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ORIGINAL REPORT

CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer

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ABSTRACT

Purpose

Metastatic esophagogastric cancer treatments after failure of second-line chemotherapy are limited. Nivolumab demonstrated superior overall survival (OS) versus placebo in Asian patients with advanced gastric or gastroesophageal junction cancers. We assessed the safety and efficacy of nivolumab and nivolumab plus ipilimumab in Western patients with chemotherapy-refractory esophagogastric cancers.

Patients and Methods

Patients with locally advanced or metastatic chemotherapy–refractory gastric, esophageal, or gastroesophageal junction cancer from centers in the United States and Europe received nivolumab or nivolumab plus ipilimumab. The primary end point was objective response rate. The association of tumor programmed death-ligand 1 status with response and survival was also evaluated.

Results

Of 160 treated patients (59 with nivolumab 3 mg/kg, 49 with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, 52 with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg), 79% had received two or more prior therapies. At the data cutoff, investigator-assessed objective response rates were 12% (95% CI, 5% to 23%), 24% (95% CI, 13% to 39%), and 8% (95% CI, 2% to 19%) in the three groups, respectively. Responses were observed regardless of tumor programmed death-ligand 1 status. With a median follow-up of 28, 24, and 22 months across the three groups, 12-month progression-free survival rates were 8%, 17%, and 10%, respectively; 12-month OS rates were 39%, 35%, and 24%, respectively. Treatment-related grade 3/4 adverse events were reported in 17%, 47%, and 27% of patients in the three groups, respectively.

Conclusion

Nivolumab and nivolumab plus ipilimumab demonstrated clinically meaningful antitumor activity, durable responses, encouraging long-term OS, and a manageable safety profile in patients with chemotherapy-refractory esophagogastric cancer. Phase III studies evaluating nivolumab or nivolumab plus ipilimumab in earlier lines of therapy for esophagogastric cancers are underway.

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INTRODUCTION

Metastatic esophagogastric cancer is a global health burden and a substantial cause of cancer-related mortality worldwide.[1,2] For patients with disease progression receiving second-line therapy, the prognosis remains poor; thus, effective treatment options are urgently needed.[3,4] The pathogenesis of esophagogastric adenocarcinoma has been linked to chronic inflammation, DNA damage that results in high microsatellite instability (MSI), high mutational burden, and overexpression of immune checkpoint proteins.[5-8] These findings suggest that immune checkpoint inhibition is a viable therapeutic strategy for patients with esophagogastric cancer. The anti–programmed death-1 (PD-1) monoclonal antibodies nivolumab and pembrolizumab have demonstrated promising activity in early clinical trials that included patients with esophagogastric cancers.[9-11]

On the basis of superior survival demonstrated in the phase III, randomized, placebo-controlled ATTRACTION-2 trial,[12] nivolumab

ASSOCIATED CONTENT

Appendix
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was approved in Japan for the treatment of patients with chemotherapy-refractory gastric and gastroesophageal junction (GEJ) cancers regardless of programmed death-ligand 1 (PD-L1) status. Also, in the United States, pembrolizumab was approved for the treatment of patients with chemotherapy-refractory PD-L1–positive gastric/GEJ cancer on the basis of the promising clinical activity observed in the KEYNOTE-059 trial.[10] Dual PD-1/cytotoxic T-lymphocyte–associated antigen 4 blockade with nivolumab plus ipilimumab has demonstrated synergistic activity in preclinical models[13,14] and has led to enhanced response rates in patients with metastatic melanoma, small-cell lung cancer, and DNA mismatch repair–deficient/MSI–high (MSI-H) metastatic colorectal cancer.[15-17] We present the safety, efficacy, long-term survival, and biomarker analyses of nivolumab and nivolumab plus ipilimumab in Western patients with chemotherapy-refractory locally advanced or metastatic esophagogastric cancer from the multicenter, phase I/II CheckMate-032 trial.

PATIENTS AND METHODS

Study Design and Treatment

CheckMate-032 is an ongoing, open-label, two-stage, multicohort, phase I/II trial. The esophagogastric cohort of CheckMate-032 enrolled patients at 18 centers in the United States and five European countries. The study protocol and all amendments were approved by local institutional review boards, and the protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, as defined by the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. All patients provided written informed consent before enrollment. Patients were randomly assigned, when multiple treatment groups were open, to one of the following: nivolumab 3 mg/kg (NIVO3) intravenously every 2 weeks; nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3) every 3 weeks for four cycles; or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3 + IPI1) every 3 weeks for four cycles. All combination regimens were followed by NIVO3 every 2 weeks until disease progression or unacceptable adverse event (AE). Treatment beyond disease progression was permitted in patients with clinical benefit on the basis of investigator assessment. Patients who were assigned to the NIVO3 group and experienced disease progression could cross over to a combination group. Dose reductions or modifications were not permitted with nivolumab or ipilimumab. Dose interruption was allowed. The criteria for treatment discontinuation and interruption are summarized in the Appendix (online only).

Patients

Key eligibility criteria for the esophagogastric cancer cohort included diagnosis of locally advanced or metastatic gastric, esophageal, or GEJ adenocarcinoma with disease progression while taking or intolerance of at least one chemotherapy regimen; measurable disease as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[18]; Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate organ function. Patients with human epidermal growth factor receptor 2–positive tumors were eligible if they had received previous treatment with trastuzumab. Key exclusion criteria included suspected autoimmune disease; hepatitis B virus or human immunodeficiency virus infection; conditions requiring corticosteroids or other immunosuppressive medications; and previous immune checkpoint inhibitor therapy.

Study Assessments

The primary end point was objective response rate (ORR), defined as the best response of complete response or partial response divided by the number of treated patients, per RECIST version 1.1.[18] ORR was assessed by investigator and by blinded independent central review (BICR). Secondary end points included overall survival (OS), progression-free survival (PFS), duration of response (DOR), and safety. Tumor response was assessed using imaging every 6 weeks for 24 weeks, then every 12 weeks until disease progression or treatment discontinuation. Survival was monitored continuously while patients were receiving treatment and every 3 months after treatment discontinuation. Clinical activity was also assessed by tumor PD-L1 and MSI status. AEs were assessed and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[19]

Tumor PD-L1 expression was assessed centrally using a validated, automated immunohistochemistry assay (Dako North America, Carpinteria, CA) of archival samples obtained before enrollment or new biopsy specimens. Samples with ≥ 100 evaluable tumor cells and ≥ 1% PD-L1 staining of tumor cell membranes were considered PD-L1–positive. MSI status was established retrospectively on available tumor/normal paired samples using a polymerase chain reaction–based assay on the basis of the

