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← Editorial

➕ Supplemental content

IMPORTANCE Immune checkpoint inhibitors have demonstrated atypical response patterns, which may not be fully captured by conventional response criteria. There is a need to better understand the potential benefit of continued immune checkpoint inhibition beyond progression.

OBJECTIVE To evaluate the safety and potential benefit of nivolumab (anti–programmed cell death receptor 1) monotherapy beyond Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression.

DESIGN, SETTING, AND PARTICIPANTS Pooled, retrospective analysis of data from phase 3 trials of nivolumab in treatment-naive patients with advanced melanoma (CheckMate 066 or CheckMate 067) conducted at academic and clinical cancer centers. Participants were patients treated beyond first disease progression, defined as those who received their last dose of nivolumab more than 6 weeks after progression (TBP group); and patients not treated beyond progression, who discontinued nivolumab therapy before or at progression (non-TBP group). Data analyses were conducted from November 6, 2015, to January 11, 2017.

INTERVENTIONS Nivolumab (3 mg/kg every 2 weeks) administered until progression or unacceptable toxic effects. Patients could be treated beyond progression if deriving apparent clinical benefit and tolerating study drug, at the investigator's discretion.

MAIN OUTCOMES AND MEASURES Tumor response and safety in TBP and non-TBP patients.

RESULTS Among 526 randomized patients (39% [n = 203] female; median age, 62 years [range, 18-90 years]), 306 (58%) experienced disease progression, including 85 (28%) TBP patients and 221 (72%) non-TBP patients. Twenty-four (28%) of the TBP patients had a target lesion reduction of greater than 30% after progression compared with baseline (TBP>30% group). At the time of this analysis, 65 (76%) TBP patients and 21 (87%) TBP>30% patients were still alive; 27 (32%) and 11 (46%), respectively, continued to receive treatment. Median (range) time from progression to last dose of treatment was 4.7 (1.4-25.8) months for TBP patients and 7.6 (2.4-19.4) months for TBP>30% patients. Median (range) time from progression to greater than 30% tumor reduction was 1.4 (0.2-7.0) months. Treatment-related select grade 3 to 4 adverse events were similar in the TBP and non-TBP groups (5 [6%] and 9 [4%], respectively).

CONCLUSIONS AND RELEVANCE A substantial proportion of selected patients treated with frontline nivolumab who were clinically stable and judged to be eligible for treatment beyond RECIST v1.1–defined progression by the treating investigators derived apparent clinical benefit without compromising safety. Further analysis will help define the potential benefit of continued nivolumab treatment beyond progression.

TRIAL REGISTRATION clinicaltrials.gov Identifiers: NCT01721772 (CheckMate 066) and NCT01844505 (CheckMate 067)

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Immune checkpoint inhibitors, which enhance antitumor immune response,[1-3] are associated with atypical response patterns[4,5] that may not be fully captured by conventional response criteria such as Response Evaluation Criteria in Solid Tumors (RECIST).[6] These atypical response patterns include responses following an apparent increase in tumor burden ("pseudoprogression") and responses in the presence of new lesions. In advanced melanoma, immune-related responses have been observed in approximately 10% of patients treated with ipilimumab (anti–cytotoxic T-lymphocyte antigen 4),[5] and in approximately 7% to 9% of patients treated with nivolumab or pembrolizumab (anti–programmed cell death receptor 1 [anti–PD-1]).[7-9]

Nivolumab is a fully human monoclonal IgG4 antibody that selectively blocks the interaction between PD-1 on activated T cells and its ligands, programmed cell death ligands 1 (PD-L1) and 2 (PD-L2), on tumor cells as well as tumor-infiltrating immune cells.[10-13] Based on phase 3 trial data showing improved overall survival (OS) and progression-free survival (PFS) compared with dacarbazine (CheckMate 066)[7] and improved PFS and objective response rate vs ipilimumab (CheckMate 067),[14] nivolumab monotherapy was approved for the treatment of advanced melanoma in many countries around the world.

