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Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

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ABSTRACT

BACKGROUND

No adjuvant treatment has been established for patients who remain at high risk for recurrence after neoadjuvant chemoradiotherapy and surgery for esophageal or gastroesophageal junction cancer.

METHODS

We conducted CheckMate 577, a global, randomized, double-blind, placebo-controlled phase 3 trial to evaluate a checkpoint inhibitor as adjuvant therapy in patients with esophageal or gastroesophageal junction cancer. Adults with resected (R0) stage II or III esophageal or gastroesophageal junction cancer who had received neoadjuvant chemoradiotherapy and had residual pathological disease were randomly assigned in a 2:1 ratio to receive nivolumab (at a dose of 240 mg every 2 weeks for 16 weeks, followed by nivolumab at a dose of 480 mg every 4 weeks) or matching placebo. The maximum duration of the trial intervention period was 1 year. The primary end point was disease-free survival.

RESULTS

The median follow-up was 24.4 months. Among the 532 patients who received nivolumab, the median disease-free survival was 22.4 months (95% confidence interval [CI], 16.6 to 34.0), as compared with 11.0 months (95% CI, 8.3 to 14.3) among the 262 patients who received placebo (hazard ratio for disease recurrence or death, 0.69; 96.4% CI, 0.56 to 0.86; P<0.001). Disease-free survival favored nivolumab across multiple prespecified subgroups. Grade 3 or 4 adverse events that were considered by the investigators to be related to the active drug or placebo occurred in 71 of 532 patients (13%) in the nivolumab group and 15 of 260 patients (6%) in the placebo group. The trial regimen was discontinued because of adverse events related to the active drug or placebo in 9% of the patients in the nivolumab group and 3% of those in the placebo group.

CONCLUSIONS

Among patients with resected esophageal or gastroesophageal junction cancer who had received neoadjuvant chemoradiotherapy, disease-free survival was significantly longer among those who received nivolumab adjuvant therapy than among those who received placebo. (Funded by Bristol Myers Squibb and Ono Pharmaceutical; CheckMate 577 ClinicalTrials.gov number, NCT02743494.)

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*A complete list of the CheckMate 577 sites and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Esophageal cancer, the seventh most common cancer globally, accounts for more than half a million deaths each year.[1] The incidence of esophageal squamous-cell carcinoma, the most common histologic type, has been stable, whereas the incidences of esophageal and gastroesophageal junction adenocarcinomas continue to increase in Western countries.[1-3]

Neoadjuvant chemoradiotherapy followed by surgery is a widely used standard of care for patients with resectable, locally advanced esophageal or gastroesophageal junction cancer.[4-6] However, the risk of recurrence after neoadjuvant chemoradiotherapy and surgery remains high, especially among the 70 to 75% of patients who do not have a pathological complete response.[7] The median overall survival among patients without a pathological complete response is shorter than that among those with a pathological complete response, and outcomes are even worse in patients with lymph node–positive disease.[7-11] Adjuvant treatments to improve outcomes are clearly needed; however, none has proved to be effective. Instead, the standard of care after neoadjuvant chemoradiotherapy and surgery is surveillance.[4,5]

In clinical trials involving patients who had previously treated, advanced gastroesophageal cancers with the histologic type adenocarcinoma or squamous-cell carcinoma, survival among those who received nivolumab, a fully human monoclonal anti–programmed death 1 (PD-1) antibody, was longer than among those who received either placebo or chemotherapy.[12,13] Here, we report the results of CheckMate 577, a global, randomized, double-blind, placebo-controlled phase 3 trial that evaluated a novel approach of using a checkpoint inhibitor as adjuvant treatment after neoadjuvant chemoradiotherapy and surgery for esophageal or gastroesophageal junction cancer.

METHODS

PATIENTS

We enrolled patients who were at least 18 years of age, had resected esophageal or gastroesophageal junction cancer, and had received neoadjuvant chemoradiotherapy. These patients were enrolled regardless of programmed death ligand 1 (PD-L1) expression. The inclusion criteria stipulated that at the initial diagnosis, the patients had stage II or III esophageal or gastroesophageal junction cancer (as defined in the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer)[14] and histologically confirmed predominant adenocarcinoma or squamous-cell carcinoma. The patients completed neoadjuvant chemoradiotherapy,[4,5] followed by complete resection, and were rendered free of disease (defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins [R0]).