Table 1. Baseline Patient and Disease Characteristics

Characteristic	NIVO3 (n = 59)	NIVO1 + IPI3 (n = 49)	NIVO3 + IPI1 (n = 52)
Median age, years (range)	60 (29-80)	53 (27-77)	58 (19-81)
Age ≥ 65 years	17 (29)	10 (20)	17 (33)
Male sex	45 (76)	34 (69)	45 (87)
Race			
White	56 (95)	46 (94)	50 (96)
Black/Asian/other	3 (5)	3 (6)	2 (4)
ECOG PS			
0	29 (49)	27 (55)	18 (35)
1	30 (51)	22 (45)	34 (65)
Primary tumor location			
Gastric	19 (32)	22 (45)	18 (35)
Esophageal	9 (15)	8 (16)	9 (17)
GEJ	31 (53)	19 (39)	25 (48)
Site of metastases			
Lymph node	39 (66)	29 (59)	32 (62)
Peritoneum	13 (22)	8 (16)	9 (17)
Liver	31 (53)	27 (55)	26 (50)
Lung	20 (34)	12 (24)	17 (33)
Prior regimens			
0	0	1 (2)	0
1	10 (17)	6 (12)	16 (31)
2	20 (34)	19 (39)	16 (31)
3	19 (32)	11 (22)	13 (25)
> 3	10 (17)	12 (24)	7 (13)
Prior therapies			
Fluoropyrimidine	59 (100)	47 (96)	50 (96)
Platinum	57 (97)	45 (92)	49 (94)
Taxane	38 (64)	33 (67)	32 (62)
Anti-HER2	14 (24)	12 (24)	16 (31)
Prior radiotherapy	24 (41)	13 (27)	26 (50)
HER2			
Positive	8 (14)	5 (10)	9 (17)
Negative	30 (51)	22 (45)	25 (48)
Unknown	21 (36)	22 (45)	18 (35)
MSI status	(n = 25)	(n = 23)	(n = 24)
MSI-H	7 (28)*	2 (9)*	2 (8)*
Non–MSI-H	18 (72)*	21 (91)*	22 (92)*
Not evaluable/missing	34 (58)	26 (53)	28 (54)
PD-L1 expression	(n = 42)	(n = 42)	(n = 43)
≥ 1	16 (38)*	10 (24)*	13 (30)*
< 1	26 (62)*	32 (76)*	30 (70)*
Not evaluable/missing	17 (29)	7 (14)	9 (17)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; MSI, microsatellite instability; MSI-H, microsatellite instability–high; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PD-L1, programmed death-ligand 1.
*Percentage of evaluable patients.

Table 2. ORR, DCR, and DOR per Investigator Assessment and BICR

Variable	NIVO3 (n = 59)		NIVO1 + IPI3 (n = 49)		NIVO3 + IPI1 (n = 52)	
	Investigator	BICR	Investigator	BICR	Investigator	BICR
ORR, No. (%; 95% CI)	7 (12; 5 to 23)	4 (7; 2 to 17)	12 (24; 13 to 39)	10 (20; 10 to 34)	4 (8; 2 to 19)	2 (4; 1 to 13)
Complete response	1 (2)	0	1 (2)	1 (2)	0	1 (2)
Partial response	6 (10)	4 (7)	11 (22)	9 (18)	4 (8)	1 (2)
Stable disease	12 (20)	18 (31)	8 (16)	13 (27)	15 (29)	17 (33)
Progressive disease	34 (58)	26 (44)	23 (47)	18 (37)	24 (46)	25 (48)
Unable to determine	6 (10)	11 (19)	6 (12)	8 (16)	9 (17)	8 (15)
DCR, No. (%)*	19 (32)	22 (37)	20 (41)	23 (47)	19 (37)	19 (37)
Median TTR, months (range)	1.6 (1.2 to 4.0)	1.4 (1.2 to 2.1)	2.7 (1.2 to 14.5)	2.6 (1.1 to 4.2)	2.6 (1.3 to 2.8)	2.0 (1.2 to 2.7)
Median DOR, months (95% CI)	7.1 (3.0 to 13.2)	14.1 (2.8 to 14.1)	7.9 (2.8 to NE)	NR (2.7 to NE)	NR (2.5 to NE)	NR (NE to NE)

Abbreviations: BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NE, not estimable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; NR, not reached; ORR, objective response rate; TTR, time to response.
*Patients with a best objective response of complete response, partial response, or stable disease.

Bethesda panel of mononucleotide and dinucleotide markers.[20] Samples positive for two or more markers of instability were classified as MSI-H.

Statistical Analyses

Each treatment group was evaluated separately for the primary end point of ORR using a modified Simon two-stage study design,[21] with 80% power to reject the null hypothesis of ORR ≤ 10% (insufficient drug activity), assuming that the true ORR was 25%, with a one-sided α of .05. Thus, the trial was not designed or powered for a formal comparison of the treatment groups. In this multicohort trial, an ORR of 25% was considered to be of clinical interest across tumor types and was not specifically selected based on the esophagogastric cancer cohort. In addition, the tests did not adjust for multiplicity across the different tumor type cohorts in CheckMate-032. In the first stage, 18 patients were enrolled per group. If at least two responses were observed, accrual was expanded in the second stage to 22 additional patients, for a total of 40 patients per group. The treatment was considered of clinical interest if at least 20% of patients (eight of 40) experienced an objective response. On the basis of the results of phase I studies in other solid tumors,[22-24] it was hypothesized that NIVO3 + IPI1 would have similar efficacy and improved safety; thus, the NIVO3 + IPI1 group was not based on a two-stage design and was started once the NIVO1 + IPI3 group proceeded to the second stage. The protocol permitted further expansion of treatment groups on the basis of the clinical activity.

The BICR assessment of the NIVO3 group was based on the March 2016 data cutoff. All other efficacy and safety assessments for the treatment groups were based on the November 2016 data cutoff. ORR was summarized by a binomial proportion and corresponding two-sided 95% exact CIs using the Clopper-Pearson method. DOR, PFS, and OS were summarized using medians and time point–specific survival rates by Kaplan-Meier and two-sided 95% CIs. Descriptive statistics were used to characterize patient characteristics and safety. Statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Patients were enrolled and treated from November 19, 2013, through June 3, 2015. At the time of the data cutoff, 160 patients received NIVO3 (n = 59), NIVO1 + IPI3 (n = 49), or NIVO3 + IPI1 (n = 52). Of the 160 patients, 79% had received two or more prior therapies; 49%, 47%, and 38% of patients across the three groups had received three or more prior lines of therapy, respectively (Table 1). Tumor samples were evaluable for PD-L1 and MSI status in 79% and 45% of patients, respectively. The NIVO3 group had higher percentages of patients with PD-L1–positive tumors (38%) and MSI-H status (28%) than either of the combination groups (NIVO1 + IPI3: PD-L1–positive, 24%, and MSI-H, 9%; NIVO3 + IPI1: PD-L1–positive, 30%, and MSI-H, 8%). Median duration of follow-up (potential time on study from first dose to database lock) in the three groups was 28 months (range, 17 to 35 months) in the NIVO3 group, 24 months (range, 21 to 33 months) in the NIVO1 + IPI3 group, and 22 months (range, 19 to 25 months) in the NIVO3 + IPI1 group; most patients in each treatment group (NIVO3, 97%; NIVO1 + IPI3, 88%; NIVO3 + IPI1, 94%) had discontinued treatment at the time of the data cutoff. The most common reason for discontinuation of treatment across all groups was disease progression (Appendix Fig A1, online only). After discontinuation of study therapy, approximately one third of patients in each treatment group (36% overall) went on to receive subsequent anticancer therapy, consisting of chemotherapy in most patients (84%).

