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ORIGINAL REPORT

Efficacy and Safety of Nivolumab Alone or in Combination With Ipilimumab in Patients With Mucosal Melanoma: A Pooled Analysis

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ABSTRACT

Purpose

Mucosal melanoma is an aggressive malignancy with a poor response to conventional therapies. The efficacy and safety of nivolumab (a programmed death-1 checkpoint inhibitor), alone or combined with ipilimumab (a cytotoxic T-lymphocyte antigen-4 checkpoint inhibitor), have not been reported in this rare melanoma subtype.

Patients and Methods

Data were pooled from 889 patients who received nivolumab monotherapy in clinical studies, including phase III trials; 86 (10%) had mucosal melanoma and 665 (75%) had cutaneous melanoma. Data were also pooled for patients who received nivolumab combined with ipilimumab (n = 35, mucosal melanoma; n = 326, cutaneous melanoma).

Results

Among patients who received nivolumab monotherapy, median progression-free survival was 3.0 months (95% CI, 2.2 to 5.4 months) and 6.2 months (95% CI, 5.1 to 7.5 months) for mucosal and cutaneous melanoma, with objective response rates of 23.3% (95% CI, 14.8% to 33.6%) and 40.9% (95% CI, 37.1% to 44.7%), respectively. Median progression-free survival in patients treated with nivolumab combined with ipilimumab was 5.9 months (95% CI, 2.8 months to not reached) and 11.7 months (95% CI, 8.9 to 16.7 months) for mucosal and cutaneous melanoma, with objective response rates of 37.1% (95% CI, 21.5% to 55.1%) and 60.4% (95% CI, 54.9% to 65.8%), respectively. For mucosal and cutaneous melanoma, respectively, the incidence of grade 3 or 4 treatment-related adverse events was 8.1% and 12.5% for nivolumab monotherapy and 40.0% and 54.9% for combination therapy.

Conclusion

To our knowledge, this is the largest analysis of data for anti–programmed death-1 therapy in mucosal melanoma to date. Nivolumab combined with ipilimumab seemed to have greater efficacy than either agent alone, and although the activity was lower in mucosal melanoma, the safety profile was similar between subtypes.

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INTRODUCTION

Ipilimumab, which blocks cytotoxic T-lymphocyte antigen-4,[1] has demonstrated long-term survival in approximately 20% of patients with advanced melanoma.[2] Another immune checkpoint inhibitor, nivolumab, blocks the interaction of the programmed death-1 receptor (PD-1) with its ligands, PD-L1 and PD-L2.[1] In phase III trials, nivolumab monotherapy showed improved overall survival (OS) and a greater objective response rate (ORR) versus dacarbazine in untreated patients with *BRAF* wild-type melanoma[3] and a greater ORR versus chemotherapy in melanoma patients who experienced disease progression and were receiving ipilimumab or ipilimumab and a BRAF inhibitor.[4] In phase II and III clinical trials, nivolumab in combination with ipilimumab improved progression-free survival (PFS) and ORR versus ipilimumab alone in treatment-naïve patients with advanced melanoma.[5,6]

ASSOCIATED CONTENT

Appendix
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Several new agents have been approved for the treatment of cutaneous melanoma since 2011, including the combination of nivolumab and ipilimumab, yet there is a paucity of published information regarding the efficacy and safety of these agents in other melanoma subtypes. In white populations, the primary sites of melanoma are cutaneous (82%), uveal (8%), acral (3%), and mucosal (2%), with approximately 5% being unknown.[7] Mucosal melanomas primarily occur in the head and neck region (eg, nasal and oral cavities), followed by the GI tract (anorectum) and female genital tract (vulva and vagina).[8,9] Accordingly, they occur at a higher incidence in females than in males.[10] Although mucosal melanomas are rare in white populations, accounting for 2% or less of all melanomas,[7,10] the incidence has been reported to be up to 23% in Chinese populations.[11] Prognosis for these patients is poor, with a 5-year survival rate less than that reported for cutaneous or uveal melanoma.[9]

