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

Yelena Y. Janjigian, Johanna Bendell, Emiliano Calvo, Joseph W. Kim, Paolo A. Ascierto, Padmanee Sharma, Patrick A. Ott, Katriona Pelhola, Dirk Jaeger, Jeffry Evans, Filippo de Braud, Ian Chau, Christopher T. Harbison, Cecile Dorange, Marina Tschaita, and Dung T. Le

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. For patients with disease progression receiving second-line therapy, the prognosis remains poor; thus, effective treatment options are urgently needed. 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. 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.

On the basis of superior survival demonstrated in the phase III, randomized, placebo-controlled ATTRACTION-2 trial, nivolumab
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.10,11 It also received approval in Canada, European countries, and Australia for patients with chemotherapy-refractory 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 models12,13 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.14-17 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.

**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 + IP13) every 3 weeks for four cycles; or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3 + IP11) 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 $\geq 100$ evaluable tumor cells and $\geq 1\%$ 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 + IP13 (n = 49) | NIVO3 + IP11 (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 (6)          | 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 (37)               | 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 (46)               | 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; IP11, ipilimumab 1 mg/kg; IP13, 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) |
|-------------------|---------------|-----------------------|-----------------------|
| ORR, No. (%) CIs  | Investigator  | BICR                  | Investigator          | BICR                  |
| Complete response | 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)         |
| 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)                |
| Progression       | 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 | 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)      | 7.9 (2.8 to NE)       | NR (2.7 to NE)         | NR (2.5 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.

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**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 antinecancer 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, 1.2 months (95% CI, 1.0 to 1.4 months) in the NIVO1 + IPI3 group, and 1.2 months (95% CI, 1.0 to 1.4 months) in the NIVO3 + IPI1 group (Table 2). 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).
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.
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. 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.

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,2,25 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 tumors15,16 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
| Response/OS | NIVO3 (n = 59) | NIVO1 + IPI3 (n = 49) | NIVO3 + IPI1 (n = 52) |
|------------|----------------|------------------------|------------------------|
| PD-L1+     |                |                        |                        |
| (n = 16)   | 3 (19; 4 to 46) | 3 (12; 2 to 30)        | 2 (29; 4 to 71)        |
| PD-L1−     | (n = 26)       | 2 (29; 4 to 71)        | 2 (11; 1 to 35)        |
| MSI-H      | (n = 7)        | 4 (40; 12 to 74)       | 7 (22; 9 to 40)        |
| Non-MSI-H  | (n = 18)       | 1 (50; 1 to 99)        | 4 (19; 5 to 42)        |
| 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. (%) | 3 (19; 4 to 46) | 3 (12; 2 to 30) | 2 (29; 4 to 71)* |

DCR, No. (%)  | 5 (31) | 11 (42) | 5 (71) | 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 (8 to 47) | 25 (11 to 42) | 50 (11 to 91) | 23 (8 to 43) |

*ORR was 7 and 13 months in the two responders in the NIVO3 group, ≥ 17.4 months in the one responder in the NIVO1 + IPI3 group, and ≥ 13.8 months in the responder in the NIVO3 + IPI1 group. | 1DOR was 3.0 and ≥ 26.5 months for the two responders in the NIVO3 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. | 2Patients with a best objective response of complete response, partial response, or stable disease. | 3Abbreviations: DCR, disease control rate; DOR, duration of response; IP11, 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. |
With emerging data highlighting the importance of MSI as a predictive biomarker of response to immune checkpoint inhibitors,\textsuperscript{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.\textsuperscript{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 vs 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.
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Table 4. Treatment-Related Adverse Events

| TRAE               | NIVO3, No. (%) (n = 59) | NIVO1 + IP1, No. (%) (n = 49) | NIVO3 + IP1, 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 | | | | | |
| AST increased      | 5 (8)     | 2 (3)    | 8 (16)    | 7 (14)   | 5 (10)    | 2 (4)     |
| ALT 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: IP1, ipilimumab 1 mg/kg; IP3, 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 + IP1 group included diarrhea (8%), adrenal insufficiency (8%), fatigue (6%), increased ALT (6%), increased AST (6%), and colitis (6%). In the NIVO3 + IP1 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 + IP1 in the first-line setting (NCT02872116) in patients with esophagogastric cancer.