Efficacy

Investigator-assessed ORR was 12% with NIVO3, 24% with NIVO1 + IPI3, and 8% with NIVO3 + IPI1 (Table 2). Median DOR was 7.1 months (95% CI, 3.0 to 13.2 months) in the NIVO3 group, 7.9 months (95% CI, 2.8 months to not estimable) in the NIVO1 + IPI3 group, and not yet reached (95% CI, 2.5 months to not estimable) in the NIVO3 + IPI1 group (Figs 1A-1C). Responses were observed with NIVO3, NIVO1 + IPI3, and NIVO3 + IPI1 regardless of tumor PD-L1 expression (Table 3; BICR in Appendix Table A1, online only). Objective responses were observed in both patients with MSI-H and those with non–MSI-H tumors (Table 3; Appendix Fig A2, online only). Additional efficacy outcomes per BICR are presented in Appendix Figure A3 (online only).

Among evaluable patients, 29%, 45%, and 27% of patients in the NIVO3, NIVO1 + IPI3, and NIVO3 + IPI1 groups, respectively, had a reduction in tumor burden from baseline per investigator assessment (Fig 1D; BICR in Appendix Fig A4, online only). The median time to response ranged from 1.6 to 2.7 months (Table 2). Disease control (complete response, partial response, and stable disease) was achieved by 32% to 41% of patients (Table 2). Stable disease for at least 12 weeks was achieved by 67%, 63%, and 67% of patients with stable disease in the NIVO3, NIVO1 + IPI3, and NIVO3 + IPI1 groups, respectively. At the time of the data cutoff, five patients in the NIVO1 + IPI3 group and two patients in the NIVO3 + IPI1 group had ongoing responses by investigator assessment (Appendix Fig A2, online only).

Median PFS by investigator assessment was 1.4 months (95% CI, 1.2 to 1.5 months) in the NIVO3 group, 1.4 months (95% CI, 1.2

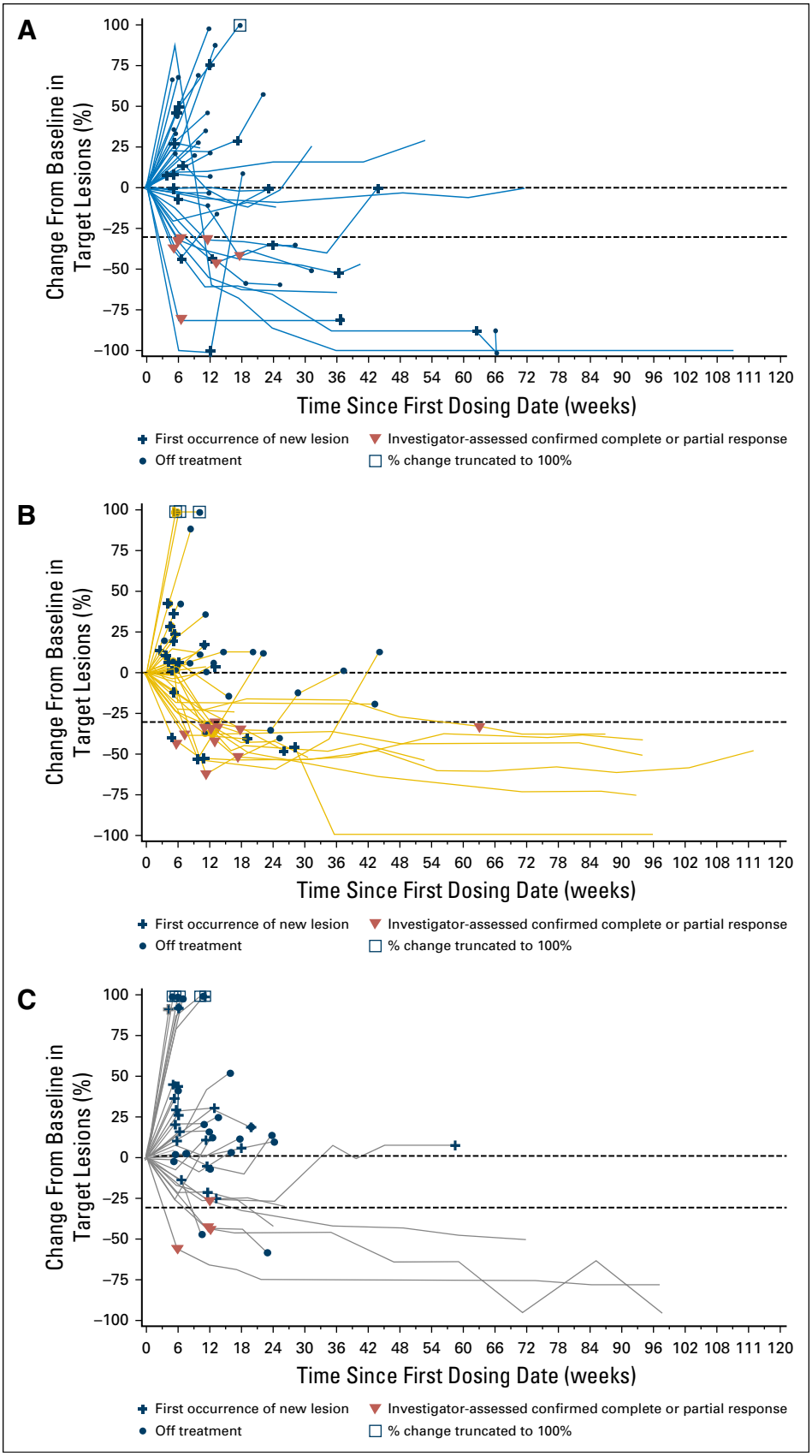

Fig 1. Changes in tumor burden per investigator assessment in individual patients. Percentage change from baseline in target lesions over time with (A) nivolumab 3 mg/kg (NIVO3), (B) nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3), (C) NIVO3 plus ipilimumab 1 mg/kg (NIVO3 + IPI1), and (D) the reduction in maximum percentage change from baseline in size of tumors by treatment group. Patients with 0% best reduction in target lesion are not shown on the plot (NIVO3, n = 2; NIVO1 + IPI3, n = 1; NIVO3 + IPI1, n = 1). Triangle indicates investigator-assessed confirmed complete or partial response, square indicates percent change truncated at 100%, closed circle represents patients off treatment, and cross represents first occurrence of a new lesion. (*) Indicates patients with a confirmed response (complete or partial response), and the bars representing patients with a percentage change in tumor burden that exceeds 100% have been truncated.

