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ORIGINAL REPORT

Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials

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ABSTRACT

Purpose
Approximately 40% of patients with advanced melanoma who received nivolumab combined with ipilimumab in clinical trials discontinued treatment because of adverse events (AEs). We conducted a retrospective analysis to assess the efficacy and safety of nivolumab plus ipilimumab in patients who discontinued treatment because of AEs.

Methods
Data were pooled from phase II and III trials of patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, every 3 weeks for four doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks (N = 409). Efficacy was assessed in all randomly assigned patients who discontinued because of AEs during the induction phase (n = 96) and in those who did not discontinue because of AEs (n = 233). Safety was assessed in treated patients who discontinued because of AEs (n = 176) at any time and in those who did not discontinue because of AEs (n = 231).

Results
At a minimum follow-up of 18 months, median progression-free survival was 8.4 months for patients who discontinued treatment because of AEs during the induction phase and 10.8 months for patients who did not discontinue because of AEs (P = .97). Median overall survival had not been reached in either group (P = .23). The objective response rate was 58.3% for patients who discontinued because of AEs during the induction phase and 50.2% for patients who did not discontinue. The vast majority of grade 3 or 4 AEs occurred during the induction phase, with most resolving after appropriate management.

Conclusion
Efficacy outcomes seemed similar between patients who discontinued nivolumab plus ipilimumab treatment because of AEs during the induction phase and those who did not discontinue because of AEs. Therefore, even after discontinuation, many patients may continue to derive benefit from combination therapy.

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INTRODUCTION

The immune checkpoint inhibitors ipilimumab (anti-cytotoxic T-cell lymphocyte antigen-4) and nivolumab (anti-programmed death-1 [PD-1]), alone and in combination, and pembrolizumab (anti–PD-1) monotherapy are approved for the treatment of advanced melanoma. Pembrolizumab has shown improved overall survival (OS) compared with ipilimumab monotherapy,[1] and the combination of nivolumab and ipilimumab has demonstrated improved objective response rate (ORR) and progression-free survival (PFS) compared with ipilimumab alone in patients with advanced melanoma in both the phase II CheckMate 069 (Study of Nivolumab Plus Ipilimumab Compared With Ipilimumab Alone in the Treatment of Previously Untreated, Unresectable, or Metastatic Melanoma; ClinicalTrials.gov identifier: NCT01927419) and the phase III CheckMate 067 (Phase 3 Study of Nivolumab or Nivolumab Plus

ASSOCIATED CONTENT

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Data Supplement

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Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma; ClinicalTrials.gov identifier: NCT01844505) trials.[2-5] Recently, nivolumab plus ipilimumab and nivolumab alone have demonstrated an improvement in OS compared with ipilimumab alone in CheckMate 067.[6]

Despite the high rate of efficacy with nivolumab and ipilimumab combination therapy, there are high rates of adverse events (AEs). Grade 3 and 4 treatment-related AEs were experienced by 54% of patients who received combination therapy in CheckMate 069, and more than one third of patients randomly assigned to the combination group discontinued treatment because of AEs.[5] Of the patients who received combination therapy in CheckMate 067, 55% reported grade 3 or 4 treatment-related AEs.[3] Forty-seven percent of those receiving combination therapy received more than four doses of nivolumab and entered the nivolumab-alone maintenance phase; 53% received between one and four doses of the combination during the nivolumab plus ipilimumab induction phase.

When using nivolumab plus ipilimumab combination therapy, what clinicians can expect when they need to discontinue treatment because of AEs is one of the most important questions in the treatment of patients. Although prior data have shown encouraging efficacy among patients who discontinued immunotherapy at any time,[4-7] no data are available on efficacy outcomes among patients who discontinued treatment early on (ie, before completion of the induction phase). Furthermore, whether severe immune-mediated AEs are a predictive marker for efficacy is still an unanswered question.[8] In this analysis, we evaluated efficacy outcomes in patients who discontinued the combination of nivolumab and ipilimumab because of treatment-related AEs during the induction phase of the CheckMate 069 and 067 studies; in addition, we characterized the safety profile of patients who discontinued treatment because of AEs.