In CheckMate 066, treatment-naive patients with BRAF wild-type melanoma treated with nivolumab had an improved OS compared with those who received dacarbazine (prepared as a citrate salt) (hazard ratio for death, 0.42; 99.8% CI, 0.25-0.73; P < .001). Whereas the objective response rate with nivolumab was high (40%), approximately 30% of patients experienced a best overall response of progressive disease.[7] Similarly, in CheckMate 067, the median PFS was significantly longer for patients who received nivolumab plus ipilimumab (11.5 months; 95% CI, 8.9-16.7 months) or nivolumab monotherapy (6.9 months; 95% CI, 4.3-9.5 months) compared with ipilimumab monotherapy (2.9 months; 95% CI, 2.8-3.4 months; P < .001 for both comparisons).[14] Progressive disease was reported in 23%, 38%, and 49% of patients treated with the combination, nivolumab monotherapy, and ipilimumab monotherapy, respectively.

Although disease progression is considered failure of treatment for nonimmunotherapeutic agents, resulting in treatment discontinuation, the possibility of delayed, immune-related responses suggests that patients with disease progression could benefit from continued treatment with immune checkpoint inhibitors. Therefore, across the nivolumab development program, patients were permitted to continue study treatment after initial investigator-assessed RECIST v1.1-defined progression, provided that they were considered to be deriving clinical benefit and tolerating the study drug. The objective of this retrospective analysis was to evaluate the safety and potential benefit of nivolumab monotherapy beyond the first RECIST v1.1-defined progression in patients with advanced melanoma.

Methods

Study Design and Treatment
This analysis pooled data from patients treated with nivolumab monotherapy in CheckMate 066 (n = 206)[7] or CheckMate 067

Key Points

Question Can patients with treatment-naive advanced melanoma derive apparent clinical benefit from nivolumab treatment beyond Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression without compromising safety?

Findings In this pooled, retrospective analysis of 85 treatment-naive patients with advanced melanoma who continued nivolumab treatment beyond RECIST v1.1-defined progression in phase 3 clinical trials (CheckMate 066, CheckMate 067), 28% had a target lesion reduction of greater than 30% after progression compared with baseline, with no new or unexpected adverse events.

Meaning Continued treatment with nivolumab may be an option to achieve further benefit without compromising safety in some patients with advanced melanoma.

(n = 313) (**Figure 1**).[14] Patients received nivolumab, 3 mg/kg, every 2 weeks by intravenous infusion until disease progression by RECIST v1.1 criteria[6] or unacceptable toxic effects. The protocols for CheckMate 066 and CheckMate 067 state that patients could be treated beyond first progression provided that they exhibited investigator-assessed clinical benefit without substantial adverse effects related to nivolumab. Assessment of clinical benefit took into account whether the patient was clinically deteriorating and unlikely to receive further benefit from continued treatment. Investigators selected patients for TBP after consultation with and approval from the study monitors.

