First-Line Nivolumab Plus Chemotherapy for Advanced Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma: 3-Year Follow-Up of the Phase III CheckMate 649 Trial

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

We report 3-year efficacy and safety results from the phase III CheckMate 649 trial. Patients with previously untreated advanced or metastatic gastroesophageal adenocarcinoma were randomly assigned to nivolumab plus chemotherapy or chemotherapy. Primary end points were overall survival (OS) and progression-free survival (PFS) by blinded independent central review (BICR) in patients whose tumors expressed PD-L1 combined positive score (CPS) ≥5. With 36.2-month minimum follow-up, for patients with PD-L1 CPS ≥5, the OS hazard ratio (HR) for nivolumab plus chemotherapy versus chemotherapy was 0.70 (95% CI, 0.61 to 0.81); 21% versus 10% of patients were alive at 36 months, respectively; the PFS HR was 0.70 (95% CI, 0.60 to 0.81); 36-month PFS rates were 13% versus 8%, respectively. The objective response rate (ORR) per BICR was 60% (95% CI, 55 to 65) with nivolumab plus chemotherapy versus 45% (95% CI, 40 to 50) with chemotherapy; median duration of response was 9.6 months (95% CI, 8.2 to 12.4) versus 7.0 months (95% CI, 5.6 to 7.9), respectively. Nivolumab plus chemotherapy also continued to show improvement in OS, PFS, and ORR versus chemotherapy in the overall population. Adding nivolumab to chemotherapy maintained clinically meaningful long-term survival benefit versus chemotherapy alone, with an acceptable safety profile, supporting the continued use of nivolumab plus chemotherapy as standard first-line treatment for advanced gastroesophageal adenocarcinoma.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

First-line nivolumab plus chemotherapy has been approved for the treatment of unresectable advanced, non–human epidermal growth factor receptor 2 (HER2)–positive gastric, gastroesophageal junction, and esophageal adenocarcinoma in over 50 countries on the basis of the results from CheckMate 649. At 12.1-month minimum follow-up, nivolumab plus chemotherapy demonstrated improvement in all efficacy measures, including superior overall survival (OS; hazard ratio [HR], 0.71 [98.4% CI, 0.59 to 0.86]; $P < .0001$) and progression-free survival (PFS) by blinded independent central review (BICR; HR, 0.68 [98% CI, 0.56 to 0.81]; $P < .0001$) versus chemotherapy in patients with PD-L1 combined positive score (CPS) ≥5. Nivolumab plus chemotherapy also showed significant improvement in OS, along with PFS benefit versus chemotherapy in the overall population, and an acceptable safety profile.[1] We report 3-year follow-up results from CheckMate 649.

METHODS

Study Design, Patients, and Procedures

Inclusion/exclusion criteria and procedures for the CheckMate 649 study have been previously described and a summary is provided in Appendix 1 (online only).[1] Details are available in the Protocol (online only).

End Points, Assessments, and Statistical Analyses

Dual primary end points for the nivolumab plus chemotherapy versus chemotherapy arms were OS and PFS by BICR per RECIST, version 1.1, in patients with PD-L1 CPS ≥5. Secondary and exploratory end points, assessments, and statistical methods have been previously described and are provided in Appendix 1.[1] The results reported here were not formally tested.

Statement of Institutional Review Board Approval and Informed Consent

The trial was done according to Good Clinical Practice guidelines developed by the International Council for Harmonisation and in compliance with the trial protocol. 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.

RESULTS

Patient Baseline Demographics

Study population is described in Appendix Figure A1. At clinical cutoff (May 31, 2022), the median follow-up was 47.4 months (range, 36.2-61.5) in the nivolumab plus chemotherapy arm and 47.3 months (range, 36.6-61.3) in the chemotherapy arm. Baseline demographics are shown in Table 1 and Appendix Table A1.

Efficacy

With 36.2-month minimum follow-up, nivolumab plus chemotherapy continued to demonstrate improvement in median OS versus chemotherapy (14.4 months [95% CI, 13.1 to 16.2] *v* 11.1 months [95% CI, 10.0 to 12.1], respectively; HR, 0.70 [95% CI, 0.61 to 0.81]) in patients with PD-L1 CPS ≥5. OS benefit was also maintained in the overall population (HR, 0.79 [95% CI, 0.71 to 0.88]). OS rates at 36 months were higher with nivolumab plus chemotherapy versus chemotherapy (Figs 1A and 1B).

Nivolumab plus chemotherapy also maintained BICR-assessed median PFS benefit compared with chemotherapy (8.3 months [95% CI, 7.0 to 9.3] *v* 6.1 months [95% CI, 5.6 to 6.9], respectively; HR, 0.70 [95% CI, 0.60 to 0.81]) in patients with PD-L1 CPS ≥5. PFS benefit was also maintained in the overall population (HR, 0.79 [95% CI, 0.71 to 0.89]). PFS rates at 36 months were numerically higher with nivolumab plus chemotherapy compared with chemotherapy (Figs 1C and 1D).

Objective response rate (ORR) by BICR continued to be higher with nivolumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS ≥5 (60% [95% CI, 54.7 to 64.8] *v* 45% [95% CI, 40.1 to 50.2]). ORR was also higher in the overall population. In patients with PD-L1 CPS ≥5, the complete response rate was 13% with nivolumab plus chemotherapy versus 7% with chemotherapy. The median duration of response was 9.6 months (95% CI, 8.2 to 12.4) versus 7.0 months (95% CI, 5.6 to 7.9), respectively. The results were similar in the overall population (Appendix Table A2 and Figs 1E and 1F).

The HRs for OS consistently favored nivolumab plus chemotherapy over chemotherapy across multiple prespecified subgroups in patients with PD-L1 CPS ≥5 and in the overall population. The magnitude of OS benefit was greater in patients with microsatellite instability-high (MSI-H) tumors, and patients with microsatellite stable (MSS) tumors had results similar to the overall population (Fig 2). The unstratified HRs for OS with nivolumab plus chemotherapy versus chemotherapy in PD-L1 CPS ≥1, ≥5, and ≥10 subgroups were 0.75, 0.69, and 0.66, respectively; in PD-L1 CPS <1, <5, and <10 subgroups, the HRs were 0.95, 0.95, and 0.91, respectively. ORR was higher across all PD-L1 CPS subgroups with nivolumab plus chemotherapy versus chemotherapy (Appendix Fig A2).

At week-18 landmark analysis of OS by response status, median OS in the nivolumab plus chemotherapy arm among measurable patients with PD-L1 CPS ≥5 and <5 and in the overall population was 20.8 (95% CI, 17.8 to 25.5), 17.7 (95% CI, 15.3 to 21.6), and 19.4 months (95% CI, 17.5 to 21.8) for responders (confirmed partial or complete response per BICR) and 11.6 (95% CI, 9.8 to 14.4), 9.7 (95% CI, 8.6 to 12.3), and 10.6 months (95% CI, 9.7 to 12.6) for nonresponders, respectively. In the chemotherapy arm, median OS was 15.5 (95% CI, 13.3 to 19.3), 15.3 (95% CI, 13.2 to 18.5), and 15.5 months (95% CI, 13.9 to 18.1) for responders and 10.8 (95% CI, 9.3 to 11.6), 11.5 (95% CI, 9.8 to 13.2), and 11.0 months (95% CI, 9.9 to 11.8) for nonresponders, respectively. The OS rates at 36 months were numerically higher for responders than for nonresponders regardless of PD-L1 CPS ≥5 or <5 (Appendix Fig A3).

Safety

Among all treated patients, median duration of treatment was 6.8 months (range, 0.1-57.7) for nivolumab plus chemotherapy and 4.9 months (range, 0.0-55.2) for chemotherapy. Any-grade treatment-related adverse events (TRAEs) occurred in 739 of 782 (95%) patients in the nivolumab plus chemotherapy arm and in 682 of 767 (89%) patients in the chemotherapy arm (grade 3 or 4, 60% *v* 45%; Appendix Table A3). No additional deaths occurred with longer follow-up.[1]

Most TRAEs with potential immunologic etiology were grade 1 or 2, and grade 3 or 4 events occurred in ≤5% of patients across organ categories (Appendix Table A4). Additional safety results are described in Appendix 1.