METHODS

Study Design and Patients

To evaluate the efficacy and safety of nivolumab combined with ipilimumab in patients with advanced melanoma who discontinued treatment because of AEs, data were pooled from the CheckMate 069 phase II trial[2] and the CheckMate 067 phase III trial[3] (Fig 1). In both multicenter, double-blinded, randomized trials, treatment-naive patients with unresectable stage III or stage IV melanoma received at least one dose of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses (induction), and then nivolumab alone at 3 mg/kg every 2 weeks (nivolumab maintenance). Additional eligibility criteria have been described previously.[2,3] Patients were treated until progression or unacceptable toxicity. Dosing delays were permitted to enable the management of drug-related AEs, and dosing was allowed to resume once the AE resolved to either baseline or grade 1 severity. No dose modifications were permitted. Patients who discontinued treatment during the induction phase were not allowed to continue with nivolumab maintenance. The protocol-specified reasons for discontinuation of treatment in both trials are provided in the Data Supplement. Each study protocol was approved by the institutional review board at each participating study site, and the studies were conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. All the patients (or their legal representatives) provided written informed consent before enrollment.

Efficacy and Safety Assessments

Patients were assessed for efficacy if they had received at least one dose each of nivolumab and ipilimumab as combination therapy and discontinued treatment because of AEs during the induction phase of treatment (n = 96) or did not discontinue treatment because of AEs (n = 233; Fig 1). For patients who discontinued before receiving nivolumab monotherapy, the induction phase was defined as the time between the first and last doses of combination treatment. Using Response Evaluation Criteria in Solid Tumors, version 1.1,[9] tumor response was assessed at baseline and at 12 weeks after the patient was randomly assigned, then every 6 weeks for the first 12 months, and then every 12 weeks until disease progression, withdrawal of consent, or study discontinuation. The efficacy outcomes assessed were PFS, OS, ORR, best overall response, time to response, duration of response, and reduction in tumor burden. Minimum follow-up was 18 months.

Patients were assessed for safety if they had received at least one dose each of nivolumab and ipilimumab as combination therapy. All patients had safety data collected continuously during the treatment period and for a minimum of 100 days from the last dose of study therapy. Two patient cohorts were included in the safety analyses: patients who discontinued and had a treatment-related AE any time (within either the induction period or the nivolumab maintenance period; n = 176) and patients who did not discontinue treatment because of AEs (n = 231; Fig 1). Safety analyses, including laboratory assessments, were conducted 14 days before the initiation of treatment and within 72 hours before the next cycle of treatment of up to seven cycles. Safety was then formally assessed at every subsequent dose.

Safety evaluations included the assessment of treatment-related AEs, which were assessed and graded according to the National Cancer Institute

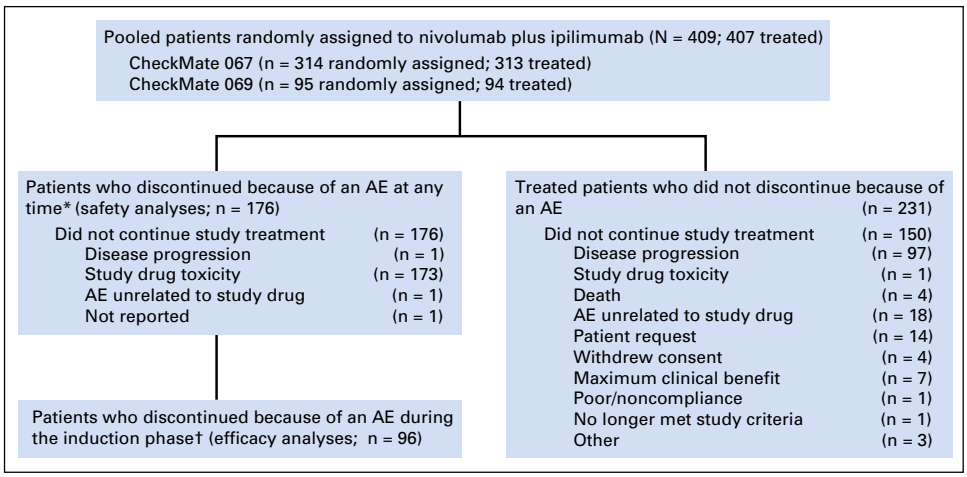

Fig 1. Patient populations included in this pooled analysis. (*) Includes patients who discontinued and had a treatment-related adverse event (AE) at any time. (†) For patients who had taken at least one dose of nivolumab monotherapy, the induction phase was defined as the time between the first dose of nivolumab plus ipilimumab up to a day before the first nivolumab monotherapy dose. For patients who discontinued before receiving nivolumab monotherapy, the induction phase was defined as the time between the first and the last dose of combination treatment.

