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Original Research

Safety and efficacy of nivolumab in patients with rare melanoma subtypes who progressed on or after ipilimumab treatment: a single-arm, open-label, phase II study (CheckMate 172)

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Abstract ***Background:*** Nivolumab has been widely studied in non-acral cutaneous melanoma; however, limited data are available in other melanoma subtypes. We report outcomes by melanoma subtype in patients who received nivolumab after progression on prior ipilimumab.
Patients and methods: CheckMate 172 was a phase II, single-arm, open-label, multicentre study that evaluated nivolumab in patients with advanced melanoma who progressed on or after ipilimumab. Patients received 3 mg/kg of nivolumab, every 2 weeks for up to 2 years. The primary end-point was incidence of grade ≥3, treatment-related select adverse events (AEs).
Results: Among 1008 treated patients, we report data on patients with non-acral cutaneous melanoma (n = 723 [71.7%]), ocular melanoma (n = 103 [10.2%]), mucosal melanoma (n = 63 [6.3%]), acral cutaneous melanoma (n = 55 [5.5%]) and other melanoma subtypes (n = 64 [6.3%]). There were no meaningful differences in the incidence of grade ≥3, treatment-related select AEs among melanoma subtypes or compared with the total population. No new safety signals emerged. At a minimum follow-up of 18 months, median overall survival was 25.3 months for non-acral cutaneous melanoma and 25.8 months for acral cutaneous melanoma, with 18-month overall survival rates of 57.5% and 59.0%, respectively. Median overall survival was 12.6 months for ocular melanoma and 11.5 months for mucosal melanoma, with 18-month overall survival rates of 34.8% and 31.5%, respectively.
Conclusions: The safety profile of nivolumab after ipilimumab is similar across melanoma subtypes. Compared with non-acral cutaneous melanoma, patients with acral cutaneous melanoma had similar survival outcomes, whereas those with ocular and mucosal melanoma had lower median overall survival.
ClinicalTrials.gov ID: : NCT02156804.

1. Introduction

Rare forms of melanoma (mucosal, ocular and acral cutaneous melanoma, each accounting for ≤5% of all melanomas [1–3]) are genetically distinct from the most common form of melanoma that arises on hair-bearing skin (non-acral cutaneous melanoma). Approximately 40–50% of patients with non-acral cutaneous melanoma have an activating mutation in the *BRAF* gene [4]. Mucosal melanoma, which originates from mucosal epithelia, and ocular melanoma, which most often develops in the middle layer of the eye (uveal melanoma), are genetically distinct [5,6]. *BRAF* mutations are rare (≤10%) in mucosal melanoma [7] and are absent in ocular melanoma [6]. Acral cutaneous melanoma, which arises on non–hair-bearing skin, is also genetically distinct, with a low frequency of *BRAF* mutations (15%) [5]. A minority (15% at most) of patients with mucosal and acral cutaneous melanoma have mutations in *KIT*, and the majority (90%) of those with ocular melanoma have mutations in *GNAQ* and *GNA11* [5].

There is some evidence to suggest that tumour mutational burden (TMB) may contribute to the likelihood of response to anti-programmed death receptor 1 (PD-1) treatment in patients with melanoma [8]. Non-acral cutaneous melanoma has a genetic signature that

is associated with ultraviolet (UV) DNA damage, and this signature contributes to the high TMB that is seen in melanoma [5,9]. In contrast, acral cutaneous melanomas and non-cutaneous melanomas are less affected by UV radiation and have a low TMB [8,10]. It is therefore possible that the clinical benefit associated with immune checkpoint inhibitors may differ between non-acral cutaneous melanoma and rare melanoma subtypes. One challenge associated with exploring this possibility is that patients with rare melanoma subtypes are often excluded from registrational studies. For example, in the phase III studies CheckMate 066 [11] and CheckMate 037 [12], which led to the approval of nivolumab (anti–PD-1) monotherapy for the treatment of metastatic melanoma, patients with ocular melanoma were not included, and clinical outcomes for those with acral cutaneous melanoma were not reported separately.

CheckMate 172 is a large, phase II clinical trial of nivolumab in patients with advanced melanoma who progressed on or after ipilimumab [13]. Eligible patients included those with different melanoma subtypes and challenging subgroups. Here, we report the safety and overall survival (OS) results by melanoma subtype in patients who received nivolumab in CheckMate 172. For additional details on the safety and efficacy of nivolumab in challenging subgroups in CheckMate 172, please see our companion manuscript [14].