Patient-Reported Outcomes

Although baseline Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) total scores were similar

TABLE 1. Baseline Demographics and Clinical Characteristics

	Patients With PD-L1 CPS ≥5		All Randomly Assigned Patients	
Characteristic	Nivolumab Plus Chemotherapy (n = 473)	Chemotherapy (n = 482)	Nivolumab Plus Chemotherapy (n = 789)	Chemotherapy (n = 792)
Age, years, median (range)	63 (18-88)	62 (23-90)	62 (18-88)	61 (21-90)
<65	266 (56)	286 (59)	473 (60)	488 (62)
≥65	207 (44)	196 (41)	316 (40)	304 (38)
Sex				
Male	331 (70)	349 (72)	540 (68)	560 (71)
Female	142 (30)	133 (28)	249 (32)	232 (29)
Race[a]				
Asian	119 (25)	117 (24)	186 (24)	189 (24)
Non-Asian	354 (75)	365 (76)	603 (76)	602 (76)
Region				
Asia	117 (25)	111 (23)	178 (23)	178 (22)
United States and Canada	67 (14)	70 (15)	131 (17)	132 (17)
Rest of the world	289 (61)	301 (62)	480 (61)	482 (61)
ECOG PS[b]				
0	193 (41)	204 (42)	327 (41)	337 (43)
1	280 (59)	278 (58)	461 (58)	452 (57)
Primary tumor location at initial diagnosis				
GC	333 (70)	334 (69)	554 (70)	556 (70)
GEJC	84 (18)	86 (18)	132 (17)	128 (16)
EAC	56 (12)	62 (13)	103 (13)	108 (14)
Tumor cell PD-L1 expression[c]				
<1%	363 (77)	361 (75)	663 (84)	661 (83)
≥1%	110 (23)	120 (25)	126 (16)	127 (16)
Previous surgery				
Yes	98 (21)	105 (22)	161 (20)	176 (22)
No	375 (79)	377 (78)	628 (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	99 (21)	96 (20)	165 (21)	179 (23)
≥2	374 (79)	386 (80)	624 (79)	613 (77)

(continued on following page)

TABLE 1. Baseline Demographics and Clinical Characteristics (continued)

Characteristic	Patients With PD-L1 CPS ≥5		All Randomly Assigned Patients	
	Nivolumab Plus Chemotherapy (n = 473)	Chemotherapy (n = 482)	Nivolumab Plus Chemotherapy (n = 789)	Chemotherapy (n = 792)
Site of metastases				
Liver	190 (40)	217 (45)	301 (38)	313 (40)
Peritoneum	102 (22)	96 (20)	188 (24)	189 (24)
CNS	1 (<1)	0	1 (<1)	0
Signet ring cell carcinoma				
Yes	72 (15)	69 (14)	145 (18)	137 (17)
No	401 (85)	413 (86)	644 (82)	655 (83)
Lauren classification				
Intestinal type	171 (36)	176 (37)	272 (34)	267 (34)
Diffuse type	137 (29)	141 (29)	254 (32)	273 (34)
Mixed	37 (8)	30 (6)	58 (7)	48 (6)
Unknown	128 (27)	135 (28)	205 (26)	204 (26)
MSI status				
MSS	424 (90)	423 (88)	696 (88)	682 (86)
MSI-H	18 (4)	16 (3)	23 (3)	21 (3)
Not reported or invalid	31 (7)	43 (9)	70 (9)	89 (11)
Chemotherapy regimen[d]				
FOLFOX	237 (51)	242 (52)	422 (54)	406 (53)
XELOX	231 (49)	223 (48)	360 (46)	361 (47)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: CPS, combined positive score; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, fluorouracil plus leucovorin plus oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; XELOX, capecitabine plus oxaliplatin.

[a]Not reported for one patient in the overall chemotherapy arm.

[b]On the basis of case report form. ECOG PS of 2 was reported in one patient treated with nivolumab plus chemotherapy and three patients treated with chemotherapy. The overall population had an ECOG performance status of 0 or 1 on the basis of interactive response technology.

[c]Indeterminate, nonevaluable, or not reported for four patients in the chemotherapy arm.

[d]Patients who received at least one dose of the assigned treatment.

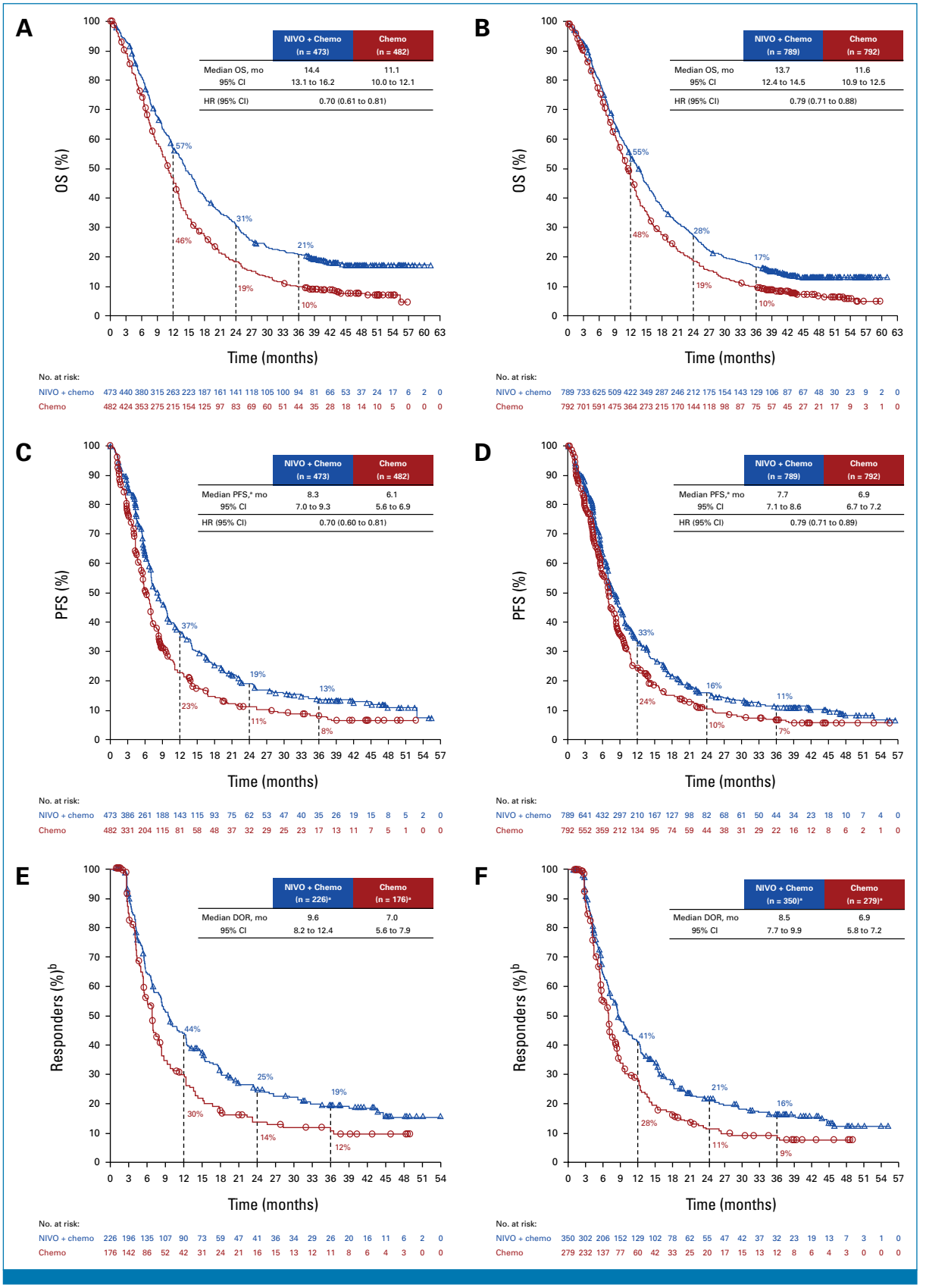

FIG 1. Kaplan-Meier estimates of OS, PFS, and duration of response in (A, C, and E) patients with PD-L1 CPS ≥5 and (B, D, and F) all randomly assigned patients. [a]Number of responders; [b]Per BICR assessment. BICR, blinded independent central review; Chemo, chemotherapy; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival.

between the nivolumab plus chemotherapy and chemotherapy arms for patients with PD-L1 CPS ≥5 and the overall population, the least squares mean difference between treatment arms continued to favor nivolumab plus chemotherapy at most time points (Appendix Figs A4A-A4B). FACT-Ga GP5 questionnaire results continued to indicate more patients reporting not being bothered at all or being bothered a little bit by side effects from treatment with nivolumab plus chemotherapy versus chemotherapy (Appendix Figs A4C-A4D).

