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Health-Related Quality of Life With Nivolumab Plus Chemotherapy Versus Chemotherapy in Patients With Advanced Gastric/Gastroesophageal Junction Cancer or Esophageal Adenocarcinoma From CheckMate 649

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DOI https://doi.org/10.1200/JCO.23.00170

ABSTRACT

PURPOSE In CheckMate 649, first-line nivolumab plus chemotherapy prolonged overall survival versus chemotherapy in patients with advanced/metastatic non–human epidermal growth factor receptor 2 (HER2)-positive gastric/gastroesophageal junction cancer (GC/GEJC) or esophageal adenocarcinoma (EAC). We present exploratory patient-reported outcomes (PROs).

METHODS In patients (N = 1,581) concurrently randomly assigned 1:1 to nivolumab plus chemotherapy or chemotherapy and in those with tumor PD-L1 expression at a combined positive score (CPS) of ≥5, health-related quality of life (HRQoL) was assessed using the EQ-5D and Functional Assessment of Cancer Therapy-Gastric (FACT-Ga), which included the FACT-General (FACT-G) and Gastric Cancer subscale (GaCS). The FACT-G GP5 item assessed treatment-related symptom burden. Longitudinal changes in HRQoL were assessed using mixed models for repeated measures in the PRO analysis population (randomly assigned patients with baseline and ≥1 postbaseline assessments). Time to symptom or definitive deterioration analyses were also conducted.

RESULTS In the PRO analysis population (n = 1,360), PRO questionnaire completion rates were mostly >80% during treatment. Patient-reported symptom burden was not increased with nivolumab plus chemotherapy versus chemotherapy. Mean improved changes from baseline were greater with nivolumab plus chemotherapy versus chemotherapy for FACT-Ga total, GaCS, and EQ-5D visual analog scale in patients with a CPS of ≥5; results were similar for the overall PRO analysis population. In CPS ≥5 and all randomly assigned populations, nivolumab plus chemotherapy reduced the risk of symptom deterioration versus chemotherapy, on the basis of FACT-Ga total score and GaCS; time to definitive deterioration was longer, and the risk of definitive deterioration in HRQoL was reduced with nivolumab plus chemotherapy across EQ-5D and most FACT-Ga measures (hazard ratio [95% CI] <1).

CONCLUSION Compared with chemotherapy alone, first-line nivolumab plus chemotherapy showed stable or better on-treatment HRQoL in patients with advanced/metastatic non–HER2-positive GC/GEJC/EAC and also showed decreased risk of definitive HRQoL deterioration.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

Accepted July 17, 2023

Published September 15, 2023

J Clin Oncol 00:1-12

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INTRODUCTION

Gastric/gastroesophageal junction cancer (GC/GEJC) and esophageal adenocarcinoma (EAC) are among the leading causes of global cancer-related mortality.[1] Strong similarities in molecular profiles between GC/GEJC and EAC suggest that these cancers could be considered a single disease entity.[2,3] Chemotherapy, the standard first-line treatment for patients with unresectable advanced or metastatic human epidermal growth factor receptor 2 (HER2)–negative GC/GEJC, has been

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CONTEXT

Key Objective

Gastric/gastroesophageal junction cancer (GC/GEJC) or esophageal adenocarcinoma (EAC) is associated with poor prognosis and high mortality. The phase III CheckMate 649 study showed clinical benefit with first-line nivolumab plus chemotherapy versus chemotherapy alone in patients with advanced GC/GEJC or EAC. This exploratory analysis evaluated the health-related quality of life (HRQoL) in patients treated with nivolumab plus chemotherapy versus chemotherapy alone using patient-reported outcomes (PROs).

Knowledge Generated

Patients treated with nivolumab plus chemotherapy versus chemotherapy alone maintained their HRQoL with a reduced risk of definitive deterioration in disease-related and overall health status and without increased treatment-related symptom burden. PRO results complement the previously reported clinically meaningful efficacy benefit with nivolumab plus chemotherapy and support its use as a first-line treatment for advanced or metastatic GE/GEJC or EAC.

Relevance *(A.H. Ko)*

These PRO data can be helpful when counseling patients with advanced or metastatic GE/GEJC or EAC, providing reassurance that the benefits of adding nivolumab to chemotherapy extend not only to improved survival, but also to preservation of their quality of life and prolonged symptom control.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

associated with poor prognosis (median overall survival [OS] is <1 year) and patient-reported symptom burden, with some regimens resulting in significant treatment-related toxicity.[4-7] Similar clinical outcomes with systemic chemotherapy have been reported for EAC.[8-10] First-line targeted therapies for HER2-negative GC/GEJC have not shown significant improvements in efficacy or safety compared with chemotherapy.[11-14] Considering the limited life expectancy of patients with advanced disease, it is important to assess the health-related quality of life (HRQoL) to weigh the benefits and risks of treatment from the patient's perspective.[15] This is especially relevant for advanced gastroesophageal cancers[16] as deterioration of HRQoL correlated with deterioration in Eastern Cooperative Oncology Group (ECOG) performance status (PS) and with disease progression in the second-line setting as shown by the RAINBOW/REGARDS studies.[17] In the first-line setting, chemotherapy showed stable or improved HRQoL versus best supportive care in patients with advanced esophagogastric cancer.[18] Recently, immunotherapy with or without chemotherapy has shown significant survival benefit versus chemotherapy alone in multiple tumor types, with no detrimental effects on HRQoL.[19,20] In patients with PD-L1–positive advanced or metastatic GC/GEJC, first-line pembrolizumab, a PD-1 inhibitor, was noninferior to chemotherapy for OS and HRQoL was similar between treatment arms.[21,22]

Nivolumab, a fully human anti–PD-1 antibody that restores antitumor T-cell function,[23,24] has shown significant survival benefit and acceptable safety, while maintaining or improving HRQoL versus standard of care in the first- or second-line setting for multiple tumor types.[25-31]

CheckMate 649 (ClinicalTrials.gov identifier: NCT02872116), a phase III, randomized open-label study, evaluated first-line nivolumab-based therapies in patients with advanced or metastatic GC/GEJC or EAC.[32] The study demonstrated superior OS along with a progression-free survival benefit and an acceptable safety profile with nivolumab plus chemotherapy versus chemotherapy in patients whose tumors expressed PD-L1 at a combined positive score (CPS) of ≥5 (primary population) or a CPS of ≥1 and in all randomly assigned patients.[32,33] On the basis of these results, first-line nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapies is approved in multiple countries for patients with advanced or metastatic GC/GEJC or EAC regardless of tumor PD-L1 expression[34,35] and in the European Union for those with a CPS of ≥5.[36] Initial analyses suggested that HRQoL was maintained with nivolumab plus chemotherapy.[32,33] Here, we present detailed results of the exploratory HRQoL analyses from CheckMate 649, using data from the July-2021 database lock.

