KEYNOTE-062 study. In the phase 3 part of the Asian ATTRACTION-4 study of previously untreated advanced gastric/GEJ cancer, nivolumab plus chemotherapy significantly improved PFS (HR 0·68; p<0·001) but not OS (HR 0·90; p=0·26) in the all randomised population.[28] The differences in efficacy observed among these three studies could be due to differences in study design (including statistical considerations, biomarker selection, patient population, geography, and treatment regimens including chemotherapy backbone) and subsequent therapies. A large proportion of patients (66%) received subsequent therapy in ATTRACTION-4.[28] The proportion (39%) of patients receiving subsequent therapy observed in CheckMate 649 was consistent with the global phase 3 KEYNOTE-062 study and may reflect the practice patterns and limited therapeutic options in some countries.

The safety profile of nivolumab plus chemotherapy was consistent with the known safety profiles of the individual treatments and no new safety signals were identified.[11,17,28–30] Duration of chemotherapy was similar among the treatment groups when comparing the same chemotherapy backbone, suggesting that the addition of nivolumab did not negatively impact chemotherapy administration. Treatment-related deaths were more common in the nivolumab plus chemotherapy group versus chemotherapy. However, seven out of 16 deaths in the nivolumab plus chemotherapy group were related to chemotherapy alone and the overall proportion of treatment-related deaths was low (2%), consistent with that observed in other first-line PD-1–inhibitor-chemotherapy regimens in gastric/GEJ adenocarcinoma.[16,28] Despite more frequent grade 3–4 TRAEs and events leading to discontinuation with nivolumab plus chemotherapy versus chemotherapy, grade 3–4 TRAEs with potential immunologic aetiology occurred in ≤5% of patients, and the overall safety profile was acceptable. There was a trend towards improved HRQoL with nivolumab plus chemotherapy, although not clinically meaningful per the predefined threshold, along with a decreased risk of TTSD while on treatment, suggesting that the addition of nivolumab maintains HRQoL. The acceptable safety profile combined with significant improvement in OS, along with PFS benefit, improved and durable objective responses, and maintained HRQoL, indicate a favourable benefit-risk profile for nivolumab plus chemotherapy.

Our study had some limitations. Based on data available at the time of study design, tumour cell PD-L1 expression was chosen as a stratification factor for CheckMate 649. Following reports which indicated that PD-L1 CPS had better enrichment for efficacy than tumour cell PD-L1 expression in advanced gastric/GEJ/oesophageal adenocarcinoma,[21–23] the protocol was amended to use PD-L1 CPS ≥5 to define the primary population. Although tumour cell PD-L1 expression remained a stratification factor, patients whose tumours expressed PD-L1 CPS ≥5 were balanced between the two treatment groups. In addition, demographics and baseline disease characteristics were balanced between treatment groups in the PD-L1 CPS

≥5 population. Patients with known HER2-positive status were excluded from CheckMate 649. However, because HER2 testing may not have been performed routinely at all study sites, patients with unknown HER2 status were permitted to be enrolled. Importantly, the proportion of these patients (~40%) was balanced across the treatment groups. Based on the known incidence of HER2-overexpressing tumours in gastric/GEJ cancer (~20%),[31–35] it is expected that the majority of patients with not reported HER2 status in this study were HER2-negative. Another limitation of CheckMate 649 is its open-label study design, which may have potentially influenced patient responses in the HRQoL questionnaires and adverse event causality assessment. However, an open-label design was considered appropriate due to the inclusion of multiple treatments with different dosing regimens. Centrally assessed primary endpoints and adverse event management using standard treatment algorithms were not expected to be impacted by bias.

In conclusion, nivolumab is the first PD-1 inhibitor to demonstrate superior OS, along with clinically meaningful PFS benefit, improved and durable objective responses, maintained HRQoL, and an acceptable safety profile, in combination with chemotherapy versus chemotherapy alone in previously untreated patients with advanced gastric/GEJ/oesophageal adenocarcinoma and represents a potential standard first-line treatment for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Declaration of interests