DISCUSSION

After 3 years of follow-up, nivolumab plus chemotherapy continued to demonstrate clinically meaningful OS improvement, with sustained separation of the Kaplan-Meier curves, higher OS rates, continued PFS benefit, and more durable responses in patients whose tumors expressed PD-L1 CPS ≥5 and in the overall population. A trend toward improved HRQoL versus chemotherapy alone was maintained over time, although there was no adjustment for

A

Category (PD-L1 CPS ≥5)	Subgroup	Median OS, Months: NIVO + Chemo	Median OS, Months: Chemo	Unstratified HR for Death (95% CI)
Overall (N = 955)		14.4	11.1	0.69 (0.60 to 0.79)
Age, years	<65 (n = 552)	14.4	11.1	0.69 (0.57 to 0.83)
	≥65 (n = 403)	14.3	11.2	0.69 (0.56 to 0.85)
Sex	Male (n = 680)	14.4	10.8	0.66 (0.56 to 0.78)
	Female (n = 275)	14.3	12.1	0.77 (0.60 to 0.99)
Region	Asia (n = 228)	16.1	11.8	0.61 (0.46 to 0.82)
	United States/Canada (n = 137)	18.2	12.6	0.65 (0.44 to 0.94)
	ROW (n = 590)	13.1	10.4	0.74 (0.62 to 0.88)
ECOG PS	0 (n = 397)	17.8	13.8	0.74 (0.59 to 0.92)
	1 (n = 558)	12.6	8.5	0.64 (0.54 to 0.77)
Primary tumor location	GC (n = 667)	15.0	10.5	0.64 (0.54 to 0.76)
	GEJC (n = 170)	13.4	13.1	0.81 (0.58 to 1.12)
	EAC (n = 118)	11.2	11.3	0.80 (0.54 to 1.19)
Signet ring cell carcinoma	Yes (n = 141)	12.1	10.1	0.67 (0.47 to 0.96)
	No (n = 814)	15.0	11.3	0.69 (0.59 to 0.80)
Liver metastases[a]	Yes (n = 407)	13.1	9.8	0.64 (0.52 to 0.79)
	No (n = 519)	15.5	11.6	0.73 (0.60 to 0.88)
Tumor cell PD-L1 expression[b]	<1% (n = 724)	14.2	11.6	0.75 (0.64 to 0.87)
	≥1% (n = 230)	16.2	8.8	0.54 (0.40 to 0.72)
MSI status[c]	MSS (n = 847)	14.3	11.1	0.71 (0.62 to 0.83)
	MSI-H (n = 34)	44.8	8.8	0.29 (0.12 to 0.71)
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.68 (0.56 to 0.83)
	XELOX (n = 454)	15.0	11.0	0.69 (0.57 to 0.85)

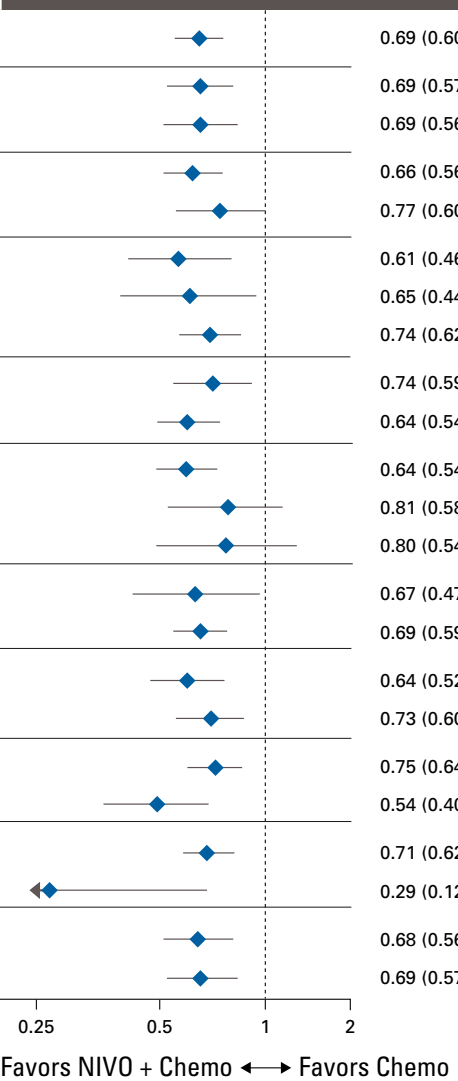

FIG 2. Forest plot of OS in prespecified subgroups with (A) PD-L1 CPS ≥5 and (B) all randomly assigned patients. [a]Not reported, n = 29; [b]indeterminate, nonevaluable, or not reported, n = 1; [c]invalid/not available, n = 74; [d]ECOG PS 2, n = 4; [e]not reported, n = 49; [f]indeterminate, nonevaluable, or not reported, n = 4; [g]invalid/not available, n = 159. Chemo, chemotherapy; CPS, combined positive score; EAC, esophageal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, fluorouracil plus leucovorin plus oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HR, hazard ratio; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NIVO, nivolumab; OS, overall survival; ROW, rest of the world; XELOX, capecitabine plus oxaliplatin. (continued on following page)

B

Category (all randomized)	Subgroup	Median OS, Months: NIVO + Chemo	Median OS, Months: Chemo	Unstratified HR for Death (95% CI)
Overall (N = 1,581)		13.7	11.6	0.78 (0.70 to 0.87)
Age, years	<65 (n = 961)	12.9	11.8	0.81 (0.71 to 0.93)
	≥65 (n = 620)	14.4	11.3	0.75 (0.63 to 0.89)
Sex	Male (n = 1,100)	14.0	11.3	0.76 (0.67 to 0.87)
	Female (n = 481)	12.6	12.1	0.83 (0.69 to 1.01)
Region	Asia (n = 356)	16.3	12.8	0.76 (0.61 to 0.96)
	United States/Canada (n = 263)	15.3	12.1	0.65 (0.50 to 0.84)
	ROW (n = 962)	12.1	10.9	0.83 (0.72 to 0.95)
ECOG PS[d]	0 (n = 664)	16.8	14.2	0.83 (0.70 to 0.98)
	1 (n = 913)	11.5	9.8	0.74 (0.64 to 0.85)
Primary tumor location	GC (n = 1,110)	14.2	11.3	0.75 (0.66 to 0.85)
	GEJC (n = 260)	12.6	12.8	0.89 (0.68 to 1.15)
	EAC (n = 211)	12.3	11.6	0.84 (0.63 to 1.12)
Signet ring cell carcinoma	Yes (n = 282)	11.1	11.2	0.90 (0.71 to 1.15)
	No (n = 1,299)	14.3	11.8	0.76 (0.67 to 0.86)
Liver metastases[e]	Yes (n = 614)	12.5	10.6	0.72 (0.60 to 0.85)
	No (n = 918)	14.2	12.3	0.84 (0.73 to 0.97)
Tumor cell PD-L1 expression[f]	<1% (n = 1,324)	13.1	12.0	0.84 (0.75 to 0.95)
	≥1% (n = 253)	16.1	9.8	0.55 (0.42 to 0.73)
MSI status[g]	MSS (n = 1,378)	13.8	11.5	0.79 (0.71 to 0.89)
	MSI-H (n = 44)	38.7	12.3	0.34 (0.16 to 0.74)
Chemotherapy regimen	FOLFOX (n = 828)	13.7	11.8	0.77 (0.66 to 0.89)
	XELOX (n = 721)	13.8	11.7	0.80 (0.69 to 0.94)

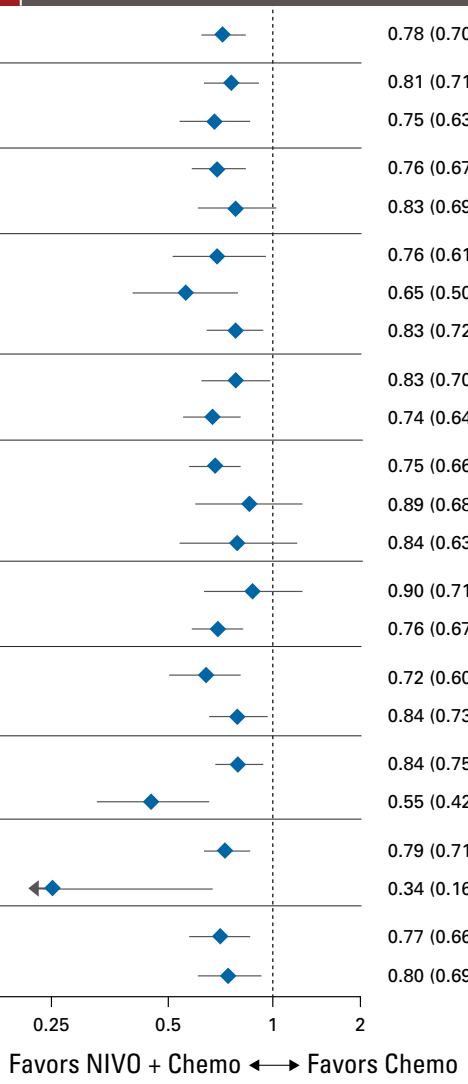

FIG 2. (Continued).

multiple comparisons.[2] OS benefit was also observed across subgroups, including in patients with poor prognostic factors, such as liver metastases. The magnitude of OS benefit was substantially greater in patients with MSI-H tumors, and the survival benefit in the MSS population was consistent with the overall population.

