First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

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Summary

Background First-line chemotherapy for advanced or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction adenocarcinoma has a median overall survival (OS) of less than 1 year. We aimed to evaluate first-line programmed cell death (PD)-1 inhibitor-based therapies in gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma. We report the first results for nivolumab plus chemotherapy versus chemotherapy alone.

Methods In this multicentre, randomised, open-label, phase 3 trial (CheckMate 649), we enrolled adults (≥18 years) with previously untreated, unresectable, non-HER2-positive gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma, regardless of PD-ligand 1 (PD-L1) expression from 175 hospitals and cancer centres in 29 countries. Patients were randomly assigned (1:1:1 while all three groups were open) via interactive web response technology (block sizes of six) to nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks) plus chemotherapy (capecitabine and oxaliplatin every 3 weeks or leucovorin, fluorouracil, and oxaliplatin every 2 weeks), nivolumab plus ipilimumab, or chemotherapy alone. Primary endpoints for nivolumab plus chemotherapy versus chemotherapy alone were OS or progression-free survival (PFS) by blinded independent central review, in patients whose tumours had a PD-L1 combined positive score (CPS) of five or more. Safety was assessed in all patients who received at least one dose of the assigned treatment. This study is registered with ClinicalTrials.gov, NCT02872116.

Findings From March 27, 2017, to April 24, 2019, of 2687 patients assessed for eligibility, we concurrently randomly assigned 1581 patients to treatment (nivolumab plus chemotherapy [n=789, 50%] or chemotherapy alone [n=792, 50%]). The median follow-up for OS was 13·1 months (IQR 6·7–19·1) for nivolumab plus chemotherapy and 11·1 months (5·8–16·1) for chemotherapy alone. 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 alone in patients with a PD-L1 CPS of five or more (minimum follow-up 12·1 months). Additional results showed significant improvement in OS, along with PFS benefit, in patients with a PD-L1 CPS of one or more and all randomly assigned patients. Among all treated patients, 462 (59%) of 782 patients in the nivolumab plus chemotherapy group and 341 (44%) of 767 patients in the chemotherapy alone group had grade 3–4 treatment-related adverse events. The most common any-grade treatment-related adverse events (≥25%) were nausea, diarrhoea, and peripheral neuropathy across both groups. 16 (2%) deaths in the nivolumab plus chemotherapy group and four (1%) deaths in the chemotherapy alone group were considered to be treatment-related. No new safety signals were identified.

Interpretation Nivolumab is the first PD-1 inhibitor to show 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, gastro-oesophageal junction, or oesophageal adenocarcinoma. Nivolumab plus chemotherapy represents a new standard first-line treatment for these patients.

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Introduction

Gastric cancer, including gastro-oesophageal junction cancer, is the fourth leading cause of cancer-related deaths worldwide.[1] Adenocarcinoma is the most common (>90%) histological type of gastric and gastro-oesophageal junction cancer[2] and accounts for

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Research in context

Evidence before this study

We searched PubMed on Nov 24, 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 Sept 1, 2018, and Dec 1, 2020, using the same key words. Our search identified 259 abstracts, from which we selected primary publications from randomised phase 3 studies of programmed cell death (PD)-1 or PD-ligand 1 (PD-L1) inhibitors in previously untreated patients with advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma. 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 gastric cancer or gastro-oesophageal junction cancer, 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 whose tumours expressed PD-L1 with a combined positive score (CPS) of one or more, 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 gastric cancer or gastro-oesophageal junction cancer expressing PD-L1 with a CPS of one or more or ten or more. In the phase 3 KEYNOTE-590 study of oesophageal cancer or gastro-oesophageal junction cancer (mainly squamous cell carcinoma histology), first-line pembrolizumab plus chemotherapy provided improved OS and PFS in advanced unresectable or metastatic gastro-oesophageal junction (Siewert type 1) or oesophageal adenocarcinoma in a subgroup analysis with a manageable safety profile. In the phase 3 JAVELIN Gastric 100 study of advanced gastric cancer and gastro-oesophageal junction cancer, avelumab maintenance after first-line chemotherapy did not show superior OS versus continued chemotherapy in the primary population of all randomly assigned patients or in patients with tumour cell PD-L1 expression of 1% or more.

Added value of this study

With nearly 1600 patients randomly assigned in the CheckMate 649 trial, nivolumab in combination with chemotherapy showed superior OS, along with PFS benefit, versus chemotherapy alone in previously untreated patients with advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma. To our knowledge, CheckMate 649 is the first global study to show 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 gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma. 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 alone, 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 an important unmet need in previously untreated patients with gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma, for whom no advances have been made in the past decade. Nivolumab is the first PD-1 inhibitor to show superior OS, along with PFS benefit and an acceptable safety profile, in combination with chemotherapy versus chemotherapy alone; this combination is now indicated in the USA as a first-line treatment in patients with advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma.

approximately 65% of oesophageal cancer cases in North America and 40% of oesophageal cancer cases in Europe.[3] Additionally, oesophageal adenocarcinoma accounts for 15% of oesophageal cancer cases worldwide.[3]

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

The programmed cell death (PD)-1 inhibitor nivolumab provided superior OS versus placebo in heavily pre-treated advanced or recurrent gastric or gastro-oesophageal junction cancer in the phase 3 ATTRACTION-2 study.[17] Chemotherapy, in addition to its direct cytotoxic properties, might contribute to antitumour immune response elicited by nivolumab through induction of immunogenic cell death.[18–20] PD-ligand 1 (PD-L1) 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, gastro-oesophageal junction, or oesophageal adenocarcinoma.[21–23]

The phase 3 CheckMate 649 study aimed to evaluate PD-1 inhibitor-based therapies in previously untreated advanced gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma; here, we report results from the nivolumab plus chemotherapy versus chemotherapy alone groups.