Common Terminology Criteria for Adverse Events, version 4.0.[10] An AE was deemed to be on-study if it occurred within 30 days after the last dose of study treatment. Additional safety evaluations included treatment-related select AEs (ie, those with a potential immunologic basis); time to onset and resolution of select AEs, defined as complete resolution or improvement to baseline grade; and serious AEs (SAEs), defined as those AEs that may lead to or result in death, are or may become life threatening, may result in or lead to in-patient hospitalization or prolongation of hospitalization, or may result in or lead to significant disability or incapacity.

Statistical Analyses

Kaplan-Meier estimates of PFS, OS, and duration of response with two-sided 95% CIs were calculated using the Brookmeyer and Crowley method, with hazard ratios estimated using an unstratified Cox proportional hazards model; *P* values were assessed using an unstratified log-rank test. The proportion of patients with a complete or partial response (ORR) was calculated using the Clopper and Pearson method; two-sided *P* values were calculated using the Cochran-Mantel-Haenszel test.

RESULTS

Patient Characteristics and Treatment

A total of 409 patients were randomly assigned to nivolumab plus ipilimumab in the CheckMate 069 and CheckMate 067 studies. All randomly assigned patients were included in the efficacy analyses. Two patients were not treated and were therefore excluded from the safety analyses (Fig 1). Among the 407 patients who received combination treatment, 176 (43%) discontinued treatment because of AEs, of whom 96 (24%) discontinued because of AEs during the induction phase (Fig 1). The remaining 231 patients did not discontinue treatment because of AEs; this group included those who discontinued treatment for other reasons (eg, 97 [42%] because of disease progression). The baseline characteristics were generally well balanced between the group of patients who discontinued during the induction phase and those who did not discontinue because of AEs; however, significantly fewer patients had M1c disease and elevated lactate dehydrogenase among those who discontinued because of AEs at any time compared with those who did not discontinue because of AEs (Data Supplement).

Patients who discontinued treatment because of AEs at any time received a median of three doses of nivolumab (range, one to 45) and ipilimumab (range, one to four). In patients who discontinued during the induction phase, the median number of doses of nivolumab and ipilimumab was three each (range, one to four). Patients who did not discontinue treatment because of AEs received a median of 14 doses of nivolumab (range, one to 58), and four doses of ipilimumab (range, one to four). The median duration of treatment was 1.5 months (95% CI, 1.4 to 2.1 months), 1.4 months (95% CI, 1.2 to 1.6 months), and 9.4 months (95% CI, 5.1 to 14.8 months) in patients who discontinued because of AEs at any time, who discontinued during the induction phase, and who did not discontinue because of AEs, respectively.

Subsequent systemic treatments were received by 61 patients (35%) who discontinued treatment because of AEs at any time, 37 patients (39%) who discontinued during the induction phase, and 55 patients (24%) who did not discontinue because of AEs (Data Supplement). The median time to subsequent systemic therapy was not reached in patients who discontinued because of AEs at any time or in patients who did not discontinue treatment because of AEs, with 115 of 176 patients (65%) and 178 of 233 patients (76%) free of systemic treatments at 12 months, respectively. The median time to subsequent systemic therapy was 25.3 months for patients who discontinued because of AEs during the induction phase, and 59 of 96 (61%) were free of systemic treatments at 12 months.

Efficacy

Investigator-assessed ORR was 58.3% (95%, CI 47.8% to 68.3%) for patients who discontinued during the induction phase and 50.2% (95% CI, 43.6% to 56.8%) for patients who did not discontinue because of AEs (*P* = .180; Table 1). The proportion of patients with a complete response and the time to response were similar across the two subgroups, and the median duration of response was not reached in either group (Table 1; Fig 2). The proportion of patients with an ongoing response was 64% for patients who discontinued treatment because of AEs during the induction phase and 80% for patients who did not discontinue because of AEs (Table 1). The median reduction in tumor burden was −51.4% for both groups (Data Supplement).