The magnitude of survival benefit continued to be enriched with nivolumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS ≥5. However, the results indicate no further meaningful clinical benefit with PD-L1 CPS ≥10. The 18-week landmark analysis of OS by response showed that patients who responded to nivolumab plus chemotherapy had longer OS and there was a numerically higher proportion of patients alive at 36 months than with nonresponders in PD-L1 CPS ≥5, <5, and the overall populations.

Recently, additional studies demonstrated benefit from adding PD-1 inhibitors to chemotherapy as first-line treatment in this patient population, expanding the existing clinical evidence in this disease setting.[3-5] Patients with claudin-18 isoform 2 (CLDN18.2)–positive, HER2-negative gastric or gastroesophageal junction adenocarcinoma have shown prolonged survival from adding a monoclonal antibody targeting CLDN18.2 to chemotherapy compared with chemotherapy alone.[6,7] These results indicate that targeted therapies in combination with

chemotherapy also provide new treatment options for patients with gastric cancer.

To our knowledge, CheckMate 649 has the longest follow-up data, including OS, for first-line anti–PD-1 plus chemotherapy treatment for patients with gastro-esophageal cancer. The data from this 3-year follow-up further support nivolumab plus chemotherapy as standard first-line treatment for patients with gastric, gastro-esophageal junction, and esophageal adenocarcinoma.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

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APPENDIX 1. ADDITIONAL METHODS

Study Design and Patients

Patients were eligible regardless of PD-L1 expression. Other key inclusion criteria were ≥1 measurable lesion or evaluable disease per RECIST, version 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with known human epidermal growth factor receptor 2–positive status were excluded. Additional eligibility criteria included patients with adequate organ function and ability to provide a fresh or archival tumor sample to determine PD-L1 status. Previous adjuvant or neoadjuvant chemotherapy, radiotherapy, and/or chemoradiotherapy (administered at least 6 months before random assignment) were allowed. Patients with untreated CNS metastases or peripheral neuropathy (above grade 1); active, known, or suspected autoimmune disease; positive test result for hepatitis B or hepatitis C virus; and known history of positive test for HIV or known AIDS were excluded. Previous systemic therapy for metastatic disease was not allowed. All patients provided written informed consent per Declaration of Helsinki principles.

Randomization and Masking

Patients were randomly assigned 1:1:1 to nivolumab plus chemotherapy, nivolumab plus ipilimumab, or chemotherapy, and then 1:1 to nivolumab plus chemotherapy versus chemotherapy once the nivolumab plus ipilimumab arm was closed. Randomization was performed using interactive web response technology with a block size of six and was stratified according to tumor cell PD-L1 status (≥1% *v* <1% or indeterminate), region (Asia *v* United States and Canada *v* rest of the world), ECOG performance status (0 *v* 1), and type of chemotherapy (capecitabine plus oxaliplatin [XELOX] *v* leucovorin plus fluorouracil plus oxaliplatin [FOLFOX]). Investigators were not blinded to treatment allocation.

Procedures

Eligible patients were at least age 18 years, with unresectable advanced or metastatic gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma. In the nivolumab plus chemotherapy arm, nivolumab was administered either at a dose of 360 mg once every 3 weeks or 240 mg once every 2 weeks with investigator's choice of chemotherapy (XELOX [capecitabine 1,000 mg/m^2 twice daily, days 1-14, and oxaliplatin 130 mg/m^2, day 1, once every 3 weeks], or FOLFOX [leucovorin 400 mg/m^2, once on day 1, fluorouracil 400 mg/m^2, once on day 1 and 1,200 mg/m^2, once on days 1-2, and oxaliplatin 85 mg/m^2, day 1, once every 2 weeks]). In the chemotherapy arm, XELOX or FOLFOX were administered as indicated above. Capecitabine was administered orally; all other treatments were administered intravenously. Treatment continued until documented disease progression, unacceptable toxicity, withdrawal of consent, or study end. Nivolumab was given for a maximum of 2 years, and chemotherapy was given per local standards. Patients in the nivolumab plus chemotherapy arm were permitted to continue treatment beyond initial disease progression (per RECIST v1.1), on the basis of the investigator's judgment. Dose reductions were not permitted for nivolumab and were permitted per local standards for chemotherapy.

End Points and Assessments

Hierarchically tested secondary end points were overall survival (OS) in patients with PD-L1 CPS ≥1 and the overall population. Additional secondary end points not formally tested included blinded independent central review (BICR)–assessed PFS and objective response rate (ORR; evaluated in all patients with at least one target or measurable lesion at baseline) in patients across PD-L1 combined positive score (CPS) cutoffs and in the overall population and OS in patients with PD-L1 CPS ≥10. Key exploratory end points included BICR-assessed duration of response; efficacy across tumor cell PD-L1 expression cutoffs; landmark survival rates; health-related quality of life; and safety and tolerability (included patients who received at least one dose of study treatment).

The exploratory OS landmark analyses were performed in patients who were alive, evaluable, and not censored before 18 weeks grouped by response status per BICR assessment at the 18-week landmark time point. Responders had complete or partial response, and nonresponders had stable or progressive disease. The 18-week landmark time point was chosen by considering the balance among the proportion of patients alive at 18 weeks, the proportion of responders measured by 18 weeks, and the proportion of patients excluded from the analysis.

Tumors were assessed using computed tomography or magnetic resonance imaging per RECIST v1.1 by BICR at baseline, every 6 weeks from the start of cycle 1 for 48 weeks, and every 12 weeks thereafter until disease progression. Adverse events were assessed per investigator throughout the treatment period and during follow-up according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and Medical Dictionary for Regulatory Activities, version 25.0. Treatment-relatedness refers to nivolumab, at least one chemotherapy drug component, or both.

Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) analysis was done for patients with PD-L1 CPS ≥5 and all randomly assigned patients who had an assessment at baseline (before administration of treatment on day of first dose) and at least one subsequent assessment while on treatment. The questionnaire completion rate was calculated and summarized using descriptive statistics. The change from baseline was a linear function of treatment groups, trial assessment, baseline score, trial stratification factors, interaction between treatment group and trial assessment, interaction between baseline score and trial assessment, and any potential confounders. A clinically meaningful difference was defined as at least a 15.1-point change from baseline in FACT-Ga total score.[8] The *P* value for the difference in least squares means was computed as the two-tailed probability using the *t* distribution. No adjustments were made for multiple comparisons.

Mean score and mean change from baseline for the FACT-Ga scale were estimated using mixed model for repeated measures. Treatment burden was assessed by the individual GP5 item of the FACT-Ga, which reads, "I am bothered by side effects of treatment" and has been described previously.[1,9] Frequencies and percentages of the GP5 item question responses (not at all, a little bit, somewhat, quite a bit, and very much) were tabulated with 10 or more patients in each group.

PD-L1 expression was assessed by two central laboratories using the PD-L1 IHC 28-8 pharmDx assay according to the manufacturer's instructions (Dako, an Agilent Technologies, Inc company, Santa Clara, CA). Tumor cell PD-L1 expression was evaluated on at least 100 viable tumor cells and shown as a percentage of tumor cells with partial or complete membrane staining. CPS was evaluated on both tumor and tumor-associated immune cells as a ratio of the number of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells within the evaluated tumor area, multiplied by 100.

Additional Results

Safety

The most common any-grade treatment-related adverse events (TRAEs) were nausea, diarrhea, and peripheral neuropathy in both arms (Appendix Table A3). The most common grade 3 or 4 TRAEs were neutropenia, decreased neutrophil count, and anemia in the nivolumab plus chemotherapy arm and neutropenia, decreased neutrophil count, diarrhea, and vomiting in the chemotherapy arm. Serious TRAEs of any grade were reported in 176 (23%) patients (grade 3 or 4, n = 134 [17%]; grade 5, n = 4 [<1%]) and in 95 (12%) patients (grade 3 or 4, n = 78 [10%]), respectively. Any TRAEs leading to discontinuation were reported in 331 patients (42%) and 198 patients (26%), respectively. Sixteen deaths in the nivolumab plus chemotherapy arm and four deaths in the chemotherapy arm were treatment-related and have been previously described.[1]

Most TRAEs with potential immunologic etiology were grade 1 or 2, and grade 3 or 4 events occurred in ≤ 5% of patients across organ categories (Appendix Table A4).