Methods

Study design and participants

We did a multicentre, randomised, open-label, phase 3 trial at 175 hospitals and cancer centres in 29 countries across Asia, Australia, Europe, North America, and South America (appendix pp 19–21). Eligible patients were aged 18 years or older, with previously untreated, unresectable advanced or metastatic gastric, gastro-oesophageal junction, 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 previous adjuvant or neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy (administered at least 6 months before randomisation) were eligible. Patients with known HER2-positive status; untreated CNS metastases; peripheral neuropathy (higher than grade 1); active, known, or suspected autoimmune disease; positive test result for hepatitis B or C virus; and known history of positive test for HIV or known AIDS were excluded.

During enrolment, the primary population was amended to patients whose tumours had a PD-L1 CPS of five or more based on results from the gastro-oesophageal cohort of CheckMate 032 and other published studies suggesting that PD-L1 CPS might 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 done according to Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the trial protocol (appendix p 22). The protocol was approved by the institutional review boards or independent ethics committees at each site. All patients provided written informed consent as per the Declaration of Helsinki principles.

Randomisation and masking

Patients were randomly assigned to nivolumab plus chemotherapy (XELOX [capecitabine and oxaliplatin] or FOLFOX [leucovorin, fluorouracil, 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 randomly assigned to nivolumab plus chemotherapy versus chemotherapy alone; results for nivolumab plus ipilimumab versus chemotherapy alone remain blinded and will be reported later.

Randomisation was done using interactive web response technology (block sizes of six) and stratified according to tumour cell PD-L1 status (≥1% *vs* <1% or indeterminate), region (Asia *vs* USA 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 masked 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/m² twice a day, days 1–14 and oxaliplatin 130 mg/m², day 1, every 3 weeks] or FOLFOX [leucovorin 400 mg/m², day 1, fluorouracil 400 mg/m², day 1 and 1200 mg/m², days 1–2, and oxaliplatin 85 mg/m², 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 CT or MRI per RECIST version 1.1, by blinded independent central review 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 done at two central laboratories using the Dako PD-L1 immunohistochemistry 28-8 pharmDx assay (Dako, Santa Clara, CA, USA), which has been analytically validated in gastric, gastro-oesophageal junction, and 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 re-scoring PD-L1 stained slides using the CPS algorithm, defined as the number of PD-L1-positive tumour cells

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See **Online** for appendix

(partial or complete membrane staining), lymphocytes, and macrophages (membrane staining or intracellular staining, or both) divided by the total number of viable tumour cells multiplied by 100.

Treatment-related adverse events 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 drug component, or both. Patients could discontinue individual treatment components and continue on other components in a combination regimen (appendix p 3). Treatment-related adverse events 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 treatment-related adverse events.

Outcomes

Dual primary endpoints for the nivolumab plus chemotherapy versus chemotherapy alone 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 blinded independent central review per RECIST version 1.1, evaluated in patients with a PD-L1 CPS of five or more. Hierarchically tested secondary endpoints were OS in patients with a PD-L1 CPS of one or more and all randomly assigned patients. Additional secondary endpoints that were not formally tested included blinded independent central review-assessed PFS and objective response rate at different PD-L1 CPS cutoffs and in all randomly assigned patients. Key prespecified exploratory endpoints included blinded independent central review-assessed duration of response; landmark survival rates; biomarkers potentially predictive of efficacy; health-related quality of life (HRQOL); and safety and tolerability.

All randomly assigned patients included all enrolled patients who were randomly assigned concurrently to either nivolumab plus chemotherapy or chemotherapy alone. The primary population comprised all randomly assigned patients whose tumours had a PD-L1 CPS of five or more. Objective response was evaluated in all randomly assigned patients who had at least one target or measurable lesion at baseline. Safety was analysed in all treated patients, which included all randomly assigned patients who received at least one dose of study treatment during the trial. Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) analysis was done for patients with a PD-L1 CPS of five or more and all randomly assigned patients who had an assessment at baseline (day 1, assessment before administration of treatment on day of first dose) and at least one subsequent assessment while on treatment. Additional details about HRQOL are shown in the appendix (p 3). Time to symptom deterioration was analysed in patients with a PD-L1 CPS of five or more and all randomly assigned patients with intent to treat. Biomarker analysis was done in all randomly assigned 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 (type I error) of 0·03 were allocated to OS and 0·02 to PFS. Upon superiority of OS in patients with a PD-L1 CPS of five or more, OS was hierarchically tested in patients with a PD-L1 CPS of one or more with a fraction of α (50% α transmitted=0·015), followed by all randomly assigned patients (100% α transmitted=0·015). The study was designed for final PFS and interim OS analyses to be assessed at 12-month minimum follow-up and final OS analysis at 24-month minimum follow-up. Lan and DeMets α-spending functions were used to establish the significance level for the interim analysis of OS.

With an assumed prevalence of 35% for patients with a PD-L1 CPS of five or more, 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 a PD-L1 CPS of five or more concurrently randomly assigned to the nivolumab plus chemotherapy or chemotherapy alone 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 a 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% CIs were calculated using the log-log transformation method. A post-hoc exploratory analysis was done 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) on OS and PFS in all randomly assigned patients using Cox models fitted with the biomarker as a 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 an interactive 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 alone were calculated using a Cox proportional hazards regression model with treatment as the covariate. Statistical analyses were done using SAS, version 9.4. An independent data monitoring committee monitored safety and efficacy data. This study is registered with ClinicalTrials.gov, NCT02872116.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the clinical study report.