In this analysis, patients treated beyond first disease progression were defined as those who received their last dose of nivolumab more than 6 weeks after progression (TBP group). A subgroup of these patients that had greater than 30% tumor reduction in target lesion after progression when compared with baseline was evaluated separately (TBP>30% group). Patients not treated beyond progression discontinued nivolumab before or at RECIST-defined progression (non-TBP group).
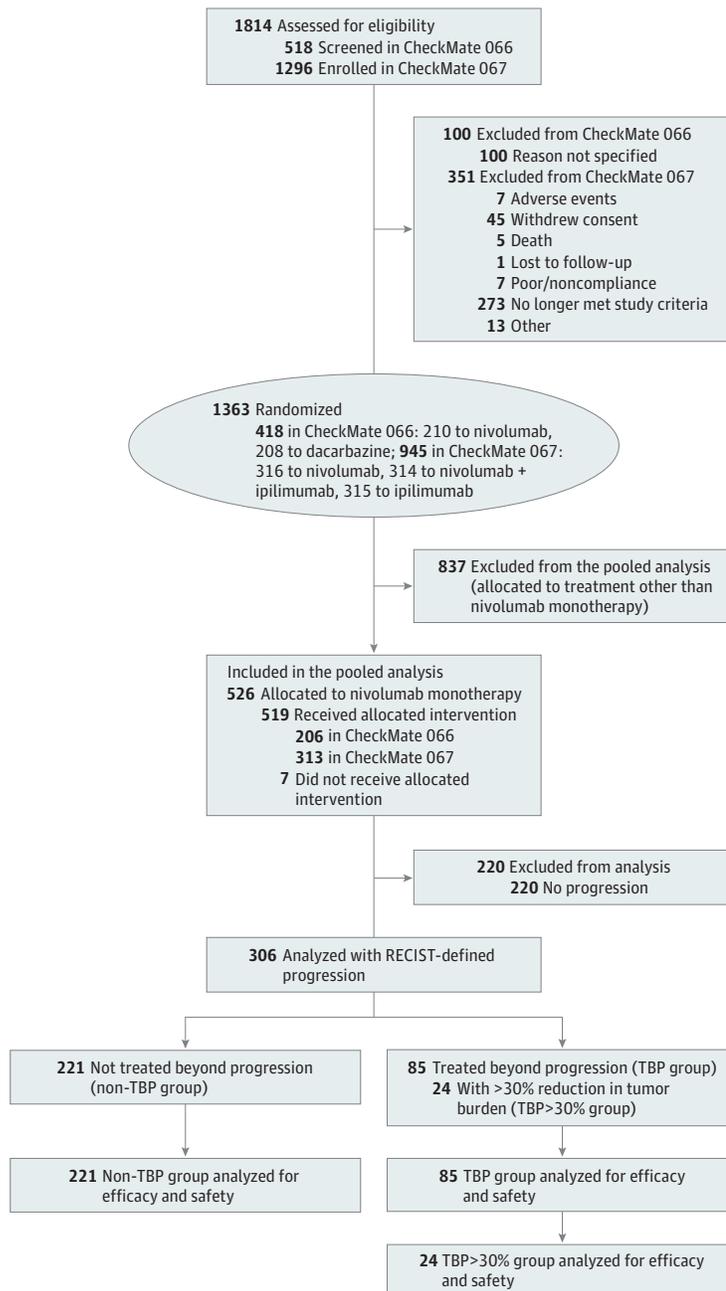
Patients
Eligible patients had histologically confirmed unresectable stage III or IV malignant melanoma and had received no prior systemic therapy for advanced disease.[7,14] Patients were at least 18 years of age, with measurable disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with active brain metastases, ocular melanoma, or autoimmune disease were excluded from both studies. In CheckMate 066, all patients had BRAF wild-type melanoma; in CheckMate 067, patients with BRAF wild-type or BRAF-mutated melanoma were eligible.[7,14] All patients provided written informed consent. The protocols were approved by either the relevant institutional review boards or ethics committees at each investigator's study site. The studies were conducted in accordance with the Declaration of Helsinki with good clinical practice as defined by the International Conference on Harmonisation.

Progression-Free Survival, Overall Survival, Tumor Response, and Safety Assessments
Progression-free survival was defined as time from randomization to investigator-assessed first clinical or radiographic

Figure 1. Consolidated Standards of Reporting Trials Flow Diagram for Patient Disposition, Showing Patient Subgroups for Analysis

1814 Assessed for eligibility
   518 Screened in CheckMate 066
   1296 Enrolled in CheckMate 067

100 Excluded from CheckMate 066
   100 Reason not specified
351 Excluded from CheckMate 067
   7 Adverse events
   45 Withdrew consent
   5 Death
   1 Lost to follow-up
   7 Poor/noncompliance
   273 No longer met study criteria
   13 Other

1363 Randomized
   418 in CheckMate 066: 210 to nivolumab, 208 to dacarbazine; **945** in CheckMate 067: 316 to nivolumab, 314 to nivolumab + ipilimumab, 315 to ipilimumab

837 Excluded from the pooled analysis (allocated to treatment other than nivolumab monotherapy)

Included in the pooled analysis
526 Allocated to nivolumab monotherapy
519 Received allocated intervention
   206 in CheckMate 066
   313 in CheckMate 067
7 Did not receive allocated intervention

220 Excluded from analysis
220 No progression

306 Analyzed with RECIST-defined progression

221 Not treated beyond progression (non-TBP group)

85 Treated beyond progression (TBP group)
24 With >30% reduction in tumor burden (TBP>30% group)

221 Non-TBP group analyzed for efficacy and safety

85 TBP group analyzed for efficacy and safety

24 TBP>30% group analyzed for efficacy and safety

Patients were assessed for eligibility and randomized in 2 separate phase 3 trials, CheckMate 066 and CheckMate 067.[7,14] Other treatments (in addition to nivolumab monotherapy) to which patients were randomized comprised dacarbazine (n = 208) in CheckMate 066 and nivolumab plus ipilimumab (n = 314) or ipilimumab monotherapy (n = 315) in CheckMate 067. TBP indicates treatment beyond progression.