The most common grade 3 or 4 TRAEs with potential immunologic etiology were diarrhea (n = 35), AST increased (n = 13), palmar-plantar erythrodysesthesia syndrome (n = 13), and pneumonitis (n = 12) with nivolumab plus chemotherapy.

TABLE A1. Additional Baseline Demographics and Disease Characteristics

Characteristic	Patients With PD-L1 CPS ≥5		All Patients	
	Nivolumab Plus Chemotherapy (n = 473)	Chemotherapy (n = 482)	Nivolumab Plus Chemotherapy (n = 789)	Chemotherapy (n = 792)
PD-L1 CPS expression				
<1	—	—	140 (18)	125 (16)
≥1	—	—	641 (81)	656 (83)
<5	—	—	308 (39)	299 (38)
≥5	—	—	473 (60)	482 (61)
Not evaluable/indeterminate/missing	—	—	8 (1)	11 (1)
Albumin				
<LLN	107 (23)	116 (24)	180 (23)	178 (22)
≥LLN	350 (74)	347 (72)	577 (73)	581 (73)
Not reported	16 (3)	19 (4)	32 (4)	33 (4)
Previous adjuvant or neoadjuvant therapy				
Adjuvant	39 (8)	27 (6)	64 (8)	56 (7)
Neoadjuvant	26 (5)	37 (8)	48 (6)	62 (8)
Metastatic disease	0	0	1 (<1)	0

NOTE. Data are No. (%).
Abbreviations: CPS, combined positive score; LLN, lower limit of normal.

TABLE A2. Response Rates and Duration of Response per BICR

Outcome	Patients With PD-L1 CPS ≥5		All Randomly Assigned Patients	
	Nivolumab Plus Chemotherapy (n = 378)[a]	Chemotherapy (n = 390)[a]	Nivolumab Plus Chemotherapy (n = 602)[a]	Chemotherapy (n = 607)[a]
Objective response rate[b]	226 (60)	176 (45)	350 (58)	279 (46)
95% CI	54.7 to 64.8	40.1 to 50.2	54.1 to 62.1	41.9 to 50.0
Best overall response[c]				
Complete response	50 (13)	29 (7)	67 (11)	40 (7)
Partial response	176 (47)	147 (38)	283 (47)	239 (39)
Stable disease	106 (28)	132 (34)	171 (28)	200 (33)
Progressive disease	25 (7)	42 (11)	41 (7)	62 (10)
Not evaluable	21 (6)	40 (10)	40 (7)	66 (11)
Time to response,[d] months, median (range)	1.5 (0.8-10.2)	1.5 (1.0-13.7)	1.5 (0.8-11.2)	1.5 (0.6-13.7)
Duration of response,[d] months, median (95% CI)	9.6 (8.2 to 12.4)	7.0 (5.6 to 7.9)	8.5 (7.7 to 9.9)	6.9 (5.8 to 7.2)
Proportion of patients with duration of response,[d] % (95% CI)				
12 months	44 (37.2 to 50.6)	30 (22.9 to 37.3)	41 (35.9 to 46.7)	28 (22.4 to 33.8)
24 months	25 (18.9 to 30.9)	14 (8.7 to 20.0)	21 (17.0 to 26.2)	12 (7.6 to 16.2)
36 months	20 (14.1 to 25.5)	12 (7.2 to 18.1)	16 (12.1 to 20.7)	9 (5.6 to 13.6)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviations: BICR, blinded independent central review; CPS, combined positive score.

[a]Randomly assigned patients who had target lesion measurements at baseline, per BICR assessment.

[b]Confirmed complete response or partial response per RECIST v1.1.

[c]Percentages may not add up to 100% because of rounding.

[d]Evaluated in patients who had a response.

TABLE A3. Summary of Treatment-Related Adverse Events in All Treated Patients

	Nivolumab Plus Chemotherapy (n = 782),[a,b]		Chemotherapy (n = 767),[a,b]	
Patients	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All events	739 (95)	473 (60)	682 (89)	346 (45)
Serious events	176 (23)	134 (17)	95 (12)	78 (10)
Events leading to discontinuation	331 (42)	147 (19)	198 (26)	73 (10)
Events in 10% or more of treated patients in either arm				
Nausea	328 (42)	21 (3)	300 (39)	19 (2)
Diarrhea	257 (33)	35 (4)	207 (27)	24 (3)
Peripheral neuropathy	228 (29)	34 (4)	194 (25)	23 (3)
Anemia	205 (26)	47 (6)	175 (23)	20 (3)
Fatigue	206 (26)	30 (4)	175 (23)	18 (2)
Vomiting	199 (25)	17 (2)	171 (22)	24 (3)
Neutropenia	196 (25)	123 (16)	185 (24)	96 (13)
Decreased appetite	158 (20)	14 (2)	139 (18)	13 (2)
Neutrophil count decreased	159 (20)	84 (11)	118 (15)	67 (9)
Thrombocytopenia	159 (20)	21 (3)	150 (20)	14 (2)
Platelet count decreased	161 (21)	20 (3)	115 (15)	19 (2)
Peripheral sensory neuropathy	137 (18)	16 (2)	119 (16)	14 (2)
AST increased	124 (16)	13 (2)	70 (9)	5 (<1)
WBC count decreased	115 (15)	24 (3)	77 (10)	13 (2)
ALT increased	91 (12)	7 (<1)	51 (7)	5 (<1)
Palmar-plantar erythrodysesthesia syndrome	98 (13)	13 (2)	85 (11)	9 (1)
Lipase increased	89 (11)	45 (6)	34 (4)	16 (2)
Rash	76 (10)	7 (<1)	11 (1)	0
Asthenia	76 (10)	7 (<1)	83 (11)	10 (1)

NOTE. Data are No. (%). Common Terminology Criteria for Adverse Events, version 4.0, and Medical Dictionary for Regulatory Activities, version 25.0.

[a]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 was attributed to either nivolumab or any of the chemotherapies or both.

[b]There were 16 treatment-related deaths in the nivolumab plus chemotherapy arm (four events of pneumonitis, two events of febrile neutropenia or neutropenic fever, and one event each of acute cerebral infarction, disseminated intravascular coagulation, GI bleeding, GI toxicity, infection, intestinal mucositis, mesenteric thrombosis, pneumonia, septic shock, and stroke) and four deaths in the chemotherapy arm (one event each of asthenia and severe loss of appetite, diarrhea, pneumonitis, and pulmonary thromboembolism). Treatment-related deaths were reported regardless of time frame.

TABLE A4. Treatment-Related Adverse Events With Potential Immunologic Etiology in All Treated Patients

	Nivolumab Plus Chemotherapy (n = 782)[a,b,c]		Chemotherapy (n = 767)[a,b,c]	
Event	Any Grade	Grade 3-4[d]	Any Grade	Grade 3-4
Endocrine	109 (14)	6 (<1)	3 (<1)	0
GI	265 (34)	43 (5)	208 (27)	25 (3)
Hepatic	211 (27)	32 (4)	140 (18)	18 (2)
Pulmonary	41 (5)	14 (2)	4 (<1)	1 (<1)
Renal	28 (4)	7 (<1)	9 (1)	2 (<1)
Skin	219 (28)	28 (4)	109 (14)	9 (1)

NOTE. Data are No. (%). Common Terminology Criteria for Adverse Events, version 4.0, and Medical Dictionary for Regulatory Activities, version 25.0.

[a]Patients who received ≥1 dose of study drug.

[b]Treatment-related adverse events with potential immunologic etiology that require frequent monitoring/intervention.

[c]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment.

[d]The most common grade 3 or 4 events (≥2%) in the nivolumab plus chemotherapy arm was diarrhea (n = 35). There were no grade 5 events.

