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Original Research

Safety and efficacy of nivolumab in challenging subgroups with advanced melanoma who progressed on or after ipilimumab treatment: A single-arm, open-label, phase II study (CheckMate 172)

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Abstract ***Background:*** Limited data are available on nivolumab in challenging subgroups with advanced melanoma. We report outcomes of nivolumab after prior ipilimumab in patients who are typically excluded from clinical trials.
Patients and methods: In this phase II, single-arm, open-label, multicentre study (CheckMate 172), patients with advanced melanoma who progressed on or after ipilimumab received nivolumab 3 mg/kg, every 2 weeks for up to 2 years. The primary objective was incidence of grade ≥3, treatment-related select adverse events (AEs).
Results: At a minimum follow-up of 18 months, grade ≥3 treatment-related select AEs with the most variation across subgroups were diarrhoea and colitis (1.1% [n = 11] and 0.3% [n = 3] for the total population [n = 1008]; 0.6% [n = 1] and 0.6% [n = 1] for patients with an asymptomatic central nervous system [CNS] metastasis [n = 165; 16.4%]; 4.5% [n = 3] and 3.0% [n = 2] for patients with an Eastern Cooperative Oncology Group performance status [ECOG PS] of 2 [n = 66; 6.5%]; 2.4% [n = 2] and 0% for those who experienced a grade 3/4 immune-related AE [irAE] with prior ipilimumab [n = 84; 8.3%]; and 0% and 0% for autoimmune disease [n = 25; 2.5%], respectively). Median overall survival was 21.4 months in the total population and was 11.6, 2.4, 21.5, and 18.6 months in patients with a CNS metastasis, ECOG PS 2, a grade 3/4 irAE with prior ipilimumab, and autoimmune disease, respectively.
Conclusions: In this large, phase II clinical trial of patients with advanced melanoma who progressed on or after ipilimumab, nivolumab demonstrated a safety profile consistent with that of prior clinical trials.
ClinicalTrials.gov ID: NCT02156804.

1. Introduction

Treatment options for patients with advanced melanoma have increased dramatically in recent years. Since 2011, eight systemic therapies have been approved by the United States Food and Drug Administration for advanced melanoma, with similar approvals being granted in other countries worldwide [1]. These treatments include BRAF inhibitors, MEK inhibitors, and antibodies that target cytotoxic T-lymphocyte antigen 4 (CTLA-4; ipilimumab) and programmed death receptor 1 (PD-1; nivolumab and pembrolizumab). Alone and in combinations, these agents have improved patient outcomes and shifted treatment goals from palliative delay in disease progression to durable response and long-term survival [1].

Despite the recent advancements in the treatment of advanced melanoma, there is limited information for many of these agents regarding outcomes in challenging subgroups because these patients are typically excluded from registrational clinical trials. For example, the approval of nivolumab was based in part on results from the phase III CheckMate 037 trial, which demonstrated improved efficacy and a better safety profile with nivolumab versus investigator's choice chemotherapy in patients who progressed after prior ipilimumab with or without a BRAF inhibitor [2,3]; however, treatment effects were not specifically investigated in challenging subgroups.

CheckMate 172 is a large, phase II clinical trial that investigated the use of nivolumab in patients with advanced melanoma who progressed on or after ipilimumab [4]. The eligibility criteria included challenging subgroups and different melanoma subtypes. Here, we report safety and overall survival (OS) results in challenging subgroups that received nivolumab in CheckMate 172. For additional details on the safety and efficacy of nivolumab in patients with different melanoma subtypes in CheckMate 172, please see our companion manuscript, which appears in this issue of the *European Journal of Cancer* [5].

2. Patients and methods

Methods are defined in detail in our companion manuscript [5] and are briefly summarised below.

2.1. Patients

Eligible patients were aged ≥18 years with previously treated, unresectable, histologically confirmed, stage III or IV melanoma (per the 7th edition of the American Joint Committee on Cancer staging system [6]) and disease progression or recurrence after prior treatment containing an anti-CTLA-4 monoclonal antibody. This analysis included patients with a central nervous system (CNS) metastasis, an Eastern Cooperative Oncology Group performance status of 2 (ECOG PS 2), a grade 3/4 immune-related adverse event (irAE) with prior ipilimumab, and autoimmune disease.