Results

From March 27, 2017, to April 24, 2019, 2687 patients were assessed for eligibility. Of these, 1581 patients were concurrently randomly assigned to receive nivolumab plus chemotherapy (n=789 [50%]) or chemotherapy alone (n=792 [50%]); 1549 patients received one or more doses of the assigned treatment: nivolumab plus chemotherapy (782 patients) or chemotherapy alone (767 patients; figure 1).

The median follow-up for OS (time from concurrent random assignment 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 alone group. 698 patients discontinued treatment with nivolumab plus chemotherapy and 728 patients discontinued treatment with chemotherapy alone; the most common reason for treatment discontinuation in both groups was disease progression (515 [66%] patients in the nivolumab plus chemotherapy group and 528 [69%] patients in the chemotherapy alone group; figure 1).

Baseline characteristics were balanced across the treatment groups in the primary population (patients with a PD-L1 CPS of ≥5) and all randomly assigned patients (table 1, appendix p 4). 473 (60%) of 789 patients in the nivolumab plus chemotherapy group and 482 (61%) of 792 patients in the chemotherapy alone group had tumours expressing PD-L1 with a CPS of five or more. Most patients were non-Asian (1206 [76%] of 1581) and most had gastric cancer (1110 [70%] of 1581), while

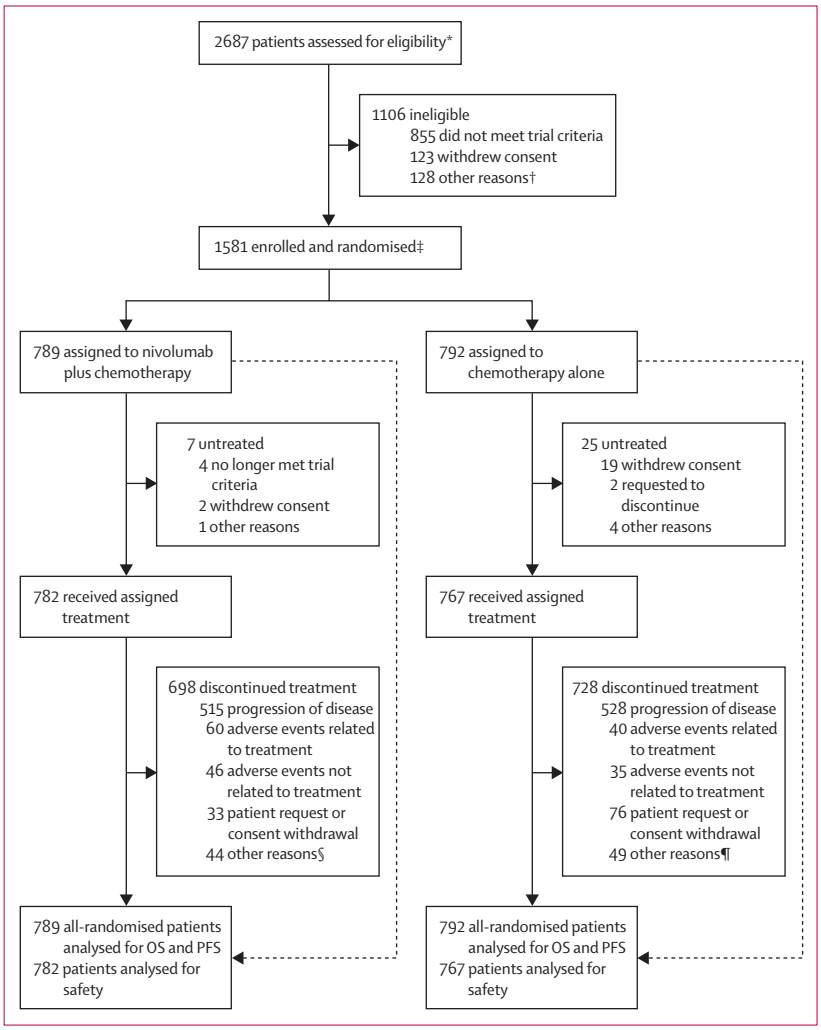

Figure 1: **Trial profile**
OS=overall survival. PFS=progression-free survival. *Enrolled patients included all concurrently randomly assigned patients to nivolumab plus chemotherapy or chemotherapy alone, and patients enrolled before the nivolumab plus ipilimumab group was closed and not assigned to any treatment group (n=2031). †Death (n=35), adverse events (n=24), poor or non-compliance (n=15), and additional reasons (n=54). ‡Patients concurrently randomly assigned to the nivolumab plus chemotherapy and chemotherapy alone groups. Relevant protocol deviations were noted in 21 (1%) patients—ie, use of prohibited on-treatment anticancer therapy (n=12), baseline Eastern Cooperative Oncology Group performance status more than 1 (n=5), incorrect cancer diagnosis (n=2), and one case each of prohibited previous anticancer therapy (at study entry) and no baseline (measurable or evaluable) disease. §Completion of treatment (n=20); maximum clinical benefit (n=10); two cases each of death, decline in performance, loss to follow-up, and patient relocation; and one case each of clinical worsening (hand synovitis grade 2), patient no longer met trial criteria, patient request to receive treatment at home, poor or non-compliance, treatment on hold due to adverse event, and unclear lung and bone lesions. ¶Maximum clinical benefit (n=25); poor or non-compliance (n=4); three cases each of patient no longer met trial criteria and death; two cases each of loss 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), cranial progression, investigator decision, patient pursuing alternative treatment, treatment delay or discontinuation (per protocol), patient unable to tolerate treatment, and patient request to discontinue.