METHODS

Study Design and Treatment

The study design for CheckMate 649 was described previously.[32] Adult patients with previously untreated advanced or metastatic non–HER2-positive (defined as HER2-negative or unknown HER2 status) GC/GEJC or EAC were initially randomly assigned 1:1:1 to receive nivolumab (360 mg once every 3 weeks or 240 mg once every 2 weeks) plus investigator's choice of chemotherapy (capecitabine and oxaliplatin [XELOX] or fluorouracil, leucovorin, and oxaliplatin [FOLFOX]), nivolumab plus ipilimumab, or chemotherapy

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alone after the nivolumab plus chemotherapy arm was added; 1:1 random assignment to nivolumab plus chemotherapy or chemotherapy continued after enrollment in the nivolumab plus ipilimumab arm was subsequently closed.[32] Results from the nivolumab plus ipilimumab arm were not included in this analysis. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or ≤2 years for nivolumab.

This study was conducted according to Good Clinical Practice guidelines developed by the International Council for Harmonisation and the Declaration of Helsinki principles. The study Protocol (online only) was approved by an institutional review board or independent ethics committee at each center. All patients provided written informed consent.

Patient-Reported Outcome Assessments and End Points

Patient-reported outcomes (PROs) were prespecified exploratory end points and collected using the three-level EQ-5D, which assessed the impact of treatment on the general health status of patients, and the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) questionnaire, which assessed the impact of treatment on cancer-related quality of life. The EQ-5D comprised a utility index (EQ-5D UI) on the basis of the UK value set and a EQ-5D visual analog scale (EQ VAS).[37,38] The FACT-Ga included the 27-item FACT-General (FACT-G) questionnaire (consisting of the physical well-being, social well-being [SWB], emotional well-being, and functional well-being subscales) and selected components, including a 19-item Gastric Cancer Subscale (GaCS).[39-41] Prespecified meaningful change thresholds (MCTs) were defined for each PRO measure (Data Supplement, Table S1, online only) on the basis of published ranges for minimally important differences for the respective scales.[38,39,41,42] Higher scores indicated better HRQoL for all PRO measures. The single FACT-G item GP5 ("I am bothered by side effects of treatment") was evaluated separately to assess the patient's experience with side effects. Scores indicating treatment bother ranged from 0 (not at all) to 4 (very much).[43]

All PRO questionnaires were completed by patients before dosing at baseline and every 6 weeks (±3 days) thereafter before treatment, regardless of the treatment schedule. To decrease patient burden, a reduced set of questionnaires were completed by patients during the follow-up period. Only the GaCS or the abbreviated 7-item version of FACT-G, FACT-G7,[44] was administered along with the EQ-5D during follow-up visits 1 (30 days [±7] after last dose) and 2 (84 days [±7] after follow-up visit 1) and every 3 months thereafter at survival follow-up visits.

Statistical Analysis

The statistical analysis for the PRO end points was descriptive and did not include hypothesis testing.

PRO questionnaire completion rates corresponded to the proportion of questionnaires received out of the expected number (ie, the number of patients still on treatment or follow-up at any given timepoint). Responses to the FACT-G GP5 item were analyzed descriptively by treatment arm at each assessment.

Mean changes from baseline in PRO scale scores were estimated from a mixed model for repeated measures (MMRM) using restricted maximum likelihood with within-patient correlations modeled by an R-side unstructured covariance structure in patients with a CPS of ≥5 and all randomly assigned patients with an evaluable PRO assessment at baseline (day 1, assessment before administration of treatment on the day of first dose) and ≥1 evaluable postbaseline PRO assessment (CPS ≥5 and overall PRO analysis populations, respectively). The change in score from baseline at each postbaseline assessment was modeled as a linear function of treatment arm, study assessment, baseline score, trial stratification factors (tumor PD-L1 expression level [≥1%, <1%, or indeterminate], geographical region [United States, Asia, or rest of the world], ECOG PS [0 or 1], planned chemotherapy regimen [XELOX or FOLFOX]), interaction terms between treatment the arm and study assessment, interaction terms between baseline score and study assessment, and any potential confounders. For the GaCS, further analyses of missing data patterns were performed to investigate missing at random assumptions. Assessments with ≥10 patients per treatment arm were included for most PRO scales/subscales; for the EQ-5D UI and FACT-G7, assessments with ≥20 patients per treatment arm in the overall PRO analysis population were included to achieve model convergence. Data from both on-treatment and follow-up PRO assessments were included if sample size requirements were met. Model-adjusted least-squares (LS) mean change in score from baseline, associated 95% CIs, and descriptive *P* values were reported at each postbaseline assessment.

Time to deterioration analyses were performed in the CPS ≥5 and all randomly assigned populations and included all PRO assessments conducted before or on the date of treatment discontinuation. Time to symptom deterioration (TTSD) was defined as the time from random assignment until the first decline in PRO score from baseline, which met or exceeded the MCT. Time to definitive deterioration (TTDD) was defined as the time from random assignment until the first decline in PRO score from baseline, which met or exceeded the MCT, when all subsequent assessments also met or exceeded the MCT. TTSD and TTDD were compared between treatment arms using stratified log-rank tests and plotted using the Kaplan-Meier (KM) product-limit method; descriptive *P* values were reported. The hazard ratio (HR) and associated two-sided 95% CIs were calculated using a stratified Cox model with the treatment group as the only covariate.

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Missing PRO assessment data were not imputed. All analyses were conducted using SAS version 9.4 or higher (SAS Institute; Cary, NC).

Additional details on treatment, PRO assessments, and statistical analyses are included in the Data Supplement.

RESULTS

Patients

Among all randomly assigned patients (N = 1,581), 60% (nivolumab plus chemotherapy; n = 473 of 789) and 61% (chemotherapy; n = 482 of 792) had a PD-L1 CPS of ≥5; the proportion of patients with a CPS of ≥5 was similar in the overall PRO analysis population (n = 1,360; 61% [422 of 694] and 60% [400 of 666], respectively; Data Supplement, Fig S1). Baseline characteristics were generally balanced between treatment arms in the CPS ≥5 PRO analysis population, between the CPS ≥5 and overall PRO analysis populations, and between the overall PRO analysis and all randomly assigned populations (Table 1).[32] The mean patient age in the CPS ≥5 PRO analysis population was 61.0 (nivolumab plus chemotherapy) and 60.5 (chemotherapy) years. Most patients were male (71%) and White (67%), had an ECOG PS of 1 (56%), and had GC as the primary tumor location at initial diagnosis (71%).