Other key inclusion criteria were residual pathological disease (i.e., the absence of a pathological complete response) with a tumor and node classification of at least ypT1 or ypN1 in the resected specimens (yp denotes the pathological stage after neoadjuvant therapy), an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores indicating greater disability), and a complete resection performed within 4 to 16 weeks before randomization. Additional eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

TRIAL DESIGN AND INTERVENTIONS

The CheckMate 577 trial is a global, randomized, double-blind, placebo-controlled phase 3 trial. After neoadjuvant chemoradiotherapy and surgery and within 4 to 16 weeks after surgery, patients were randomly assigned in a 2:1 ratio to receive either nivolumab (administered intravenously at a dose of 240 mg over 30 minutes every 2 weeks for 16 weeks, followed by 480 mg over 30 minutes every 4 weeks beginning at week 17), or placebo (according to the same schedule). Randomization was stratified according to tumor-cell PD-L1 expression (≥1% or <1%, indeterminate, or could not be evaluated), pathological lymph-node status (≥ypN1 or ypN0), and histologic type (squamous-cell carcinoma or adenocarcinoma). The use of nivolumab or placebo continued until disease recurrence, unacceptable toxic effects, or withdrawal of consent occurred. The maximum duration of the trial intervention period was 1 year. Dose modifications were not permitted, but nivolumab or placebo could be interrupted or delayed for a maximum of 6 weeks

during the first 16 weeks or for a maximum of 10 weeks during the remainder of the trial intervention period. Additional trial-design methods are detailed in the Supplementary Appendix.

Challenges in enrollment and evidence to support disease-free survival as a surrogate for overall survival[15] among patients receiving adjuvant therapy led to a protocol amendment (before the completion of enrollment) in which disease-free survival became the single primary end point and overall survival changed from the coprimary end point to the first secondary end point to be tested hierarchically.

TRIAL OVERSIGHT

Bristol Myers Squibb (the sponsor), in collaboration with Ono Pharmaceutical, funded the trial, provided the trial agents, and collaborated with the academic authors on the design of the trial and the collection, analysis, and interpretation of the data. The trial was conducted in accordance with the Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the trial protocol (available at NEJM.org). The protocol was approved by the institutional review board or independent ethics committee at each site. All the patients provided written informed consent according to the principles of the Declaration of Helsinki. An independent data monitoring committee provided oversight of safety and efficacy data.

The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The authors had access to the trial data, participated in developing or revising the manuscript, and provided final approval to submit the manuscript for publication. Medical-writing support, including development of the first draft of the manuscript under the guidance of the first and last authors, was funded by the sponsor.

END POINTS AND ASSESSMENTS

The primary end point was disease-free survival (the time from the date of randomization to the first date of disease recurrence or death, whichever occurred first, before subsequent anticancer therapy). Recurrence was defined as the appearance of one or more new lesions (local, regional, or distant in location from the primary resected site, confirmed by imaging or by cytologic or pathological evaluation) as assessed by the investigators. The secondary end points were overall survival and survival at 1, 2, and 3 years. Exploratory end points included safety, distant metastasis–free survival, and patient-reported outcomes (evaluated with the Functional Assessment of Cancer Therapy–Esophageal [FACT-E] scale and the three-level version of the European Quality of Life–5 Dimensions questionnaire [EQ-5D-3L]). The methods for assessment of these end points are provided in the Supplementary Appendix.

Disease recurrence was evaluated with the use of contrast-enhanced computed tomography (CT) or magnetic resonance imaging at baseline and every 12 weeks from the first date of administration of nivolumab or placebo (±7 days) in the first year, every 12 weeks (±14 days) in the second year, and according to local standards (a minimum of one imaging assessment every 6 to 12 months) between years 3 and 5 (until distant recurrence). If a new lesion was equivocal or unclear, either because of the lesion size or an ambiguous cause, the suspected lesion was confirmed by means of cytologic or histopathologic assessment or by a follow-up imaging evaluation within 4 weeks (if biopsy was not possible). If cytologic or histopathologic assessment or repeat imaging confirmed recurrence, then recurrence was recorded according to the date of the initial imaging. In cases of clinically clear recurrence, the diagnosis could be made on the basis of imaging alone. Lymph-node metastasis was determined by means of CT on the basis of a lymph-node diameter of at least 1 cm in the short axis.

Tumor-cell PD-L1 expression, defined as the percentage of viable tumor cells with partial or complete membrane staining in at least 100 viable tumor cells, was evaluated at two central laboratories with the use of the PD-L1 IHC 28-8 pharmDX assay with the Dako Autostainer Link 48 system (Dako, Agilent Technologies), according to the manufacturer's instructions. A combined positive score was generated as part of a post hoc exploratory analysis by using a formula to rescore the PD-L1–stained slides. The combined positive score was defined as the number of PD-L1–positive tumor cells (with partial or complete membrane staining), lymphocytes, and

macrophages (with membrane staining, intracellular staining, or both) divided by the total number of viable tumor cells and multiplied by 100.