260 (16%) had gastro-oesophageal junction 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 of May 27, 2020) of 12·1 months, nivolumab plus chemotherapy showed superior OS, with a 29% reduction in the risk of death compared with chemotherapy alone (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]) in patients with a PD-L1 CPS of five or more (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 alone (46% [42–51]). Nivolumab plus chemotherapy also provided superior PFS in patients with a PD-L1 CPS of five or more, with a 32% reduction in the risk of progression or death versus chemotherapy alone (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 6·0 months (5·6–6·9) with chemotherapy alone. The 12-month PFS estimate was 36% (95% CI 32–41) with nivolumab plus chemotherapy versus 22% (18–26) with chemotherapy alone.

In addition to the primary population, nivolumab plus chemotherapy showed a significant improvement in OS in patients with a PD-L1 CPS of one or more (HR 0·77 [99·3% CI 0·64–0·92]; p<0·0001) and all randomly assigned patients (0·80 [0·68–0·94]; p=0·0002) versus chemotherapy alone (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, providing support that the proportional assumptions were not violated (appendix p 5). Although not formally tested, HRs indicated that PFS benefit was also observed with nivolumab plus chemotherapy versus chemotherapy alone in patients with a PD-L1 CPS of one or more (HR 0·74 [95% CI 0·65–0·85]) and all randomly assigned patients (0·77 [0·68–0·87]; figure 3B, C).

The unstratified HR for OS with nivolumab plus chemotherapy versus chemotherapy alone for patients with a PD-L1 CPS of less than one was 0·92 (95% CI 0·70–1·23) and for those with a PD-L1 CPS of less than five was 0·94 (0·78–1·13); unstratified HRs for PFS were 0·93 (0·69–1·26) for patients with a PD-L1 CPS of less than one and 0·93 (0·76–1·12) for patients with a PD-L1 CPS of less than five (appendix p 11). Interaction analysis of OS by PD-L1 CPS cutoffs showed significant interaction by PD-L1 CPS at the cutoff of five (p=0·011) but not at the cutoff of one (p=0·2041; appendix p 11).

The HRs for OS favoured nivolumab plus chemotherapy over chemotherapy alone across multiple prespecified subgroups in patients with a PD-L1 CPS of five or more and in all randomly assigned patients (appendix pp 12–13). The unstratified HR for OS with nivolumab plus chemotherapy versus chemotherapy alone was 0·33 (95% CI 0·12–0·87) for patients with microsatellite instability-high tumours and 0·73 (0·62–0·85) for microsatellite stable tumours, in patients with a PD-L1 CPS of five or more, and 0·37 (0·16–0·87)

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
Median age, 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				
Men	331 (70%)	349 (72%)	540 (68%)	560 (71%)
Women	142 (30%)	133 (28%)	249 (32%)	232 (29%)
Race				
Asian	119 (25%)	117 (24%)	186 (24%)	189 (24%)
White	328 (69%)	327 (68%)	556 (70%)	541 (68%)
American Indian or Alaska Native	10 (2%)	10 (2%)	12 (2%)	14 (2%)
Black or African American	2 (<1%)	7 (1%)	7 (1%)	11 (1%)
Other	14 (3%)	21 (4%)	28 (4%)	36 (5%)
Not reported	0	0	0	1 (<1%)
Region				
Asia	117 (25%)	111 (23%)	178 (23%)	178 (22%)
USA 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				
Gastric cancer	333 (70%)	334 (69%)	554 (70%)	556 (70%)
Gastro-oesophageal junction cancer	84 (18%)	86 (18%)	132 (17%)	128 (16%)
Oesophageal adenocarcinoma	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%)
Previous 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%)

(Table 1 continues on next page)

for patients with microsatellite instability-high tumours and 0·80 (0·71–0·91) for microsatellite stable tumours, in all randomly assigned patients. Post-hoc interaction analyses indicated no evident interaction of treatment effect on OS by most of the baseline demographics and disease characteristic 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 alone group had an objective response (per blinded independent central review assessment). The proportion of patients with a complete response was 12% in the nivolumab plus chemotherapy group and 7% in the chemotherapy alone group, and median duration of response was 9·5 months (95% CI 8·0–11·4) in the nivolumab plus chemotherapy group versus 7·0 months (5·7–7·9) in the chemotherapy alone group (appendix pp 6, 15). Consistent results were observed in all randomly assigned patients (appendix pp 6, 15). In the nivolumab plus chemotherapy group, the proportion of patients with a PD-L1 CPS of less than one who had an objective response was 51% (47 of 93) and for those with a PD-L1 CPS of less than five was 55% (121 of 219). In the chemotherapy alone group, the proportion of patients with a PD-L1 CPS of less than one who had an objective response was 41% (35 of 85 patients) and for those patients with a PD-L1 CPS of less than five was 46% (97 of 209 patients; appendix p 11).

Among all randomly assigned patients, 297 (38%) of 789 in the nivolumab plus chemotherapy group and 326 (41%) of 792 in the chemotherapy alone group received at least one subsequent therapy for advanced gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma. The most common subsequent therapy in both groups was systemic anticancer therapy (268 [34%] of 789 in the nivolumab plus chemotherapy group and 311 [39%] of 792 patients in the chemotherapy alone group); 12 (2%) patients in the nivolumab plus chemotherapy group and 64 (8%) patients in the chemotherapy alone group received subsequent immunotherapy (appendix p 7).