This study was conducted in accordance with Good Clinical Practices as defined by the International Conference on Harmonisation. It was compliant with the study protocol, which was approved by the institutional review board/independent ethics committee of the participating sites before trial initiation. All patients provided written, informed consent before enrolment.

2.2. Study design

This phase II, single-arm, open-label study (NCT02156804) was conducted at 156 sites in 20 European countries. Patients were treated with nivolumab 3 mg/kg administered intravenously every 2 weeks for up to 2 years until progression or unacceptable toxicity (Supplementary Fig. S1). Treatment beyond progression was permitted for patients who tolerated the study drug and who had investigator-assessed clinical benefit.

2.3. End points and study assessments

The primary objective was to determine the incidence of grade ≥3 treatment-related select adverse events (AEs) in patients with melanoma who progressed on or after ipilimumab and were treated with nivolumab. Select AEs consist of a list of preferred terms grouped by specific category. They include AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity. Secondary end points included the incidence of all grade ≥3 select AEs, median time to onset and resolution of grade 3/4 select AEs, and OS. Exploratory end points included safety, tolerability, and OS in patients with different melanoma subtypes, CNS metastases, ECOG PS 2, a grade 3/4 irAE with prior ipilimumab, and autoimmune disease.

Safety and OS analyses were based on patients who received ≥1 dose of nivolumab. Safety was assessed weekly for patients with known immune-related AEs of grade 3 or 4 during treatment with prior anti-CTLA-4 therapy. All on-study AEs, treatment-related AEs, serious AEs, and treatment-related serious AEs were assessed using the worst grade per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, classified by system organ class and Medical Dictionary for Regulatory Activities preferred term. Treatment modifications were based on specific laboratory and AE criteria. OS was defined as the time between the start of treatment and the date of death due to any cause. OS was assessed while patients were on nivolumab and every 3 months after treatment discontinuation.

2.4. Statistical analysis

Safety results are presented as a number and a percentage of patients with AEs. OS was estimated using Kaplan–Meier methodology. Median OS and two-sided 95% confidence interval (CI) were calculated using the Brookmeyer and Crowley method. The 18-month OS rates and 95% CIs are also reported. The number of doses received is reported as a median and a range, and as a count and a percentage.

3. Results

3.1. Patients and treatment

Results are from a database lock on March 23, 2018, with a minimum follow-up of 18 months. Median follow-up in months was 14.3 for the total population ($N = 1008$), 7.5 for CNS metastasis ($n = 165$), 2.5 for ECOG PS 2 ($n = 66$), 15.8 for patients who experienced a grade 3/4 irAE with prior ipilimumab ($n = 84$), and 18.2 for autoimmune disease ($n = 25$). At the cutoff date for this analysis, most patients were off treatment (Supplementary Table S1). The most common reason for treatment discontinuation was disease progression (59.6% in the total population, 66.1% in patients with a CNS metastasis, 69.7% in patients with ECOG PS 2, 48.8% in patients who experienced a grade 3/4 irAE with

prior ipilimumab, and 52.0% in those with autoimmune disease).

At baseline, most patients had stage IV disease, *BRAF* wild-type tumours, and received 1 or 2 prior therapies (Table 1). In patients with ECOG PS 2, 27.3%

Table 1
Baseline characteristics.