PRO Questionnaire Completion Rates

In the CPS ≥5 and overall PRO analysis populations, >95% of patients had an evaluable baseline assessment. In the CPS ≥5 and overall PRO analysis populations, EQ-5D and FACT-Ga questionnaire completion rates were >80% on most

TABLE 1. Baseline Characteristics of Patients in the CPS ≥5 and Overall PRO Analysis Populations

	CPS ≥5 PRO Analysis Population (n = 822)		Overall PRO Analysis Population (n = 1,360)	
Characteristic	NIVO + Chemo (n = 422)	Chemo (n = 400)	NIVO + Chemo (n = 694)	Chemo (n = 666)
Age, years, mean (SD)	61.0 (11.8)	60.5 (11.4)	60.1 (12.0)	59.6 (11.8)
Male, No. (%)	293 (69)	292 (73)	476 (69)	475 (71)
Race, No. (%)				
White	284 (67)	265 (66)	473 (68)	444 (67)
Asian	117 (28)	103 (26)	181 (26)	170 (26)
Others	21 (5)	32 (8)	40 (6)	52 (8)
Region, No. (%)				
United States	55 (13)	54 (14)	108 (16)	104 (16)
Asia	116 (27)	100 (25)	174 (25)	164 (25)
Rest of the world	251 (59)	246 (62)	412 (59)	398 (60)
ECOG performance status, No. (%)				
0	184 (44)	178 (45)	316 (46)	303 (45)
1	238 (56)	222 (56)	378 (54)	363 (55)
Weight, kg, mean (SD)	68.4 (17.1)	67.8 (16.0)	68.4 (16.9)	67.8 (17.0)
Primary tumor location at initial diagnosis, No. (%)				
GC	307 (73)	277 (69)	500 (72)	471 (71)
GEJC	70 (17)	74 (19)	111 (16)	107 (16)
EAC	45 (11)	49 (12)	83 (12)	88 (13)
Disease state at initial diagnosis, No. (%)				
Stage I	3 (1)	4 (1)	6 (1)	4 (1)
Stage II	14 (3)	16 (4)	23 (3)	32 (5)
Stage III	55 (13)	56 (14)	90 (13)	96 (14)
Stage IV	349 (83)	323 (81)	573 (83)	533 (80)
Not reported	1 (0)	1 (0)	2 (0)	1 (0)
Disease status, No. (%)				
Locally recurrent	2 (0)	0 (0)	2 (0)	1 (0)
Metastatic	405 (96)	383 (96)	667 (96)	639 (96)
Locally advanced	15 (4)	17 (4)	25 (4)	26 (4)

NOTE. Percentages may not sum to 100 because of rounding.
Abbreviations: Chemo, chemotherapy; CPS, combined positive score; EAC, esophageal adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; GC, gastric cancer; GEJC, gastroesophageal junction cancer; NIVO, nivolumab; PRO, patient-reported outcome; SD, standard deviation.

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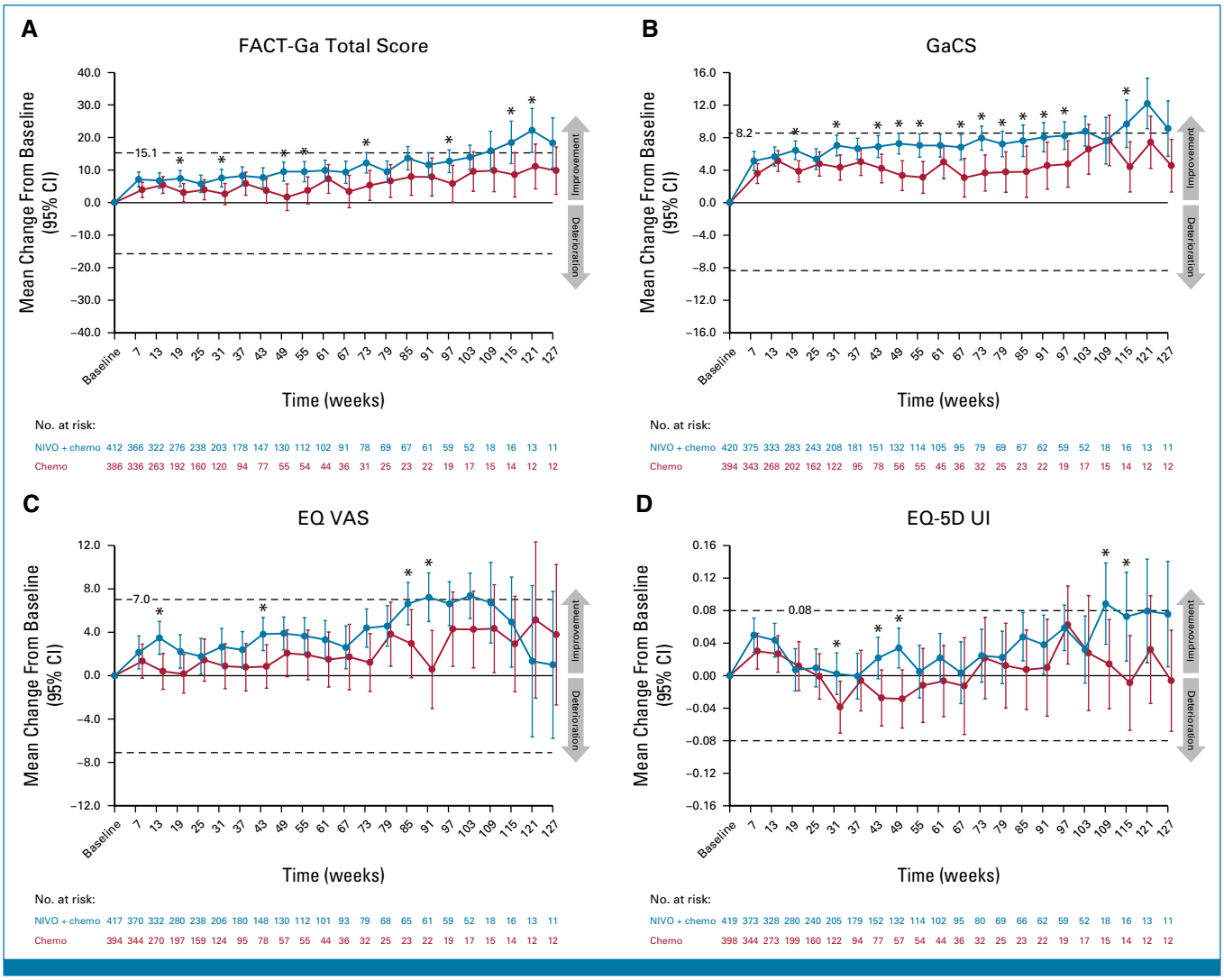

FIG 1. Least-squares mean change (95% CI) from baseline in (A) FACT-Ga total score, (B) GaCS, (C) EQ VAS, and (D) EQ-5D UI scores in the CPS ≥5 PRO analysis population. Dashed lines indicate MCTs. Circles indicate point estimates, and vertical bars indicate 95% CIs. *P < .05 was not formally tested. Only timepoints with ≥10 patients per treatment arm were included. Chemo, chemotherapy; CPS, combined positive score; EQ-5D UI, EQ-5D utility index; EQ VAS, EQ-5D visual analog scale; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; GaCS, Gastric Cancer Subscale; MCT, meaningful change threshold; NIVO, nivolumab; PRO, patient-reported outcome.

on-treatment assessments with ≥10 patients (until week 133) in both treatment arms; EQ-5D completion rates during follow-up were slightly lower (Data Supplement, Table S2).