RECIST progression, or death. Overall survival was defined as time from randomization to death. Tumor assessments included objective response rate based on investigator-assessed RECIST v1.1 criteria, time to response, and duration of response, defined as time from complete or partial response to first disease progression. Tumors were assessed at baseline, every 6 weeks from randomization for the first year, and every 12 weeks thereafter, until disease progression or treatment discontinuation, whichever occurred later. After treatment discontinuation, patients were evalu-ated every 3 months for survival and safety. Adverse events (AEs) were graded using the National Cancer Institute Com-mon Terminology Criteria for Adverse Events v4.0. Select AEs, defined as those with a potential immunologic cause, were analyzed by organ category.

Statistical Analyses

Objective response rate was defined as the number of patients with a best overall response of complete or partial response di-vided by the number of randomized patients for each group, with

Table 1. Patient Characteristics at Progression

Characteristic	Patients Who Experienced Disease Progression (n = 306)		
	Non-TBP (n = 221)	TBP (n = 85)	TBP>30%[a] (n = 24)
Eastern Cooperative Oncology Group performance status of 0, No. (%)	111 (50)	66 (78)	20 (83)
LDH > ULN, No. (%)	132 (60)	19 (22)	0
LDH > 2 × ULN, No. (%)	61 (28)	2 (2)	0
Change in tumor volume at progression, mean (range), %[b]	15 (−100 to 353)	−9 (−100 to 176)	−45 (−87 to 64)
Progression due to increase in target lesions only, No. (%)[c]	35 (16)	24 (28)	...
Progression due to appearance of new lesions only, No. (%)[c]	67 (30)	39 (46)	...
Increase in target lesions and appearance of new lesions, No. (%)	65 (29)	16 (19)	...
Progression in nontarget lesions only, No. (%)	54 (24)	6 (7)	...

Abbreviations: LDH, lactate dehydrogenase; TBP, treatment beyond progression; ULN, upper limit of normal.

[a] The TBP>30% group is a subset of the TBP group. Patients in this subset had greater than a 30% tumor reduction in target lesion after progression compared with baseline.

[b] Change in size of target lesions per Response Evaluation Criteria in Solid

Tumors v1.1; does not include new lesions.

[c] The percentage of patients with an increase in target lesions and/or appearance of new lesions does not total 100% because not all factors attributed to progressive disease are shown in the table (eg, progression of nontarget lesions).

2-sided, 95% CIs for the response rate based on the Clopper-Pearson method. Progression-free survival and OS were estimated using Kaplan-Meier methodology; 2-sided, 95% CIs for median PFS and OS were computed by the Brookmeyer and Crowley method. Tumor burden change (sum of diameters of target lesions) over time for each patient was displayed graphically.

Results

Patient Characteristics at Baseline and Progression

Median time from randomization to last known date alive or death in the TBP, non-TBP, and TBP>30% groups was 14.3 (range, 5.0-27.9), 9.9 (range, 0.3-27.6), and 15.0 (range, 10.4-24.7) months, respectively. Of 526 patients allocated to nivolumab monotherapy, 306 (58%) experienced disease progression; 85 (28%) patients with progressing disease were in the TBP group and 221 (72%) were in the non-TBP group (eTable 1 in the Supplement; Figure 1). The remaining 220 (42%) patients did not experience disease progression with nivolumab (Figure 1). Among the 85 TBP patients, 30 were from CheckMate 066 and 55 were from CheckMate 067. Twenty-four TBP patients (28%) had a target lesion reduction of greater than 30% after progression when compared with baseline (eTable 1 in the Supplement; Figure 1).

Formal hypothesis testing was not conducted; however, numerical differences were noted between TBP and non-TBP patients. Relative to non-TBP patients, TBP patients were more likely to have a baseline ECOG performance status of 0 (71 [84%] vs 145 [66%]) and less likely to have poor prognostic features at baseline, including stage M1c disease (41 [48%] vs 152 [69%]) and lactate dehydrogenase (LDH) levels above the upper limit of normal (ULN) (25 [29%] vs 109 [49%]) (eTable 1 in the Supplement). Relative to the TBP group overall, TBP patients who had a tumor reduction of greater than 30% after first progression were less likely to have poor prognostic features at baseline (M1c disease: 8 [33%] vs 41 [48%]; LDH > ULN: 5 [21%] vs 25 [29%]; LDH > 2 × ULN: 0 vs 4 [5%]). Twenty percent of pa-

tients in both the TBP (17 patients) and non-TBP (45 patients) groups, and 33% of those in the TBP>30% group (8 patients), had BRAF mutation–positive melanoma. Patients with PD-L1-positive status (5% cutoff) included 23 (27%) TBP patients, 43 (19%) non-TBP patients, and 5 (21%) TBP>30% patients.