Adverse events were assessed throughout the trial treatment period and during follow-up. These events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

STATISTICAL ANALYSIS

For the primary end point, we estimated that at least 440 events of disease recurrence or death would provide approximately 91% power for the trial to detect an average hazard ratio of 0.72 at a two-sided alpha of 0.05, with accounting for a prespecified interim analysis of disease-free survival, which was triggered when at least 85% of all 440 events had been observed. The boundary for statistical significance based on 396 events of disease recurrence or death observed at this interim analysis required the P value to be less than 0.036. Disease-free survival was compared in the nivolumab and placebo groups in all patients who underwent randomization (intention-to-treat population) with the use of the two-sided log-rank test, stratified according to the three randomization stratification factors.

The hazard ratio with its corresponding two-sided 100 × (1 − adjusted alpha) confidence interval was estimated with the use of a stratified Cox proportional-hazards model with the trial group as the only covariate in the model. Disease-free survival in each group was estimated and plotted according to the Kaplan–Meier method. A two-sided 95% confidence interval for median disease-free survival in each group was computed with the Kaplan–Meier method and the log–log transformation method. Additional details on censoring of patient data in the analysis of disease-free survival are included in the Supplementary Appendix.

RESULTS

PATIENTS

From July 2016 through August 2019, a total of 1085 patients at 170 sites in 29 countries were assessed for eligibility, and 794 patients were randomly assigned to receive nivolumab (532 patients) or placebo (262 patients) (Fig. S1 in the Supplementary Appendix). A total of 792 patients received at least one dose of nivolumab or placebo as assigned (2 patients in the placebo group did not). The median follow-up for this interim analysis (the time from randomization to the clinical data cutoff date on May 12, 2020) was 24.4 months (range, 6.2 to 44.9). A total of 501 of 532 patients (94%) in the nivolumab group and 241 of 260 patients (93%) in the placebo group discontinued the assigned regimen. The primary reason for discontinuation of the regimen was completion of the intervention in the nivolumab group (in 229 of 532 patients [43%]) and disease progression in the placebo group (in 113 of 260 patients [43%]).

The demographic and baseline clinical characteristics were balanced between the two groups (Table 1). Most patients (563 of 794 [71%]) had adenocarcinoma, and 457 of 794 patients (58%) had a pathological lymph-node status of at least ypN1. Baseline tumor-cell PD-L1 expression of 1% or greater was detected in 89 of 532 patients (17%) in the nivolumab group and in 40 of 262 patients (15%) in the placebo group. In a post hoc analysis, a baseline PD-L1 combined positive score of 5 or higher (on a scale of 0 to 100, with higher scores indicating greater PD-L1 expression in tumor, immune cells, or both) was observed in 246 of 435 patients (57%) in the nivolumab group and in 125 of 231 patients (54%) in the placebo group. Approximately one third of the patients were from the United States or Canada, one third were from Europe, and one third were from Asia or the rest of the world. Table S1 provides details regarding chemotherapy and radiotherapy in the patients who received neoadjuvant treatment. The demographic and baseline clinical characteristics of the patients who began the regimen less than 10 weeks after surgery and those who began the regimen 10 or more weeks after surgery are shown in Table S2 (post hoc analysis).

EFFICACY

The median disease-free survival was 22.4 months (95% confidence interval [CI], 16.6 to 34.0) among patients who received nivolumab and 11.0 months (95% CI, 8.3 to 14.3) among those who received placebo (hazard ratio for disease recurrence or death, 0.69; 96.4% CI, 0.56 to 0.86; P<0.001) (Fig. 1A). Disease-free survival was significantly longer among patients who received adjuvant nivolumab than among those who received placebo, and there was a sustained separation of the disease-free survival curves. In a