2. Patients and methods

Methods are defined in detail below and are briefly summarised in our companion manuscript [14].

2.1. Patients

Eligible patients were aged ≥18 years with previously treated, unresectable, histologically confirmed, stage III or IV melanoma (based on the 7th edition of the American Joint Committee on Cancer Guidelines [15]) and disease progression or recurrence after prior treatment containing an anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibody. Patients were required to have evaluable disease by computed tomography or magnetic resonance imaging scan per Response Evaluation Criteria In Solid Tumors version 1.1 or clinically apparent disease that the investigator could follow for response. Previous chemotherapy, interferon in the adjuvant setting, interleukin 2, BRAF/MEK inhibitors and KIT inhibitors were permitted. Patients must have completed previous chemotherapy or immunotherapy at least 4 weeks before nivolumab treatment was initiated, with all adverse events (AEs) having either returned to baseline or stabilised. Patients with central nervous system (CNS) metastases (treated or untreated) with a life expectancy of >3 months were eligible if they were asymptomatic or neurologically returned to baseline. Patients with untreated, symptomatic CNS metastases and conditions requiring treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of nivolumab were excluded.

This study was conducted in accordance with Good Clinical Practices as defined by the International Conference on Harmonisation and in compliance with the study protocol, which was approved by the institutional review board/independent ethics committee of each study centre. All patients provided written, informed consent before enrolment.

2.2. Study design

In this phase II, single-arm, open-label study (NCT02156804) conducted at 156 sites in 20 European countries, patients received 3 mg/kg of nivolumab intravenously every 2 weeks for up to 2 years until progression or unacceptable toxicity (Supplementary Fig. S1). Patients who tolerated study drug and had investigator-assessed clinical benefit were eligible for treatment beyond progression.

2.3. End-points and study assessments

The primary end-point was the incidence of grade ≥3 treatment-related select AEs in patients with advanced melanoma who received nivolumab after progression on or after ipilimumab. Select AEs consist of a list of preferred terms organised by category. They include AEs that may differ from or may be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity. The secondary end-points included incidence of all grade ≥3 select AEs, median time to onset and resolution of grade 3/4 select AEs and OS. Safety, tolerability and OS were exploratory end-points in patients with non-acral cutaneous melanoma and rare melanoma subtypes (ocular, mucosal, acral cutaneous and other melanoma subtypes).

Safety assessments and OS 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. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to assess all on-study AEs, treatment-related AEs, serious AEs and treatment-related serious AEs using worst grade. Events were classified by system organ class and by preferred term per Medical Dictionary for Regulatory Activities. Dose delay or discontinuation was based on specific laboratory and AE criteria. OS was defined as the time between the start of nivolumab treatment and date of death due to any cause. OS was evaluated while patients were on treatment and every 3 months after discontinuation.

2.4. Statistical analysis

Demographic characteristics and baseline disease characteristics in the total population and in melanoma subtypes were reported as counts and percentages or as a median and range (age). Safety data were presented as the number and percentage of patients with an AE. OS was estimated using Kaplan-Meier methodology and associated statistics. Median OS and two-sided 95% confidence intervals (CIs) were assessed by the Brookmeyer and Crowley method. OS rates at 18 months and 95% CIs were also reported. Dosing information was reported as a median and range (number of doses received and duration of therapy) or as a count and percentage (number of doses received: 1, 2, 3, 4 or ≥4).

3. Results

3.1. Patients and treatment

The current analysis is based on a minimum follow-up of 18 months (database lock: March 23, 2018) and a

Table 1
Baseline characteristics.