The median PFS for patients who discontinued treatment during the induction phase because of AEs was 8.4 months (95% CI, 5.8 to 16.7 months) and 10.8 months (95% CI, 5.9 to 23.0 months) for patients who did not discontinue because of AEs (hazard ratio, 0.99; 95% CI, 0.72 to 1.37; *P* = .966; Fig 3A). PFS rates at 18 months were 38% and 49% for patients who discontinued because of AEs during the induction phase and patients who did not discontinue because of AEs, respectively. Similarly, there was no difference in OS between these groups (Fig 3B), with the medians not reached in either group (hazard ratio, 0.79; 95% CI, 0.54 to 1.17; *P* = .2344). OS rates at 18 months were 67% for patients who discontinued because of AEs during the induction phase and 62% for those who did not discontinue because of AEs.

Table 1. Response to Treatment

Response	Patients Who Discontinued Because of AEs During Induction Phase (n = 96)	Patients Who Did Not Discontinue Because of AEs (n = 233)
Objective response		
No. (%)	56 (58.3)	117 (50.2)
95% CI	47.8 to 68.3	43.6 to 56.8
Best overall response, No. (%)		
Complete response	11 (11.5)	28 (12.0)
Partial response	45 (46.9)	89 (38.2)
Stable disease	18 (18.8)	25 (10.7)
Progressive disease	19 (19.8)	63 (27.0)
Unable to determine*	3 (3.1)	28 (12.0)
Median time to response, months (range)	2.7 (1.9-10.3)	2.8 (1.4-17.1)
Median duration of response, months (95% CI)	NR (8.6 to NR)	NR (NR to NR)
Ongoing responders, No. of No. (%)	36 of 56 (64.3)	94 of 117 (80.3)

Abbreviations: AE, adverse event; NR, not reached.
*Includes never treated, death before disease assessment, early discontinuation because of adverse events, and other.

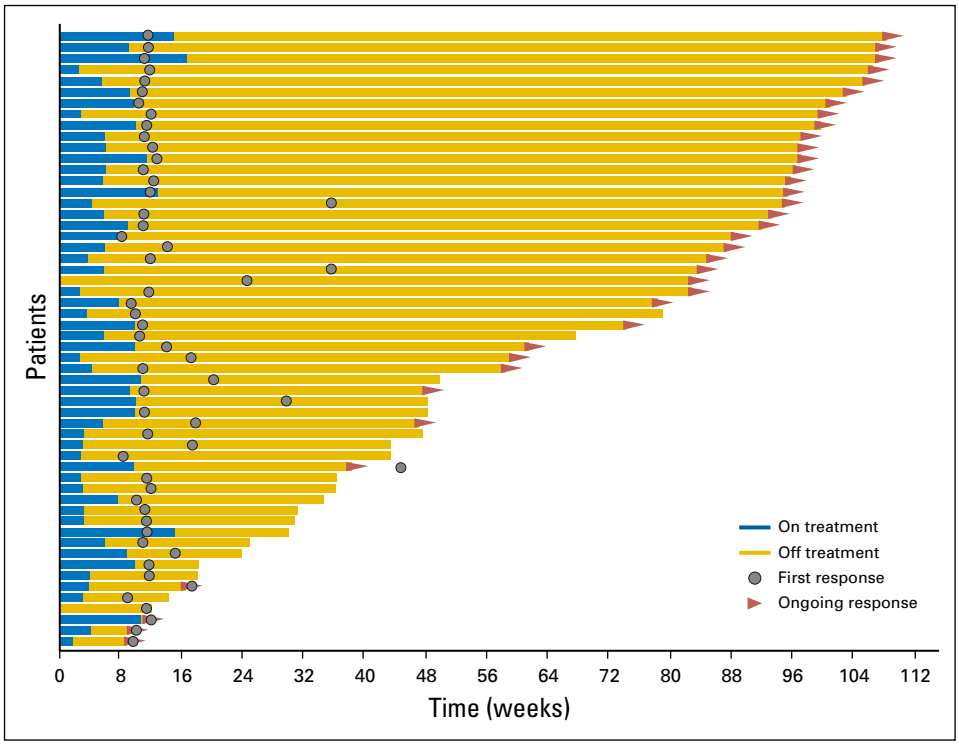

Fig 2. Time to and duration of response in patients who discontinued treatment because of adverse events during the induction phase of treatment.