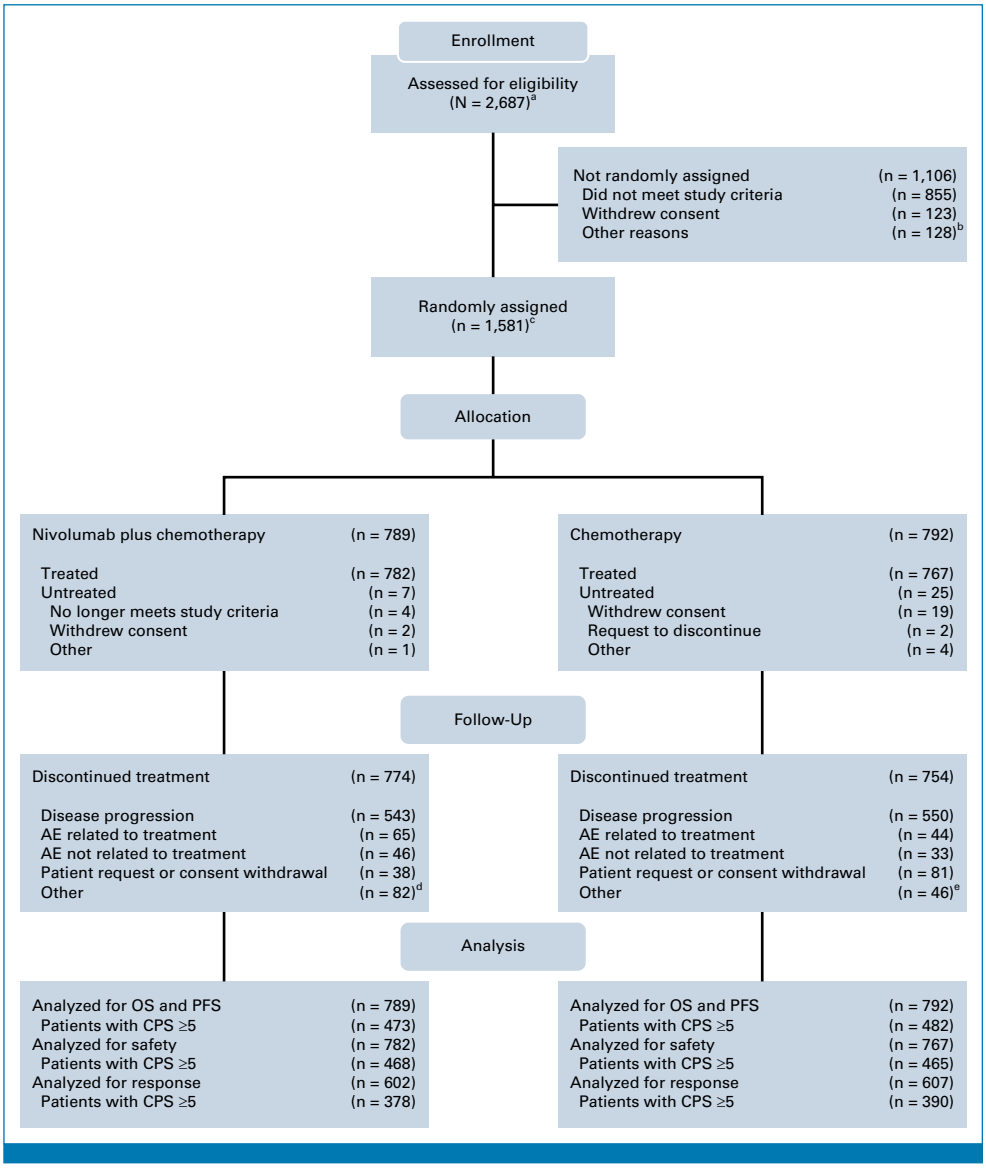

FIG A1. CONSORT diagram. [a]Enrolled patients included all concurrently randomly assigned patients to nivolumab plus chemotherapy and chemotherapy as well as patients enrolled before the nivolumab plus ipilimumab arm was closed and not randomly assigned to any of the treatment arms. [b]Included death (n = 35), AEs (n = 24), poor/noncompliance (n = 15), and additional reasons (n = 54). [c]Includes patients concurrently randomly assigned to the nivolumab plus chemotherapy and chemotherapy arms. [d]Included completion of treatment (n = 55), maximum clinical benefit (n = 12), lost to follow-up (n = 2), no longer met study criteria (n = 1), poor/noncompliance (n = 1), and other (n = 11). [e]Included maximum clinical benefit (n = 30), poor/noncompliance (n = 4), lost to follow-up (n = 2), death (n = 1), and other (n = 9). AE, adverse event; CPS, combined positive score; OS, overall survival; PFS, progression-free survival.

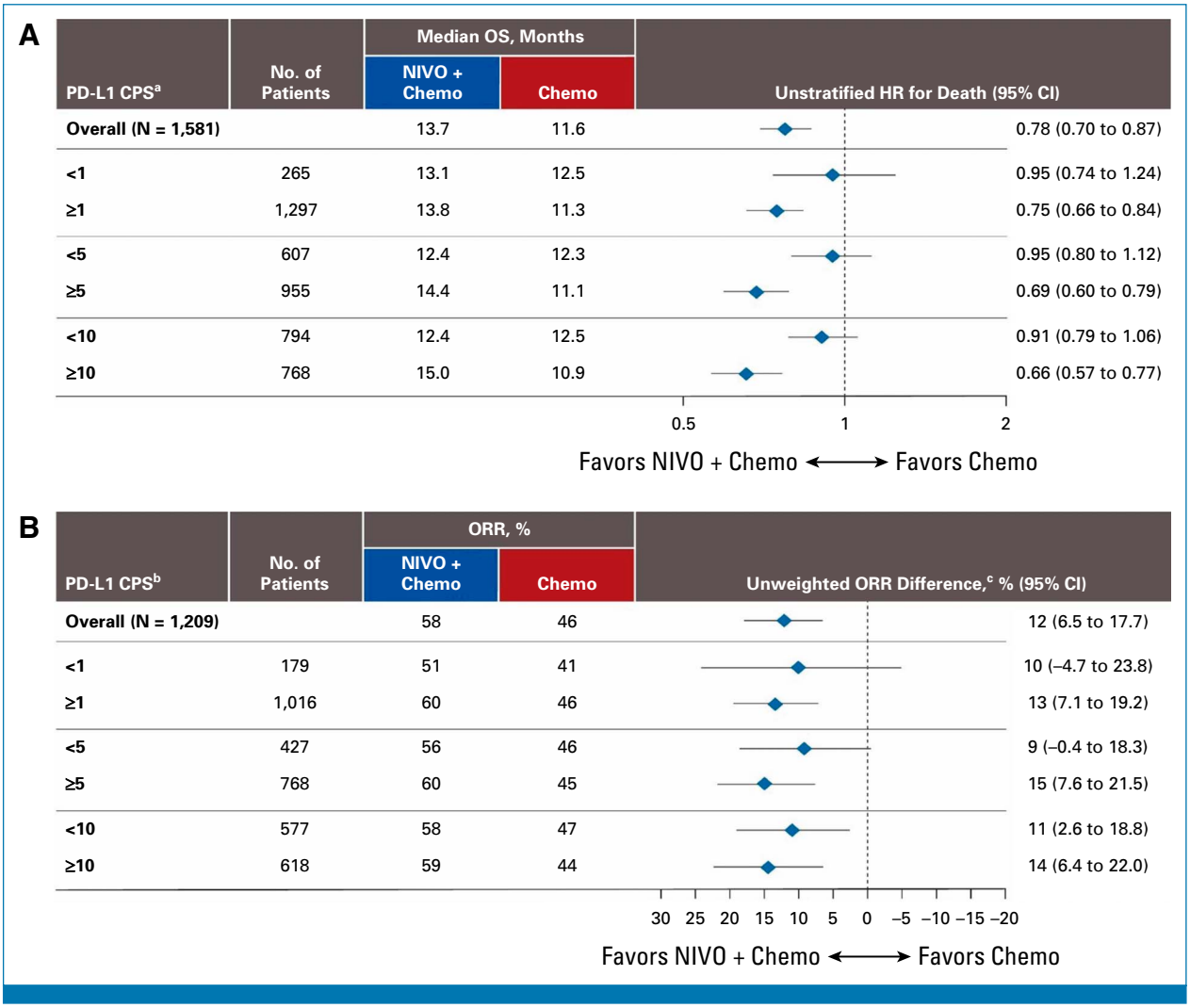

FIG A2. Subgroup analysis by PD-L1 CPS subpopulation for (A) OS and (B) objective rate response. [a]PD-L1 CPS expression indeterminate/not reported, n = 19; [b]PD-L1 CPS expression indeterminate/not reported, n = 14; [c]randomly assigned patients who had target lesion measurements at baseline, per BICR; [d]percentages may not reflect an exact difference because of rounding. BICR, blinded independent central review; Chemo, chemotherapy; CPS, combined positive score; HR, hazard ratio; NIVO, nivolumab; ORR, objective response rate; OS, overall survival.