Mucosal melanoma is an aggressive subtype that is largely resistant to traditional therapies.[11,12] A major challenge with mucosal melanoma is that well-established protocols for staging and treatment are lacking, and in the absence of discernable signs or symptoms recognizable by the patient, diagnosis often occurs at late stages.[9] Anatomic location often precludes complete surgical resection because negative margins are difficult to achieve.[9] Response rates with chemotherapy are poor and are generally similar to those observed in cutaneous melanoma.[13] Patients with mucosal, acral, and chronically sun-damaged melanomas infrequently have *BRAF* mutations, but amplifications or activating mutations in the receptor tyrosine kinase, KIT, are common.[14,15] Although typically of short duration, antitumor activity with KIT inhibitors such as imatinib has been observed in mucosal melanoma with certain *KIT* mutations.[14,15]

Although ipilimumab and anti–PD-1 agents have demonstrated activity in mucosal melanoma, the evidence is based on small study populations, retrospective analyses, and single case reports.[16-20] In two retrospective analyses and data from an expanded access program, ipilimumab treatment resulted in an ORR of 7% to 12%, median PFS of 2.3 to 4.3 months, and median OS of 6.4 months in patients with metastatic mucosal melanoma.[16-18] In a phase II study, 1-year OS rates of 38% and 14% were reported for ipilimumab-treated patients with cutaneous (n = 83) and mucosal (n = 7) melanoma, respectively.[19] A patient with mucosal melanoma was reported to achieve a durable, near-complete response when treated with an anti–PD-1 agent after ipilimumab.[20] To better understand the benefit of anti–PD-1–based therapy in this melanoma subtype, we conducted a pooled analysis of data from patients with mucosal melanoma who received nivolumab alone or combined with ipilimumab in clinical trials.

PATIENTS AND METHODS

Study Population

Patients included in the current analyses had a confirmed histologic diagnosis of unresectable stage III or stage IV (advanced) melanoma. Those with primary uveal melanoma were excluded from four of the six nivolumab clinical trials from which the data in these analyses were derived, but patients with primary mucosal melanoma were eligible to participate in all studies. In these studies, M staging of mucosal melanomas was based on cutaneous melanoma criteria. Information regarding the exact location of the primary site of mucosal melanomas was not collected during the trials.

Clinical Trials

Data were pooled from 889 patients with advanced melanoma who had received nivolumab monotherapy (3 mg/kg every 2 weeks until progression or unacceptable toxicity) in one of five ongoing clinical trials: (1) a phase I dose-ranging study in previously treated patients (CA209-003; n = 17)[21]; (2) a phase I biomarker study to evaluate the immunomodulatory effects of nivolumab (CA209-038; n = 85)[22]; (3) a phase III trial of nivolumab versus chemotherapy in treatment-naïve patients with wild-type *BRAF* (CheckMate 066; n = 206)[3]; (4) a phase III trial of nivolumab versus chemotherapy in patients who experienced disease progression after ipilimumab or ipilimumab and a BRAF inhibitor if positive for a *BRAF* V600 mutation (CheckMate 037; n = 268)[4]; and (5) a phase III trial of nivolumab monotherapy or nivolumab plus ipilimumab versus ipilimumab monotherapy in treatment-naïve patients (CheckMate 067; n = 313).[6]

To evaluate the efficacy and safety of nivolumab combined with ipilimumab in mucosal melanoma, data were pooled from CheckMate 067 and an ongoing phase II trial (CheckMate 069) of nivolumab plus ipilimumab versus ipilimumab alone in treatment-naïve patients.[5] Across melanoma subtypes, 407 patients (313 from CheckMate 067; 94 from CheckMate 069) had received nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks for up to four doses, and after combination therapy, patients could have received nivolumab monotherapy at 3 mg/kg every 2 weeks until progression or unacceptable toxicity; 357 patients had received ipilimumab monotherapy (3 mg/kg every 3 weeks for four doses).