Among all treated patients, the median treatment duration was 6·8 months (IQR 3·7–13·3) with nivolumab plus chemotherapy and 4·9 months (2·5–8·4) with chemotherapy alone (appendix p 8). The most common treatment-related adverse events were nausea, diarrhoea, and peripheral neuropathy across both groups (table 2). Grade 3–4 treatment-related adverse events occurred in 462 (59%) of 782 patients in the nivolumab plus chemotherapy group and 341 (44%) of 767 patients in the chemotherapy alone group, and any-grade treatment-related adverse events leading to discontinuation were reported in 284 (36%) patients in the nivolumab plus chemotherapy group and 181 (24%) patients in the chemotherapy alone group (table 2). Any-grade serious treatment-related adverse events were reported in 172 (22%) of 782 patients given nivolumab plus chemotherapy (grade 3–4: 131 [17%] patients; four grade 5 events), and in 93 (12%) of 767 patients given chemotherapy (grade 3–4: 77 [10%] patients, no grade 5 events). 16 (2%) deaths in the nivolumab plus chemotherapy group and four (1%) deaths in the chemotherapy alone group were considered treatment related. Preferred terms for cause of death were per investigator assessment. 12 treatment-related deaths in the nivolumab plus chemotherapy group were due to three cases of pneumonitis, two cases of febrile neutropenia or 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 alone group (n=4; one for each event) were due to diarrhoea, asthenia and severe loss of appetite, pulmonary thromboembolism, and pneumonitis. Of the 16 deaths in the nivolumab plus chemotherapy group, four were deemed to be related to nivolumab, five to nivolumab plus chemotherapy, and

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
(Continued from previous page)				
Site of metastases				
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%)
Microsatellite instability status				
Microsatellite stable	423 (89%)	423 (88%)	695 (88%)	682 (86%)
Microsatellite instability-high	18 (4%)	16 (3%)	23 (3%)	21 (3%)
Not reported or invalid	32 (7%)	43 (9%)	71 (9%)	89 (11%)
Chemotherapy regimen§				
FOLFOX	237/468 (51%)	242/465 (52%)	422/782 (54%)	406/767 (53%)
XELOX	231/468 (49%)	223/465 (48%)	360/782 (46%)	361/767 (47%)

Data are median (IQR) or n (%). PD-L1=programmed cell death ligand 1. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. XELOX=capecitabine and oxaliplatin. *Based on case report form. All randomly assigned patients had ECOG performance status of 0 or 1 based on interactive response technology. †Includes indeterminate tumour cell PD-L1 expression. ‡Per WHO histological classification. §Patients who received at least one dose of the assigned treatment.

Table 1: **Baseline characteristics**

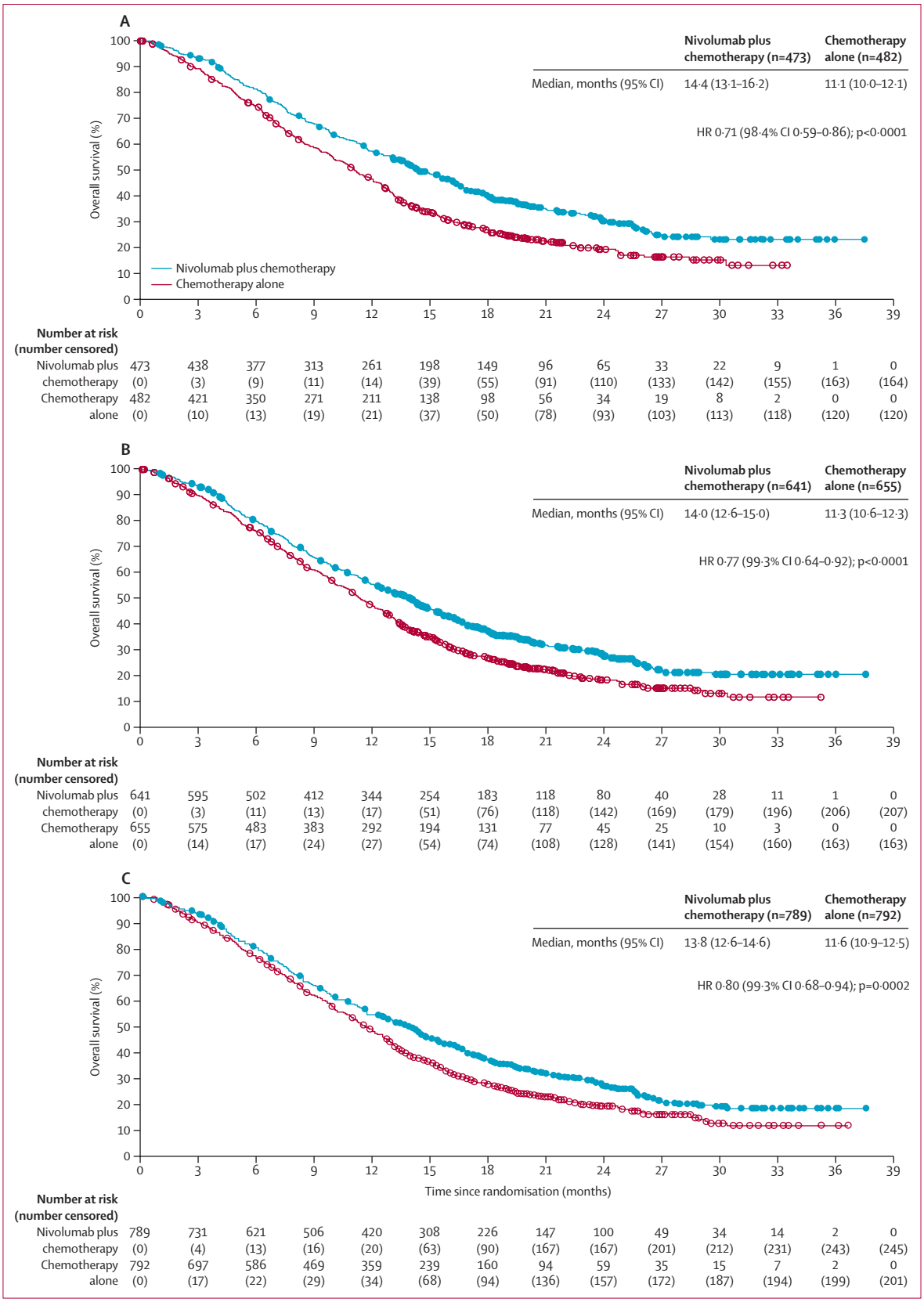

Figure 2: **Overall survival**
Overall survival for patients with a PD-L1 CPS of five or more (A), in which the 12-month rate was 57% (95% CI 53–62) for nivolumab plus chemotherapy and 46% (42–51) for chemotherapy alone; a CPS of one or more (B), in which the 12-month rate was 56% (95% CI 52–59) for nivolumab plus chemotherapy and 47% (43–51) for chemotherapy alone; and all randomly assigned patients (C), in which the 12-month rate was 55% (95% CI 51–58) for nivolumab plus chemotherapy and 48% (44–51) for chemotherapy alone. PD-L1=programmed cell death ligand 1. CPS=combined positive score. HR=hazard ratio.