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Nivolumab (N = 532)	Placebo (N = 262)
Median age (range) — yr	62 (26–82)	61 (26–86)
Male sex — no. (%)	449 (84)	222 (85)
Race — no. (%)†		
White	432 (81)	216 (82)
Asian	83 (16)	34 (13)
Black	7 (1)	2 (<1)
Other	10 (2)	9 (3)
Not reported	0	1 (<1)
Geographic region — no. (%)		
Europe	202 (38)	101 (39)
United States or Canada	167 (31)	88 (34)
Asia	77 (14)	29 (11)
Rest of the world‡	86 (16)	44 (17)
ECOG performance-status score — no. (%)§		
0	308 (58)	156 (60)
1	224 (42)	106 (40)
Disease stage at initial diagnosis — no. (%)		
II	179 (34)	99 (38)
III	351 (66)	163 (62)
Not reported	2 (<1)	0
Tumor location at initial diagnosis — no. (%)		
Esophagus	320 (60)	155 (59)
Gastroesophageal junction	212 (40)	107 (41)
Histologic type — no. (%)¶		
Adenocarcinoma	376 (71)	187 (71)
Squamous-cell carcinoma	155 (29)	75 (29)
Other	1 (<1)	0
Tumor-cell PD-L1 expression at trial entry — no. (%)‖		
<1%	374 (70)	196 (75)
≥1%	89 (17)	40 (15)
Indeterminate or could not be evaluated	69 (13)	26 (10)
Pathological lymph-node status at trial entry — no. (%)**		
≥ypN1	305 (57)	152 (58)
ypN0	227 (43)	109 (42)
Not known	0	1 (<1)
Pathological tumor status at trial entry — no. (%)**		
ypT0	31 (6)	16 (6)
ypT1 or ypT2	202 (38)	106 (40)
ypT3 or ypT4	296 (56)	140 (53)
Not known	3 (<1)	0

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group, and PD-L1 programmed death ligand 1.
† Race was reported by the patients.
‡ The "rest of the world" category comprised Argentina, Australia, Brazil, Israel, Mexico, and Turkey.
§ ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ One patient in the nivolumab group had a histologic type of "other" (protocol deviation).
‖ In most patients, tumor-cell PD-L1 expression was determined with the use of the PD-L1 IHC 28–8 pharmDX assay (Dako, Agilent Technologies) from a tumor tissue specimen obtained from the patient after completion of chemoradiotherapy. However, tumor tissue from 40 patients was quantifiable only before chemoradiotherapy.
** Pathological lymph-node status and tumor status are classified according to the criteria of the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.