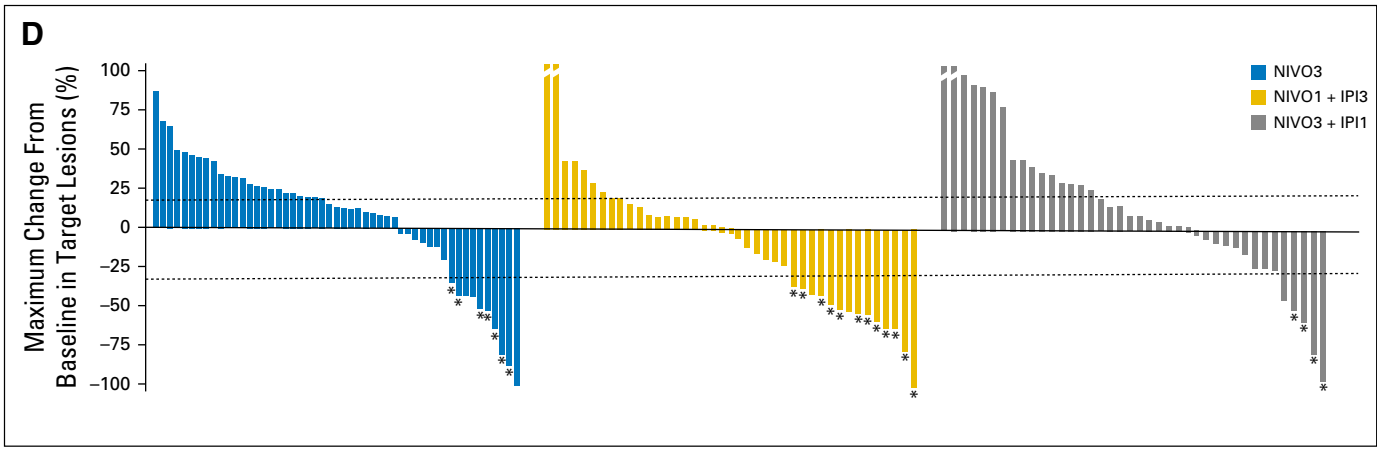

Fig 1. (Continued).

to 3.8 months) in the NIVO1 + IPI3 group, and 1.6 months (95% CI, 1.4 to 2.6 months) in the NIVO3 + IPI1 group (Fig 2A; BICR in Appendix Fig A5, online only). The 12-month PFS rate was 8% (95% CI, 3% to 17%) in the NIVO3 group, 17% (95% CI, 8% to 29%) in the NIVO1 + IPI3 group, and 10% (95% CI, 3% to 20%) in the NIVO3 + IPI1 group. The median OS was 6.2 months (95% CI, 3.4 to 12.4 months) in the NIVO3 group, 6.9 months (95% CI, 3.7 to 11.5 months) in the NIVO1 + IPI3 group, and 4.8 months (95% CI, 3.0 to 8.4 months) in the NIVO3 + IPI1 group (Fig 2B). The 12-month OS rate was 39% (95% CI, 26% to 52%) in the NIVO3 group, 35% (95% CI, 22% to 49%) in the NIVO1 + IPI3 group, and 24% (95% CI, 13% to 37%) in the NIVO3 + IPI1 group. The 12-month OS rates by PD-L1 and MSI status are listed in Table 3.

Safety

Treatment-related AEs (TRAEs) occurred in 69% of patients in the NIVO3 group, 84% of patients in the NIVO1 + IPI3 group, and 75% of patients in the NIVO3 + IPI1 group. The most common (≥ 15%) TRAEs across all treatment groups included fatigue, pruritus, rash, diarrhea, decreased appetite, and increased ALT and AST levels (Table 4). Grade 3/4 TRAEs were reported in 17%, 47%, and 27% of patients receiving NIVO3, NIVO1 + IPI3, and NIVO3 + IPI1, respectively. TRAEs resulted in treatment discontinuation in 3% of patients in the NIVO3 group, 20% of patients in the NIVO1 + IPI3 group, and 13% of patients in the NIVO3 + IPI1 group. Serious TRAEs occurred in 10%, 43%, and 25% of patients receiving NIVO3, NIVO1 + IPI3, and NIVO3 + IPI1, respectively. One death due to tumor lysis syndrome, deemed by the investigator to be possibly treatment related, occurred in the NIVO3 + IPI1 group.

DISCUSSION

Results of the CheckMate-032 study reported here demonstrate for the first time that nivolumab and nivolumab plus ipilimumab provide clinically meaningful and durable antitumor activity with a manageable safety profile in heavily pretreated Western patients with chemotherapy-refractory esophagogastric cancer. Notably, the clinical activity with nivolumab monotherapy in our study was consistent with that reported with nivolumab in Asian patients in the ATTRACTION-2 study.[12] Taken together with other reports on anti–PD-1 therapy,[9,25] these findings suggest that despite the morphologic and molecular heterogeneity of esophagogastric cancer, immune checkpoint blockade provides a consistent therapeutic benefit across Asian and Western patients.

Considering the aggressive biology of metastatic esophagogastric cancer, combined immune checkpoint blockade may further improve the efficacy of single-agent anti–PD-1 therapy by avoiding tumor immune escape through synergistic T-cell antitumor activity.[13,14] NIVO1 + IPI3 has demonstrated clinical activity and a manageable safety profile in other solid tumors[15,16] and is Food and Drug Administration approved for the treatment of melanoma.[26] The results with NIVO1 + IPI3 therapy reported here demonstrate an ORR of 24%; however, despite the numerically higher ORR achieved in patients receiving NIVO1 + IPI3 than in those receiving NIVO3, median OS was similar between these groups. One explanation for this observation may be the higher proportion of patients with MSI-H and PD-L1–positive tumors in the NIVO3 group. The enhanced clinical benefit observed with NIVO1 + IPI3 was accompanied by a numerically higher incidence of grade 3/4 AEs than observed with NIVO3. These events were primarily diarrhea and elevated liver enzyme levels and were manageable using protocol-specified AE management algorithms. In contrast, NIVO3 + IPI1 had comparable clinical activity and a numerically higher overall rate of AEs compared with NIVO3. These findings suggest that the lower ipilimumab dose may not have been sufficient to enhance anti–PD-1–mediated immune responses in this patient population. On the basis of the numerically higher overall response and landmark OS rates in the NIVO1 + IPI3 arm, this combination was considered more likely to offer clinical benefit relative to currently available treatment regimens for first-line metastatic esophagogastric cancer and was selected for further evaluation in the phase III CheckMate-649 study (NCT02872116).

To identify potential biomarkers of response to nivolumab and nivolumab plus ipilimumab, treatment response and outcomes were explored by tumor PD-L1 and MSI status. Responses were observed regardless of tumor PD-L1 status across the treatment groups. Although the ORR seemed numerically higher in patients with PD-L1–positive versus PD-L1–negative tumors, the sample size was small, with overlapping CIs between these subgroups. Of note, tumor PD-L1 status was not predictive of survival with nivolumab in patients with gastric/GEJ cancer in the phase III ATTRACTION-2 trial.[12]

Table 3. Investigator-Assessed Response and OS by PD-L1 and MSI Status

	NIVO3 (n = 59)				NIVO1 + IPI3 (n = 49)				NIVO3 + IPI1 (n = 52)			
Response/OS	PD-L1+ (n = 16)	PD-L1− (n = 26)	MSI-H (n = 7)	Non–MSI-H (n = 18)	PD-L1+ (n = 10)	PD-L1− (n = 32)	MSI-H (n = 2)	Non–MSI-H (n = 21)	PD-L1+ (n = 13)	PD-L1− (n = 30)	MSI-H (n = 2)	Non–MSI-H (n = 22)
ORR, No. (%; 95% CI)	3 (19; 4 to 46)	3 (12; 2 to 30)	2 (29; 4 to 71)*	2 (11; 1 to 35)†	4 (40; 12 to 74)	7 (22; 9 to 40)	1 (50; 1 to 99)*	4 (19; 5 to 42)†	3 (23; 5 to 54)	0 (0; 0 to 12)	1 (50; 1 to 99)*	1 (5; 0.1 to 23.0)†
DCR, No. (%)‡	5 (31)	11 (42)	5 (71)	5 (28)	5 (50)	13 (41)	1 (50)	9 (43)	5 (38)	10 (33)	1 (50)	8 (36)
OS rate, months, % (95% CI)												
12	34 (12 to 57)	45 (25 to 63)	57 (17 to 84)	33 (14 to 55)	50 (18 to 75)	32 (16 to 48)	50 (1 to 91)	32 (16 to 48)	23 (6 to 47)	25 (11 to 42)	50 (1 to 91)	23 (8 to 43)
18	13 (2 to 35)	28 (13 to 47)	29 (4 to 61)	17 (4 to 37)	50 (18 to 75)	24 (10 to 40)	50 (1 to 91)	30 (12 to 51)	15 (3 to 39)	8 (2 to 23)	50 (1 to 91)	6 (0 to 23)

Abbreviations: DCR, disease control rate; DOR, duration of response; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; MSI-H, microsatellite instability–high; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PD-L1−, programmed death-ligand 1–negative; PD-L1+, programmed death-ligand 1–positive.