YYJ reports receiving consulting/advisory board fees from AstraZeneca, Daiichi Sankyo, Imugene, Jounce Therapeutics, Merck Serono, Michael J. Hennessy Associates, Paradigm Medical Communications, LLC, Pfizer, Seattle, Genetics, Zymeworks Inc.; receiving consulting/advisory and research funding from Eli Lilly, Bristol Myers Squibb, Merck & Co, Inc; receiving research funding from Bayer, Boehringer Ingelheim, Genentech/Roche, MSK Cancer Center Support Grant/Core Grant (P30 CA008748), and Ono Pharmaceutical Company; receiving speaker's bureau fees from the American Society of Clinical Oncology; and receiving stock options from Rgenix, outside the submitted work. KS reports receiving personal fees for advisory roles from AbbVie, Inc., Bristol Myers Squibb, GlaxoSmithKline, Novartis, Ono Pharmaceutical Company, Pfizer Inc, and Takeda; receiving advisory role/research funding from Astellas Pharma, Eli Lilly, Merck Pharmaceutical, and Taiho Pharmaceutical; receiving honoraria (lecture fee) from AbbVie Inc, Novartis, and Yakult Honsha; receiving research funding from Chugai Pharma, Daiichi Sankyo, Dainippon Sumitomo Pharma, and Medi Science, outside the submitted work. MM reports receiving research grants from AIO, Amgen, German Federal Ministry of Education and Research, Bristol Myers Squibb, European Organisation for Research and Treatment of Cancer, German Cancer Aid, Merck Serono, Merck Sharpe & Dohme, and Pfizer; receiving personal fees from Bristol Myers Squibb, Falk Foundation, Lilly, MCI Group, Merck Serono, Merck Sharpe & Dohme, Pfizer, and Roche; and receiving non-financial support from AIO, Amgen, Bristol Myers Squibb, German Federal Ministry of Education and Research, European Organisation for Research and Treatment of Cancer, and German Cancer Aid, outside the submitted work. MG reports receiving grants and personal fees from Bristol Myers Squibb and Novartis; and receiving personal fees from Merck Sharpe & Dohme and Roche, outside the submitted work. KY reports receiving grants and personal fees from Daiichi-Sankyo, Ono Pharmaceutical Company, Taiho Pharmaceutical, and Yakult Honsha; receiving personal fees from

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Research in context

Evidence before this study

We searched PubMed in November 2020 for English language articles, using the terms "Gastric OR Gastroesophageal Junction OR Esophagogastric Junction OR Esophageal adenocarcinoma OR Oesophageal adenocarcinoma," and "PD-1 OR PD-L1," and "First-line OR Previously untreated OR Treatment naive" in the title or abstract, with no time limits. To identify results from clinical trials that were not yet published in peer-reviewed journals, we also searched the American Society of Clinical Oncology and European Society for Medical Oncology congress websites for publications between September 1, 2018, and December 1, 2020, using the same key words. Our search identified 259 abstracts, from which we selected primary publications from randomised phase 3 studies of PD-1 or PD-L1 inhibitors in previously untreated patients with advanced gastric cancer and/or gastroesophageal junction cancer and/or oesophageal adenocarcinoma (GC/GEJC/EAC). Using these criteria, four studies with efficacy and safety data were identified: ATTRACTION-4, KEYNOTE-062, KEYNOTE-590, and JAVELIN Gastric 100. In the phase 3 ATTRACTION-4 study of previously untreated Asian patients with advanced GC/GEJC, nivolumab plus chemotherapy significantly improved progression-free survival (PFS) but not overall survival (OS) in the all randomised population with a manageable safety profile. Similarly, in the global, phase 3 KEYNOTE-062 study, which enrolled patients with PD-L1 combined positive score (CPS) ≥1, pembrolizumab plus chemotherapy did not provide superior OS benefit but provided a modest improvement in PFS and objective response with a manageable safety profile in patients with advanced or recurrent GC/GEJC with PD-L1 CPS ≥1 or ≥10. In the phase 3 KEYNOTE-590 study of oesophageal/GEJC (mainly squamous cell carcinoma histology), first-line pembrolizumab plus chemotherapy provided improved OS and PFS in advanced unresectable or metastatic gastroesophageal junction (Siewert type 1) or oesophageal adenocarcinoma in a subgroup analysis and a manageable safety profile. In the phase 3 JAVELIN Gastric 100 study of advanced GC/GEJC, avelumab maintenance after first-line chemotherapy did not demonstrate superior OS versus continued chemotherapy in the primary population of all randomised patients or in patients with tumour cell PD-L1 expression ≥1%.

Added value of this study

With nearly 1600 patients randomised in the CheckMate 649 trial, nivolumab in combination with chemotherapy demonstrated superior OS, along with PFS benefit, versus chemotherapy alone in previously untreated patients with advanced GC/GEJC/EAC. To our knowledge, CheckMate 649 is the first global study to demonstrate superior OS with a median OS exceeding 1 year in the first-line setting for patients with non–human epidermal growth factor receptor 2-positive GC/GEJC/EAC. The safety profile of nivolumab plus chemotherapy was consistent with the known safety profiles of the individual treatment components and no new safety signals were identified. Although grade 3–4 treatment-related adverse events and events leading to discontinuation were more frequent with nivolumab plus chemotherapy versus chemotherapy, the safety profile was acceptable in the context of the significant improvement in OS, along with PFS

benefit, improved and durable objective responses, and maintained health-related quality of life.