Characteristic	Total patients (N = 1008)	Melanoma subtype				
		Non-acral cutaneous (n = 723)	Ocular (n = 103)	Mucosal (n = 63)	Acral cutaneous (n = 55)	Other (n = 64)[a]
Median age, years (range)	62 (18–89)	61 (18–89)	63 (27–84)	63 (34–86)	67 (37–83)	60 (21–87)
Age ≥65 years, *n* (%)	425 (42.2)	298 (41.2)	44 (42.7)	30 (47.6)	29 (52.7)	24 (37.5)
Male, *n* (%)	557 (55.3)	421 (58.2)	56 (54.4)	23 (36.5)	28 (50.9)	29 (45.3)
ECOG PS, *n* (%)						
0–1	941 (93.4)	678 (93.8)	100 (97.1)	54 (85.7)	52 (94.5)	57 (89.1)
2	66 (6.5)	44 (6.1)	3 (2.9)	9 (14.3)	3 (5.5)	7 (10.9)
Not reported	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Disease stage, *n* (%)						
Stage III	43 (4.3)	38 (5.3)	1 (1.0)	0 (0)	3 (5.5)	1 (1.6)
Stage IV	965 (95.7)	685 (94.7)	102 (99.0)	63 (100.0)	52 (94.5)	63 (98.4)
M stage at study entry, *n* (%)						
M0	32 (3.2)	26 (3.6)	1 (1.0)	1 (1.6)	3 (5.5)	1 (1.6)
M1a	122 (12.1)	100 (13.8)	3 (2.9)	6 (9.5)	9 (16.4)	4 (6.3)
M1b	160 (15.9)	126 (17.4)	5 (4.9)	10 (15.9)	15 (27.3)	4 (6.3)
M1c with brain metastases	165 (16.4)	137 (18.9)	4 (3.9)	9 (14.3)	7 (12.7)	8 (12.5)
M1c without brain metastases	508 (50.4)	320 (44.3)	88 (85.4)	34 (54.0)	21 (38.2)	45 (70.3)
Not reported	21 (2.1)	14 (1.9)	2 (1.9)	3 (4.8)	0 (0)	2 (3.1)
CNS metastases, *n* (%)						
Yes	165 (16.4)	137 (18.9)	4 (3.9)	9 (14.3)	7 (12.7)	8 (12.5)
No	822 (81.5)	572 (79.1)	97 (94.2)	51 (81.0)	48 (87.3)	54 (84.4)
Not reported	21 (2.1)	14 (1.9)	2 (1.9)	3 (4.8)	0 (0)	2 (3.1)
Treatment status of CNS metastasis, *n* (%)						
Treated	120 (11.9)	98 (13.6)	3 (2.9)	8 (12.7)	4 (7.3)	7 (10.9)
Untreated	42 (4.2)	37 (5.1)	1 (1.0)	1 (1.6)	2 (3.6)	1 (1.6)
Treated leptomeningeal	13 (1.3)	10 (1.4)	0 (0)	2 (3.2)	0 (0)	1 (1.6)
***BRAF* mutation status, *n* (%)**						
Wild-type	567 (56.3)	386 (53.4)	45 (43.7)	54 (85.7)	45 (81.8)	37 (57.8)
Mutant	336 (33.3)	294 (40.7)	6 (5.8)	6 (9.5)	9 (16.4)	21 (32.8)
Not reported	105 (10.4)	43 (5.9)	52 (50.5)	3 (4.8)	1 (1.8)	6 (9.4)
Number of prior therapies, *n* (%)[b]						
0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1	399 (39.6)	278 (38.5)	42 (40.8)	32 (50.8)	21 (38.2)	26 (40.6)
2	375 (37.2)	272 (37.6)	41 (39.8)	22 (34.9)	16 (29.1)	24 (37.5)
≥3	234 (23.2)	173 (23.9)	20 (19.4)	9 (14.3)	18 (32.7)	14 (21.9)
Baseline LDH, *n* (%)						
≤ULN	482 (47.8)	375 (51.9)	33 (32.0)	26 (41.3)	24 (43.6)	24 (37.5)
>ULN	514 (51.0)	340 (47.0)	70 (68.0)	33 (52.4)	31 (56.4)	40 (62.5)
≤2× ULN	839 (83.2)	617 (85.3)	72 (69.9)	48 (76.2)	51 (92.7)	51 (79.7)
>2× ULN	157 (15.6)	98 (13.6)	31 (30.1)	11 (17.5)	4 (7.3)	13 (20.3)
Not reported	12 (1.2)	8 (1.1)	0 (0)	4 (6.3)	0 (0)	0 (0)
Prior use of immune-modulating medication, *n* (%)						
Yes	354 (35.1)	265 (36.7)	24 (23.3)	20 (31.7)	25 (45.5)	20 (31.3)
No	654 (64.9)	458 (63.3)	79 (76.7)	43 (68.3)	30 (54.5)	44 (68.8)

CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal.