Characteristic	Total patients (N = 1008)	Subgroup			
		CNS metastasis (n = 165)	ECOG PS 2 (n = 66)	Grade 3/4 irAE with ipilimumab (n = 84)	Autoimmune disease (n = 25)
Median age, years (range)	62 (18–89)	58 (19–87)	59 (23–81)	58 (21–81)	62 (35–84)
Age ≥65 years, *n* (%)	425 (42.2)	64 (38.8)	24 (36.4)	29 (34.5)	11 (44.0)
Male, *n* (%)	557 (55.3)	101 (61.2)	33 (50.0)	53 (63.1)	10 (40.0)
ECOG PS, *n* (%)					
0-1	941 (93.4)	147 (89.1)	0 (0)	77 (91.7)	24 (96.0)
2	66 (6.5)	18 (10.9)	66 (100.0)	7 (8.3)	1 (4.0)
Not reported	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Disease stage, *n* (%)					
Stage III	43 (4.3)	1 (0.6)	2 (3.0)	4 (4.8)	3 (12.0)
Stage IV	965 (95.7)	164 (99.4)	64 (97.0)	80 (95.2)	22 (88.0)
M stage at study entry, *n* (%)					
M0	32 (3.2)	0 (0)	1 (1.5)	4 (4.8)	1 (4.0)
M1a	122 (12.1)	0 (0)	5 (7.6)	11 (13.1)	7 (28.0)
M1b	160 (15.9)	0 (0)	3 (4.5)	12 (14.3)	4 (16.0)
M1c with brain metastases	165 (16.4)	165 (100.0)	18 (27.3)	14 (16.7)	6 (24.0)
M1c without brain metastases	508 (50.4)	0 (0)	38 (57.6)	40 (47.6)	6 (24.0)
Not reported	21 (2.1)	0 (0)	1 (1.5)	3 (3.6)	1 (4.0)
CNS metastases, *n* (%)					
Yes	165 (16.4)	165 (100.0)	18 (27.3)	14 (16.7)	6 (24.0)
No	822 (81.5)	0 (0)	47 (71.2)	67 (79.8)	18 (72.0)
Not reported	21 (2.1)	0 (0)	1 (1.5)	3 (3.6)	1 (4.0)
Treatment status of CNS metastasis, *n* (%)					
Treated	120 (11.9)	119 (72.1)	11 (16.7)	6 (7.1)	4 (16.0)
Untreated	42 (4.2)	41 (24.8)	6 (9.1)	9 (10.7)	2 (8.0)
Treated leptomeningeal	13 (1.3)	13 (7.9)	0 (0)	0 (0)	1 (4.0)
Melanoma subtype, *n* (%)					
Mucosal	63 (6.3)	9 (5.5)	9 (13.6)	4 (4.8)	3 (12.0)
Cutaneous	723 (71.7)	137 (83.0)	44 (66.7)	56 (66.7)	17 (68.0)
Acral	55 (5.5)	7 (4.2)	3 (4.5)	5 (6.0)	2 (8.0)
Ocular/uveal	103 (10.2)	4 (2.4)	3 (4.5)	10 (11.9)	1 (4.0)
Other	64 (6.3)	8 (4.8)	7 (10.6)	9 (10.7)	2 (8.0)
***BRAF* mutation status, *n* (%)**					
Wild-type	567 (56.3)	81 (49.1)	38 (57.6)	50 (59.5)	19 (76.0)
Mutant	336 (33.3)	67 (40.6)	25 (37.9)	28 (33.3)	5 (20.0)
Not reported	105 (10.4)	17 (10.3)	3 (4.5)	6 (7.1)	1 (4.0)
Number of prior therapies, *n* (%)[a]					
0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1	399 (39.6)	58 (35.2)	23 (34.8)	39 (46.4)	10 (40.0)
2	375 (37.2)	66 (40.0)	24 (36.4)	29 (34.5)	9 (36.0)
≥3	234 (23.2)	41 (24.8)	19 (28.8)	16 (19.0)	6 (24.0)
Baseline LDH, *n* (%)					
≤ULN	482 (47.8)	64 (38.8)	13 (19.7)	46 (54.8)	19 (76.0)
>ULN	514 (51.0)	98 (59.4)	52 (78.8)	37 (44.0)	5 (20.0)
≤2 × ULN	839 (83.2)	126 (76.4)	35 (53.0)	68 (81.0)	22 (88.0)
>2 × ULN	157 (15.6)	36 (21.8)	30 (45.5)	15 (17.9)	2 (8.0)
Not reported	12 (1.2)	3 (1.8)	1 (1.5)	1 (1.2)	1 (4.0)
Type of autoimmune disorder, *n* (%)					
Endocrine	14 (1.4)	4 (2.4)	1 (1.5)	3 (3.6)	14 (56.0)
Gastrointestinal	2 (0.2)	0 (0)	0 (0)	2 (2.4)	2 (8.0)
Hepatic	1 (0.1)	0 (0)	0 (0)	1 (1.2)	1 (4.0)
Skin	7 (0.7)	2 (1.2)	0 (0)	4 (4.8)	7 (28.0)
Other[b]	1 (0.1)	0 (0)	0 (0)	1 (1.2)	1 (4.0)
Not reported	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Condition of autoimmune disorder, *n* (%)					
Active	13 (1.3)	2 (1.2)	1 (1.5)	4 (4.8)	13 (52.0)
Not active	12 (1.2)	4 (2.4)	0 (0)	7 (8.3)	12 (48.0)