Descriptive Analyses of Treatment-Related Symptom Burden

In the CPS ≥5 and overall PRO analysis populations, most patients in both treatment arms reported that they were not at all or a little bothered by treatment-related side effects, as assessed by the FACT-G GP5 item. The proportion of patients reporting not at all bothered by treatment-related side effects increased over time in the nivolumab plus chemotherapy arm and was higher than that in the chemotherapy arm at most postbaseline timepoints (Data Supplement, Fig S2). In the CPS ≥5 PRO analysis population, the proportion of patients reporting not at all or a little bothered by treatment side effects at postbaseline assessments ranged from 63% (not at all, n = 91 of 336; a little, n = 120 of 336) at week 13 to 94% (n = 12 of 16; n = 3 of 16) at week 115 for nivolumab plus chemotherapy and 62% (n = 92 of 347; n = 124 of 347) at week 7 to 84% (n = 11 of 25; n = 10 of 25) at week 79 for chemotherapy; in the overall PRO analysis population, the proportions ranged from 62% (n = 137 of 538; n = 196 of 538) at week 13 to 100% (n = 11 of 11; n = 0 of 11) at week 133 and 60% (n = 60 of 282; n = 109 of 282) at week 25 to 86% (n = 18 of 44; n = 20 of 44) at week 79, respectively.

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Analyses of Changes in PROs Over Time

In the CPS ≥5 PRO analysis population, FACT-Ga total, GaCS, and EQ VAS scores generally improved from baseline at most on-treatment assessments for both treatment arms. LS mean changes from baseline favored nivolumab plus chemotherapy over chemotherapy for all three measures (Figs 1A-1C). EQ-5D UI scores showed a trend toward improvement from baseline over time with nivolumab plus chemotherapy but showed minimal changes from baseline with chemotherapy (Fig 1D). Similar results were observed for the overall PRO analysis population (Figs 2A-2D). LS mean changes in FACT-G total, including the abbreviated FACT-G7, from baseline were generally similar across both treatment arms in both the CPS ≥5 and overall PRO analysis populations (Data Supplement, Figs S3A-S3D).

Time to Deterioration Analyses

In the CPS ≥5 randomly assigned population, nivolumab plus chemotherapy delayed TTSD and reduced the risk of symptom deterioration versus chemotherapy during treatment, on the basis of the FACT-Ga total score (HR, 0.75 [95% CI, 0.58 to 0.97]), GaCS (HR, 0.65 [95% CI, 0.50 to 0.83]), and EQ-5D UI (HR, 0.80 [95% CI, 0.65 to 0.99]; Figs 3A, 3B and 4A; Data Supplement, Fig S4). TTSD also favored nivolumab plus chemotherapy over chemotherapy on the basis of EQ VAS, FACT-G total, and the four FACT-G