Data Analyses

For comparisons of patient demographics between subtypes, *P* values were based on the χ^2 test for categorical variables and two-sample *t* test for continuous variables. Median PFS was based on Kaplan-Meier estimates, with two-sided 95% CIs computed using the Brookmeyer and Crowley method. Hazard ratios and corresponding 95% CIs were estimated using an unstratified Cox proportional hazards model. In an exploratory analysis, *P* values for comparisons of PFS between treatment groups within each subtype were calculated using an unstratified log-rank test. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in all studies except CA209-003, in which RECIST version 1.0 (with modification) was used.[3-6,21,22] The proportion of patients with a confirmed complete or partial response (ORR) was calculated for each pooled data set, with 95% CIs on the basis of the Clopper-Pearson method. Kaplan-Meier methodology was used to calculate the duration of response, defined as the time between the date of the first documented objective response and the date of the first subsequent disease progression or death, whichever occurred first. OS was not included in the analyses because of the lack of mature data for most of the studies. No formal comparisons were made between subtypes for any efficacy end point.

ORR and PFS were also evaluated in the pooled data sets according to PD-L1 status, which was evaluated with a verified immunohistochemical assay using a rabbit monoclonal antihuman antibody (clone 28-8), described previously.[23] Each biopsied tissue sample was scored with a cutoff of $\geq$ 5% or $<$ 5% of tumor cells having cell-surface PD-L1 staining of any intensity in a section with at least 100 evaluable tumor cells. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Patients were evaluated for safety if they had received at least one dose of nivolumab monotherapy or one dose each of nivolumab and ipilimumab as combination therapy.

RESULTS

Patient Characteristics and Treatment

Among 889 patients who received nivolumab monotherapy, 86 (10%) with mucosal melanoma and 665 (75%) with cutaneous melanoma were included in the analyses. For those who received nivolumab combined with ipilimumab (n = 407), 35 patients (9%)

with mucosal melanoma and 326 (80%) with cutaneous melanoma were included; 36 of 357 patients (10%) with mucosal melanoma and 269 (75%) with cutaneous melanoma had received ipilimumab monotherapy. The remaining 11% to 15% of patients within each pooled group were diagnosed with acral melanoma, uveal melanoma, or unknown primaries.

Baseline demographics were balanced between mucosal and cutaneous melanoma subtypes and across treatment groups, age, Eastern Cooperative Oncology Group performance status, and M stage (Table 1). However, relative to cutaneous melanoma, a higher percentage of patients with mucosal melanoma were female ($P = .0035$ for nivolumab monotherapy; $P = .0114$ for combination therapy), and a lower percentage had tumor PD-L1 expression $\geq 5\%$ ($P = .0071$ for nivolumab monotherapy). Although the differences were not statistically significant, more patients with mucosal melanoma had elevated lactate dehydrogenase (LDH) levels. More patients with cutaneous melanoma had a *BRAF* mutation, consistent with the known molecular pathology of this subtype compared with mucosal melanoma. Other genetic abnormalities, such as mutations in *KIT*, were not tested in our study population.

Patients with mucosal melanoma who were treated with nivolumab monotherapy had received a median of 7.0 doses (range, 1 to 34), and those with cutaneous melanoma had received a median of 11.0 doses (range, 1 to 61 doses). In the combination group, a median of 4.0 doses (range, 1 to 28 doses) of nivolumab and 4.0 doses (range, 1 to 4 doses) of ipilimumab were received by patients with mucosal melanoma; patients with cutaneous melanoma received similar dosing (nivolumab, median of 4.0 doses [range, 1 to 39 doses]; ipilimumab, median of 4.0 doses [range, 1 to 4 doses]). Patients treated with ipilimumab monotherapy, regardless of melanoma subtype, received a median of 4.0 doses (range, 1 to 4 doses). In the three treatment groups, median follow-up times ranged from 6.2 to 8.6 months for mucosal melanoma and 10.0 to 11.7 months across melanoma subtypes.