The TBP patients were more likely than the non-TBP patients to have first progression defined by either an increase in target lesions or appearance of new lesions, but less likely to have both of these disease characteristics together (Table 1). Fewer patients in the TBP than non-TBP group had LDH levels above the ULN at progression (19 [22%] vs 132 [60%]), but more patients had an ECOG performance status of 0 (66 [78%] vs 111 [50%]) (Table 1). None of the TBP>30% patients had LDH levels above the ULN at progression and 20 (83%) had an ECOG performance status of 0. The median change in tumor volume (size in target lesions as per RECIST v1.1 criteria) at progression was an increase of 15% (range, −100% to 353%) in non-TBP patients and a decrease of 9% (range, −100% to 176%) and 45% (range, −87% to 64%) in TBP and TBP>30% patients, respectively. In TBP patients, progression in many cases was due to the appearance of new lesions despite a decrease in target lesions (Table 1).

Response Before First Progression and Time to Progression

In the period from the start of nivolumab treatment to first disease progression, non-TBP and TBP groups had a similar objective response rate (33 [15%] vs 16 [19%]), median PFS (2.6 [95% CI, 2.30-2.66] vs 2.8 [95% CI, 2.69-3.15] months), and median time to objective response (non-TBP, 2.6 [range, 1.9-5.3] months; TBP, 2.6 [range, 2.0-7.6] months). Compared with non-TBP patients, TBP patients had a shorter median duration of objective response (4.4 vs 5.6 months). The majority of TBP patients who experienced RECIST v1.1-defined progression did so at the time of first scan (Figures 2 and 3).

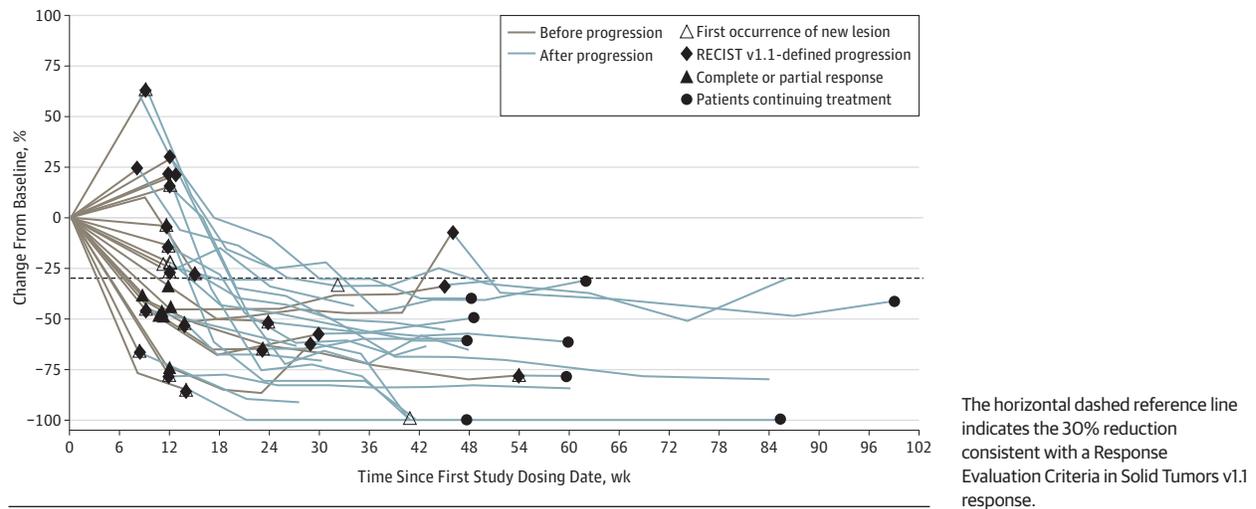### Duration of Treatment and Survival

In the TBP group, 65 patients (76%) were alive and 27 (32%) were continuing treatment at the time of the analysis (Figure 2). In the TBP>30% group, 21 patients (87%) were alive and 11 (46%) were