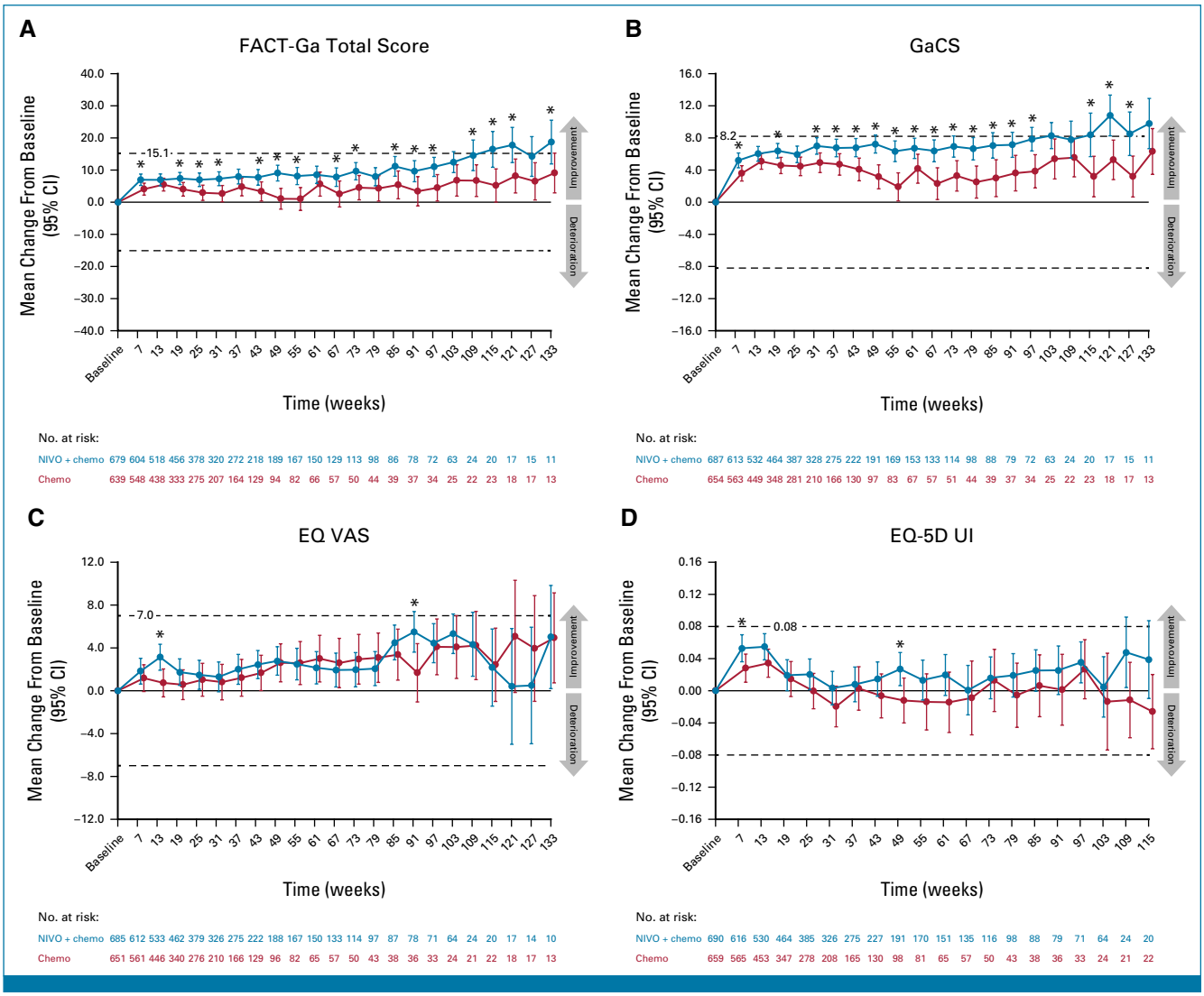

FIG 2. Least-squares mean change (95% CI) from baseline in (A) FACT-Ga total score, (B) GaCS, (C) EQ VAS, and (D) EQ-5D UI scores in the overall PRO analysis population. Dashed lines indicate MCTs. Circles indicate point estimates, and vertical bars indicate 95% CIs. *P < .05 was not formally tested. Only timepoints with ≥10 patients per treatment arm were included for FACT-Ga total score, GaCS, and EQ VAS; timepoints with ≥20 patients per treatment arm were included for EQ-5D UI. Chemo, chemotherapy; CPS, combined positive score; EQ-5D UI, EQ-5D utility index; EQ VAS, EQ-5D visual analog scale; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; GaCS, Gastric Cancer Subscale; MCT, meaningful change threshold; NIVO, nivolumab; PRO, patient-reported outcomes.

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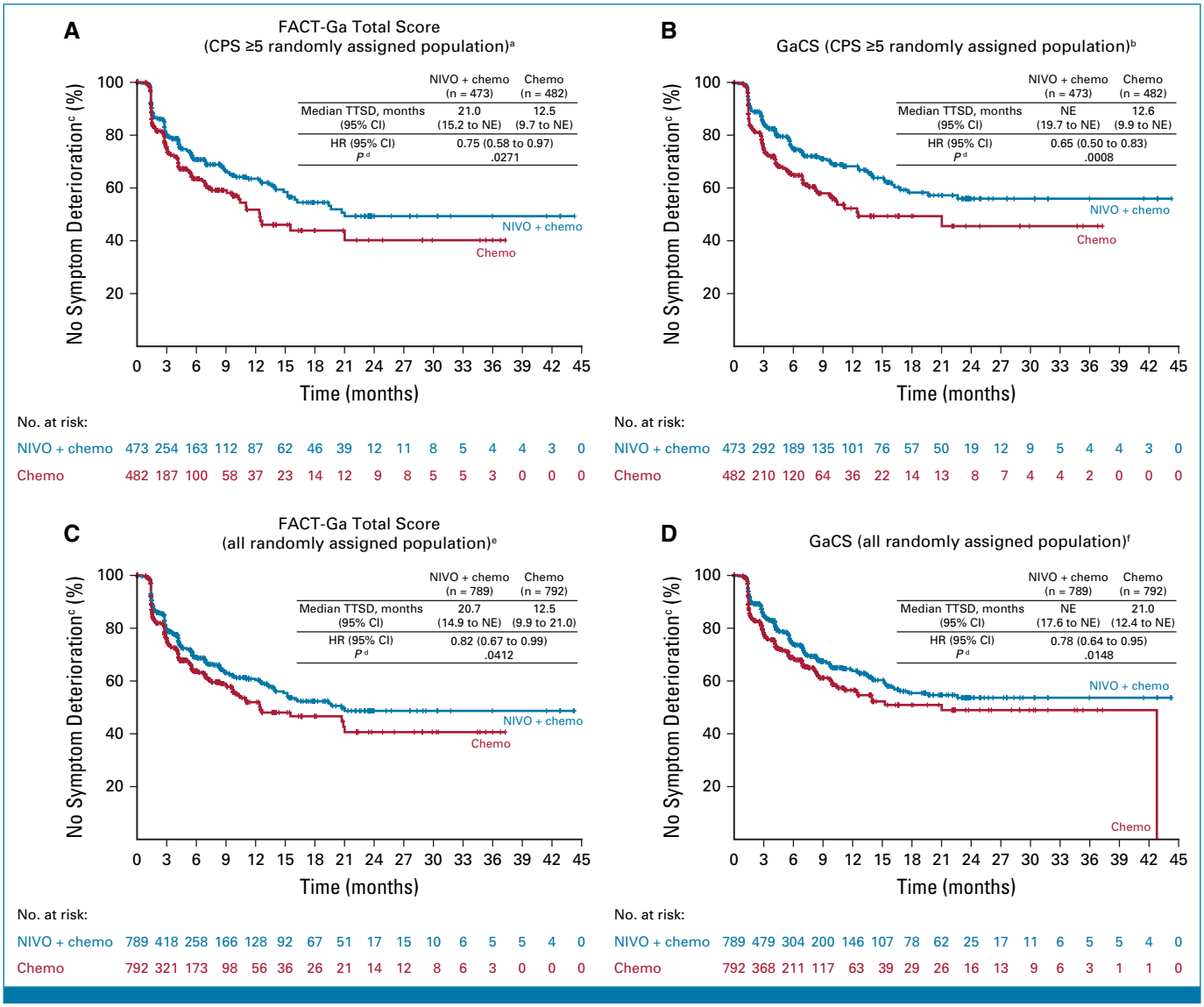

FIG 3. TTSD on the basis of FACT-Ga total score and GaCS in the (A and B) CPS ≥5 and (C and D) all randomly assigned populations. [a]One hundred twenty-five (26.4%) patients in the NIVO + chemo arm and 122 (25.3%) patients in the chemo arm showed symptom deterioration; [b]116 (24.5%) patients in the NIVO + chemo arm and 127 (26.3%) patients in the chemo arm showed symptom deterioration; [c]MCTs were 15.1 points for FACT-Ga total score and 8.2 points for GaCS; [d]$P < .05$ was not formally tested; [e]213 (27.0%) patients in the NIVO + chemo arm and 200 (25.2%) patients in the chemo arm showed symptom deterioration; [f]199 (25.2%) patients in the NIVO + chemo arm and 195 (24.6%) patients in the chemo arm showed symptom deterioration. Chemo, chemotherapy; CPS, combined positive score; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; GaCS, Gastric Cancer Subscale; HR, hazard ratio; MCT, meaningful change threshold; NE, nonestimable; NIVO, nivolumab; PRO, patient-reported outcomes; TTSD, time to symptom deterioration.

subscales (HR <1 for all measures); however, these results were not statistically significant (Fig 4A; Data Supplement, Figs S4B and S4C). Results were generally consistent between the CPS ≥5 and all randomly assigned populations (Figs 3 and 4; Data Supplement, Fig S4).

Nivolumab plus chemotherapy showed a statistically significant and clinically meaningful delay in TTDD and reduced the risk of definitive deterioration in HRQoL versus chemotherapy during treatment in the CPS ≥5 randomly assigned population across all PRO measures (HR [95% CI] <1; Figs 4A, 5A and 5B; Data Supplement, Figs S5A-S5C). Similar results were observed in all randomly assigned patients for all components of the EQ-5D and FACT-Ga measures except for the SWB subscale (Figs 4B, 5C and 5D; Data Supplement, Figs S5D-S5F).