Implications of all the available evidence

The CheckMate 649 trial addresses a high unmet need in previously untreated patients with GC/GEJC/EAC, where no advances have been made in recent years. Nivolumab is the first PD-1 inhibitor to demonstrate superior OS, along with PFS benefit and an acceptable safety profile, in combination with chemotherapy versus chemotherapy alone and represents a potential standard first-line treatment in patients with advanced GC/GEJC/EAC.

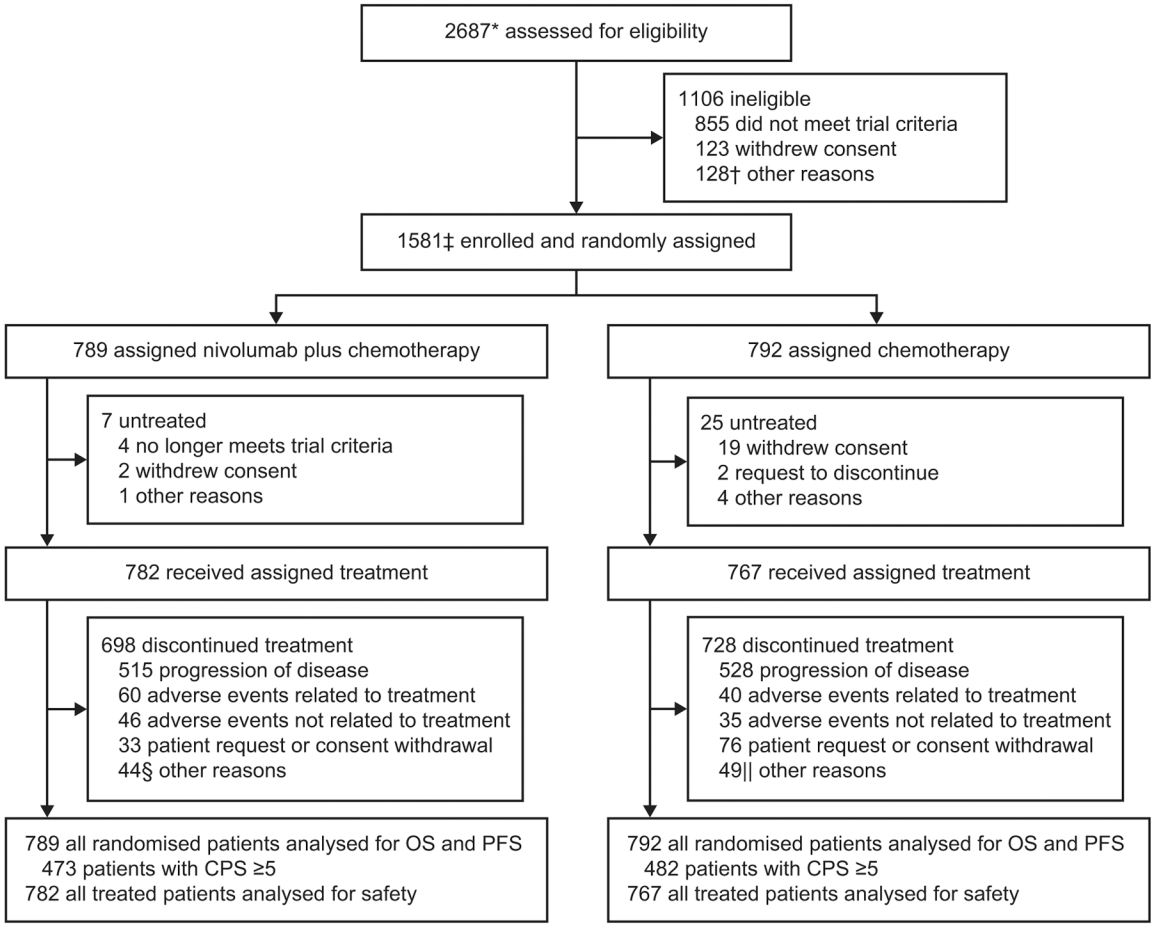
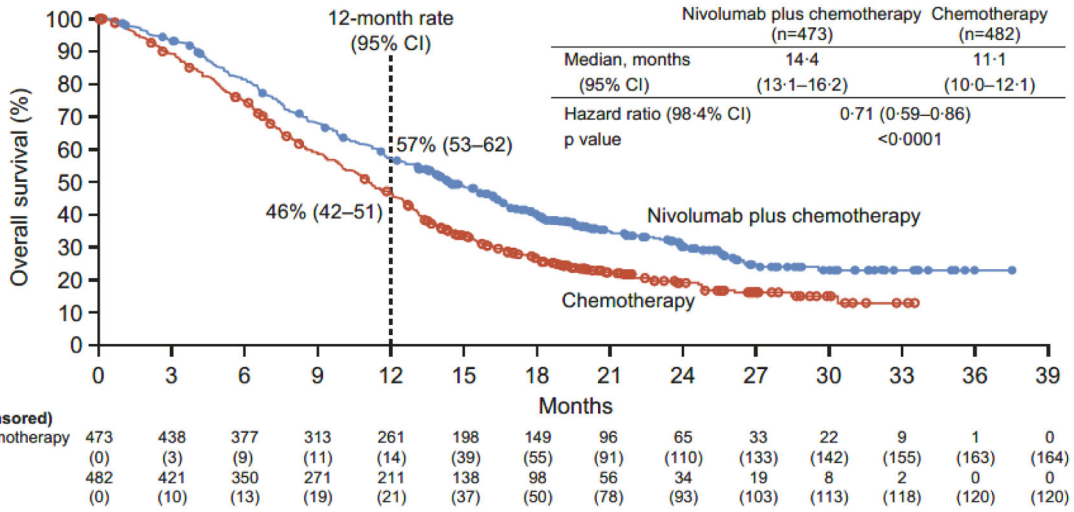