Authors’ Disclosures of Potential Conflicts of Interest

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

References

1. International Agency for Research on Cancer: Stomach cancer: GLOBOCAN 2012: Estimated incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=stomach
2. International Agency for Research on Cancer: Oesophageal cancer: GLOBOCAN 2012: Estimated incidence, mortality and prevalence. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=oesophagus
3. Anandappa G, Chau I: Emerging novel therapeutic agents in the treatment of patients with gastroesophageal and gastric adenocarcinoma. Hematol Oncol Clin North Am 31:529-544, 2017
4. Wagner AD, Syn NL, Moehler M, et al: Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 8:C0004064, 2017
5. Janjigian YY, Sanchez-Vega F, Jonsson P, et al: Genetic predictors of response to systemic therapy in esophagogastric cancer. Cancer Discov 8:49-58, 2018
6. Cancer Genome Atlas Research Network: Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513:202-209, 2014
7. Cancer Genome Atlas Research Network: Integrated genomic characterization of oesophageal carcinoma. Nature 541:169-175, 2017
8. Zhang M, Dong Y, Liu H, et al: The clinicopathological and prognostic significance of PD-L1 expression in gastric cancer: A meta-analysis of 10 studies with 1,901 patients. Sci Rep 6:37933, 2016
9. Muro K, Chung HC, Shankaran V, et al: Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): A multicentre, open-label, phase 1b trial. Lancet Oncol 17:717-726, 2016
10. Fuchs CS, Doi T, Jiang RW, et al: Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: Phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 4:e1800013, 2018
11. Janjigian Y, Bendell JC, Calvo E, et al: CheckMate 032: Phase II, open-label study of safety and activity of nivolumab (NIVO) alone or with ipilimumab (IP1) in advanced and metastatic (AM) gastric cancer (GC). J Clin Oncol 36:773-779, 2018
12. Kang YK, Boku N, Satoh T, et al: Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 390: 2461-2471, 2017
13. Curran MA, Montalvo W, Ygita H, et al: PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA 107:2275-2280, 2010
14. Selby M, Englishdt J, Lu L-S, et al: Antitumor activity of concurrent blockade of immune checkpoint molecules CTLA-4 and PD-1 in preclinical models. J Clin Oncol 31, 2013 (suppl; abstr 3061)
15. Larkin J, Chiorion-Sileni V, Gonzalez R, et al: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373: 23-34, 2015
16. Antonia SJ, López-Martín JA, Bendell J, et al: Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): A multicentre, open-label, phase 1/2 trial. Lancet Oncol 18:883-895, 2016
17. Overman MJ, Lonardi S, Wong KYM, et al: Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 36:773-779, 2018
18. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:289-247, 2009
19. National Cancer Institute: NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Bethesda, MD, National Cancer Institute, 2009
20. Umar A, Boland CR, Terdiman JP, et al: Revised Bethesda guidelines for hereditary non-polyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 96: 261-268, 2004

Author Contributions

Conception and design: Yelena Y. Janjigian, Marina Tschaika, Dung T. Le
Provision of study materials or patients: Emiliano Calvo, Katriina Peltola, Dung T. Le
Collection and assembly of data: Yelena Y. Janjigian, Johanna Bendell, Emiliano Calvo, Joseph W. Kim, Paolo A. Ascierito, Padmanee Sharma, Patrick A. Ott, Katriina Peltola, Dirk Jaeger, Jeffry Evans, Filippo de Braud, Ian Chau, Dung T. Le
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors
21. Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1-10, 1989
22. Wolchok JD, Kluger H, Callahan MK, et al: Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369:122-133, 2013
23. Hammers HJ, Plimack ER, Infante JR, et al: Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The CheckMate 016 Study. J Clin Oncol 35:3851-3858, 2017
24. Hellmann MD, Rizvi NA, Goldman JW, et al: Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study. Lancet Oncol 18:31-41, 2017
25. Muro K, Fuchs CS, Jang RW, et al: KEYNOTE-059 cohort 1: Pembrolizumab (Pembro) monotherapy in previously treated advanced gastric or gastro-esophageal junction (G/GEJ) cancer in patients (Pts) with PD-L1+ tumors: Asian subgroup analysis. J Clin Oncol 36, 2018 (suppl, abstr 723)
26. Opdivo (nivolumab) US prescribing information: Princeton, NJ, Bristol-Myers Squibb, 2018
27. Le DT, Durham JN, Smith KN, et al: Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357:409-413, 2017
28. Le DT, Uram JN, Wang H, et al: PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509-2520, 2015