Safety

Overall, 156 of 407 treated patients (38%) discontinued treatment because of any-grade treatment-related AE, the vast majority of which were grade 3 or 4 AEs (Table 2). Colitis was the most frequently reported treatment-related AE, which led to discontinuation in 40 patients (10%), followed by elevated alanine aminotransferase (5%) and aspartate aminotransferase (4%).

Treatment-related SAEs led to hospitalization in 125 (71%) of the 176 patients who discontinued because of an AE at any time and 131 (57%) of the 231 patients who did not discontinue because of an AE. Colitis was the main SAE leading to hospitalization; it occurred in 37 (21.0%) of the patients who discontinued because of AEs and in six (2.6%) of the patients who did not discontinue because of AEs.

Treatment-related select AEs were pooled and assessed by organ category. The most frequently observed grade 3 or 4 treatment-related select AEs for patients who discontinued because of AEs at any time were GI, and included diarrhea (20%) and colitis (20%; Data Supplement). For patients who did not discontinue because of AEs, grade 3 or 4 hepatic AEs were most frequently observed (10%). Fifty percent of patients who discontinued because of an AE at any time and 19% of patients who did not discontinue because of AEs experienced AEs in two or more select organ categories (Data Supplement). Less than 2% of patients in either subgroup experienced AEs in three or more organ categories.

In both treatment subgroups, the majority of grade 3 and 4 select AEs seemed to occur during the induction phase, with skin AEs typically developing the fastest (2 to 3 weeks), followed by GI AEs (6 to 11 weeks), hepatic AEs (8 to 10 weeks), and endocrine AEs (11 to 12 weeks; Fig 4). The vast majority of grade 3 and 4 select AEs resolved after the use of established safety algorithms, typically within 3 to 5 weeks, with the exception of endocrine AEs (Table 3). Most endocrine AEs did not resolve, because patients requiring long-term hormone and/or corticosteroid replacement therapy were not considered to have resolved by definition.

Systemic corticosteroids were the most common immunosuppressive agents used for AE management; they were used in 91% of patients who discontinued because of an AE and in 55% of patients who did not. Infliximab was used in 10% compared with 1% of patients, likely as a result of the higher number of patients with colitis among those who discontinued because of an AE. Administration of infliximab on tumor kinetics was assessed in the subgroup of patients who discontinued because of colitis at any time and who were treated with infliximab (Data Supplement). Treatment with infliximab did not seem to affect the development of a response or the durability of response; however, a few patients who received infliximab did seem to progress after an initial response.

Overall, as reported previously, three patients died as a result of treatment-related AEs.[2,3,5] One patient with a history of cardiac issues died 29 days after one dose of treatment as a result of ventricular arrhythmia; a second patient who received three doses of treatment died 69 days after the last treatment as a result of pneumonitis and iatrogenic pneumothorax; and a third patient died 86 days after the last treatment, with the cause of death listed as panhypopituitarism with cortisol deficiency and adrenal crisis.

DISCUSSION

In this post hoc, retrospective analysis of data from patients with advanced melanoma who received nivolumab plus ipilimumab combination therapy, most who discontinued because of AEs did so during the induction phase, before receiving all four doses of the combination. PFS, OS, and ORR seemed to be similar in patients