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Total patients (N = 1008)	Subgroup			
		CNS metastasis (n = 165)	ECOG PS 2 (n = 66)	Grade 3/4 irAE with ipilimumab (n = 84)	Autoimmune disease (n = 25)
Prior use of immune-modulating medication, *n* (%)					
Yes	354 (35.1)	68 (41.2)	25 (37.9)	37 (44.0)	12 (48.0)
No	654 (64.9)	97 (58.8)	41 (62.1)	47 (56.0)	13 (52.0)

CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; irAE, immune-related adverse event; LDH, lactate dehydrogenase; OS, overall survival; ULN, upper limit of normal.
[a] Excluding anti-CTLA-4 treatment.
[b] Includes myasthenia gravis.

had M1c disease with brain metastases and 78.8% had lactate dehydrogenase levels greater than the upper limit of normal. Treatment exposure in patients who experienced a grade 3/4 irAE with prior ipilimumab and those with autoimmune disease was similar to that observed in the total population, with the subgroups receiving a median of 12.0 (range, 1–52) and 13.0 (range, 1–52) doses of nivolumab, respectively; the median duration of therapy was 26.8 (range, 0.1–110.1) and 24.1 (range, 0.1–104.1) weeks, respectively (Supplementary Table S2). Patients with a CNS metastasis and those with ECOG PS 2 received a median of 7.0 (range, 1–55) and 4.0 (range, 1–63) doses of nivolumab, respectively; the median duration of therapy was 13.3 (range, 0.1–130.9) and 6.1 (range, 0.1–128.1) weeks, respectively. Subsequent therapy of any type was received by 35.2% of patients in the total population, 30.9% with a CNS metastasis, 15.2% with ECOG PS 2, 29.8% of those who had a grade 3/4 irAE with prior ipilimumab, and 44.0% with autoimmune disease (Supplementary Table S3).

3.2. Safety

Grade 3/4 treatment-related AEs occurred in 18.2% of patients in the total population, 17.6% with a CNS metastasis, 13.6% with ECOG PS 2, 11.9% who had a grade 3/4 irAE with prior ipilimumab, and 16.0% with autoimmune disease; these events led to treatment discontinuation in 4.8%, 6.1%, 3.0%, 2.4%, and 4.0% of patients, respectively. Three treatment-related deaths were reported in the total population, including one patient (0.6%) in the CNS metastasis subgroup (Table 2).

The organ system most commonly affected by grade 3/4 treatment-related select AEs was the liver for the total population (n = 28, 2.8%), for the CNS metastasis group (n = 5, 3.0%), and for those who experienced a grade 3/4 irAE with prior ipilimumab (n = 3, 3.6%) (Table 3). In patients with ECOG PS 2, the most common grade 3/4 treatment-related select AEs were gastrointestinal AEs (n = 4, 6.1%). Only one (4.0%) grade 3/4 treatment-related select AE (diabetes mellitus) was reported in those with autoimmune disease.

3.3. Efficacy

Patients who experienced a grade 3/4 irAE with prior ipilimumab and those with autoimmune disease had the longest median OS (21.5 months [95% CI, 15.4–30.6] and 18.6 months [95% CI, 9.4–30.6], respectively) among the subgroups, with survival outcomes that were similar to those observed in the total population (median OS, 21.4 months [95% CI, 18.4–24.5]) (Fig. 1 and Supplementary Table S4). OS for these two subgroups and the total population was similar over time. Patients with a CNS metastasis and those with ECOG PS 2 had lower median OS (11.6 months [95% CI, 8.2–18.1] and 2.4 months [95% CI, 1.5–4.1], respectively). The 18-month OS rate was 53.8% in the total population and was 42.3%, 18.8%, 59.3%, and 58.2% in patients with a CNS metastasis, with an ECOG PS 2, who experienced a grade 3/4 irAE with prior ipilimumab, and with autoimmune disease, respectively (Supplementary Table S4).