*DOR was 7 and 13 months in the two responders in the NIVO3 group, ≥ 17.4 in the one responder in the NIVO1 + IPI3 group, and ≥ 13.8 months in the responder in the NIVO3 + IPI1 group.

†DOR was 3.0 and ≥ 26.5 months for the two responders in the NIVO 3 group, and 2.5 months in the one responder in the NIVO3 + IPI1 group. The median DOR was 4.53 months (95% CI, 2.76 months to not estimable) in the four responders in the NIVO1 + IPI3 group.

‡Patients with a best objective response of complete response, partial response, or stable disease.

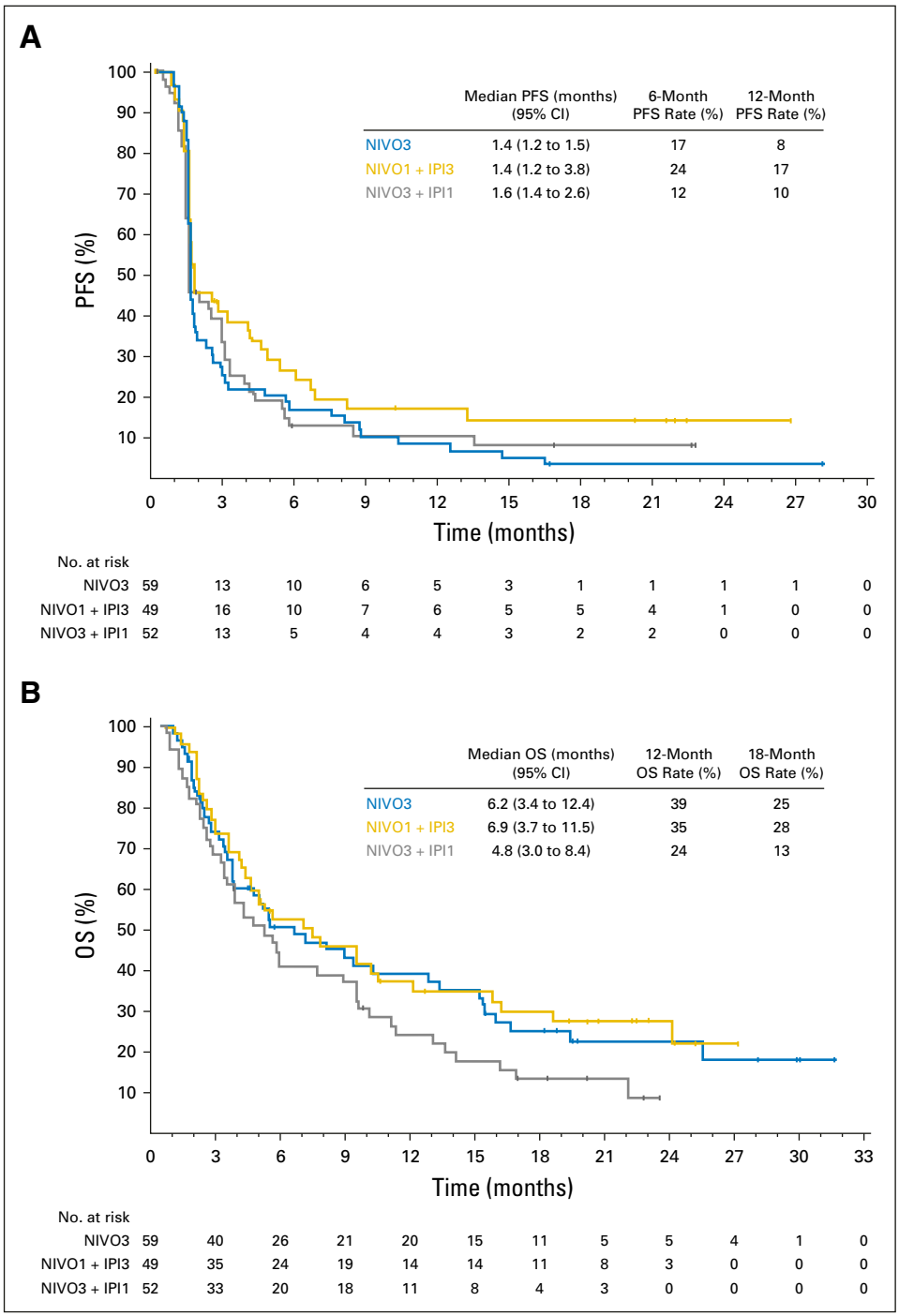

Fig 2. Kaplan-Meier curves of (A) investigator-assessed progression-free survival (PFS) and (B) overall survival (OS) in all enrolled patients by treatment group: nivolumab 3 mg/kg (NIVO3), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3), and NIVO3 plus ipilimumab 1 mg/kg (NIVO3 + IPI1). Hash marks indicate censored observations.

With emerging data highlighting the importance of MSI as a predictive biomarker of response to immune checkpoint inhibitors,[27,28] our exploratory analysis revealed that responses were observed in patients with both MSI-H and non–MSI-H tumors. The ORR seemed numerically higher in the MSI-H subgroup; however, because of the small sample size, these data are only hypothesis generating, and research in larger patient subsets is needed to confirm these findings.

This study adds to the current body of evidence supporting the role of immune checkpoint inhibitors for the treatment of patients with advanced esophagogastric cancers.[9,10,12] Limitations of this phase I/II study include the absence of a standard-of-care comparator and that the study was not designed for formal comparisons across treatment groups. In addition, identification of potential biomarkers of response was limited by the small sample size. Ongoing studies may identify biomarker-defined subgroups of patients likely to gain greater benefit from nivolumab-based therapy. Thus, the optimal approach of when (earlier *v* later lines of therapy) and how (alone or in combination) to incorporate nivolumab and nivolumab plus ipilimumab into clinical practice is yet to be determined.