Figure 2. Duration of Treatment and Survival
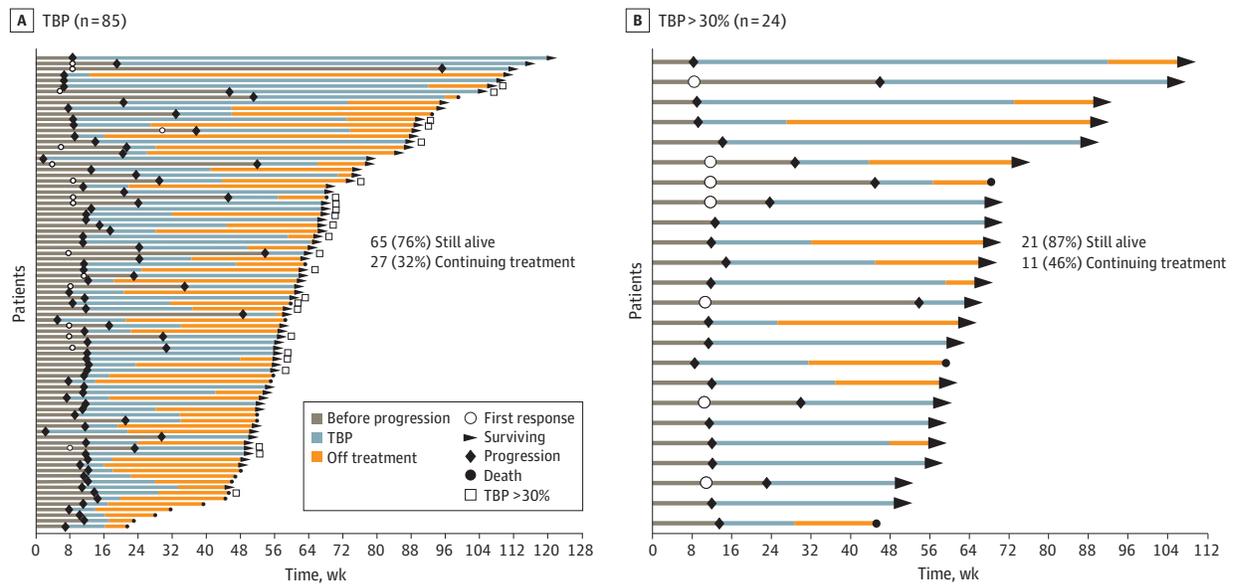
A, All patients treated beyond progression. B, Patients treated beyond progression with greater than 30% tumor reduction in target lesion after progression when compared with baseline. TBP indicates treatment beyond progression.

Figure 3. Tumor Burden Change Over Time in 24 Patients Treated Beyond Progression With Greater Than 30% Tumor Reduction in Target Lesion After Progression Compared With Baseline

The horizontal dashed reference line indicates the 30% reduction consistent with a Response Evaluation Criteria in Solid Tumors v1.1 response.

continuing treatment (Figure 2). The median number of nivolumab doses received after progression was 9.0 (range, 3-53) for the TBP group overall and 16.5 (range, 5-41) for the TBP>30% group. The median time from progression to last dose of study treatment was 4.7 months (range, 1.4-25.8 months) for TBP patients and 7.6 months (range, 2.4-19.4 months) for TBP>30% patients. The median time from progression to greater than 30% tumor reduction compared with baseline was 1.4 months (range, 0.2-7.0 months) in TBP>30% patients. Of the 85 TBP patients, 36 (42%) had a reduction in tumor burden after first progression (eFigure 1 in the Supplement). The TBP patients who

achieved subsequent tumor reduction after initial disease progression did so before week 24 (Figure 3).

Median OS from randomization to nivolumab treatment was not reached (95% CI, 21.5 to not reached) for TBP patients and was 10.6 months (95% CI, 8.1-14.2 months) for non-TBP patients, with 24-month OS rates of 59% (95% CI, 36%-76%) and 25% (95% CI, 16%-35%), respectively (eFigure 2 in the Supplement).