Figure 1: Trial profile

OS=overall survival. PFS=progression-free survival. CPS=combined positive score. *Enrolled patients included all concurrently randomised patients to nivolumab plus chemotherapy or chemotherapy, as well as patients enrolled before the nivolumab plus ipilimumab group was closed and not randomised to any of the treatment groups. The total number of patients randomised to three groups was 2031. The nivolumab plus ipilimumab group will remain blinded until final analysis, and the results will be reported at a later time. †Included death (n=35), adverse events (n=24), poor/noncompliance (n=15), and additional reasons (n=54). ‡Includes patients concurrently randomised to the nivolumab plus chemotherapy and chemotherapy groups. Relevant protocol deviations were noted in 21 (1%) patients. This included usage of prohibited on-treatment anti-cancer therapy (n=12), baseline ECOG PS > 1 (n=5), incorrect cancer diagnosis (n=2), and one case each of prohibited prior anti-cancer therapy (at study entry) and no baseline (measurable or evaluable) disease. §Included completion of treatment (n=20); maximum clinical benefit (n=10); two cases each of death, decline in performance, lost to follow-up, and patient relocation; and one case each of clinical worsening (hand synovitis G2), patient no longer met trial criteria, patient request to receive treatment at home, poor/noncompliance, treatment on hold due to adverse event, and unclear lung and bone lesions. ||Included maximum clinical benefit (n=25); poor/noncompliance (n=4); three cases each of patient no longer met trial criteria and death; two cases each of lost to follow-up and surgery; and

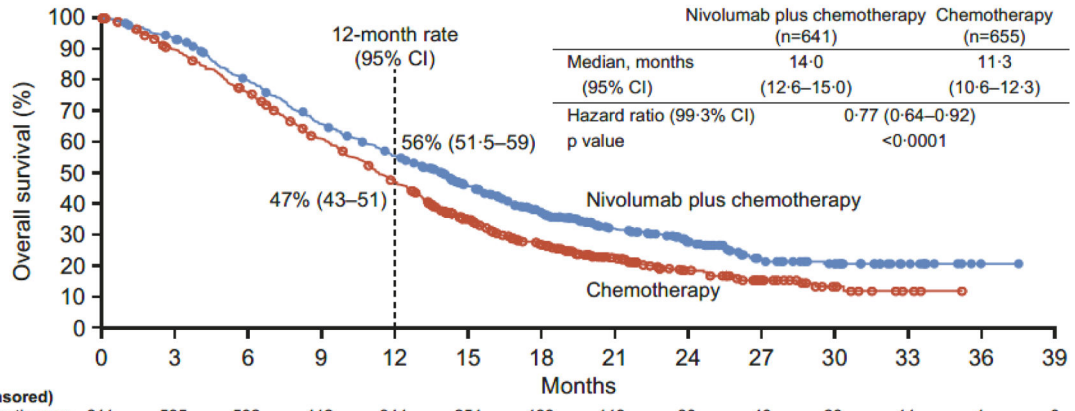
one case each of bad performance status, carcinomatoses meninges, clinical progression, disease progression confirmed by central imaging (per blinded independent central review), failure after cranial progression, investigator decision, patient pursuing alternative treatment, treatment delay/discontinuation (per protocol), patient unable to tolerate treatment, and patient request to discontinue.