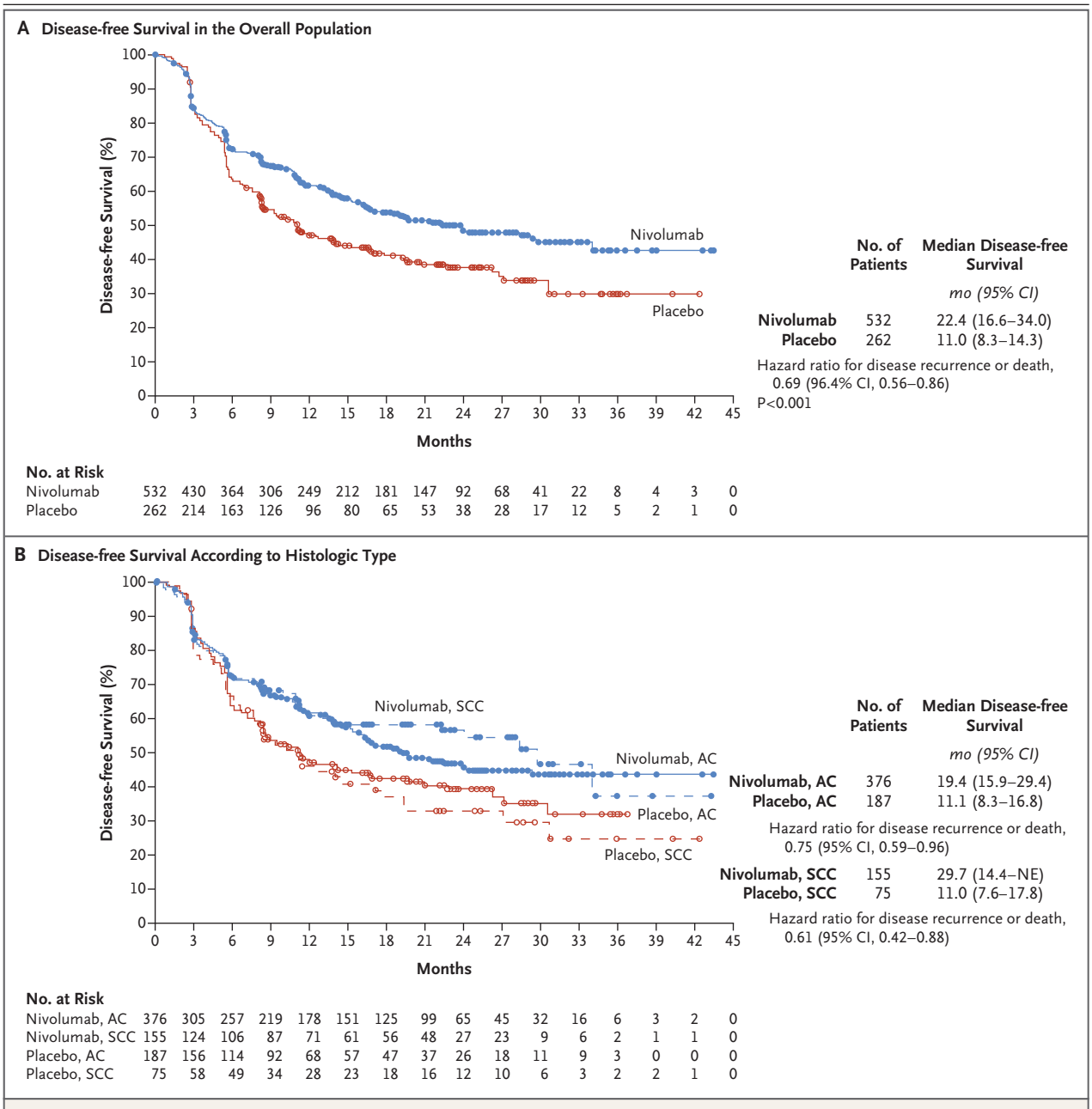


Figure 1. Disease-free Survival in the Intention-to-Treat Population.

Kaplan–Meier estimates of disease-free survival in the overall population (Panel A) and according to histologic type (Panel B) are shown. At 6 months, 72% (95% confidence interval [CI], 68 to 76) of the patients in the nivolumab group and 63% (95% CI, 57 to 69) of those in the placebo group were alive without disease recurrence. AC denotes adenocarcinoma, NE could not be estimated, and SCC squamous-cell carcinoma.

post hoc analysis, the disease-free survival benefit was observed regardless of histologic type (Figs. 1B and 2). Hazard ratios for disease recurrence or death consistently favored nivolumab across prespecified subgroups based on demographic and baseline disease characteristics, including tumor-cell PD-L1 expression (Fig. 2). Post hoc analyses showed a disease-free survival benefit

of nivolumab (hazard ratio, <1) in patients with tumors with a PD-L1 combined positive score of at least 5 and in those with a score of less than 5, as well as across reported doses of neoadjuvant radiotherapy (Fig. S2).

Among the 396 observed events of disease recurrence or death (90% of 440 events), 366 were recurrences and 30 were deaths. Distant recurrence was less frequent in the nivolumab group than in the placebo group (in 154 of 532 patients [29%] and in 103 of 262 patients [39%], respectively), as was locoregional recurrence (in 65 of 532 patients [12%] and in 44 of 262 patients [17%], respectively). The median distant metastasis–free survival was 28.3 months (95% CI, 21.3 to could not be estimated) in the nivolumab group and 17.6 months (95% CI, 12.5 to 25.4) in the placebo group; thus, the risk of distant recurrence or death was 26% lower with nivolumab than with placebo (hazard ratio, 0.74; 95% CI, 0.60 to 0.92) (Fig. 3).

A total of 157 of 532 patients (30%) in the nivolumab group and 111 of 262 patients (42%) in the placebo group received subsequent therapy, including systemic anticancer therapy, radiotherapy, and surgery (Table S3). Few of these patients received subsequent immunotherapy (4 of 532 patients [<1%] and 19 of 262 patients [7%], respectively).

EXPOSURE AND SAFETY

The median duration of the trial intervention period in the safety population was 10.1 months (range, 0.03 to 14.2) in the nivolumab group (532 patients) and 9.0 months (range, 0.03 to 15.0) in the placebo group (260 patients) (Table S4). The percentages of patients with dose delays were similar in the two groups. Among the patients who received nivolumab, 459 of 532 (86%) had a relative dose intensity of 90% or more.

Grade 3 or 4 adverse events of any cause occurred in 183 of 532 patients (34%) in the nivolumab group and 84 of 260 patients (32%) in the placebo group, and serious adverse events of any grade occurred in 30% of the patients in each group (158 of 532 and 78 of 260, respectively) (Table 2). Adverse events that were considered by the investigators to be related to the trial regimen were more common with nivolumab than with placebo, including grade 3 or 4 events (in 71 of 532 patients [13%] and 15 of 260 patients [6%], respectively) and events leading to discontinuation (in 48 of 532 patients [9%] and 8 of 260 patients [3%], respectively). The incidence of serious adverse events of any grade related to the trial regimen was 8% in the nivolumab group and 3% in the placebo group. The most common adverse events of any grade that were considered to be related to the trial regimen were fatigue, diarrhea, pruritus, and rash in patients receiving nivolumab and diarrhea and fatigue in those receiving placebo.