[a] Among the 64 patients with other melanoma subtypes, 17 were classified as unknown.

[b] Excluding anti–CTLA-4 treatment.

median follow-up (in months) of 14.3 for the total population ($N = 1008$), 16.8 for non-acral cutaneous melanoma ($n = 723$), 10.2 for ocular melanoma ($n = 103$), 6.6 for mucosal melanoma ($n = 63$), 18.5 for acral cutaneous melanoma ($n = 55$) and 10.1 for other melanoma subtypes ($n = 64$). Nearly all patients had discontinued treatment by the cut-off date for this analysis (Supplementary Table S1). The most common reason for treatment discontinuation across all melanoma subtypes and the total population was disease progression.

Baseline characteristics were generally similar across all melanoma subtypes (Table 1). However, the percentage of patients with an Eastern Cooperative Oncology Group performance status of 2 was highest (14.3%) in patients with mucosal melanoma and lowest in those with ocular melanoma (2.9%). CNS metastases were more common in patients with non-acral cutaneous melanoma (18.9%) than in patients with any of the other subtypes, and they were present the least often in those with ocular melanoma (3.9%).

The median number of nivolumab doses received was 12.0 (range, 1–73) for the total population, 13.0 (range, 1–73) for non-acral cutaneous melanoma, 10.0 (range, 1–55) for ocular melanoma, 8.0 (range, 1–53) for mucosal melanoma, 17.0 (range, 2–52) for acral cutaneous melanoma and 12.0 (range, 1–63) for other melanoma subtypes, with a median duration of therapy (in weeks) of 25.1 (range, 0.1–146.2), 26.4 (range, 0.1–146.2), 20.0 (0.1–113.4), 16.7 (range, 0.1–104.4), 34.4 (range, 2.1–106.5) and 23.3 (range, 0.1–131.1), respectively (Supplementary Table S2). Subsequent therapy of any type was received by 35.2% of patients in the total population, 36.9% with non-acral cutaneous melanoma, 25.2% with ocular melanoma, 27.0% with mucosal melanoma, 45.5% with acral cutaneous melanoma and 31.3% with other melanoma subtypes (Supplementary Table S3).

3.2. Safety

Grade 3/4 treatment-related AEs occurred in 18.2% of patients in the total population, 18.8% with non-acral cutaneous melanoma, 14.6% with ocular melanoma, 20.6% with mucosal melanoma, 25.5% with acral cutaneous melanoma and 7.8% with other melanoma subtypes; these events led to treatment discontinuation in 4.8%, 5.3%, 4.9%, 1.6%, 5.5% and 1.6% of patients, respectively. Three treatment-related deaths were reported in the total population; all were in the non-acral cutaneous melanoma 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%), non-acral cutaneous melanoma ($n = 21$, 2.9%) and acral cutaneous melanoma ($n = 3$, 5.5%) (Table 3). Grade 3/4 treatment-related select AEs affected the skin, liver and pulmonary system ($n = 2$

Table 2
Safety summary[a].

n (%)	Total patients ($N = 1008$)		Melanoma subtype									
			Non-acral cutaneous ($n = 723$)		Ocular ($n = 103$)		Mucosal ($n = 63$)		Acral cutaneous ($n = 55$)		Other ($n = 64$)	
	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 grade	Grade 3/4
Any AEs	973 (96.5)	460 (45.6)	694 (96.0)	336 (46.5)	101 (98.1)	43 (41.7)	63 (100.0)	27 (42.9)	53 (96.4)	30 (54.5)	62 (96.9)	24 (37.5)
Treatment-related AEs	681 (67.6)	183 (18.2)	490 (67.8)	136 (18.8)	65 (63.1)	15 (14.6)	42 (66.7)	13 (20.6)	42 (76.4)	14 (25.5)	42 (65.6)	5 (7.8)
Serious AEs	507 (50.3)	312 (31.0)	357 (49.4)	229 (31.7)	44 (42.7)	19 (18.4)	43 (68.3)	26 (41.3)	32 (58.2)	22 (40.0)	31 (48.4)	16 (25.0)
Treatment-related serious AEs	107 (10.6)	73 (7.2)	80 (11.1)	55 (7.6)	6 (5.8)	3 (2.9)	10 (15.9)	8 (12.7)	7 (12.7)	4 (7.3)	4 (6.3)	3 (4.7)
AEs leading to discontinuation	181 (18.0)	108 (10.7)	132 (18.3)	81 (11.2)	25 (24.3)	14 (13.6)	6 (9.5)	4 (6.3)	8 (14.5)	6 (10.9)	10 (15.6)	3 (4.7)
Treatment-related AEs leading to discontinuation	73 (7.2)	48 (4.8)	60 (8.3)	38 (5.3)	6 (5.8)	5 (4.9)	1 (1.6)	1 (1.6)	4 (7.3)	3 (5.5)	2 (3.1)	1 (1.6)
Any AEs that required IMM	482 (47.8)	208 (20.6)	346 (47.9)	153 (21.2)	47 (45.6)	22 (21.4)	27 (42.9)	15 (23.8)	35 (63.6)	10 (18.2)	27 (42.2)	8 (12.5)
Treatment-related deaths[b]	3 (0.3)		3 (0.4)		0 (0)		0 (0)		0 (0)		0 (0)	