A PD-L1 CPS ≥5



Number at risk (censored)														
Nivolumab plus chemotherapy	473	438	377	313	261	198	149	96	65	33	22	9	1	0
	(0)	(3)	(9)	(11)	(14)	(39)	(55)	(91)	(110)	(133)	(142)	(155)	(163)	(164)
Chemotherapy	482	421	350	271	211	138	98	56	34	19	8	2	0	0
	(0)	(10)	(13)	(19)	(21)	(37)	(50)	(78)	(93)	(103)	(113)	(118)	(120)	(120)

B PD-L1 CPS ≥1



Number at risk (censored)														
Nivolumab plus chemotherapy	641	595	502	412	344	254	183	118	80	40	28	11	1	0
	(0)	(3)	(11)	(13)	(17)	(51)	(76)	(118)	(142)	(169)	(179)	(196)	(206)	(207)
Chemotherapy	655	575	483	383	292	194	131	77	45	25	10	3	0	0
	(0)	(14)	(17)	(24)	(27)	(54)	(74)	(108)	(128)	(141)	(154)	(160)	(163)	(163)

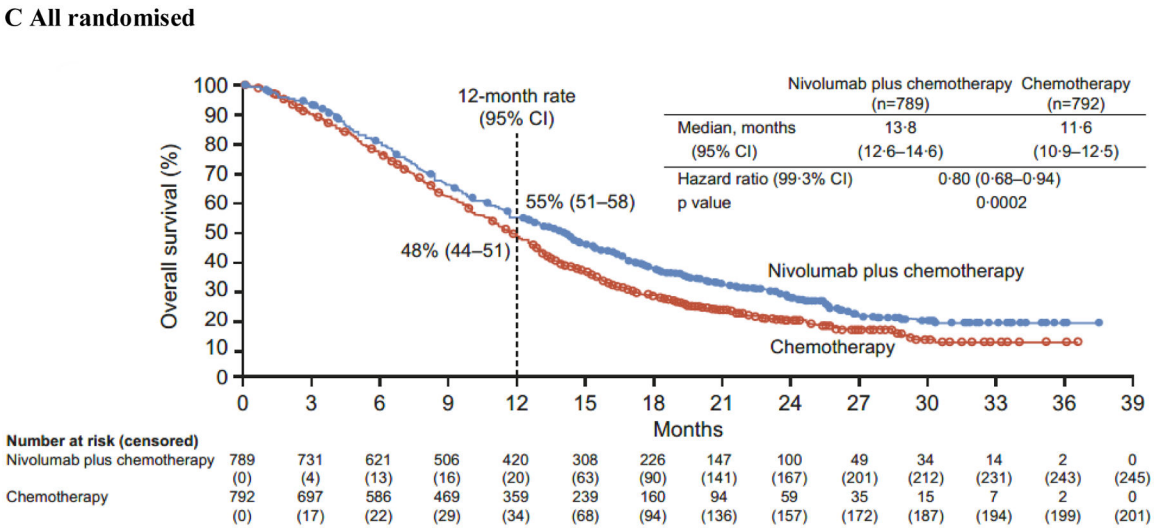
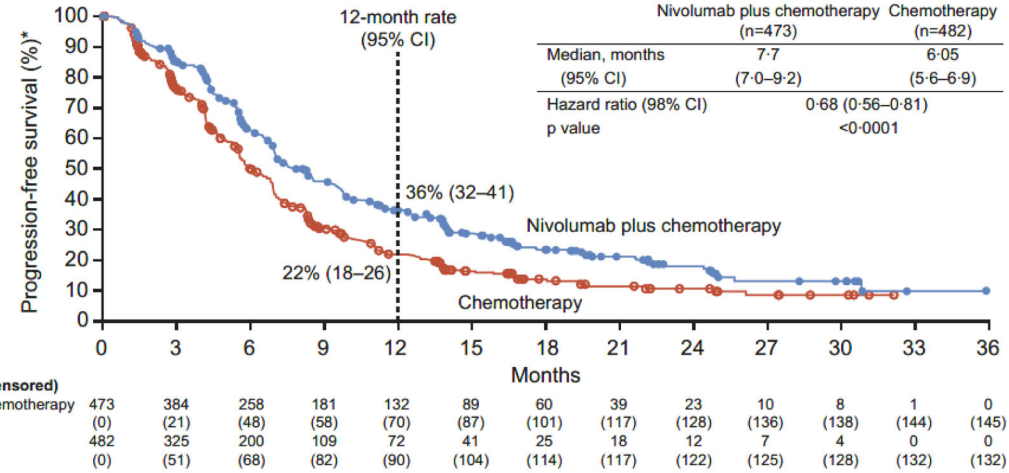