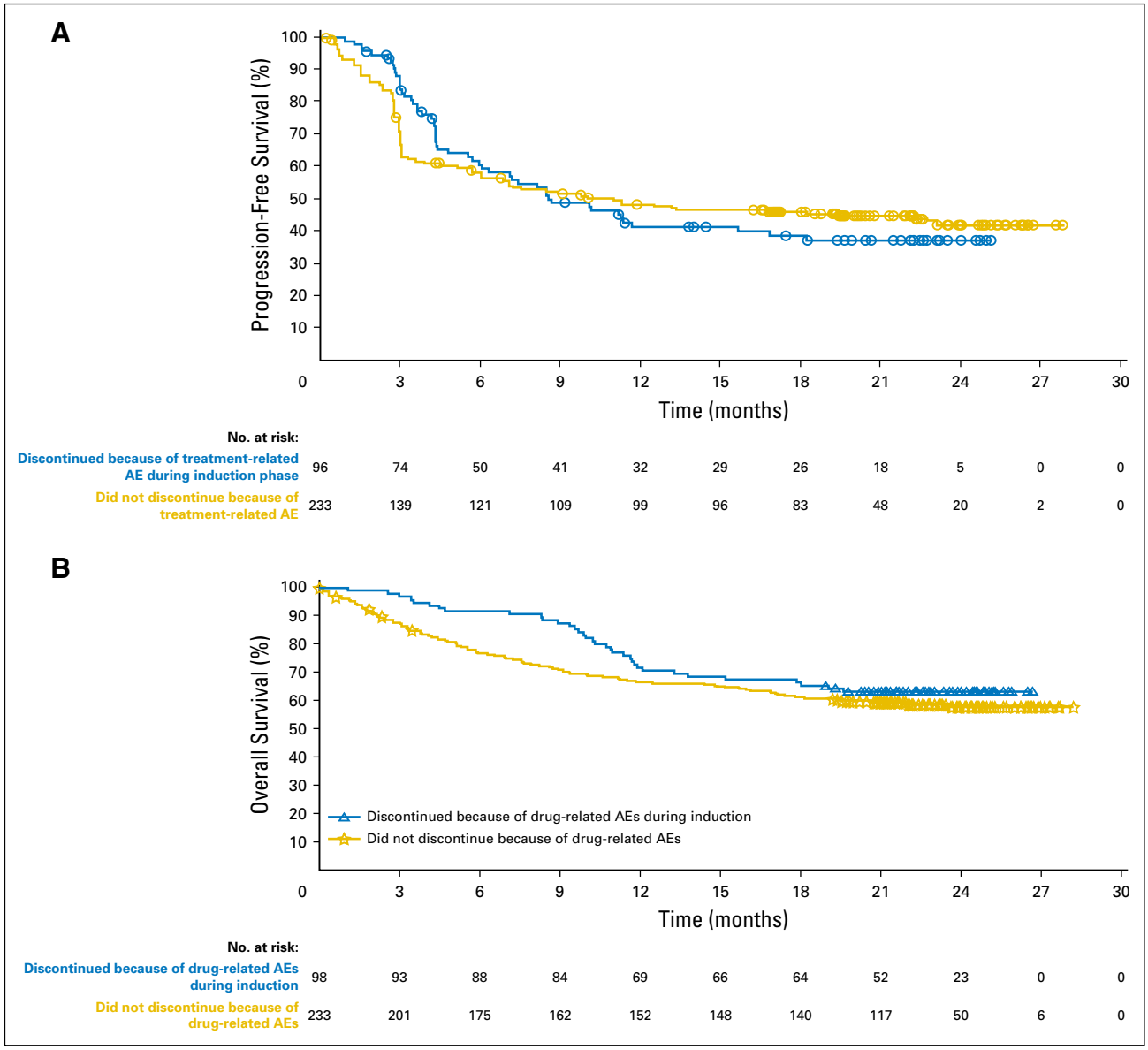

Fig 3. (A) Progression-free survival and (B) overall survival for patients who discontinued treatment because of adverse events (AEs) during the induction phase and for patients who did not discontinue because of AEs. Differences between the two subgroups were not statistically significant for either progression-free survival or overall survival.

who discontinued treatment because of AEs during the induction phase and in those who did not discontinue because of AEs. The median duration of response has not yet been reached in either group. The median time to subsequent systemic therapy was not reached for those patients who discontinued treatment because of AEs at any time or for those patients who did not discontinue because of AEs, and was 25 months in patients who discontinued because of AEs during the induction phase.