AE, adverse event; IMM, immune-modulating medication.
[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 end-point).

Select AE category, *n* (%)	Total patients ($N = 1008$)		Melanoma subtype									
			Non-acral cutaneous ($n = 723$)		Ocular ($n = 103$)		Mucosal ($n = 63$)		Acral cutaneous ($n = 55$)		Other ($n = 64$)	
	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 grade	Grade 3/4
Skin	**266 (26.4)**	**12 (1.2)**	**196 (27.1)**	**8 (1.1)**	**17 (16.5)**	**2 (1.9)**	**14 (22.2)**	**0 (0)**	**22 (40.0)**	**1 (1.8)**	**17 (26.6)**	**1 (1.6)**
Pruritus	78 (7.7)	1 (0.1)	58 (8.0)	1 (0.1)	4 (3.9)	0 (0)	4 (6.3)	0 (0)	5 (9.1)	0 (0)	7 (10.9)	0 (0)
Generalised pruritus	70 (6.9)	2 (0.2)	48 (6.6)	1 (0.1)	6 (5.8)	0 (0)	3 (4.8)	0 (0)	6 (10.9)	1 (1.8)	7 (10.9)	0 (0)
Rash	68 (6.7)	3 (0.3)	53 (7.3)	2 (0.3)	6 (5.8)	0 (0)	1 (1.6)	0 (0)	4 (7.3)	0 (0)	4 (6.3)	1 (1.6)
Maculopapular rash	16 (1.6)	1 (0.1)	12 (1.7)	0 (0)	2 (1.9)	1 (1.0)	1 (1.6)	0 (0)	1 (1.8)	0 (0)	0 (0)	0 (0)
Erythema	13 (1.3)	1 (0.1)	8 (1.1)	1 (0.1)	1 (1.0)	0 (0)	1 (1.6)	0 (0)	2 (3.6)	0 (0)	1 (1.6)	0 (0)
Generalised rash	12 (1.2)	2 (0.2)	10 (1.4)	1 (0.1)	1 (1.0)	1 (1.0)	0 (0)	0 (0)	1 (1.8)	0 (0)	0 (0)	0 (0)
Papular rash	7 (0.7)	1 (0.1)	7 (1.0)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	2 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Autoimmune dermatitis	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pemphigoid	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endocrine	**170 (16.9)**	**18 (1.8)**	**123 (17.0)**	**17 (2.4)**	**14 (13.6)**	**0 (0)**	**8 (12.7)**	**0 (0)**	**10 (18.2)**	**0 (0)**	**15 (23.4)**	**1 (1.6)**
Hypothyroidism	102 (10.1)	2 (0.2)	74 (10.2)	1 (0.1)	8 (7.8)	0 (0)	2 (3.2)	0 (0)	7 (12.7)	0 (0)	11 (17.2)	1 (1.6)
Increased blood TSH	13 (1.3)	1 (0.1)	9 (1.2)	1 (0.1)	0 (0)	0 (0)	2 (3.2)	0 (0)	0 (0)	0 (0)	2 (3.1)	0 (0)
Adrenal insufficiency	7 (0.7)	4 (0.4)	5 (0.7)	4 (0.6)	1 (1.0)	0 (0)	0 (0)	0 (0)	1 (1.8)	0 (0)	0 (0)	0 (0)
Hypophysitis	6 (0.6)	4 (0.4)	5 (0.7)	4 (0.6)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypopituitarism	6 (0.6)	2 (0.2)	5 (0.7)	2 (0.3)	0 (0)	0 (0)	1 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diabetes mellitus	5 (0.5)	3 (0.3)	5 (0.7)	3 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Autoimmune thyroiditis	5 (0.5)	1 (0.1)	4 (0.6)	1 (0.1)	0 (0)	0 (0)	1 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Type 1 diabetes mellitus	2 (0.2)	2 (0.2)	2 (0.3)	2 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Lymphocytic hypophysitis	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Secondary adrenocortical insufficiency	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal	**136 (13.5)**	**14 (1.4)**	**93 (12.9)**	**11 (1.5)**	**17 (16.5)**	**0 (0)**	**8 (12.7)**	**1 (1.6)**	**12 (21.8)**	**1 (1.8)**	**6 (9.4)**	**1 (1.6)**
Diarrhoea	131 (13.0)	11 (1.1)	88 (12.2)	9 (1.2)	17 (16.5)	0 (0)	8 (12.7)	0 (0)	12 (21.8)	1 (1.8)	6 (9.4)	1 (1.6)
Colitis	10 (1.0)	3 (0.3)	9 (1.2)	3 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)
Autoimmune colitis	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)	1 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic	**83 (8.2)**	**28 (2.8)**	**62 (8.6)**	**21 (2.9)**	**9 (8.7)**	**2 (1.9)**	**2 (3.2)**	**1 (1.6)**	**5 (9.1)**	**3 (5.5)**	**5 (7.8)**	**1 (1.6)**
Increased ALT	45 (4.5)	13 (1.3)	36 (5.0)	10 (1.4)	3 (2.9)	1 (1.0)	2 (3.2)	1 (1.6)	3 (5.5)	1 (1.8)	1 (1.6)	0 (0)
Increased AST	41 (4.1)	8 (0.8)	31 (4.3)	6 (0.8)	4 (3.9)	1 (1.0)	1 (1.6)	0 (0)	3 (5.5)	1 (1.8)	2 (3.1)	0 (0)
Increased blood AP	22 (2.2)	3 (0.3)	14 (1.9)	2 (0.3)	6 (5.8)	1 (1.0)	0 (0)	0 (0)	1 (1.8)	0 (0)	1 (1.6)	0 (0)
Increased GGT	18 (1.8)	9 (0.9)	14 (1.9)	7 (1.0)	1 (1.0)	1 (1.0)	0 (0)	0 (0)	2 (3.6)	1 (1.8)	1 (1.6)	0 (0)
Autoimmune hepatitis	10 (1.0)	9 (0.9)	7 (1.0)	6 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.6)	2 (3.6)	1 (1.6)	1 (1.6)
Increased blood bilirubin	10 (1.0)	2 (0.2)	9 (1.2)	2 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)
Increased transaminases	6 (0.6)	2 (0.2)	5 (0.7)	2 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)