4. Discussion

To the best of our knowledge, this is the largest analysis of efficacy and safety data with nivolumab monotherapy in challenging subgroups that are commonly treated in clinical practice but are often excluded from clinical trials. Overall, the safety profile of nivolumab in this large, phase II clinical trial was consistent with that reported in prior clinical trials [3,7–9]. The organ system most commonly affected by grade ≥3 treatment-related select AEs was the liver for the total population, the CNS metastasis group, and those who experienced a grade 3/4 irAE with prior ipilimumab; the gastrointestinal tract and endocrine system were most commonly affected in the ECOG PS 2 and autoimmune disease groups, respectively.

Previous studies of nivolumab have excluded patients with untreated brain metastases despite more than one-third of patients with advanced melanoma having brain metastases at diagnosis [10]. In the current analysis, 17.6% of patients with a CNS metastasis experienced grade 3/4 treatment-related AEs, which

Table 2
Safety summary[a].

n (%)	Total patients ($N = 1008$)		Subgroup							
			CNS metastasis ($n = 165$)		ECOG PS 2 ($n = 66$)		Grade 3/4 irAE with ipilimumab ($n = 84$)		Autoimmune disease ($n = 25$)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AEs	973 (96.5)	460 (45.6)	160 (97.0)	81 (49.1)	65 (98.5)	24 (36.4)	80 (95.2)	39 (46.4)	25 (100.0)	14 (56.0)
Treatment-related AEs	681 (67.6)	183 (18.2)	100 (60.6)	29 (17.6)	26 (39.4)	9 (13.6)	53 (63.1)	10 (11.9)	17 (68.0)	4 (16.0)
Serious AEs	507 (50.3)	312 (31.0)	109 (66.1)	68 (41.2)	54 (81.8)	18 (27.3)	53 (63.1)	33 (39.3)	16 (64.0)	12 (48.0)
Treatment-related serious AEs	107 (10.6)	73 (7.2)	21 (12.7)	17 (10.3)	6 (9.1)	4 (6.1)	12 (14.3)	6 (7.1)	5 (20.0)	3 (12.0)
AEs leading to discontinuation	181 (18.0)	108 (10.7)	32 (19.4)	20 (12.1)	16 (24.2)	7 (10.6)	20 (23.8)	12 (14.3)	2 (8.0)	1 (4.0)
Treatment-related AEs leading to discontinuation	73 (7.2)	48 (4.8)	13 (7.9)	10 (6.1)	3 (4.5)	2 (3.0)	6 (7.1)	2 (2.4)	1 (4.0)	1 (4.0)
Any AEs that required IMM	482 (47.8)	208 (20.6)	87 (52.7)	48 (29.1)	21 (31.8)	11 (16.7)	48 (57.1)	18 (21.4)	17 (68.0)	7 (28.0)
Treatment-related deaths[b]	3 (0.3)		1 (0.6)		0 (0)		0 (0)		0 (0)	

AE, adverse event; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IMM, immune-modulating medication; irAE, immune-related adverse event.
[a] Includes events reported between the first dose and 30 days after the last dose of study therapy.
[b] Based on the overall study follow-up.

Table 3
Treatment-related select adverse events of grade ≥3 (primary endpoint).