Overall Safety

Any-grade, treatment-related select AEs were similar, but generally occurred more frequently, in the TBP group than in the

Table 2. Treatment-Related Select Adverse Events (AEs)[a,b]

| AE Type | No. (%) | | | |
| | Non-TBP (n = 221) | | TBP (n = 85) | |
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All treatment-related select AEs	97 (44)	9 (4)	57 (67)	5 (6)
Skin	58 (26)	2 (1)	43 (51)	1 (1)
Pruritus	25 (11)	1 (<1)	23 (27)	0
Rash	23 (10)	0	23 (27)	0
Gastrointestinal	32 (14)	2 (1)	18 (21)	1 (1)
Diarrhea	31 (14)	2 (1)	18 (21)	1 (1)
Colitis	1 (<1)	0	1 (1)	0
Endocrine	18 (8)	1 (<1)	13 (15)	1 (1)
Hypothyroidism	13 (6)	0	7 (8)	0
Hyperthyroidism	5 (2)	1 (<1)	5 (6)	0
Hepatic	7 (3)	4 (2)	5 (6)	2 (2)
Alanine aminotransferase increased	3 (1)	2 (1)	1 (1)	0
Aspartate aminotransferase increased	2 (1)	1 (<1)	1 (1)	0
Pulmonary	3 (1)	0	2 (2)	0
Pneumonitis	2 (1)	0	1 (1)	0
Renal	4 (2)	0	0	0
Blood creatinine increased	2 (1)	0	0	0
Renal failure	2 (1)	0	0	0

Abbreviation: TBP, treatment beyond progression.

[a] Most common select AEs (defined as those with a potential immunologic cause) in each organ category are listed.

[b] These data were not adjusted for differences in treatment exposure.

non-TBP group (Table 2). The frequency of treatment-related select grade 3 to 4 AEs was similar in non-TBP and TBP groups (9 [4%] and 5 [6%], respectively). The most common treatment-related select AEs of any grade involved the skin (58 [26%] in the non-TBP group and 43 [51%] in the TBP group) and of grade 3 to 4 involved the liver (4 [2%] in the non-TBP and 2 [2%] in the TBP group). In an exposure-adjusted safety analysis, the incidence of treatment-related AEs was lower in TBP vs non-TBP patients (eTable 2 in the Supplement).

Subsequent Therapy

Following first progression, fewer patients in the TBP group received subsequent anticancer treatment than in the non-TBP group (56 [66%] vs 166 [75%]) (eTable 3 in the Supplement). Although the type of subsequent anticancer treatments received was similar in both groups (eTable 3 in the Supplement), more patients in the TBP group than in the non-TBP group received surgery (19 [22%] vs 28 [13%]) and fewer received any subsequent systemic therapy (41 [48%] vs 146 [66%]). Among TBP>30% patients, 1 (4%) received surgery and 9 (37%) received any subsequent systemic therapy (eTable 3 in the Supplement). The brain was the most common site of subsequent radiotherapy in TBP and non-TBP groups (2 [2%] and 9 [4%] of patients, respectively) (eTable 4 in the Supplement). The most common type of subsequent surgery was local tumor treatment surgery, which was reported in 7 (8%) of TBP patients and 3 (1%) of non-TBP patients (eTable 4 in the Supplement).

Discussion

This retrospective, pooled analysis of data from the phase 3 studies CheckMate 066 and CheckMate 067 suggests that a pro-

portion of patients with treatment-naive advanced melanoma who receive nivolumab beyond RECIST v1.1-defined progression may derive apparent clinical benefit. Although the data in this report are still immature, given the lack of OS data from CheckMate 067, 76% of patients treated with nivolumab beyond first progression were alive at the time of this analysis, while 32% continued to receive treatment. We also identified differences in OS between TBP and non-TBP patients (24-month OS rate, 59% and 25%, respectively). The safety profile associated with TBP was similar to that reported in a large pooled analysis of data from 576 patients who received nivolumab monotherapy.[15] Patients who continued nivolumab therapy were less likely than non-TBP patients to require any subsequent cancer therapy and were more likely to have surgery, which could suggest that nivolumab TBP resulted in tumor shrinkage that allowed for surgical resection or that progression was isolated and not reflective of the total tumor burden.

Atypical response patterns have been noted in patients treated with nivolumab beyond RECIST-defined progression in melanoma,[7,16] non–small-cell lung cancer,[17] and renal cell carcinoma.[18,19] They have also been observed with use of other immune checkpoint inhibitors,[8,9,20,21] although it is worth noting that we found delayed response to be rare after 24 weeks in patients treated beyond progression. Immune-related response criteria (irRC) were proposed to enable more appropriate monitoring of response in patients receiving immunotherapy. These criteria base antitumor response on total measurable tumor burden, so that the appearance of new lesions, for example, would not necessarily represent progressive disease if accompanied by an overall reduction in burden of all measurable lesions. To date, trials of immune checkpoint inhibitors have not consistently reported response rates

based on the irRC, and rigorous comparison of clinical outcomes using RECIST and irRC has not been made. Although irRC are not likely to be widely used in clinical practice, they have helped to raise awareness of atypical response patterns with immune checkpoint inhibitors and that stopping treatment at first signs of apparent tumor progression may be inappropriate in a patient who is otherwise tolerating treatment well. For example, ipilimumab treatment may result in delayed onset of effect, and some patients who initially responded or had stable disease with ipilimumab, but later experienced disease progression, achieved further disease control on ipilimumab retreatment.[22]