(*continued on next page*)

Table 3 (*continued*)

Select AE category, *n* (%)	Total patients (N = 1008)		Melanoma subtype									
			Non-acral cutaneous (n = 723)		Ocular (n = 103)		Mucosal (n = 63)		Acral cutaneous (n = 55)		Other (n = 64)	
	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 grade	Grade 3/4
Increased conjugated bilirubin	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Acute hepatitis	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary	**22 (2.2)**	**5 (0.5)**	**17 (2.4)**	**2 (0.3)**	**2 (1.9)**	**2 (1.9)**	**1 (1.6)**	**1 (1.6)**	**0 (0)**	**0 (0)**	**2 (3.1)**	**0 (0)**
Pneumonitis	20 (2.0)	4 (0.4)	15 (2.1)	1 (0.1)	2 (1.9)	2 (1.9)	1 (1.6)	1 (1.6)	0 (0)	0 (0)	2 (3.1)	0 (0)
Acute respiratory failure	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Renal	**17 (1.7)**	**3 (0.3)**	**14 (1.9)**	**3 (0.4)**	**1 (1.0)**	**0 (0)**	**1 (1.6)**	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1.6)**	**0 (0)**
Tubulointerstitial nephritis	2 (0.2)	2 (0.2)	2 (0.3)	2 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Renal failure	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypersensitivity/infusion reaction	**13 (1.3)**	**1 (0.1)**	**8 (1.1)**	**1 (0.1)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**4 (7.3)**	**0 (0)**	**1 (1.6)**	**0 (0)**
Infusion-related reaction	10 (1.0)	1 (0.1)	6 (0.8)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (5.5)	0 (0)	1 (1.6)	0 (0)

AE, adverse event; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; TSH, thyroid-stimulating hormone.

each, 1.9%) in the ocular melanoma subgroup and the gastrointestinal tract, liver and pulmonary system (n = 1 each, 1.6%) in the mucosal melanoma subgroup.