Figure 2: Overall survival

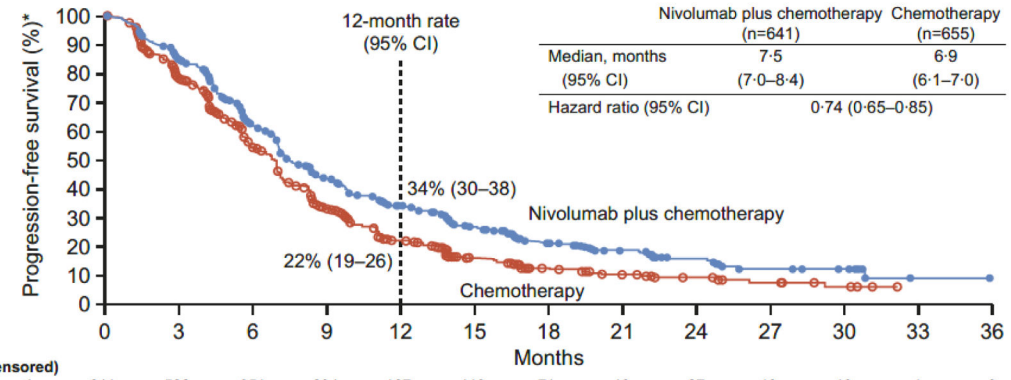
PD-L1=programmed death ligand 1. CPS=combined positive score. CI=confidence interval.

A PD-L1 CPS ≥5



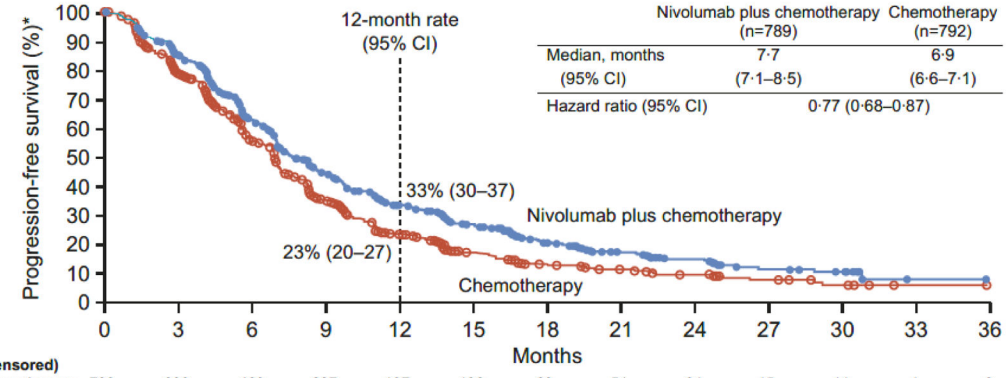
Number at risk (censored)													
Nivolumab plus chemotherapy	473	384	258	181	132	89	60	39	23	10	8	1	0
	(0)	(21)	(48)	(58)	(70)	(87)	(101)	(117)	(128)	(136)	(138)	(144)	(145)
Chemotherapy	482	325	200	109	72	41	25	18	12	7	4	0	0
	(0)	(51)	(68)	(82)	(90)	(104)	(114)	(117)	(122)	(125)	(128)	(132)	(132)

B PD-L1 CPS ≥1



Number at risk (censored)													
Nivolumab plus chemotherapy	641	522	351	234	167	113	71	46	27	13	10	1	0
	(0)	(26)	(60)	(76)	(93)	(115)	(135)	(153)	(166)	(175)	(178)	(186)	(187)
Chemotherapy	655	452	291	167	99	53	31	21	13	8	4	0	0
	(0)	(71)	(99)	(114)	(129)	(151)	(162)	(167)	(173)	(176)	(179)	(183)	(183)

C All randomised



Number at risk (censored)													
Nivolumab plus chemotherapy	789	639	429	287	197	136	83	51	31	15	11	1	0
	(0)	(38)	(84)	(105)	(125)	(149)	(173)	(193)	(207)	(217)	(220)	(229)	(230)
Chemotherapy	792	544	351	202	120	65	38	28	18	12	6	1	0
	(0)	(92)	(133)	(155)	(173)	(199)	(211)	(216)	(222)	(225)	(229)	(234)	(235)

Figure 3: Progression-free survival

PD-L1=programmed death ligand 1. CPS=combined positive score. CI=confidence interval. *Per blinded independent central review assessment.