Two general hypotheses were considered before this analysis. First, the group who did not discontinue because of AEs would have improved efficacy because they generally were receiving treatment for a longer period than were those who did discontinue because of AEs during the induction phase. The second hypothesis was that high immune-mediated AEs in patients who discontinued because of AEs could be a signal that an immune reaction had been activated. Our results support the second hypothesis, because the group who discontinued because of AEs during the induction phase had efficacy outcomes similar to those who did not discontinue because of AEs.

Caution should be taken in the interpretation of these findings, given that this analysis is retrospective. Notably, the proportion of patients with M1c disease and elevated lactate dehydrogenase was lower in those patients who discontinued because of AEs compared with those who did not discontinue because of AEs at any time, which suggests that patients who did not discontinue because of AEs may have had a worse prognosis. In addition, interpretation of these data is complex because it is difficult to assess the respective role of two variables that may

Table 2. Treatment-Related Adverse Events That Led to Discontinuation in ≥ 1% of Patients

Treatment-Related AE	Treated Patients (N = 407)	
	Any Grade	Grade 3 or 4
Patients with any event	156 (38.3)	124 (30.5)
GI disorders	72 (17.7)	60 (14.7)
Colitis	40 (9.8)	32 (7.9)
Diarrhea	30 (7.4)	25 (6.1)
Autoimmune colitis	5 (1.2)	4 (1.0)
Investigations	37 (9.1)	33 (8.1)
Increased alanine aminotransferase	20 (4.9)	18 (4.4)
Increased aspartate aminotransferase	18 (4.4)	15 (3.7)
Increased transaminases	7 (1.7)	6 (1.5)
Increased lipase	4 (1.0)	3 (0.7)
Hepatobiliary disorders	13 (3.2)	10 (2.5)
Hepatotoxicity	6 (1.5)	4 (1.0)
Hepatitis	4 (1.0)	4 (1.0)
Respiratory, thoracic, and mediastinal disorders	13 (3.2)	7 (1.7)
Pneumonitis	10 (2.5)	4 (1.0)
Endocrine disorders	10 (2.5)	3 (0.7)
Hypothyroidism	4 (1.0)	0 (0.0)
Other disorders		
Nervous system	9 (2.2)	8 (2.0)
Renal and urinary	6 (1.5)	4 (1.0)
Musculoskeletal and connective tissue	5 (1.2)	1 (0.2)
Metabolism and nutrition	4 (1.0)	3 (0.7)
Skin and subcutaneous tissue	4 (1.0)	3 (0.7)

NOTE. Table includes only events reported between the first dose and 30 days after the last dose of study therapy. Data are presented as No. (%).

influence efficacy: duration of treatment, and immune-related AEs as a marker of a strong immune reaction. It has been suggested that the development of select treatment-related AEs may be associated with response; however, not all evidence supports this.[8] Finally, there was a relatively short follow-up period in the current analysis; a longer follow-up of the patients (particularly for PFS and OS) will be required to determine if continued treatment among those who did not discontinue because of AEs results in better outcomes compared with those who discontinued because of AEs.

Patients who discontinued nivolumab plus ipilimumab because of AEs had a pattern of select treatment-related AEs similar to that of patients who did not discontinue because of AEs, albeit with a greater frequency. It also seems that patients who discontinued because of AEs had select treatment-related AEs occur earlier (by a few weeks) compared with patients who did not discontinue because of AEs. Importantly, the wide range of onset suggests that physicians and patients need to remain vigilant over time because some AEs can occur late. Most grade 3 and 4 select treatment-related AEs in both patient groups resolved within a few weeks with appropriate temporary immunosuppression. The lack of an obvious effect of infliximab on response in our study is consistent with the results of a recent pooled analysis of data from the CheckMate 069 and CheckMate 067 trials.[11] In that analysis, OS outcomes were similar between patients with immune-related GI AEs who received corticosteroids, with or without infliximab, and those who had immune-related GI AEs but did not receive immunosuppressive agents.[11]

New, prospective trials are required to better address the role of anti–PD-1 maintenance therapy after induction with nivolumab plus ipilimumab. It is possible that patients who discontinue combination therapy because of AEs may still benefit from additional treatment with anti–PD-1 monotherapy, provided there is complete resolution of their AEs. However, recurrence of an AE is an important consideration in the continued treatment of these patients.[12] More evidence is needed to determine whether patients should discontinue therapy after they have demonstrated a clinical response and to determine the optimal duration of treatment required to reach a maximum response. In addition, there is interest in understanding the predictive capacity of onset of AEs on efficacy outcomes. The randomized discontinuation trial design has been implemented successfully to evaluate the efficacy of treatments for a variety of diseases.[13-15] This trial design may help address unanswered questions in future trials of combination therapy in advanced melanoma.