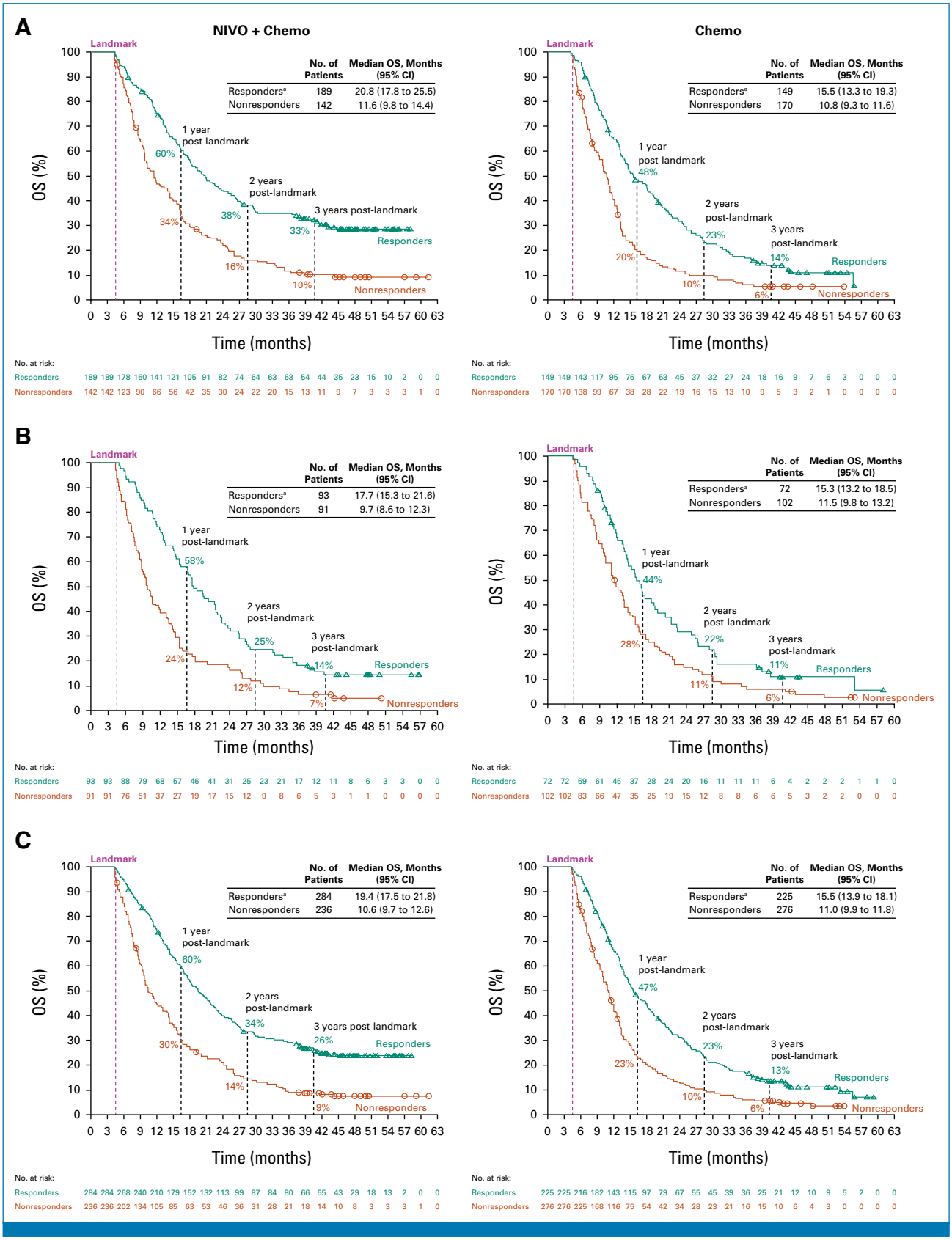

FIG A3. OS by response status at week 18 landmark in patients with (A) PD-L1 CPS ≥5, (B) PD-L1 CPS <5, and (C) all randomly assigned patients. Patients had measurable disease per BICR at baseline, had a tumor evaluation before or at 18 weeks, and were alive, evaluable, and not censored before 18 weeks. [a]Patients who had achieved confirmed partial response or complete response per BICR before or at the time of landmark. BICR, blinded independent central review; Chemo, chemotherapy; CPS, combined positive score; NIVO, nivolumab; OS, overall survival.

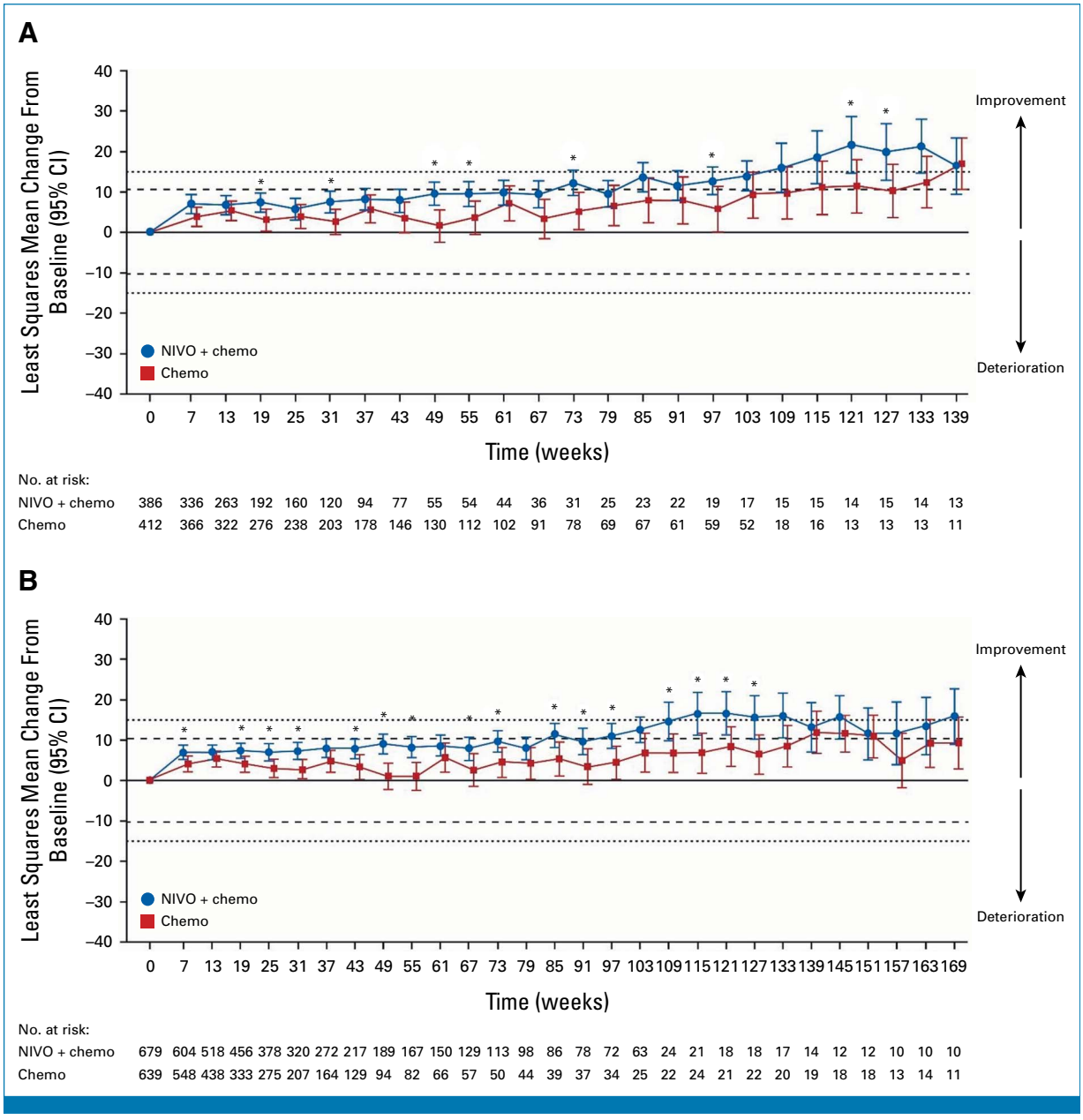

FIG A4. Least squares mean change (95% CI) in FACT-Ga total score and FACT-Ga GP5 ("I am bothered by side effects of treatment") item values in (A and C) patients with PD-L1 CPS ≥5 and (B and D) the overall population. Least squares mean (95% CI) change from baseline in FACT-Ga total score with nivolumab plus chemotherapy versus chemotherapy in (A) patients with PD-L1 CPS ≥5 (completion at baseline: nivolumab plus chemotherapy, n = 412; chemotherapy, n = 386) and (B) the overall population (completion at baseline: nivolumab plus chemotherapy, n = 679; chemotherapy, n = 639). Data in A and B are presented as least squares mean change from baseline and 95% CI. Top and bottom dotted and dashed lines indicate minimally important difference in score. The primary meaningful change threshold is 15.1 (dotted lines) and the sensitivity threshold is 10.4 (dashed lines). The *P* value for the difference in least squares means was computed as the two-tailed probability using the *t* distribution. No adjustments were made for multiple comparisons. *$P < .05$ for contrast between nivolumab plus chemotherapy versus chemotherapy; not formally tested. FACT-Ga GP5 ("I am bothered by side effects of treatment") item values in (C) patients with PD-L1 CPS ≥5 and (D) the overall population. Chemo, chemotherapy; CPS, combined positive score; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; NIVO, nivolumab. (continued on following page)