Table 1:

Demographics and baseline clinical characteristics

	Patients with PD-L1 CPS ≥5		All randomised patients	
	Nivolumab plus chemotherapy (n=473)	**Chemotherapy (n=482)**	**Nivolumab plus chemotherapy (n=789)**	**Chemotherapy (n=792)**
Median age (IQR), years	63 (54–69)	62 (54–68)	62 (54–69)	61 (53–68)
<65	266 (56%)	286 (59%)	473 (60%)	488 (62%)
≥65	207 (44%)	196 (41%)	316 (40%)	304 (38%)
Sex				
Male	331 (70%)	349 (72%)	540 (68%)	560 (71%)
Female	142 (30%)	133 (28%)	249 (32%)	232 (29%)
Race				
Asian	119 (25%)	117 (24%)	186 (24%)	189 (24%)
Non-Asian	354 (75%)	365 (76%)	603 (76%)	603 (76%)
Region				
Asia	117 (25%)	111 (23%)	178 (23%)	178 (22%)
United States and Canada	67 (14%)	70 (15%)	131 (17%)	132 (17%)
Rest of world	289 (61%)	301 (62%)	480 (61%)	482 (61%)
ECOG performance status *				
0	194 (41%)	203 (42%)	326 (41%)	336 (42%)
1	279 (59%)	278 (58%)	462 (59%)	452 (57%)
2	0	0	1 (<1%)	3 (<1%)
Not reported	0	1 (<1%)	0	1 (<1%)
Primary tumour location at initial diagnosis				
GC	333 (70%)	334 (69%)	554 (70%)	556 (70%)
GEJC	84 (18%)	86 (18%)	132 (17%)	128 (16%)
EAC	56 (12%)	62 (13%)	103 (13%)	108 (14%)
Tumour cell PD-L1 expression				
<1%†	363 (77%)	362 (75%)	663 (84%)	664 (84%)
≥1%	110 (23%)	120 (25%)	126 (16%)	127 (16%)
Prior surgery				
Yes	97 (21%)	105 (22%)	160 (20%)	176 (22%)
No	376 (79%)	377 (78%)	629 (80%)	616 (78%)
Disease stage				
Metastatic	454 (96%)	461 (96%)	757 (96%)	756 (95%)
Locally advanced	16 (3%)	20 (4%)	27 (3%)	34 (4%)
Locally recurrent	3 (<1%)	1 (<1%)	5 (<1%)	2 (<1%)
Organs with metastases				
1	98 (21%)	105 (22%)	164 (21%)	183 (23%)
≥2	361 (76%)	362 (75%)	602 (76%)	583 (74%)
Site of metastases				

	Patients with PD-L1 CPS ≥5		All randomised patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy (n=792)
Liver	191 (40%)	217 (45%)	301 (38%)	314 (40%)
Peritoneum	101 (21%)	96 (20%)	188 (24%)	188 (24%)
CNS	1 (<1%)	0	1 (<1%)	0
Signet ring cell carcinoma ‡				
Yes	72 (15%)	69 (14%)	145 (18%)	136 (17%)
No	401 (85%)	413 (86%)	644 (82%)	656 (83%)
Lauren classification				
Intestinal type	171 (36%)	176 (37%)	272 (34%)	267 (34%)
Diffuse type	137 (29%)	141 (29%)	254 (32%)	273 (34%)
Mixed	37 (8%)	30 (6%)	58 (7%)	48 (6%)
Unknown	128 (27%)	135 (28%)	205 (26%)	204 (26%)
MSI status				
MSS	423 (89%)	423 (88%)	695 (88%)	682 (86%)
MSI-H	18 (4%)	16 (3%)	23 (3%)	21 (3%)
Not reported or invalid	32 (7%)	43 (9%)	71 (9%)	89 (11%)
Chemotherapy regimen §				
FOLFOX	237 (51%)	242 (52%)	422 (54%)	406 (53%)
XELOX	231 (49%)	223 (48%)	360 (46%)	361 (47%)

Data are n (%), unless otherwise stated. PD-L1=programmed death ligand 1. CPS=combined positive score. IQR=interquartile range. ECOG=Eastern Cooperative Oncology Group. GC=gastric cancer. GEJC=gastroesophageal junction cancer. EAC=oesophageal adenocarcinoma. CNS=central nervous system. MSI=microsatellite instability. MSS=microsatellite stable. MSI-H=microsatellite instability-high. FOLFOX=5-fluorouracil plus leucovorin plus oxaliplatin. XELOX=capecitabine plus oxaliplatin.

* Based on case report form. All randomised patients had ECOG performance status of 0 or 1 based on interactive response technology.