Select AE category, *n* (%)	Total patients ($N = 1008$)		Subgroup							
			CNS metastasis ($n = 165$)		ECOG PS 2 ($n = 66$)		Grade 3/4 irAE with ipilimumab ($n = 84$)		Autoimmune disease ($n = 25$)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Skin	**266 (26.4)**	**12 (1.2)**	**39 (23.6)**	**2 (1.2)**	**11 (16.7)**	**0 (0)**	**23 (27.4)**	**0 (0)**	**7 (28.0)**	**0 (0)**
Generalised pruritus	70 (6.9)	2 (0.2)	8 (4.8)	1 (0.6)	5 (7.6)	0 (0)	7 (8.3)	0 (0)	3 (12.0)	0 (0)
Palmar-plantar erythrodysaesthesia syndrome	2 (0.2)	1 (0.1)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	1 (1.2)	0 (0)	0 (0)	0 (0)
Endocrine	**170 (16.9)**	**18 (1.8)**	**25 (15.2)**	**3 (1.8)**	**6 (9.1)**	**0 (0)**	**10 (11.9)**	**2 (2.4)**	**4 (16.0)**	**1 (4.0)**
Hypophysitis	6 (0.6)	4 (0.4)	2 (1.2)	1 (0.6)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	0 (0)	0 (0)
Diabetes mellitus	5 (0.5)	3 (0.3)	3 (1.8)	1 (0.6)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	1 (4.0)	1 (4.0)
Type 1 diabetes mellitus	2 (0.2)	2 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	0 (0)	0 (0)
Lymphocytic hypophysitis	1 (0.1)	1 (0.1)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Secondary adrenocortical insufficiency	1 (0.1)	1 (0.1)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal	**136 (13.5)**	**14 (1.4)**	**18 (10.9)**	**2 (1.2)**	**9 (13.6)**	**4 (6.1)**	**17 (20.2)**	**2 (2.4)**	**7 (28.0)**	**0 (0)**
Diarrhoea	131 (13.0)	11 (1.1)	18 (10.9)	1 (0.6)	9 (13.6)	3 (4.5)	16 (19.0)	2 (2.4)	7 (28.0)	0 (0)
Colitis	10 (1.0)	3 (0.3)	1 (0.6)	1 (0.6)	2 (3.0)	2 (3.0)	1 (1.2)	0 (0)	0 (0)	0 (0)
Autoimmune colitis	1 (0.1)	1 (0.1)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic	**83 (8.2)**	**28 (2.8)**	**16 (9.7)**	**5 (3.0)**	**3 (4.5)**	**1 (1.5)**	**7 (8.3)**	**3 (3.6)**	**0 (0)**	**0 (0)**
Increased ALT	45 (4.5)	13 (1.3)	6 (3.6)	3 (1.8)	0 (0)	0 (0)	6 (7.1)	1 (1.2)	0 (0)	0 (0)
Increased AST	41 (4.1)	8 (0.8)	6 (3.6)	1 (0.6)	0 (0)	0 (0)	5 (6.0)	0 (0)	0 (0)	0 (0)
Increased blood AP	22 (2.2)	3 (0.3)	3 (1.8)	0 (0)	2 (3.0)	0 (0)	2 (2.4)	1 (1.2)	0 (0)	0 (0)
Increased GGT	18 (1.8)	9 (0.9)	4 (2.4)	1 (0.6)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	0 (0)	0 (0)
Autoimmune hepatitis	10 (1.0)	9 (0.9)	3 (1.8)	3 (1.8)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	0 (0)	0 (0)
Increased transaminases	6 (0.6)	2 (0.2)	2 (1.2)	0 (0)	2 (3.0)	1 (1.5)	1 (1.2)	1 (1.2)	0 (0)	0 (0)
Renal	**17 (1.7)**	**3 (0.3)**	**3 (1.8)**	**1 (0.6)**	**2 (3.0)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (4.0)**	**0 (0)**
Renal failure	1 (0.1)	1 (0.1)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; GGT, gamma-glutamyl transferase; irAE, immune-related adverse event. Bold indicates organ categories.