Table 4. Treatment-Related Adverse Events

TRAE	NIVO3, No. (%) (n = 59)		NIVO1 + IPI3, No. (%) (n = 49)		NIVO3 + IPI1, No. (%) (n = 52)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE	41 (69)	10 (17)	41 (84)	23 (47)	39 (75)	14 (27)
Serious TRAEs*	6 (10)	3 (5)	21 (43)	17 (35)	13 (25)	9 (17)
TRAEs leading to treatment discontinuation	2 (3)	2 (3)	10 (20)	10 (20)	7 (13)	5 (10)
TRAEs in ≥ 15% of patients in any treatment group						
ALT increased	5 (8)	2 (3)	8 (16)	7 (14)	5 (10)	2 (4)
AST increased	7 (12)	3 (5)	8 (16)	5 (10)	2 (4)	1 (2)
Decreased appetite	9 (15)	0	5 (10)	0	3 (6)	0
Diarrhea	9 (15)	1 (2)	15 (31)	7 (14)	5 (10)	1 (2)
Fatigue	20 (34)	1 (2)	14 (29)	3 (6)	10 (19)	0
Pruritus	10 (17)	0	9 (18)	1 (2)	12 (23)	0
Rash	5 (8)	0	10 (20)	0	8 (15)	0

Abbreviations: IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; TRAE, treatment-related adverse event.
*The most common (≥ 5%) serious TRAEs in the NIVO1 + IPI3 group included diarrhea (8%), adrenal insufficiency (8%), fatigue (6%), increased ALT (6%), increased AST (6%), and colitis (6%). In the NIVO3 + IPI1 group, pneumonitis was reported as a serious TRAE in 8% of patients. No serious TRAEs ≥ 5% were reported in the NIVO3 group.

In summary, our findings suggest that nivolumab and nivolumab plus ipilimumab represent a potential therapeutic approach for patients with advanced esophagogastric cancer. Ongoing phase III studies are investigating nivolumab in the adjuvant setting (NCT02743494) and NIVO1 + IPI3 in the first-line setting (NCT02872116) in patients with esophagogastric cancer.

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Disclosures provided by the authors are available with this article at jco.org.

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CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients with Metastatic Esophagogastric Cancer

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Appendix

Supplementary Study Design

The criteria for discontinuation of treatment included the following treatment-related adverse events: grade 2 uveitis, grade 3 nonskin events lasting ≥ 7 days, grade 3 laboratory abnormalities of thrombocytopenia or liver function, all grade 4 events, and laboratory abnormalities, except for asymptomatic amylase or lipase elevations. The criteria for dose delay (until resolution of the treatment-related adverse event to grade 1 or lower) of nivolumab, ipilimumab, or both include the following treatment-related adverse events: grade 2 or worse nonskin events (except for grade 2 fatigue or laboratory abnormalities, which do not require a treatment delay), grade 3 skin events, and grade 3 laboratory abnormalities (except for asymptomatic amylase and lipase increases). If the patient had normal AST, ALT, or total bilirubin concentrations at baseline, the dose would be delayed for grade 2 or worse adverse events; if these laboratory parameters were grade 1 at baseline, the dose would be delayed for grade 3 or worse adverse events.

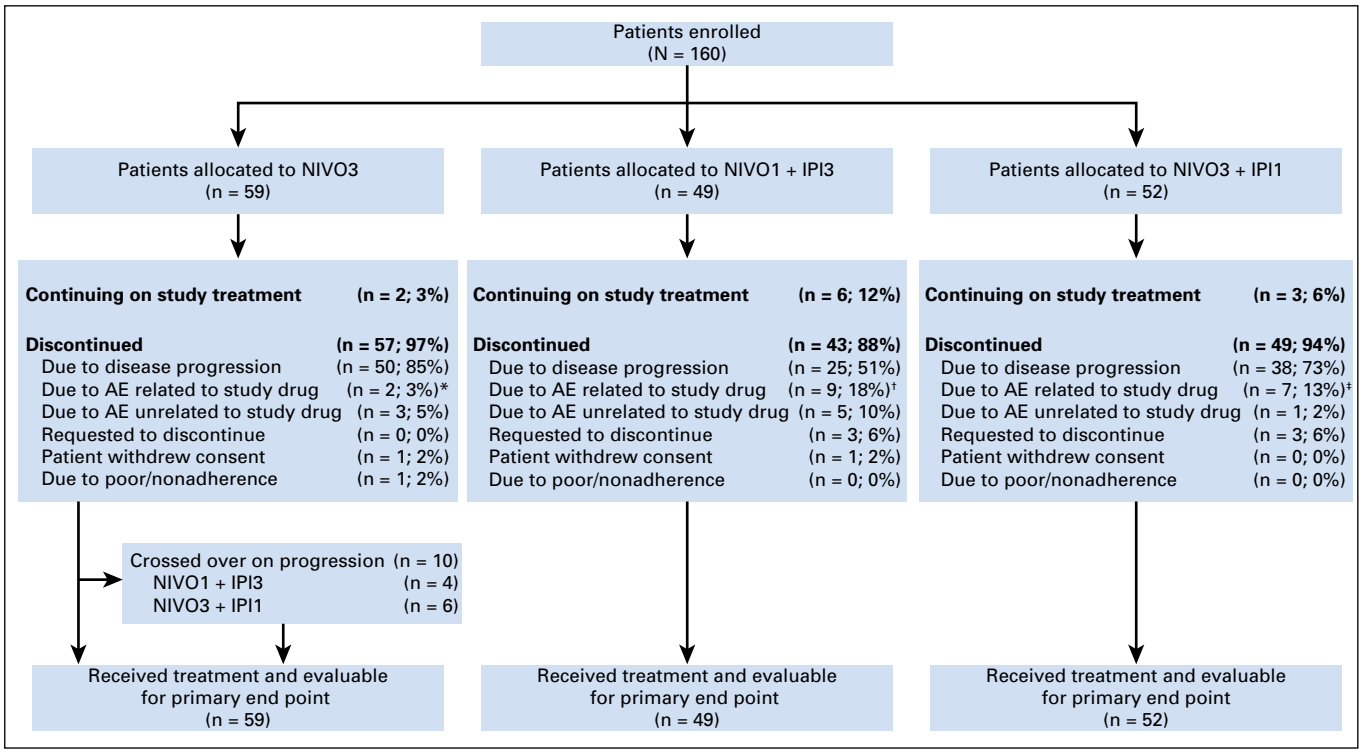

Fig A1. CONSORT diagram for study design and patient disposition. (*) Increased ALT/AST (n = 1 patient) and pneumonitis (n = 1 patient). (†) Increased ALT/AST (n = 3 patients); colitis (n = 2 patients); diarrhea (n = 2 patients); colitis, cystitis, and transaminitis (n = 1 patient); and diarrhea and hyperthyroidism (n = 1 patient). (‡) Acute renal failure, autoimmune hepatitis, diarrhea, enteritis, increased ALT/AST, lymphocytic myocarditis, and pneumonitis (n = 1 patient each). AE, adverse event; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg.