3.3. Efficacy

Median OS was similar in patients with acral cutaneous melanoma (25.8 months [95% CI, 15.1–30.6]) and non-acral cutaneous melanoma (25.3 months [95% CI, 20.9–28.9]), with 18-month OS rates of 59.0% and 57.5%, respectively (Fig. 1 and Supplementary Table S4). Compared with these groups, a lower median OS was observed in patients with ocular melanoma (12.6 months [95% CI, 10.2–15.1]) and mucosal melanoma (11.5 months [95% CI, 6.4–15.0]), with 18-month OS rates of 34.8% and 31.5%, respectively.

4. Discussion

This analysis represents the largest report to date of the safety and efficacy of nivolumab in patients with rare melanoma subtypes who were treated in a single study. The safety profile of nivolumab after ipilimumab was similar across the study population, regardless of melanoma subtype. There were no meaningful differences in the incidence of grade 3/4 treatment-related select AEs, and no new safety signals were identified in any melanoma subtype.

Acral cutaneous melanoma has a lower TMB than non-acral cutaneous melanoma [10], which may be due to reduced UV exposure at acral sites. This raises the possibility that patients with acral cutaneous melanoma may experience reduced clinical benefit with immune checkpoint inhibitors. The data in this study of 55 patients with metastatic melanoma arising from acral sites suggested that there was no reduction of clinical benefit with nivolumab in patients with acral cutaneous melanoma compared with those with non-acral cutaneous melanoma.

The subgroup of 103 nivolumab-treated patients with ocular melanoma is the largest group of anti–PD-1-treated patients with ocular melanoma described to date; however, lower median OS was observed in this population. The median OS of 12.6 months in our analysis of patients with ocular melanoma was comparable with that reported in the largest case series of patients with ocular melanoma (n = 56 eligible patients, median OS of 7.6 months) [16], and the 18-month OS rate in that analysis (~30%) is similar to that reported here (34.8%). Studies have also evaluated clinical outcomes with ipilimumab in patients with ocular melanoma, with some evidence to suggest benefit in a small proportion of patients (GEM-1 study: n = 1 [7.7%] with partial response and n = 6 [46%] with stable disease [17]; DeCOG study: no responses and n = 16 [47%] with