DISCUSSION

In CheckMate 649, nivolumab plus chemotherapy demonstrated superior OS versus chemotherapy in first-line advanced or metastatic non–HER2-positive GC/GEJC or EAC.[32] Here, we

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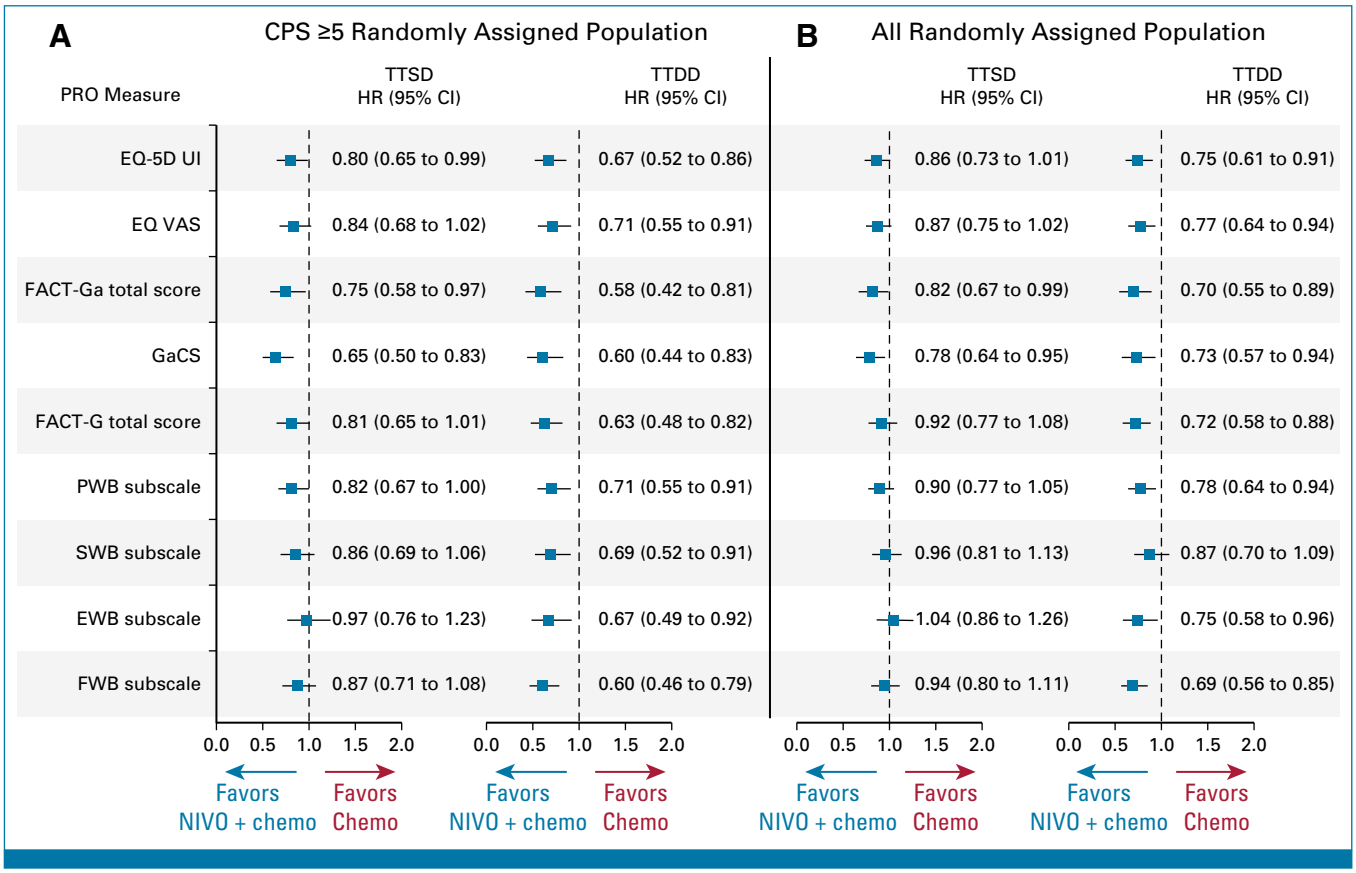

FIG 4. TTSD and TTDD in the (A) CPS ≥5 and (B) all randomly assigned populations for all PRO measures. HR reports NIVO + chemo versus chemo. Chemo, chemotherapy; CPS, combined positive score; EQ-5D UI, EQ-5D utility index; EQ VAS, EQ-5D visual analog score; EWB, emotional well-being subscale; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; FWB, functional well-being subscale; GaCS, Gastric Cancer Subscale; HR, hazard ratio; NIVO, nivolumab; PRO, patient-reported outcome; PWB, physical well-being subscale; SWB, social well-being subscale; TTSD, time to symptom deterioration; TTDD, time to definitive deterioration.

report that relative to patients treated with chemotherapy alone, patients treated with nivolumab plus chemotherapy also experienced clinically meaningful HRQoL benefits, as assessed by both gastric cancer–specific and overall health status PRO instruments using prespecified MCTs.[38,39,41,42] These findings are consistent with initial results from the study.[32,33] Previous studies on chemotherapy-based combination regimens, mainly in elderly patients, have shown early declines in HRQoL during the initial follow-up period in the combination therapy arm versus the control arm.[16,45,46] However, the addition of immunotherapy to chemotherapy has shown stable or improved HRQoL versus chemotherapy alone in the first-line setting in other advanced solid tumor types.[20,47-49] In this study, it is notable that the addition of nivolumab to chemotherapy did not negatively affect HRQoL or increase treatment-related symptom burden, despite a difference in safety profiles in the nivolumab plus chemotherapy versus chemotherapy arms (38% *v* 25% of patients discontinued treatment because of treatment-related adverse events).[33]

Longitudinal MMRM analyses showed a trend toward improved HRQoL with nivolumab plus chemotherapy versus chemotherapy although conclusions may be limited by smaller sample sizes in the chemotherapy arm at later time points. These results complement the clinical findings of the CheckMate 649 2-year update,[33] in which nivolumab plus chemotherapy continued to improve OS versus chemotherapy in both the CPS ≥5 (HR, 0.70; 95% CI, 0.61 to 0.81) and all randomly assigned populations (HR, 0.79; 95% CI, 0.71 to 0.88). The longer median durations of response (CPS ≥5: 9.7 *v* 7.0 months; all randomly assigned: 8.5 *v* 6.9 months) and higher proportions of patients with ongoing response (CPS ≥5: 13% *v* 6%; all randomly assigned: 11% *v* 4%) in the nivolumab plus chemotherapy versus chemotherapy arms may also correlate with the improvement in disease-related health status over time observed in patients treated with nivolumab plus chemotherapy.[33] Further analyses are needed to explore the correlation between PROs and clinical outcomes in this study.