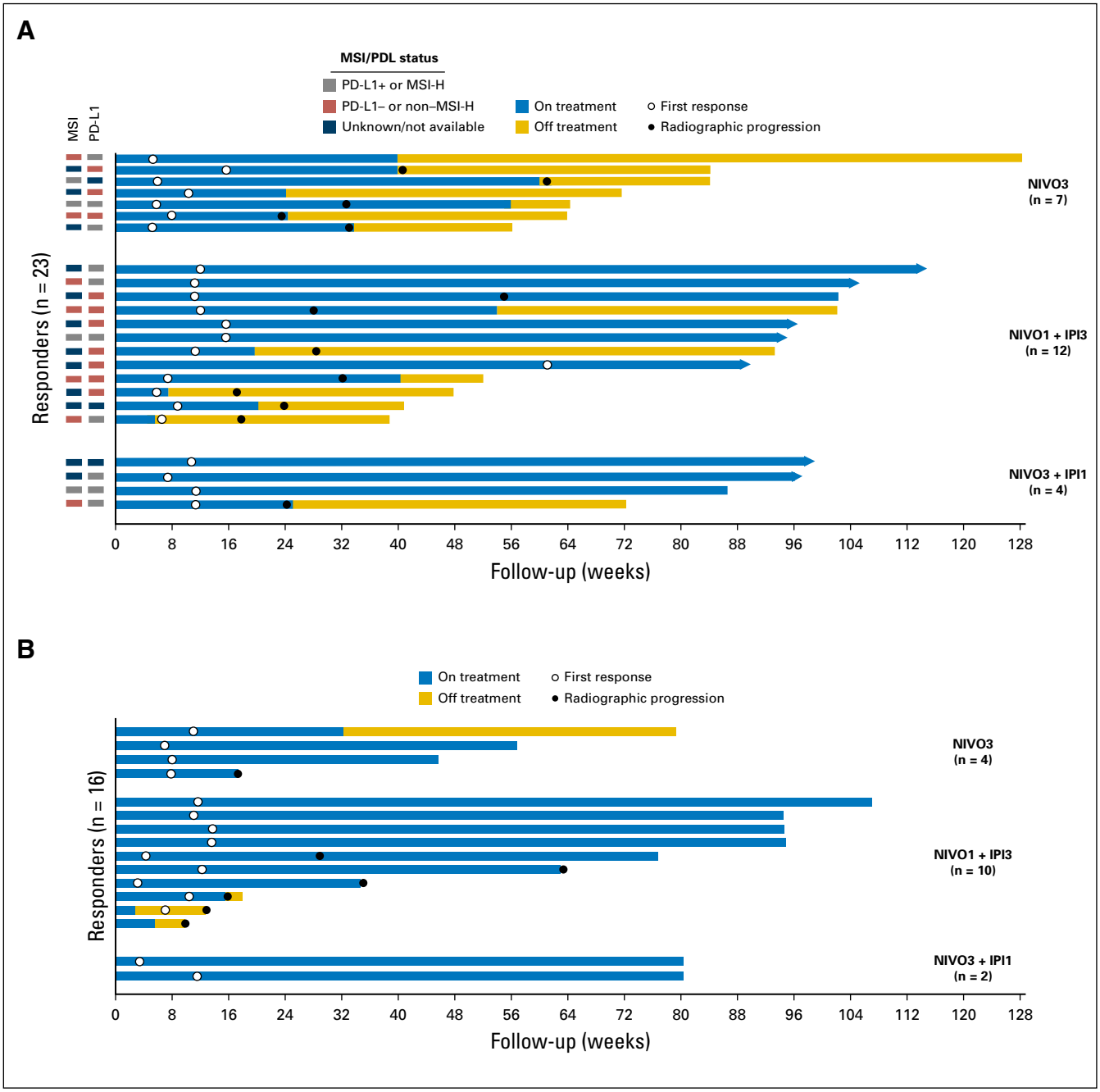

Fig A2. Response characteristics in all responders by (A) investigator assessment and (B) blinded independent central review assessment. IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; MSI, microsatellite instability; MSI-H, microsatellite instability–high; NIVO1, nivolumab 1 mg/kg; NIVO3 nivolumab 3 mg/kg; PDL, programmed death ligand; PD-L1+, programmed death-ligand 1–positive; PD-L1−, programmed death-ligand 1–negative.

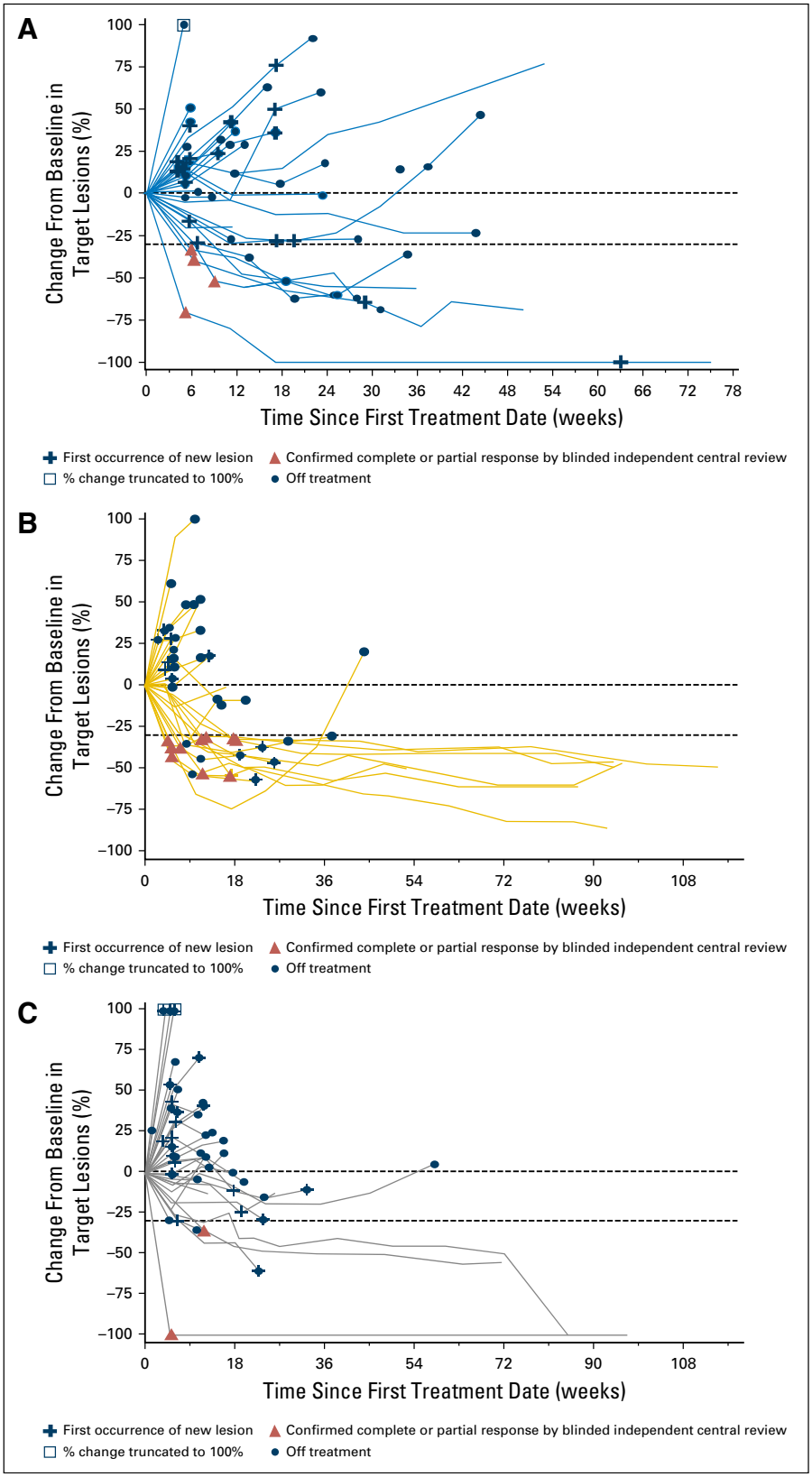

Fig A3. Changes from baseline in target lesions over time per blinded independent central review assessment in patients treated with (A) nivolumab 3 mg/kg monotherapy, (B) nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, or (C) nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. All data are based on the November 2016 database cutoff, except for the blinded independent central review data for the nivolumab 3 mg/kg group, which are based on the March 2016 database cutoff. The + signs indicate the occurrence of a new lesion, closed circles indicate off treatment, open squares represent percentage changes from baseline truncated at 100%, and red triangles indicate investigator-assessed confirmed complete or partial responses.