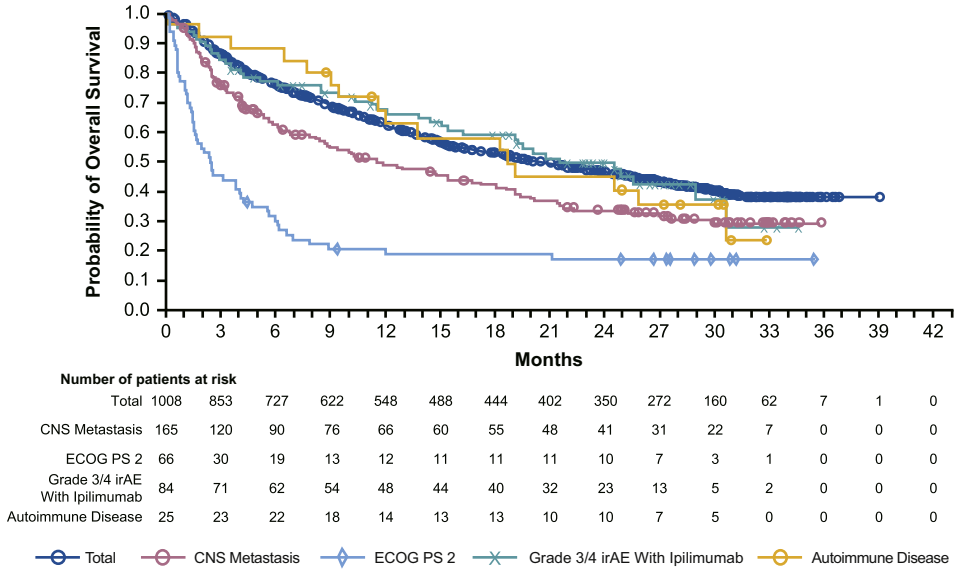

Fig. 1. OS at a minimum follow-up of 18 months in the total population and in challenging subgroups. Median OS (in months) was 21.4 (95% CI, 18.4–24.5) for the total population, 11.6 (95% CI, 8.2–18.1) for CNS metastasis, 2.4 (95% CI, 1.5–4.1) for ECOG PS 2, 21.5 (95% CI, 15.4–30.6) for those who experienced a grade 3/4 irAE with prior ipilimumab, and 18.6 (95% CI, 9.4–30.6) for autoimmune disease, with 18-month OS rates of 53.8% (95% CI, 50.5–57.0), 42.3% (95% CI, 34.1–50.2), 18.8% (95% CI, 10.4–29.2), 59.3% (95% CI, 47.4–69.3), and 58.2% (95% CI, 36.0–75.0), respectively. CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; irAE, immune-related adverse event; OS, overall survival.

was similar to the percentage reported in the total population (18.2%) and in the phase II Anti-PD-1 Brain Collaboration (ABC) study (16.0%), which included a cohort of patients (cohort B, n = 25) with asymptomatic melanoma brain metastases who received nivolumab monotherapy [11]. Although nivolumab was tolerated in patients with melanoma brain metastases in CheckMate 172 and the ABC study, survival outcomes were worse in our analysis, with a median OS of 11.6 and 18.5 months (cohort B), respectively [11]. This discrepancy may be due to differences in baseline characteristics. For example, 10.9% of patients with a CNS metastasis in CheckMate 172 had an ECOG PS of 2 versus 0% in the ABC study (cohort B) [11]. In addition, 5.5% of patients with a CNS metastasis in CheckMate 172 had mucosal melanoma, an aggressive malignancy with a poor response to conventional therapies [12]. In the ABC study, a higher proportion of patients achieved an intracranial response with nivolumab plus ipilimumab than with nivolumab alone, suggesting that patients with melanoma brain metastases may benefit from first-line treatment with nivolumab plus ipilimumab [11].

Patients with an ECOG PS 2 had the poorest survival outcomes, which is consistent with previous findings [13]. However, among these 66 patients, 27.3% had M1c disease with brain metastases, 13.6% had mucosal melanoma, and 78.8% had lactate dehydrogenase levels greater than the upper limit of normal. These data indicate that some patients in the ECOG PS 2 group also had other baseline characteristics that may have contributed to the poor survival outcomes. There are limited published data to guide oncologists regarding the use of immune checkpoint inhibitors in patients with a poor performance status [14]. Treatment decisions may depend on potential benefits and toxicities given other concurrent conditions (e.g. high-dose steroids in the case of progressive brain metastases) and the use of best supportive care.

Previous studies of immune checkpoint inhibitors have also excluded patients with pre-existing autoimmune diseases, such as ulcerative colitis, Crohn's disease, and rheumatoid arthritis. Exclusion of these patients was based primarily on the concern that patients who already have heightened and aberrant immune function could be at an increased risk for additional organ inflammation with immune-activating agents [15]. In this analysis, which included a limited number of patients with autoimmune disease (n = 25), the rate of grade 3/4 treatment-related AEs was similar between the autoimmune disease subgroup and the total population (16.0% versus 18.2%, respectively); however, more patients with autoimmune disease had an AE that required immune-modulating medication (28.0% versus 20.6%, respectively). In addition, the median OS in patients with autoimmune disease was similar to that reported in the total population (18.6 versus 21.4 months). Retrospective series and case reports suggest that autoimmunity is often exacerbated by immune checkpoint inhibitors but is generally manageable with standard treatment algorithms [15]. In a retrospective analysis of 52 patients with advanced melanoma and autoimmune disease, 33% of patients achieved a response

to anti-PD-1 treatment and only 2 patients (4%) discontinued treatment because of flaring of their autoimmune disorder [16]. Similar results were reported in another retrospective analysis (n = 19), in which 32% of patients with advanced melanoma and autoimmune disease achieved a response and no patients discontinued treatment because of flaring of their autoimmune disorder [17]. These data suggest that autoimmune disease may not preclude treatment with immune checkpoint inhibitors [15].