Time to deterioration analyses also demonstrated favorable HRQoL outcomes with nivolumab plus chemotherapy over chemotherapy in both the CPS ≥5 and all randomly assigned populations. Patients treated with nivolumab plus chemotherapy showed reduced risk of disease-related symptom

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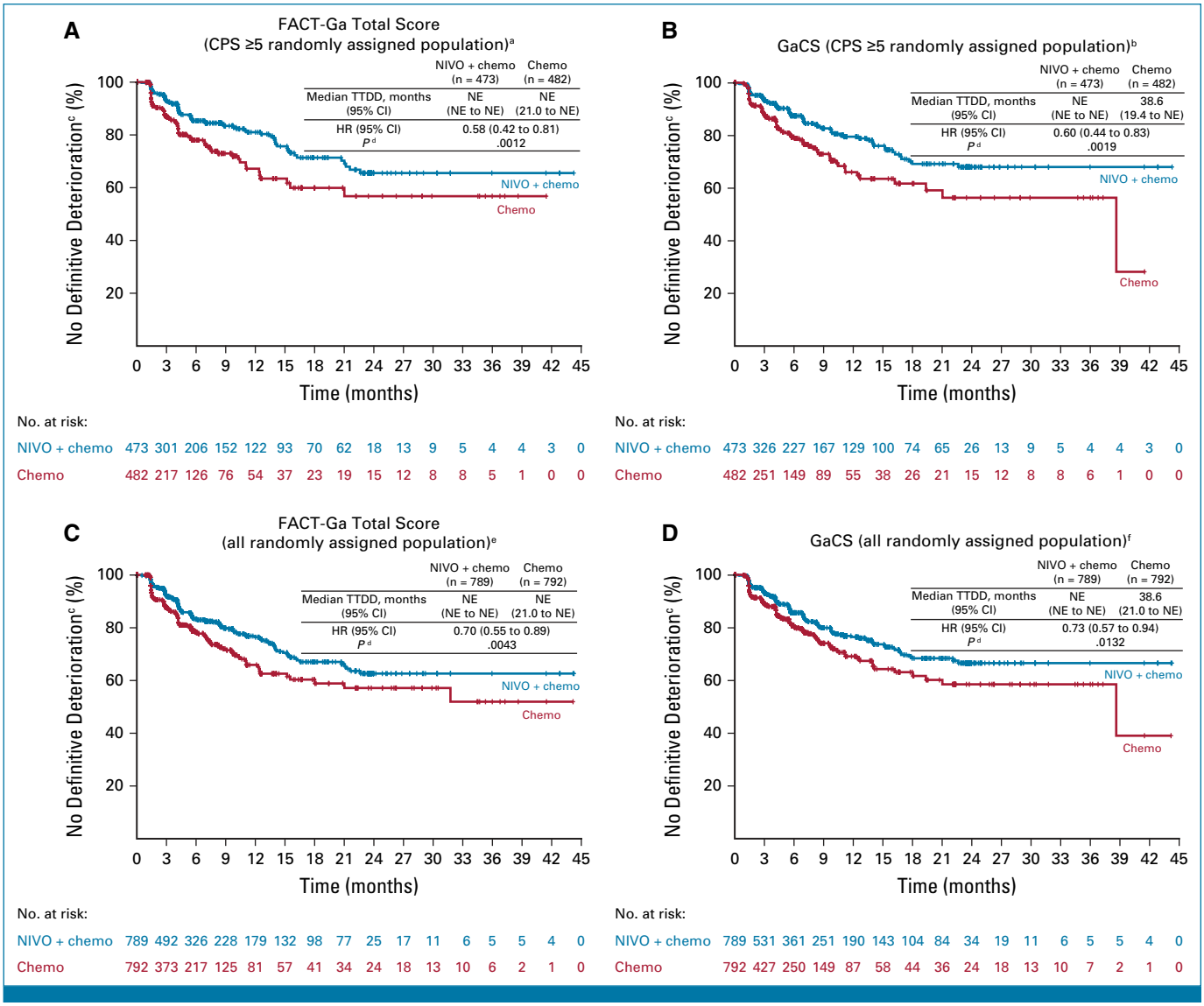

FIG 5. Time to definitive deterioration on the basis of FACT-Ga total score and GaCS in the (A and B) CPS ≥5 and (C and D) all randomly assigned populations. [a]Seventy-two (15.2%) patients in the NIVO + chemo arm and 79 (16.4%) patients in the chemo arm showed definitive deterioration; [b]75 (15.9%) patients in the NIVO + chemo arm and 85 (17.6%) patients in the chemo arm showed definitive deterioration; [c]MCTs were 15.1 points for FACT-Ga total score and 8.2 points for GaCS; [d]*P* <.05 was not formally tested; [e]131 (16.6%) patients in the NIVO + chemo arm and 132 (16.7%) patients in the chemo arm showed definitive deterioration; [f]129 (16.3%) patients in the NIVO + chemo arm and 131 (16.5%) patients in the chemo arm showed definitive deterioration. Chemo, chemotherapy; CPS, combined positive score; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; GaCS, Gastric Cancer Subscale; HR, hazard ratio; MCT, meaningful change threshold; NE, nonestimable; NIVO, nivolumab; TTDD, time to definitive deterioration.

deterioration versus chemotherapy during treatment, as assessed by the FACT-Ga total score and GaCS. The reduced risk of symptom deterioration with nivolumab plus chemotherapy appeared to be more pronounced in patients with a CPS of ≥5 versus all randomly assigned patients, given the earlier separation of the KM curves for FACT-Ga total score in the CPS ≥5 population. Notably, in both populations, nivolumab plus chemotherapy prolonged TTDD and reduced the risk of definitive deterioration in HRQoL versus chemotherapy during treatment across most components of the EQ-5D and FACT-Ga. The delay in definitive deterioration of overall health status with nivolumab plus chemotherapy versus chemotherapy, as assessed by the EQ-5D UI, was greater in the CPS ≥5 versus all randomly assigned populations (10.7 *v* 7.6 months), which may correlate with the enriched survival benefit in patients with a CPS of ≥5 in CheckMate 649 analyses.[32,33] However, it should be noted that sample sizes in the chemotherapy arm were smaller than those in the nivolumab plus chemotherapy arm at later timepoints in both the CPS ≥5 and all randomly assigned populations, reflecting a possible source of bias in the TTDD analyses.