In conclusion, most patients who discontinued the combination of nivolumab and ipilimumab did so before receiving all four

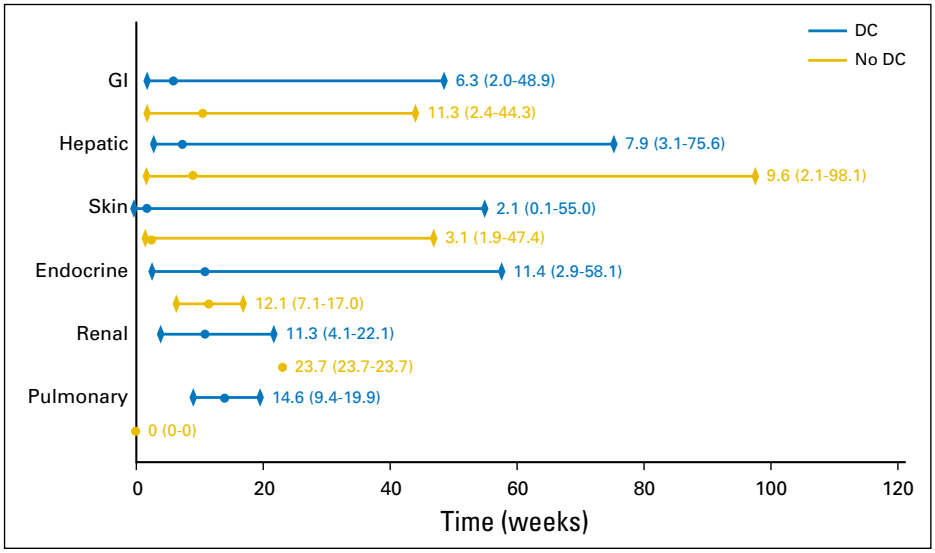

Fig 4. Time to onset of treatment-related select grade 3 or 4 adverse events in all patients with one or more events and resolution of treatment-related select grade 3 or 4 adverse events in patients treated with immune-modulating medication. DC, discontinuation.

Table 3. Resolution of Treatment-Related Select Grade 3 or 4 AEs in Patients Treated With Immune-Modulating Medication

	Treated Patients Who Discontinued Because of AEs (n = 176)		Treated Patients Who Did Not Discontinue Because of AEs (n = 231)	
Select Organ Category	Resolution of Grade 3 or 4 AE, No. of No. (%)	Median Time to Resolution, Weeks (95% CI)	Resolution of Grade 3 or 4 AE, No. of No. (%)	Median Time to Resolution, Weeks (95% CI)
GI	38 of 38 (100)	2.9 (1.9 to 4.3)	2 of 2 (100)	39.7 (5.7 to 73.7)
Hepatic	28 of 28 (100)	3.3 (2.4 to 4.4)	6 of 6 (100)	4.1 (1.0 to 8.6)
Skin	10 of 10 (100)	5.1 (2.1 to 9.7)	4 of 6 (67)	3.0 (0.7 to NR)
Endocrine	4 of 6 (67)	12.1 (1.6 to NR)	2 of 9 (22)	NR (2.0 to NR)
Renal	1 of 1 (100)	1.7 (NR to NR)	1 of 1 (100)	0.4 (NR to NR)
Pulmonary	1 of 1 (100)	0.29 (NR to NR)	0	—

Abbreviations: AE, adverse event; NR, not reached.

doses of the combination. Efficacy of nivolumab plus ipilimumab seemed to be similar for those who did and did not discontinue because of AEs. This suggests that patients may continue to derive benefit from combination therapy even after treatment is stopped because of AEs. Whether AEs are a precondition for this post-discontinuation benefit remains an open question.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials

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