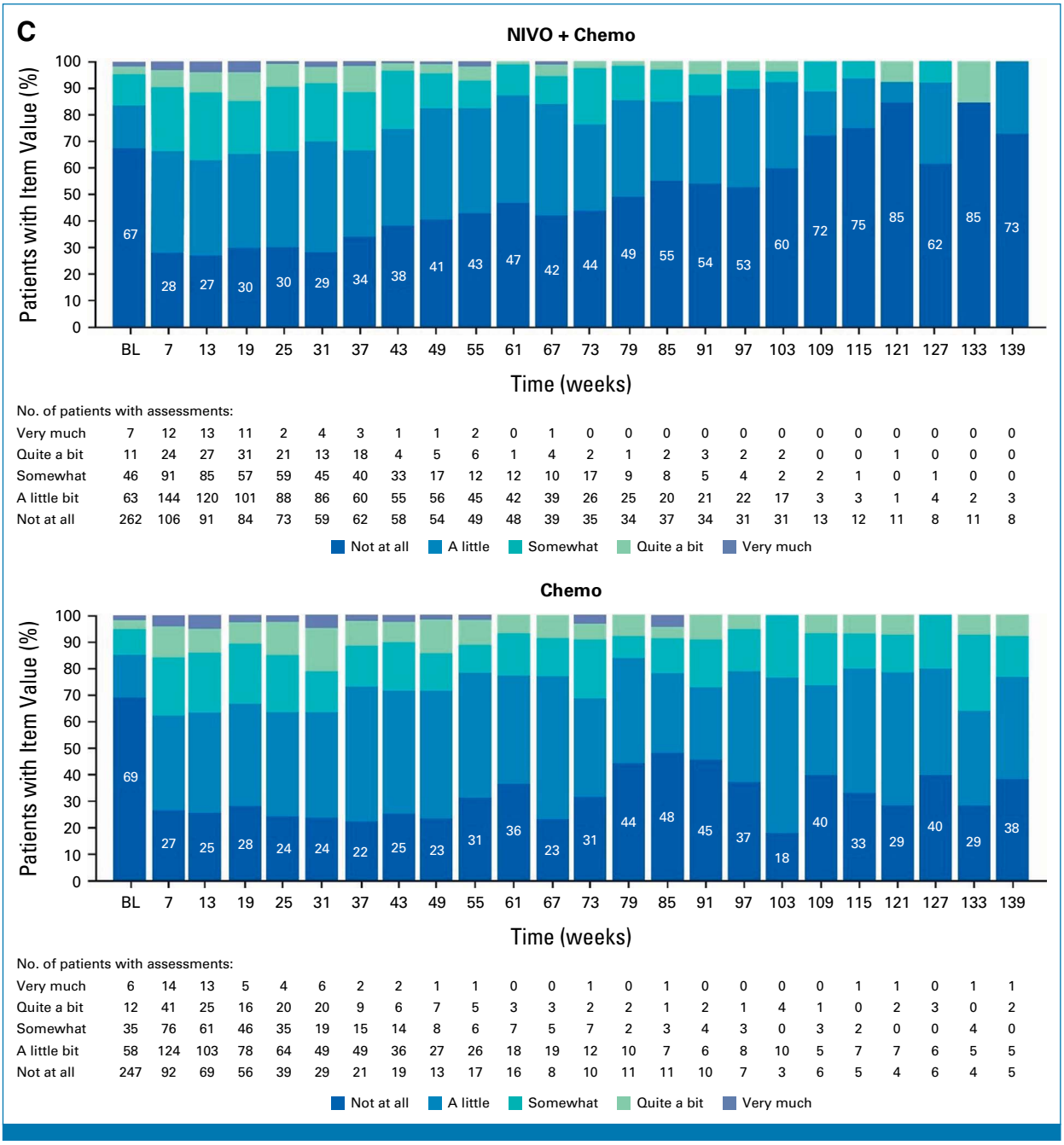

FIG A4. (Continued).

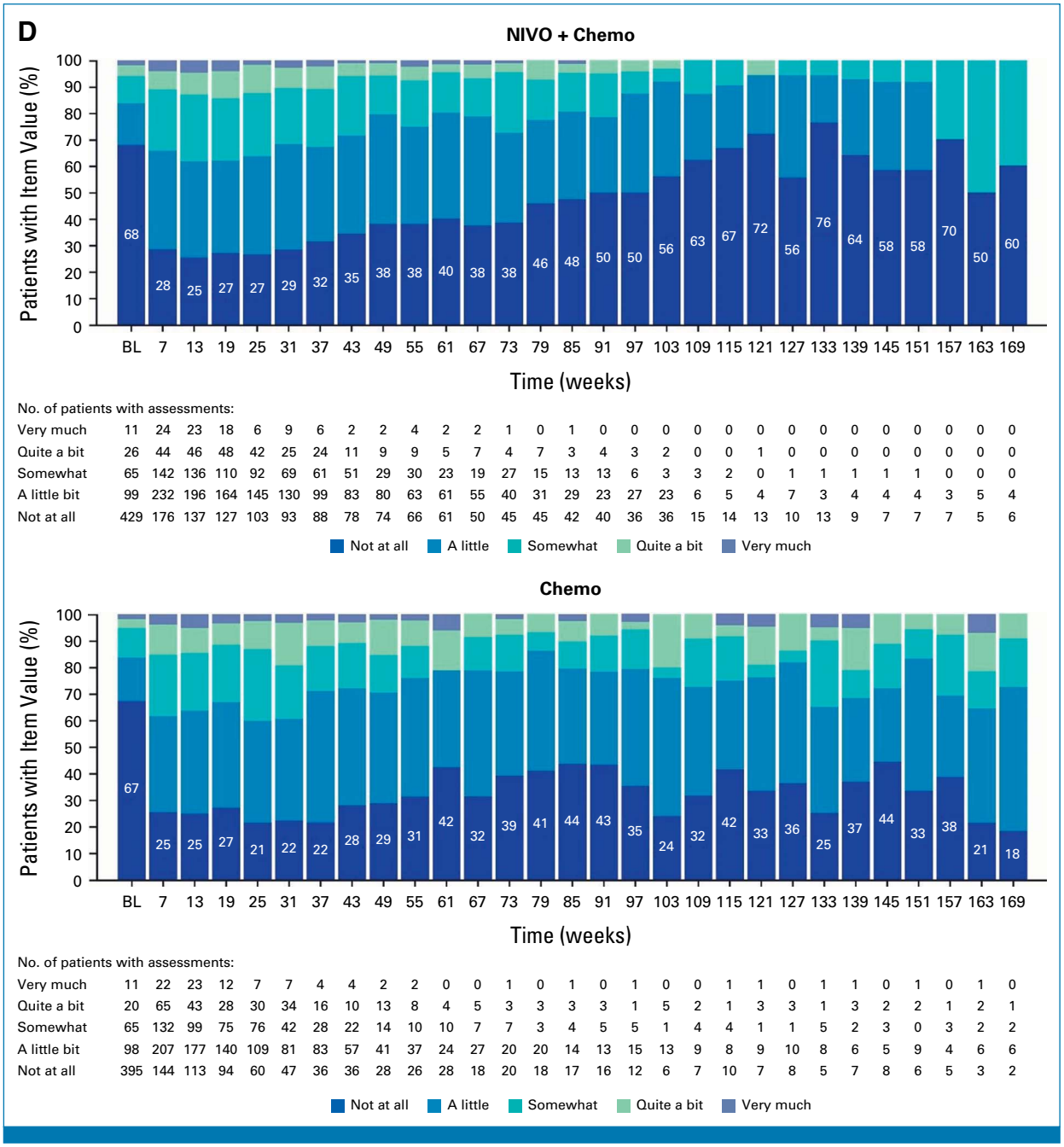

FIG A4. (Continued).