The majority of select adverse events with a potential immunologic cause that were considered to be related to nivolumab or placebo were grade 1 or 2; grade 3 or 4 events in any organ class occurred in 1% or less of the patients in the nivolumab group, and there were no grade 5 events in this category (Table S5). The most common grade 3 or 4 select nivolumab-related adverse events in the nivolumab group were pneumonitis (in 4 patients [<1%]) and rash (in 4 patients [<1%]); these events occurred in 1 patient each (<1%) in the placebo group.

PATIENT-REPORTED OUTCOMES

At least 95% of the patients completed the FACT-E assessment and the EQ-5D-3L questionnaire at baseline, and approximately 90% completed these assessments at 12 months during the treatment period. A longitudinal mixed-model analysis that was used to compare the least-squares mean score differences between the two groups showed similar improvement from baseline at most time points through week 53 with both nivolumab and placebo in the FACT-E total score, on the EQ-5D-3L visual analogue scale, and in the EQ-5D-3L utility index score. A clinically meaningful improvement with both nivolumab and placebo was observed at several time points on the EQ-5D-3L visual analogue scale, but neither group had a clinically meaningful improvement in the FACT-E total score or the EQ-5D-3L utility index score. These findings indicate that health-related quality of life was maintained during the treatment period (Fig. S3). The percentages of patients who replied "I am not at all bothered by side effects of treatment" on the FACT-E GP5 item were similar in the two groups (Fig. S4).

Subgroup	No. of Patients	Median Disease-free Survival		Unstratified Hazard Ratio (95% CI)
		Nivolumab	Placebo	
		mo		
Overall	794	22.4	11.0	0.70 (0.58–0.86)
Age				
<65 yr	507	24.4	10.8	0.65 (0.51–0.84)
≥65 yr	287	17.0	13.9	0.80 (0.57–1.12)
Sex				
Male	671	21.4	11.1	0.73 (0.59–0.91)
Female	123	Not reached	11.0	0.59 (0.35–1.00)
Race				
White	648	21.3	10.9	0.71 (0.57–0.88)
Asian	117	24.0	10.2	0.70 (0.41–1.22)
Black	9	14.4	8.3	0.43 (0.06–3.06)
Other	20	Not reached	14.1	0.48 (0.11–2.02)
Region				
Asia	106	24.0	14.3	0.78 (0.43–1.41)
Other	688	21.4	11.0	0.69 (0.56–0.86)
ECOG performance-status score				
0	464	29.4	11.1	0.73 (0.56–0.96)
1	330	17.0	10.9	0.66 (0.48–0.89)
Disease stage at initial diagnosis				
II	278	34.0	13.9	0.72 (0.51–1.02)
III	514	19.4	8.5	0.68 (0.53–0.88)
Tumor location at initial diagnosis				
Esophagus	462	24.0	8.3	0.61 (0.47–0.78)
Gastroesophageal junction	332	22.4	20.6	0.87 (0.63–1.21)
Histologic type				
Adenocarcinoma	563	19.4	11.1	0.75 (0.59–0.96)
Squamous-cell carcinoma	230	29.7	11.0	0.61 (0.42–0.88)
Tumor-cell PD-L1 expression				
≥1%	129	19.7	14.1	0.75 (0.45–1.24)
<1%	570	21.3	11.1	0.73 (0.57–0.92)
Indeterminate or could not be evaluated	95	Not reached	9.5	0.54 (0.27–1.05)
Pathological lymph-node status				
ypN0	336	Not reached	27.0	0.74 (0.51–1.06)
≥ypN1	457	14.8	7.6	0.67 (0.53–0.86)
Pathological tumor status				
ypT0	47	34.0	5.2	0.35 (0.15–0.82)
ypT1 or ypT2	308	28.3	9.3	0.60 (0.44–0.83)
ypT3 or ypT4	436	18.9	14.1	0.84 (0.64–1.11)
Histologic grade				
1 or 2	438	29.4	13.9	0.68 (0.51–0.91)
3 or 4	253	14.1	9.2	0.73 (0.52–1.02)
Not assessed	101	Not reached	11.1	0.65 (0.37–1.16)
Time from complete resection to randomization				
<10 wk	256	24.0	14.1	0.84 (0.57–1.22)
≥10 wk	538	21.4	10.8	0.66 (0.52–0.84)
HER2 status				
Positive	63	19.6	7.6	0.78 (0.40–1.55)
Negative	207	21.4	9.4	0.69 (0.46–1.03)
Not reported	522	24.0	11.1	0.70 (0.55–0.90)