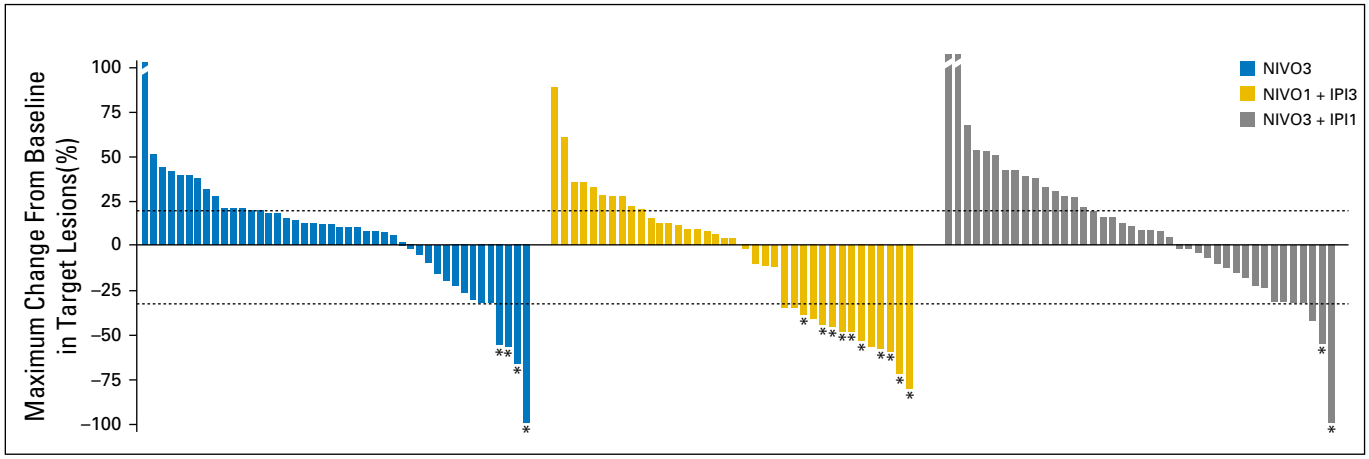

Fig A4. Waterfall plot showing maximum percentage change from baseline in size of tumors in patients treated with nivolumab 3 mg/kg (NIVO3), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3), and NIVO3 plus ipilimumab 1 mg/kg (NIVO3 + IPI1) per blinded independent central review. All data are based on the November 2016 database cutoff, except for the blinded independent central review data for the NIVO3 group, which are based on the March 2016 database cutoff. Patients with 0% best reduction in target lesion are not shown on the plot (NIVO1 + IPI3; n = 1). (*) Indicates patients with a confirmed response. Bars representing patients with a percentage change in tumor burden that exceeded 100% have been truncated.

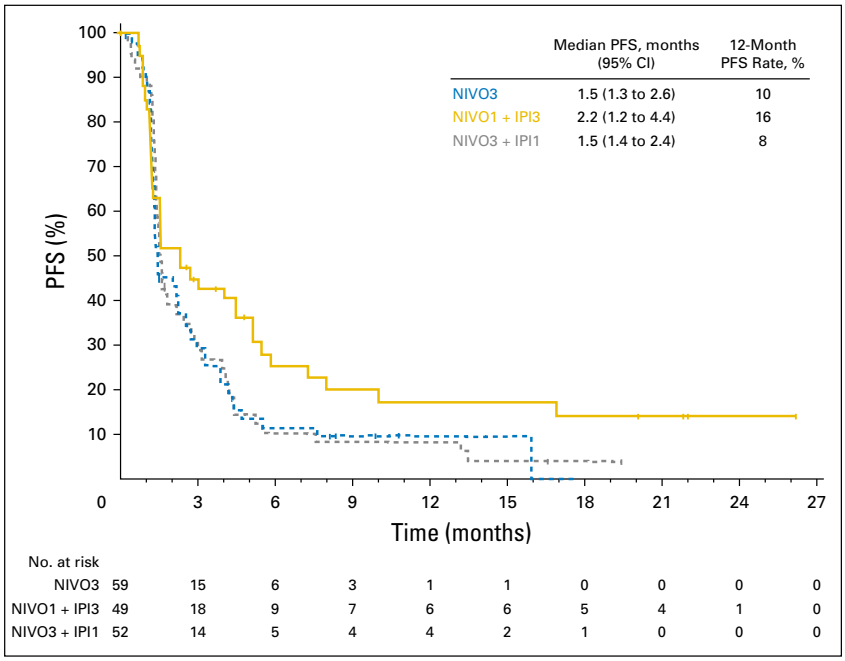

Fig A5. Kaplan-Meier curves of progression-free survival (PFS) in patients treated with nivolumab 3 mg/kg (NIVO3), nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3), and NIVO3 plus ipilimumab 1 mg/kg (NIVO3 + IPI1) per blinded independent central review. All data are based on the November 2016 database cutoff, except for the blinded independent central review data for the NIVO3 group, which are based on the March 2016 database cutoff.

Table A1. Best Overall Response per Blinded Independent Central Review by PD-L1 Status

	NIVO3 (n = 59)		NIVO1 + IPI 3 (n = 49)		NIVO3 + IPI1 (n = 52)	
Response	PD-L1+ (n = 16)	PD-L1− (n = 26)	PD-L1+ (n = 10)	PD-L1− (n = 32)	PD-L1+ (n = 13)	PD-L1− (n = 30)
ORR, No. (%; 95% CI)	2 (13; 2 to 38)	1 (4; 0 to 20)	4 (40; 12 to 74)	6 (19; 7 to 36)	1 (8; 0 to 36)	0 (0; 0 to 12)
Complete response	0	0	1 (10)	0	0	0
Partial response	2 (13)	1 (4)	3 (30)	6 (19)	1 (8)	0
Stable disease	3 (19)	12 (46)	1 (10)	10 (31)	3 (23)	12 (40)
Progressive disease	8 (50)	10 (39)	4 (40)	12 (38)	9 (69)	12 (40)
Unable to determine	3 (19)	3 (12)	1 (10)	4 (13)	0	6 (20)

NOTE. All data are based on the November 2016 database cutoff, except for the blinded independent central review data for the NIVO3 group, which are based on the March 2016 database cutoff. Data presented as No. (%) unless otherwise indicated.

Abbreviations: IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO 1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; ORR, objective response rate; PD-L1+, programmed death-ligand 1–positive; PD-L1−, programmed death ligand 1–negative.