Affiliations

Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; Johanna Bendell, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; Emiliano Calvo, START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; Joseph W. Kim, Yale Cancer Center, New Haven, CT; Paolo A. Ascierto, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples; Filippo de Braud, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; Padmance Sharma, The University of Texas MD Anderson Cancer Center, Houston, TX; Patrick A. Ott, Dana-Farber Cancer Institute, Boston, MA; Katrinya Peltola, Docrates Cancer Center, Helsinki, Finland; Dirk Jaeger, University Hospital Heidelberg, Heidelberg, Germany; Jeffry Evans, University of Glasgow, Glasgow; Ian Chau, Royal Marsden Hospital, London and Surrey, United Kingdom; Christopher T. Harbison, Cecile Dorange, Marina Tschaika, Bristol-Myers Squibb, Princeton, NJ; and Dung T. Le, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD.

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Yelena Y. Janjigian
Consulting or Advisory Role: Eli Lilly, Bristol-Myers Squibb, Merck, Roche/Genentech
Research Funding: Boehringer Ingelheim, Merck, Bristol-Myers Squibb

Johanna Bendell
Research Funding: Eli Lilly (Inst), Genentech/Roche (Inst), Incyte (Inst), Gilead Sciences (Inst), Bristol-Myers Squibb (Inst), Leap Therapeutics (Inst), AstraZeneca/MedImmune (Inst), Boston Biomedical (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Array BioPharma (Inst), Taiho Pharmaceutical (Inst), Celgene (Inst), OncoMed (Inst), Oncogenex (Inst), Daiichi Sankyo (Inst), Bayer (Inst), Apexigen (Inst), Kolltan Pharmaceuticals (Inst), SynDevRx (Inst), Merck (Inst), Macrogenics (Inst), Daiichi Sankyo (Inst), Bayer (Inst), Apexigen (Inst), Kolltan Pharmaceuticals (Inst), SynDevRx (Inst), Merck (Inst), Macrogenics (Inst), Five Prime Therapeutics (Inst), EMD Serono (Inst), TG Therapeutics (Inst), Boehringer Ingelheim (Inst), Forty Seven (Inst), Stem CentRx (Inst), Onyx (Inst), Sanofi (Inst), Takeda (Inst), Abbott/AbbVie (Inst), Eisai (Inst), Celldex (Inst), Agios (Inst), ARMO BioSciences (Inst), CytomX Therapeutics (Inst), Nektar (Inst), Ipsen (Inst), Merrimack (Inst), Novartis (Inst), Tarveda (Inst), Tyrogenex (Inst), Marshall Edwards (Inst), Pieris Pharmaceuticals (Inst), Mersana (Inst), Calithera Biosciences (Inst), Blueprint Medicines (Inst), Gritstone Oncology (Inst), Evelo Therapeutics (Inst), FORMA Therapeutics (Inst), Merus (Inst), Jacobio (Inst), eFFECTOR Therapeutics (Inst)

Emiliano Calvo
Employment: START, HM Hospitales Group
Leadership: START
Stock and Other Ownership Interests: START, Oncoart Associated, International Cancer Consultants
Honorary: HM Hospitales Group
Consulting or Advisory Role: Novartis, Janssen-Cilag, PsiOxus Therapeutics, Seattle Genetics, EUSA Pharma, Abbvie, Celgene, AstraZeneca, Guidepoint Global, GLG, SERVIER, Amcure, Roche/Genentech, Nanobiotix, Pfizer
Speakers’ Bureau: Novartis
Research Funding: Novartis, AstraZeneca, Beigene, START
Travel, Accommodations, Expenses: Roche/Genentech
Other Relationship: President and Founder of Foundation INTHEOS (Investigational Therapeutics in Oncological Sciences)

Joseph W. Kim
Consulting or Advisory Role: Voluntis, TRM Oncology, AstraZeneca/MedImmune, Clovis Oncology
Research Funding: Immune Design

Paulo A. Asciento
Consulting or Advisory Role: Bristol-Myers Squibb, Roche/Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array BioPharma, Merck Serono, Pierre Fabre, Newlink Genetics, Genmab, Incyte, MedImmune, AstraZeneca, Syndax
Research Funding: Bristol-Myers Squibb (Inst), Roche/Genentech (Inst), Array BioPharma (Inst)