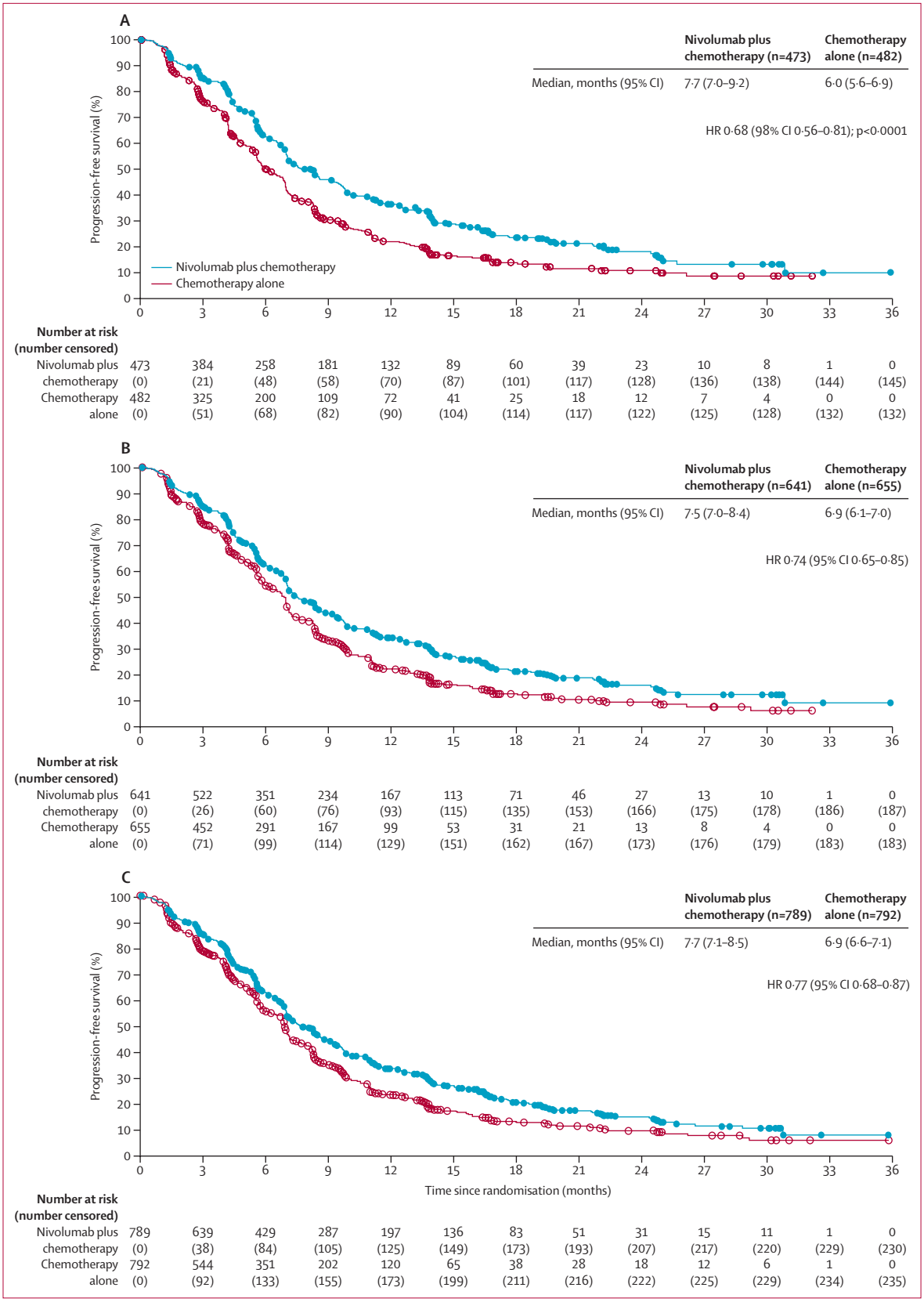

Figure 3: **Progression-free survival**
Progression-free survival (per blinded independent central review assessment) shown for patients with a PD-L1 CPS of five or more (A), in which the 12-month rate was 36% (95% CI 32–41) for nivolumab plus chemotherapy and 22% (18–26) for chemotherapy alone; a CPS of one or more (B), in which the 12-month rate was 34% (95% CI 30–38) for nivolumab plus chemotherapy and 22% (19–26) for chemotherapy alone; and all randomly assigned patients (C), in which the 12-month rate was 33% (95% CI 30–37) for nivolumab plus chemotherapy and 23% (20–27) for chemotherapy alone. PD-L1=programmed cell death ligand 1. CPS=combined positive score. HR=hazard ratio.

	Nivolumab plus chemotherapy (n=782)*				Chemotherapy alone (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
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 (%). 16 deaths in the nivolumab plus chemotherapy group and four deaths in the chemotherapy alone group were considered treatment-related. *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. Adverse events were assessed according to the 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 alone group.