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The PRO results in this study further support the use of nivolumab plus chemotherapy as standard first-line treatment for advanced or metastatic non–HER2-positive GC/GEJC or EAC. Furthermore, a recent analysis showed that patients treated with nivolumab plus chemotherapy in CheckMate 649 experienced significantly longer quality-adjusted survival time spent without symptoms of disease progression or toxicity versus those treated with chemotherapy alone.[50] Although cross-trial comparisons should be made with caution owing to differences in study design and PRO instruments, the PRO findings reported here are consistent with previous PRO studies that showed clinical benefit with first-line nivolumab and other PD-1 inhibitors with/without chemotherapy, with stable or improved HRQoL in patients, across several solid cancers, including advanced GC/GEJC.[22,51-54] As patients with advanced or metastatic GC/GEJC or EAC are generally elderly and have other prognostic factors that limit the long-term use of chemotherapy, immunotherapy-based regimens with a favorable benefit-risk profile offer first-line treatment options without the burden of added toxicity.[7,55,56] In addition, to extend the antitumor benefit beyond first-line treatment, maintenance immunotherapy is being increasingly considered for several tumor types, including GC/GEJC, to ensure optimal continuum of care for patients.[57,58] Further research into long-term maintenance immunotherapy that helps maintain or improve HRQoL in patients with advanced or metastatic GC/GEJC or EAC is warranted.

Strengths of this study include the use of both general health-related and disease-specific PRO instruments, high PRO questionnaire completion rates at baseline and during treatment, and same timing of PRO evaluation between treatment groups. This study was limited by an open-label trial design, which might have potentially influenced patient responses to questionnaires.[59] However, recent reports comparing PROs between study arms across multiple cancer trials found no differences in patient-reported symptoms despite significant disparities in treatment-related toxic effects.[59,60] Other data also showed that patients were not reluctant to report symptomatic adverse event outcomes, and bias may be less pronounced for symptoms that are proximal outcomes to the physiology of the disease and treatment than other more distal outcomes.[61] This study also used prespecified thresholds for meaningful change (Data Supplement, Table S1), which, in some cases, may be higher than what might be regarded as minimally important. Lower estimates of 4-7 points for the FACT-G total score, 3-5 points for the GaCS, and 7-10 points for FACT-Ga could be supported on the basis of a previous report[62] and literature in other primary cancer types.[63,64] Finally, sensitivity analyses were not performed in this study as data are not available at this time. Nonetheless, results from this PRO analysis indicated that nivolumab plus chemotherapy delayed definitive deterioration of HRQoL versus chemotherapy alone and, notably, demonstrated that the addition of immunotherapy to chemotherapy did not worsen HRQoL in patients with advanced or metastatic GC/GEJC or EAC.

In conclusion, nivolumab plus chemotherapy showed stable or better on-treatment HRQoL as it did not increase treatment-related symptom burden and decreased the risk of definitive HRQoL deterioration during treatment versus chemotherapy alone. These PRO results, in combination with the previously demonstrated clinically meaningful efficacy benefit and manageable safety profile,[32,33] further support the use of nivolumab plus chemotherapy as a tolerable and efficacious first-line treatment for patients with advanced or metastatic non–HER2-positive GC/GEJC or EAC.

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PRIOR PRESENTATION

Presented in part at ASCO Annual Meeting, virtual, June 4-8, 2021; the Korean Society for Medical Oncology Annual Meeting, virtual, September 2-3, 2021; the ASCO Quality Care Symposium, Boston, MA, September 24-25, 2021; and the Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie Annual Meeting, Berlin, Germany, October 1-2, 2021.

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SUPPORT

Supported by Bristol Myers Squibb.

CLINICAL TRIAL INFORMATION

NCT02872116

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00170.

DATA SHARING STATEMENT

Data are available upon reasonable request. BMS policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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ACKNOWLEDGMENT

The authors thank the patients and their families for making the study possible, as well as the investigators and clinical study teams at Bristol Myers Squibb (Princeton, NJ) and Ono Pharmaceutical Co Ltd (Osaka, Japan). Dako (an Agilent Technologies company, Santa Clara, CA) participated in the collaborative development of the PD-L1 IHC 28-8 pharmDx assay. Professional medical writing assistance was provided by Melissa Mehalick, PhD, of RTI Health Solutions at the time of study and Vidya Rajagopalan, PhD, of Evidence Scientific Solutions Inc, funded by Bristol Myers Squibb.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Health-Related Quality of Life With Nivolumab Plus Chemotherapy Versus Chemotherapy in Patients With Advanced Gastric/Gastroesophageal Junction Cancer or Esophageal Adenocarcinoma From CheckMate 649

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Research Funding: Novartis, Bristol Myers Squibb, Taiho Pharmaceutical, Roche/Genentech, Amgen, Lilly/ImClone, Merck, Delta-Fly Pharma, Gilead Sciences, Takeda, ProLynx, Zymeworks, Daiichi Sankyo, Astellas Pharma (Inst)
Patents, Royalties, Other Intellectual Property: I have research funding from: Genentech, Roche, BMS, Taiho, MedImmune, Merck, Amgen, Lilly

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Consulting or Advisory Role: Pfizer, Merck, Bristol Myers Squibb, Merck Serono, Daiichi Sankyo, Rgenix, Bayer, Imugene, AstraZeneca, Lilly, Zymeworks, Basilea Pharmaceutical, Michael J. Hennessy Associates, Paradigm, Seagen, AmerisourceBergen, Arcus Biosciences, Geneos, GlaxoSmithKline, Imedex, Lynx Health, Peerview, Silverback Therapeutics, Mersana, Research to Practice, AskGene Pharma, Phanes Therapeutics
Research Funding: Bayer (Inst), Rgenix (Inst), Bristol Myers Squibb (Inst), Merck (Inst), Lilly (Inst), NCI (Inst), Department of Defense (Inst), Cycle for Survival (Inst), Fred's Team (Inst), Genentech/Roche (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb Japan
Other Relationship: Clinical Care Options, Axis Medical Education, Research to Practice

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Speakers' Bureau: Bristol Myers Squibb, Bayer, Merck
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst)
Expert Testimony: AstraZeneca
Travel, Accommodations, Expenses: Roche

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Research Funding: Nanjing Yaojieankang Biotechnology (Inst), Baiji Shenzhou (Beijing) Biotechnology (Inst), Beijing Xiantong Biomedical Technology (Inst), QiLu Pharmaceutical (Inst), Zaiding Pharmaceutical (Inst), Jacobio (Inst), CANbridge Pharmaceuticals (Inst)

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Research Funding: Ono Pharmaceutical (Inst), Taiho Pharmaceutical (Inst), Daiichi Sankyo (Inst), Lilly (Inst), Gilead Sciences (Inst), Yakult Honsha (Inst), Chugai Pharma (Inst), Boehringer Ingelheim (Inst), Eisai (Inst), MSD Oncology (Inst), Sanofi (Inst), Bristol Myers Squibb (Inst)

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Research Funding: BMS, MSD Oncology, Novartis, Roche, Astellas Pharma, Lilly, Gemabiotech, Nektar, Poliphor, AstraZeneca, Pfizer
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No other potential conflicts of interest were reported.

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