In our analysis, 24 patients had greater than 30% tumor reduction in target lesion after progression when compared with baseline, representing approximately 5% of all patients allocated to nivolumab monotherapy (N = 526), which is consistent with known estimates of atypical immune-related response patterns observed in other anti–PD-1 studies (approximately 7%-9%).[7-9] Two main hypotheses have been proposed to account for the apparent disease progression ("pseudoprogression") that sometimes precedes responses in patients treated with immune checkpoint inhibitors.[5] First, patients with relatively high immune suppression within the tumor microenvironment may have a comparatively slow antitumor immune response that is ultimately sufficient to reduce tumor burden, allowing for continued tumor growth of target lesions or the appearance of new lesions in the interim. Alternatively, treatment may induce a transient immune cell infiltration into the tumor, accompanied by edema, giving the appearance of increased tumor burden on imaging. This type of inflammatory reaction has been confirmed by biopsy in patients treated with ipilimumab[5,23,24] and in patients treated with anti–PD-1 combination therapy.[25] Because disease progression is defined by RECIST as a 20% or more increase in tumor target lesion size or the appearance of new lesions, an inflammatory reaction with immune checkpoint therapy may be mistaken for disease progression, leading to treatment discontinuation before realization of treatment benefits.[26]

Two retrospective analyses of the efficacy and safety of nivolumab in patients with renal cell carcinoma treated beyond progression[18,19] suggested that continued nivolumab treatment benefited a proportion of patients in terms of tumor reduction, as well as longer median OS compared with patients not treated beyond progression, with no new or unexpected AEs observed. A third analysis of the same phase 3 data by the US Food and Drug Administration defined TBP differently,[27] thus resulting in a lower number of patients with progressive disease followed by a decrease of at least 30% in tumor after continued treatment with nivolumab. Nevertheless, similar to our findings, the investigators' decision to treat with nivolumab beyond progression may have been based in part on patient characteristics, such that patients with poor clinical characteristics were unlikely to receive continued treatment. In our analysis, patients who had, for example, LDH level greater than ULN at progression, or an increase in target lesions and appearance of new lesions at progression together, were less likely than those without these characteristics to be treated beyond progression. Similarly, in the aforementioned renal cell carcinoma analysis, patients with high incidence of new bone lesions and low quality of life scores were less likely than those without these characteristics to be considered for continued nivolumab treatment.[18,19] Additional evaluation of factors influencing the decision to continue treatment beyond progression (eg, lack of other alternatives at the time of the decision) may help investigators to identify appropriate candidates for this approach.

Limitations

Although our analysis provides insights into the extended use of nivolumab beyond disease progression, interpretation of these results is limited by several factors, including the use of retrospective data, the relatively small number of patients treated beyond disease progression, and selection of patients for extended treatment by investigators based on factors that have not been systematically explored. In the absence of randomized data, it is unclear that these patients would not have survived as long without being exposed to further nivolumab treatment. Future studies should examine outcomes among patients treated beyond disease progression in large, prospective cohorts that are randomized on progression to further treatment or to observation only. Randomized trials would also allow for better assessment of the safety of continued treatment compared with alternative care on progression. Although no new or unexpected AEs were observed in patients treated beyond progression in our analysis, continued treatment may be associated with risks, as observed in renal cell carcinoma.[27]

Conclusions

In summary, our analysis shows that patients treated beyond their first disease progression can experience a tumor response with continued nivolumab treatment, with a safety profile consistent with that observed in patients who did not receive further treatment. Although patients selected for continued treatment were typically healthier than those who were not selected, it is possible that patients with less favorable clinical characteristics would have also benefited from further nivolumab therapy after progression. The results of this analysis suggest that continued treatment with nivolumab may be an option to achieve further apparent clinical benefit in some patients with advanced melanoma.

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