Table 2: **Summary of treatment-related adverse events in all treated patients**

seven to chemotherapy alone (appendix p 9). Dose delays due to any-grade treatment-related adverse events were observed in 524 (67%) of 782 patients in the nivolumab plus chemotherapy group and 447 (58%) of 767 patients in the chemotherapy alone group. Modifications in chemotherapy doses were similar across groups (appendix p 8). Most treatment-related adverse events with potential immunological cause were grade 1 or 2; grade 3–4 events occurred in 5% or less of patients (appendix p 10).

The proportion of patients with a PD-L1 CPS of five or more and all randomly assigned patients completing the FACT-Ga questionnaire was 90% or more at baseline and 80% or more at most subsequent assessments for which at least ten patients responded (until week 109). Baseline mean FACT-Ga total scores were similar between the nivolumab plus chemotherapy (127·6 [SD 27·4]) and chemotherapy alone groups (127·6 [26·4]) for patients with a PD-L1 CPS of five or more and between the nivolumab plus chemotherapy (126·6 [28·3]) and chemotherapy alone groups (126·8 [26·8]) for all randomly assigned patients, with an improvement from baseline in FACT-Ga total score at all on-treatment assessments. In patients with a PD-L1 CPS of five or more and all randomly assigned patients, the least squares mean difference between treatment groups favoured nivolumab plus chemotherapy versus chemotherapy alone (at timepoints with ≥50 patients in each group). However, this result 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 than the chemotherapy alone group while on treatment (patients with a PD-L1 CPS ≥5, HR 0·64 [95% CI 0·49–0·83] and all randomly assigned 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 our knowledge, to show 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, gastro-oesophageal junction, or oesophageal adenocarcinoma, for which treatment options are limited and no advances have been made in the past decade. With more than

1580 patients randomly assigned, nivolumab plus chemotherapy provided a significant and clinically meaningful OS benefit in patients with a PD-L1 CPS of five or more or one or more, as well as in all randomly assigned patients. PFS benefit was also observed in these populations, including when statistically tested in patients with a PD-L1 CPS of five or more. On the basis of CheckMate 649, the US Food and Drug Administration approved nivolumab in combination with chemotherapy containing fluoropyrimidine and platinum for the treatment of patients with advanced or metastatic gastric cancer, gastric-oesophageal junction cancer, or oesophageal adenocarcinoma.

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

The efficacy results show significant survival advantage with nivolumab plus chemotherapy for each endpoint prespecified by statistical hierarchical testing (patients with a PD-L1 CPS of ≥5 and ≥1, and all randomly assigned patients). The relatively large proportion of patients whose tumours expressed PD-L1 with a CPS of five or more in the overall study population affects the magnitude of the benefit observed in patients with a PD-L1 CPS of one or more and all randomly assigned patients. In an exploratory analysis, the unstratified HRs for OS with nivolumab plus chemotherapy versus chemotherapy alone in patients with a PD-L1 CPS of less than one and less than five were higher than in all randomly assigned 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 five but not at the cutoff of one. However, the higher objective response observed with nivolumab plus chemotherapy relative to chemotherapy alone across PD-L1 CPS cutoffs, including CPS less than one and less than five, coupled with the potential for delayed treatment effect often seen with immuno-oncology therapy, suggests the magnitude of survival benefit could 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, gastro-oesophageal junction, or oesophageal adenocarcinoma. A study amendment to define the primary population assumed a conservative prevalence of 35% for patients with a PD-L1 CPS of five or more based on limited available data in this disease setting.[21–23] The prevalence of patients with a PD-L1 CPS of five or more (60% of all randomly assigned patients) observed in this large, randomised controlled trial was numerically higher than that reported in previous studies in gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma (17–50%).[22,24,25] This variation in prevalence of patients with a PD-L1 CPS of five or more could 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, gastro-oesophageal junction, and oesophageal adenocarcinoma.

OS consistently favoured nivolumab plus chemotherapy versus chemotherapy alone across multiple prespecified baseline demographics and disease characteristics in the primary population and all randomly assigned patients. Particularly, survival benefit with nivolumab plus chemotherapy occurred regardless of microsatellite instability status, although the 3% of patients with microsatellite instability-high tumours had greater reduction in the risk of death than those with microsatellite stable tumours. Post-hoc interaction analyses confirmed that most of the baseline demographics and disease characteristics were not determinant of the OS benefit. Although 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 of 1% or more and less than 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, gastro-oesophageal junction, and oesophageal adenocarcinoma who might derive the greatest clinical benefit from immunotherapies.