Padmanee Sharma
Stock or Other Ownership: Jounce Therapeutics, Neon Therapeutics, Jounce Therapeutics (I), Neon Therapeutics (I), Constellation Pharmaceuticals, Oncolytics, BioAtla, Forty Seven, Apricity Therapeutics, Polaris, Markers Therapeutics, Codik Biosciences, BioAtla (I), Forty Seven (I), Apricity (I), Polaris (I), Marker Therapeutics (I), Codik Biosciences (I)
Consulting or Advisory Role: Constellation Pharmaceuticals, Jounce Therapeutics, Kite Pharma, Neon Therapeutics, BioAtla, Pieris Pharmaceuticals, Oncolytics Biotech, Merck, BioMx, Forty Seven, Polaris, Apricity Therapeutics, Marker Therapeutics, Codik Biosciences, Jounce Therapeutics (I), Kite Pharma (I), Neon Therapeutics (I), Amgen, Apricity Therapeutics (I), Polaris (I), Marker Therapeutics (I), Codik Biosciences (I)

Patrick A. Ott
Consulting or Advisory Role: Bristol-Myers Squibb, CytomX Therapeutics, Celldex, Genentech, Neon Therapeutics, Novartis, Pfizer, Merck
Research Funding: Bristol-Myers Squibb (Inst), Merck (Inst), AstraZeneca/MedImmune (Inst), Celldex (Inst), ARMO BioSciences (Inst)

Katriina Peltola
Employment: Orion Pharma
Stock or Other Ownership: Faron Pharmaceuticals
Consulting or Advisory Role: MSD Oncology, Eli Lilly, Orion Pharma, Pfizer, Bristol-Myers Squibb, Novartis, Roche, Ipsen
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Dirk Jaeger
Consulting or Advisory Role: Bristol-Myers Squibb, Roche, Genentech, Bayer, CureVac, Novartis, AmeGen

Jeffry Evans
Consulting or Advisory Role: Bristol-Myers Squibb (Inst), Karus Therapeutics (Inst), Eisai (Inst), Immunova (Inst)
Speakers’ Bureau: Bristol-Myers Squibb, Eisai
Research Funding: AstraZeneca (Inst), Celgene (Inst), Basilea (Inst), Eisai (Inst), Merck (Inst), Daiichi Sankyo (Inst), Verastem (Inst), Immunocore (Inst), TC Biopharm (Inst), Roche/Genentech (Inst), GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Eisai

Filippo de Braud
Consulting or Advisory Role: Ignuya, Pfizer, Amgen, Novartis, Daiichi Sankyo, Bristol-Myers Squibb, Servier, Celgene, Tiziana Life Sciences, Dompe
Speakers’ Bureau: MSD, Novartis, Bristol-Myers Squibb, Roche, Menarini, Pfizer, Servier
Research Funding: Novartis (Inst), Ignuya (Inst), MedImmune (Inst), Nektar, Bristol-Myers Squibb (Inst), Bayer (Inst), Eli Lilly (Inst)
Travel, Accommodations, Expenses: Roche, Amgen, Bristol-Myers Squibb, Daiichi Sankyo
Ian Chau  
**Honoraria:** Taiho Pharmaceutical, Pfizer, Eli Lilly, Amgen, Gilead Sciences  
**Consulting or Advisory Role:** Sanofi, Eli Lilly, Bristol-Myers Squibb, MSD Oncology, Bayer, Roche/Genentech, Five Prime Therapeutics, Merck Serono  
**Research Funding:** Janssen-Cilag (Inst), Sanofi (Inst), Merck Serono (Inst), Eli Lilly (Inst)  
**Travel, Accommodations, Expenses:** MSD, Merck Serono, Sanofi, Eli Lilly, Bristol-Myers Squibb  

Christopher T. Harbison  
**Employment:** Bristol-Myers Squibb  
**Stock or Other Ownership:** Bristol-Myers Squibb  

Cecile Dorange  
**Employment:** Bristol-Myers Squibb  
**Stock or Other Ownership:** Bristol-Myers Squibb  

Marina Tschaika  
**Employment:** Bristol-Myers Squibb  
**Stock or Other Ownership:** Bristol-Myers Squibb  

Dung T. Le  
**Honoraria:** Merck  
**Consulting or Advisory Role:** Merck, Bristol-Myers Squibb  
**Research Funding:** Bristol-Myers Squibb  
**Patents, Royalties, Other Intellectual Property:** Checkpoint blockade and microsatellite instability
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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, 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

| Response          | NIVO3 (n = 59) | NIVO1 + IPI 3 (n = 49) | NIVO3 + IPI1 (n = 52) |
|-------------------|----------------|------------------------|------------------------|
|                   | 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. (%)      | 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.