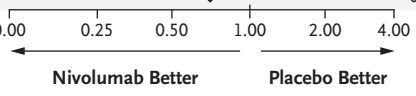


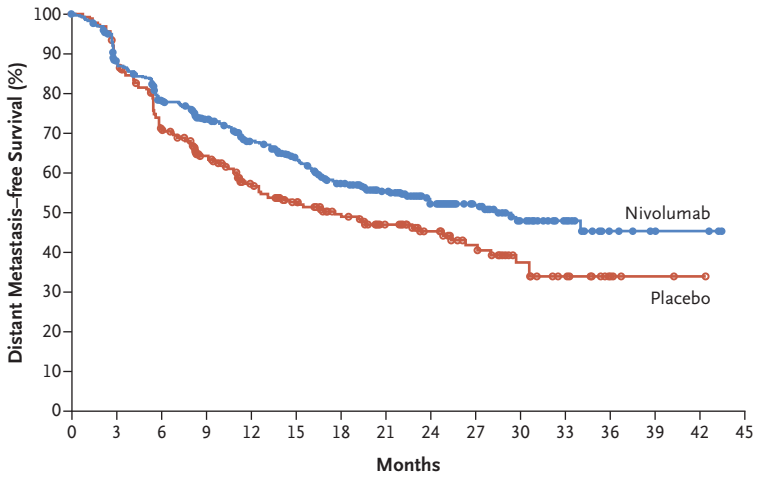
Figure 2 (facing page). Disease-free Survival, According to Subgroups.

Confidence intervals were not adjusted for multiplicity. Race was reported by the patients. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Pathological lymph-node status and tumor status are classified according to the criteria of the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer. Human epidermal growth factor receptor 2 (HER2) status was unknown in two patients. PD-L1 denotes programmed death ligand 1.

DISCUSSION

Neoadjuvant chemoradiotherapy followed by surgery is a well-established standard of care for resectable, locally advanced esophageal or gastroesophageal junction cancer.[4-6] However, a pathological complete response is often not achieved, and most patients have a poor prognosis.[7] Currently, the standard management after neoadjuvant chemoradiotherapy and surgery is surveillance,[4,5] and the development of an effective adjuvant treatment has been an elusive goal. In our CheckMate 577 trial involving patients with resectable, locally advanced esophageal or gastroesophageal junction cancer, nivolumab adjuvant therapy showed superior efficacy over placebo in the primary end point of disease-free survival. The trial population consisted of patients with residual pathological disease and a high risk of recurrence, which is reported in 70 to 75% of patients with esophageal or gastroesophageal junction cancer who do not have a pathological complete response after neoadjuvant chemoradiotherapy and surgery.[7] More than half the trial patients had lymph node–positive disease, which is associated with particularly poor outcomes. Despite the poor prognostic factors in these patients, nivolumab was associated with significant improvement in disease-free survival, with a 31% reduction in the risk of recurrence or death, and the median disease-free survival was twice as long in the nivolumab group as in the placebo group. Moreover, the sustained separation of the Kaplan–Meier curves indicates a durable benefit.

The hazard ratios favored nivolumab over pla-



	No. of Patients	Median Distant Metastasis–free Survival (mo (95% CI))
Nivolumab	532	28.3 (21.3–NE)
Placebo	262	17.6 (12.5–25.4)

Hazard ratio for distant recurrence or death, 0.74 (95% CI, 0.60–0.92)

Figure 3. Distant Metastasis–free Survival in the Intention-to-Treat Population.

At 6 months, the Kaplan–Meier estimates of distant metastasis–free survival were 78% (95% CI, 74 to 82) in the nivolumab group and 71% (95% CI, 65 to 76) in the placebo group. Confidence intervals were not adjusted for multiplicity.

Table 2. Adverse Events in the Safety Population.*

Event	Nivolumab (N = 532)		Placebo (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event†	510 (96)	183 (34)	243 (93)	84 (32)
Serious adverse event	158 (30)	107 (20)	78 (30)	53 (20)
Adverse event leading to discontinuation of trial regimen	68 (13)	38 (7)	20 (8)	16 (6)
Any adverse event related to nivolumab or placebo†‡	376 (71)	71 (13)	119 (46)	15 (6)
Serious adverse event related to nivolumab or placebo‡	40 (8)	29 (5)	7 (3)	3 (1)
Related adverse event leading to discontinuation of trial regimen‡	48 (9)	26 (5)	8 (3)	7 (3)
Adverse event related to nivolumab or placebo in ≥5% of patients in either group†				
Fatigue	90 (17)	6 (1)	29 (11)	1 (<1)
Diarrhea	88 (17)	2 (<1)	39 (15)	2 (<1)
Pruritus	53 (10)	2 (<1)	9 (3)	0
Rash	52 (10)	4 (<1)	10 (4)	1 (<1)
Hypothyroidism	50 (9)	0	4 (2)	0
Nausea	47 (9)	0	13 (5)	0
Hyperthyroidism	35 (7)	0	1 (<1)	0
Arthralgia	30 (6)	1 (<1)	4 (2)	0
Increase in AST level	29 (5)	2 (<1)	10 (4)	0
Asthenia	28 (5)	0	4 (2)	0
Decreased appetite	26 (5)	0	5 (2)	0