Pembrolizumab plus chemotherapy did not result in a significant improvement in OS versus chemotherapy alone in patients with advanced or recurrent gastric or gastro-oesophageal junction adenocarcinoma and patients with a PD-L1 CPS of one or more (HR 0·85; p=0·05) and ten or more (HR 0·85; p=0·16) in the smaller KEYNOTE-062 study.[16] In the phase 3 stage of the Asian ATTRACTION-4 study of previously untreated advanced gastric cancer and gastro-oesophageal junction 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 CheckMate 649, KEYNOTE-062, and ATTRACTION-4 could be due to differences in study design (eg, 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 of patients receiving subsequent therapy observed in CheckMate 649 (39%) was consistent with the global phase 3 KEYNOTE-062 study and might reflect the practice patterns and limited therapeutic options and approval of immunotherapies 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 affect chemotherapy administration. Treatment-related deaths were more common in the nivolumab plus chemotherapy group versus chemotherapy alone. However, seven 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 and gastro-oesophageal junction adenocarcinoma.[16,28] Despite more frequent grade 3–4 treatment-related adverse events and events leading to discontinuation with nivolumab plus chemotherapy versus chemotherapy alone, grade 3–4 treatment-related adverse events with potential immunological cause occurred in 5% or less of patients, and the overall safety profile was acceptable. There was a trend towards improved HRQOL with nivolumab plus chemotherapy, although this change was not clinically meaningful per the predefined threshold. This trend, along with a decreased risk of time to symptom deterioration while on treatment, suggested that the addition of nivolumab maintained 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. On the basis of data available at the time of study design, tumour cell PD-L1 expression was chosen as a stratification factor for CheckMate 649. Following reports that indicated that PD-L1 CPS had better enrichment for efficacy than tumour cell PD-L1 expression in advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma,[21–23] the protocol was amended to use expression of PD-L1 with a CPS of five or more to define the primary population. Although tumour cell PD-L1 expression remained a stratification factor, patients whose tumours expressed PD-L1 with a CPS of five or more were balanced between the two treatment groups. In addition, demographics and baseline disease characteristics were balanced between treatment groups in the population with a PD-L1 CPS of five or more. Patients with known HER2-positive status were excluded from CheckMate 649. However, because HER2 testing might not have been done routinely at all study sites, patients with unknown HER2 status were permitted to be enrolled. Importantly, the proportion of these patients (around 40%) was balanced across the treatment groups. On the basis of the known incidence of HER2-overexpressing tumours in gastric cancer and gastro-oesophageal junction cancer (around 20%),[31–35] it is expected that most patients without reported HER2 status in this study were HER2-negative. Another limitation of CheckMate 649 is its open-label study design, which might 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 affected by bias.

In conclusion, nivolumab is the first PD-1 inhibitor to show 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. These results have led to approval in the USA and support nivolumab plus chemotherapy as a new standard first-line treatment for previously untreated patients with advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma.

Contributors

YYJ, KS, MM, and JAA contributed to the conception and design of the study in collaboration with Bristol Myers Squibb. All authors gathered the data. VP, DC, MLe, HX, MLi, and KK verified the data. VP, DC, MLe, HX, and MLi analysed the data and all authors interpreted the data. All authors had access to all the data in the study, participated in developing or reviewing the manuscript, and provided final approval to submit the manuscript for publication.

Declaration of interests

YYJ reports receiving consulting or advisory board fees from AstraZeneca, Daiichi Sankyo, Imugene, Jounce Therapeutics, Merck Serono, Michael J Hennessy Associates, Paradigm Medical Communications, Pfizer, Seattle, Genetics, and Zymeworks; receiving consulting or advisory and research funding from Eli Lilly, Bristol Myers Squibb, and Merck & Co; receiving research funding from Bayer, Boehringer Ingelheim, Genentech/Roche, MSK Cancer Center Support Grant/Core Grant (P30 CA008748), and Ono Pharmaceutical; 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, Bristol Myers Squibb, GlaxoSmithKline, Novartis, Ono Pharmaceutical Company, Pfizer, and Takeda; receiving advisory role or research funding from Astellas Pharma, Eli Lilly, Merck Pharmaceutical, and Taiho Pharmaceutical; receiving honoraria (lecture fees) from AbbVie, Novartis, and Yakult Honsha; and 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 Sharp & Dohme, and Pfizer; receiving personal fees from Bristol Myers Squibb, Falk Foundation, Lilly, MCI Group, Merck Serono, Merck Sharp & 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 Sharp & 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 Chugai, Lilly, and Takeda; receiving grants from Sanofi; and receiving personal fees from Bristol Myers Squibb, Merck Serono, and Takeda, outside the submitted

work. MS reports receiving personal fees for clinical research from Bristol Myers Squibb, during the conduct of the study; and receiving personal fees for clinical research from Astellas, AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, and Roche, outside the submitted work. MT reports receiving research funding from Bristol Myers Squibb, during the conduct of the study. RK reports receiving grants from Amgen, AstraZeneca, Athenex, Eli Lilly, Nektar, and Sanofi; receiving grants and non-financial support from Roche; grants and personal fees from Astellas and Novartis; grants, personal fees, and non-financial support from Bristol Myers Squibb, Merck Sharp & Dohme, and Pfizer; and personal fees from Gador, outside the submitted work. MVK reports serving in an advisory role for Bristol Myers Squibb, Merck Sharp & Dohme, Ipsen, Roche, Sandoz, Sanofi, and Servier, outside the submitted work. RB reports serving as a medical adviser for Merck Serono and Novartis; receiving clinical research funding from Novartis; serving as a medical adviser and speaker for AstraZeneca, Bristol Myers Squibb, and Pfizer; receiving clinical research funding from Bristol Myers Squibb, Merck Sharp & Dohme, and Roche; and serving as a speaker for Merck, during the conduct of the study. TZ reports receiving personal advisory board fees from AstraZeneca, Bristol Myers Squibb, Lilly, Merck Sharp & Dohme, Novartis, Roche, and Sanofi, outside the submitted work. JMC reports personal fees and consulting and travel support from Bristol Myers Squibb; and research funding from AstraZeneca, Esperas Pharma, Merck, and Tesaro, outside the submitted work. VP, DC, MLe, HX, KK, and MLi report employment with Bristol Myers Squibb and ownership of stock in Bristol Myers Squibb. JAA reports receiving clinical research grants and receiving personal advisory board fees from Bristol Myers Squibb, during the conduct of the study. All other authors declare no competing interests.

Data sharing

The Bristol Myers Squibb data sharing policy can be found online. Bristol Myers Squibb will honour legitimate requests for our clinical trial data from qualified researchers. Data will be shared with external researchers whose proposed use of the data has been approved. Complete de-identified patient data sets will be eligible for sharing 2 years after completion of the CheckMate 649 study. Before data are released, the researcher(s) must sign a Data Sharing Agreement, after which the de-identified and anonymised datasets can be accessed within a secured portal.

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