Treatment with ipilimumab is associated with irAEs resulting from increased immune activation, likely due to its mechanism of action [18]. Some data suggest a potential association between clinical benefit and the induction of irAEs with anti-CTLA-4 [19] and anti-PD-1 [20] treatment in patients with advanced melanoma. Owing to the different, but also immune-activating, mechanism of action of nivolumab, patients who experienced a grade 3/4 irAE with prior ipilimumab were excluded from pivotal studies of immune checkpoint inhibitors. In this analysis, patients who experienced a grade 3/4 irAE with prior ipilimumab had a lower incidence of grade 3/4 treatment-related AEs in response to nivolumab than did patients in the total population (11.9% versus 18.2%, respectively). These data suggest that some patients who experience a grade 3/4 irAE with an immune checkpoint inhibitor in the first-line setting may be able to safely receive an immune checkpoint inhibitor in the second-line setting.

This large, phase II clinical trial of patients with advanced melanoma who progressed on or after ipilimumab demonstrated a safety profile for nivolumab that is consistent with that of prior clinical trials. This study provides important information regarding safety and survival outcomes in challenging subgroups who are often excluded from clinical trials. These findings support further evaluation of these patient populations to better reflect the clinical characteristics of patients with advanced melanoma.

Data sharing

Bristol-Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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D. Schadendorf has received grants, personal fees, and non-financial support from Bristol-Myers Squibb and Novartis for participation in advisory boards; has received speaker honoraria and patients' fees paid to his institution from Bristol-Myers Squibb and Novartis; has received personal fees and non-financial support from Roche, MSD/Merck, Amgen, Merck-EMD, Pierre Fabre, Philogen, and Incyte for participation in advisory boards; has received speaker honoraria and patients' fees paid to his institution from Roche, MSD/Merck, Amgen, Merck-EMD, Pierre Fabre, Philogen, and Incyte; has received non-financial support and patients' fees paid to his institution from Regeneron; has received speaker's honoraria and personal fees for participation in advisory boards from Sanofi; has received personal fees and non-financial support for participation in advisory boards and patients' fees paid to his institution from 4SC; and has received personal fees from Array and Pfizer for participation in advisory boards. P.A. Ascierto declares a consulting or advisory role for Bristol-Myers Squibb, Roche-Genentech, MSD, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, New-Link Genetics, MedImmune, AstraZeneca, Syndax, Sun Pharmaceuticals, Sanofi, Idera, Ultimovacs, Sandoz, and Immunocore; has received research funds from Bristol-Myers Squibb and Array; and has received travel support from MSD. J. Haanen has received grants from Bristol-Myers Squibb, Novartis, MSD, and Neon Therapeutics for research performed at his institution; and has received financial compensation paid to his institution from AstraZeneca, Celsius Therapeutics, Bayer, Bristol-Myers Squibb, MSD, Merck Serono, Pfizer, GSK, Neon Therapeutics, Immunocore, Seattle Genetics, Roche/Genentech, and Gadeta for serving as an advisor. E. Espinosa has received personal fees from Bristol-Myers Squibb for participation in advisory boards. L. Demidov has received grants from Novartis for research performed at his institution; has received personal fees from Novartis, Bristol-Myers Squibb, MSD, and BIOCAD for travel and accommodations during congresses; and has received personal fees from Roche, Bristol-Myers Squibb, and BIOCAD for participation in advisory boards. C. Garbe has received grants and personal fees from Bristol-Myers Squibb, Novartis, Roche, and Sanofi for participation in advisory boards; has also received personal fees from Amgen, MSD, and Pierre Fabre for participation in advisory boards; and has received grants and personal fees from NeraCare and personal fees from Philogen for serving as an advisor. M. Guida has received grants from Bristol-Myers

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Appendix A. Supplementary data

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