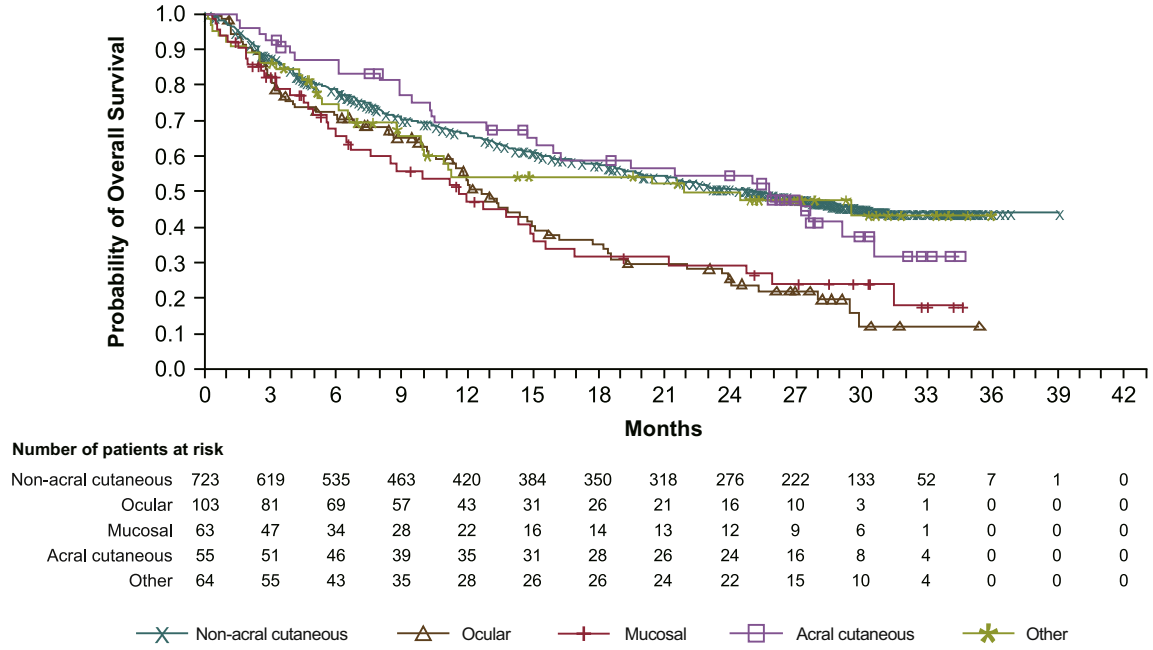

Fig. 1. OS at a minimum follow-up of 18 months in patients with non-acral cutaneous, ocular, mucosal, acral cutaneous and other melanoma subtypes. Median OS (in months) was 25.3 (95% CI, 20.9–28.9) for non-acral cutaneous melanoma, 12.6 (95% CI, 10.2–15.1) for ocular melanoma, 11.5 (95% CI, 6.4–15.0) for mucosal melanoma, 25.8 (95% CI, 15.1–30.6) for acral cutaneous melanoma and 21.8 (95% CI, 9.8–not reached) for other melanoma subtypes, with 18-month OS rates of 57.5% (95% CI, 53.7–61.2), 34.8% (95% CI, 24.8–45.0), 31.5% (95% CI, 19.0–44.7), 59.0% (95% CI, 44.2–71.1) and 54.0% (95% CI, 40.3–65.9), respectively. CI, confidence interval; OS, overall survival.

stable disease [18]). Overall, further investigation is needed in this population.

In a pooled analysis that assessed the benefit of anti–PD-1 therapy in 86 patients with mucosal melanoma, the median progression-free survival (PFS) with nivolumab monotherapy was 3.0 months for patients with mucosal melanoma and 6.2 months for those with non-acral cutaneous melanoma [1]. OS data were not reported. In our analysis, the median OS was 11.5 months for the subgroup of 63 patients with mucosal melanoma and 25.3 months for those with non-acral cutaneous melanoma. Survival data from both studies (PFS in the pooled analysis and OS in our analysis) suggest that patients with mucosal melanoma have ~50% of the clinical benefit when compared with patients who have non-acral cutaneous melanoma. D′Angelo et al [1] also reported a numerically higher median PFS with nivolumab plus ipilimumab (5.9 months) compared with nivolumab alone (3.0 months) in patients with mucosal melanoma, suggesting that nivolumab plus ipilimumab may be a better treatment option than nivolumab monotherapy in some patients with mucosal melanoma.

This large, phase II clinical trial provides important information regarding safety and survival outcomes with nivolumab in patients with rare melanoma subtypes. The safety profile of nivolumab after prior ipilimumab was generally similar between non-acral cutaneous melanoma and rare melanoma subtypes. There were clear differences in survival outcomes between subtypes. Immunotherapy is given with the aim of gaining durable disease control [19]. This study provides evidence that the likelihood of achieving disease control is similar between patients with acral cutaneous melanoma and those with non-acral cutaneous melanoma. Although the median OS for patients with ocular and mucosal melanoma was similar in this study, additional research is needed to determine whether there is a cohort of patients with mucosal melanoma who may derive durable disease control with nivolumab.

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.

Role of the funding source

This work was supported by Bristol-Myers Squibb (Princeton, NJ, USA).

Conflict of interest statement

P.N. has received personal fees from Bristol-Myers Squibb for participation in trial steering committees and

advisory boards and has received fees for advisory boards or speaker′s bureau from AstraZeneca, Immunocore, Ipsen, Merck, MSD, Novartis, Pfizer, Pierre Fabre and Roche. P.A.A. declares a consulting or advisory role for Bristol-Myers Squibb, Roche-Genentech, MSD, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, NewLink Genetics, MedImmune, AstraZeneca, Syndax Pharmaceuticals, 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.H. 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. 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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.07.010.

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