* The safety population included all the patients who had received at least one dose of nivolumab or placebo. AST denotes aspartate aminotransferase.
† These events were reported between the first dose and 30 days after the last dose of nivolumab or placebo.
‡ One grade 5 nivolumab-related adverse event was recorded (a cardiac arrest in the nivolumab group that was deemed to be not related to nivolumab by the investigator after database lock).

cebo across most prespecified subgroups, including histologic type (squamous-cell carcinoma and adenocarcinoma) and pathological lymph-node status (≥ypN1 and ypN0). No major disparities were noted between White and Asian subpopulations of patients; however, Black patients were underrepresented in this trial.

In patients with previously treated advanced gastroesophageal cancer, nivolumab has shown clinical benefit regardless of tumor-cell PD-L1 expression,[12,13] and PD-L1 expression as defined by a combined positive score of 5 or greater has shown better enrichment for the efficacy of checkpoint inhibitors than tumor-cell PD-L1 expression alone.[16] In our CheckMate 577 trial, the similar hazard ratios for disease recurrence or death with tumor-cell PD-L1 expression either below 1% or 1% or higher indicate that adjuvant nivolumab was similarly effective regardless of tumor-cell PD-L1 expression.

The hazard ratio for disease recurrence or death favored nivolumab more in the subgroup of patients with esophageal cancer than in the subgroup of patients with gastroesophageal junction cancer. Among the patients who received nivolumab, the median disease-free survival was similar in the esophageal cancer and gastroesophageal junction cancer subgroups; however, among

the patients who received placebo, the median disease-free survival was longer among those with gastroesophageal junction cancer than among those with esophageal cancer. Furthermore, given that adenocarcinoma is the most common histologic type of gastroesophageal junction cancer, it is notable that the hazard ratio (0.75) in the adenocarcinoma subgroup (regardless of tumor location) was intermediate between the hazard ratios for esophageal cancer (0.61) and gastroesophageal junction cancer (0.87), and among patients with adenocarcinoma, the median disease-free survival was 8.3 months longer with nivolumab than with placebo.

In patients who received nivolumab, the magnitude of benefit with respect to disease-free survival was greater in those in whom nivolumab was initiated at least 10 weeks after surgery than in those in whom nivolumab was initiated less than 10 weeks after surgery. This finding suggests that a prolonged recovery may be needed after intensive preoperative therapy followed by surgery, especially esophagectomy.[17,18] However, both patient subgroups stratified according to time from complete resection to randomization had an approximately 10-month-longer median disease-free survival with nivolumab than with placebo, and no clear imbalances in baseline characteristics associated with an increased risk of recurrence were identified in these two subgroups.

In addition to a disease-free survival benefit, the risk of distant recurrence or death was 26% lower and distant metastasis–free survival was 10.7 months longer with adjuvant nivolumab than with placebo. Our trial is ongoing, and an analysis of the secondary end point of overall survival is planned.

With the positive results of our CheckMate 577 trial, esophageal or gastroesophageal junction cancer is the second tumor type, after melanoma, for which nivolumab has provided a benefit as adjuvant treatment.[19] There are limited data to compare the results of neoadjuvant chemoradiotherapy with the results of perioperative chemotherapy (a standard treatment option for resectable esophageal, gastroesophageal junction, and gastric adenocarcinomas). The recent German FLOT4-AIO trial of perioperative chemotherapy did not include patients with esophageal cancer,[20] and the results cannot be directly compared with those of our CheckMate 577 trial of adjuvant therapy. Data are lacking to determine whether the results of perioperative chemotherapy could be improved by adding checkpoint inhibitors.

The safety profile of adjuvant nivolumab was in line with that in previous trials involving patients with gastroesophageal and other solid tumors.[12,13,19,21,22] Serious adverse events related to nivolumab and adverse events leading to discontinuation of the trial regimen in the nivolumab group were reported in less than 10% of the patients. Most of the patients in the adjuvant nivolumab group (86%) received at least 90% of the planned dose.

In patients with resected esophageal or gastroesophageal junction cancer after neoadjuvant chemoradiotherapy, nivolumab adjuvant therapy was associated with a significantly longer disease-free survival than placebo. The safety profile of nivolumab was similar to that seen in other types of solid tumors.

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APPENDIX

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