† Includes indeterminate tumour cell PD-L1 expression.

‡ Per World Health Organization histologic classification.

§ Patients who received at least one dose of the assigned treatment.

Table 2:

Summary of treatment-related adverse events in all treated patients

	Nivolumab plus chemotherapy (n=782)*				Chemotherapy (n=767)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5†	Grade 1–2	Grade 3	Grade 4	Grade 5
All events	272 (35%)	358 (46%)	104 (13%)	4 (<1%)	338 (44%)	285 (37%)	56 (7%)	0
Serious events	37 (5%)	97 (12%)	34 (4%)	4 (<1%)	16 (2%)	63 (8%)	14 (2%)	0
Events leading to discontinuation	148 (19%)	109 (14%)	23 (3%)	4 (<1%)	114 (15%)	58 (8%)	9 (1%)	0
Events leading to death ‡	16§ (2%)				4‖ (<1%)			
Any-grade events in 10% or more of treated patients in either group								
Nausea	303 (39%)	20 (3%)	0	0	273 (36%)	19 (2%)	0	0
Diarrhoea	218 (28%)	33 (4%)	2 (<1%)	0	182 (24%)	23 (3%)	1 (<1%)	0
Peripheral neuropathy	190 (24%)	29 (4%)	2 (<1%)	0	168 (22%)	22 (3%)	0	0
Vomiting	178 (23%)	17 (2%)	0	0	142 (19%)	24 (3%)	0	0
Fatigue	172 (22%)	30 (4%)	0	0	156 (20%)	16 (2%)	1 (<1%)	0
Anaemia	156 (20%)	44 (6%)	3 (<1%)	0	150 (20%)	20 (3%)	1 (<1%)	0
Decreased appetite	143 (18%)	14 (2%)	0	0	126 (16%)	12 (2%)	1 (<1%)	0
Thrombocytopenia	138 (18%)	15 (2%)	4 (<1%)	0	132 (17%)	12 (2%)	1 (<1%)	0
Platelet count decreased	136 (17%)	17 (2%)	3 (<1%)	0	96 (13%)	15 (2%)	4 (<1%)	0
Peripheral sensory neuropathy	121 (15%)	16 (2%)	0	0	105 (14%)	14 (2%)	0	0
Aspartate aminotransferase increased	110 (14%)	12 (2%)	0	0	64 (8%)	5 (<1%)	0	0
White blood cell count decreased	89 (11%)	20 (3%)	3 (<1%)	0	64 (8%)	12 (2%)	1 (<1%)	0
Alanine aminotransferase increased	83 (11%)	6 (<1%)	0	0	45 (6%)	5 (<1%)	0	0
Palmar-plantar erythrodysesthesia syndrome	83 (11%)	11 (1%)	0	0	75 (10%)	6 (<1%)	0	0
Neutrophil count decreased	75 (10%)	60 (8%)	23 (3%)	0	51 (7%)	50 (7%)	17 (2%)	0
Neutropenia	73 (9%)	87 (11%)	31 (4%)	0	88 (11%)	70 (9%)	23 (3%)	0
Asthenia	66 (8%)	7 (<1%)	0	0	71 (9%)	9 (1%)	1 (<1%)	0
Lipase increased	44 (6%)	34 (4%)	11 (1%)	0	18 (2%)	14 (2%)	2 (<1%)	0

Data are n (%).

* Patients who received at least one dose of the assigned treatment. Includes events reported between first dose and 30 days after last dose of trial therapy. Treatment-relatedness in the nivolumab plus chemotherapy group refers to nivolumab, at least one chemotherapy component, or both. National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and Medical Dictionary for Regulatory Activities, version 23.0.

[†]There were four grade 5 events in the nivolumab plus chemotherapy group, one case each of cerebrovascular accident, febrile neutropenia, gastrointestinal inflammation, and pneumonia. There were no grade 5 events in the chemotherapy group.

[‡]Preferred terms for cause of death were per investigator assessment.

[§]Twelve treatment-related deaths in the nivolumab plus chemotherapy group were due to three cases of pneumonitis, two cases of febrile neutropenia/neutropenic fever, and one case each of gastrointestinal bleeding, gastrointestinal toxicity, infection, intestinal mucositis, pneumonia, septic shock, and stroke. An additional four deaths due to "Other" reasons were specified as related to treatment by the investigator. These included one case each of acute cerebral infarction, mesenteric thrombosis, disseminated intravascular coagulation, and pneumonitis.

[//]Treatment-related deaths in the chemotherapy group (n=4; one for each event) were due to diarrhoea, asthenia and severe loss of appetite, pulmonary thromboembolism, and pneumonitis.