Efficacy

Median PFS was 3.0 months (95% CI, 2.2 to 5.4 months), 5.9 months (95% CI, 2.2 to not reached), and 2.7 months (95% CI, 2.6 to 2.8 months) for patients with mucosal melanoma who

Table 1. Baseline Characteristics of the Patients

Characteristic	Nivolumab Monotherapy, No. (%)		Combination Therapy, No. (%)		Ipilimumab Monotherapy, No. (%)	
	Mucosal (n = 86)	Cutaneous (n = 665)	Mucosal (n = 35)	Cutaneous (n = 326)	Mucosal (n = 36)	Cutaneous (n = 269)
Median age, years (range)	61 (22-89)	60 (18-90)	65 (35-86)	62 (18-87)	61 (31-80)	62 (18-89)
Age category, years						
< 65	49 (57.0)	412 (62.0)	17 (48.6)	191 (58.6)	24 (66.7)	150 (55.8)
≥ 65 and < 75	23 (26.7)	167 (25.1)	8 (22.9)	106 (32.5)	9 (25.0)	81 (30.1)
≥ 75	14 (16.3)	86 (12.9)	10 (28.6)	29 (8.9)	3 (8.3)	38 (14.1)
Sex						
Male	42 (48.8)	432 (65.0)	16 (45.7)	219 (67.2)	17 (47.2)	180 (66.9)
Female	44 (51.2)	233 (35.0)	19 (54.3)	107 (32.8)	19 (52.8)	89 (33.1)
ECOG performance status						
0	57 (66.3)	454 (68.3)	24 (68.6)	253 (77.6)	25 (69.4)	193 (71.7)
1	27 (31.4)	209 (31.4)	10 (28.6)	72 (22.1)	11 (30.6)	76 (28.3)
2	0	0	1 (2.9)	1 (0.3)	0	0
Not reported	2 (2.3)	2 (0.3)	0	0	0	0
M stage*						
M0/M1a/M1b	28 (32.6)	240 (36.1)	12 (34.3)	142 (43.6)	16 (44.4)	111 (41.3)
M1c	57 (66.3)	409 (61.5)	22 (62.9)	184 (56.4)	19 (52.8)	158 (58.7)
Not reported	1 (1.2)	16 (2.4)	1 (2.9)	0	1 (2.8)	0
LDH						
≤ ULN	43 (50.0)	399 (60.0)	18 (51.4)	219 (67.2)	19 (52.8)	182 (67.7)
> ULN	41 (47.7)	253 (38.0)	17 (48.6)	106 (32.5)	16 (44.4)	86 (32.0)
≤ 2 × ULN	69 (80.2)	576 (86.6)	28 (80.0)	295 (90.5)	31 (86.1)	249 (92.6)
> 2 × ULN	15 (17.4)	76 (11.4)	7 (20.0)	30 (9.2)	4 (11.1)	19 (7.1)
Not reported	2 (2.3)	13 (2.0)	0	1 (0.3)	1 (2.8)	1 (0.4)
History of brain metastases						
Yes	1 (1.2)	59 (8.9)	3 (8.6)	8 (2.5)	0	11 (4.1)
No	84 (97.7)	595 (89.5)	32 (91.4)	318 (97.5)	36 (100)	258 (95.9)
Not reported	1 (1.2)	11 (1.7)	0	0	0	0
BRAF status						
Mutant	4 (4.7)	151 (22.7)	2 (5.7)	114 (35.0)	4 (11.1)	95 (35.3)
Wild-type	79 (91.9)	496 (74.6)	33 (94.3)	212 (65.0)	32 (88.9)	174 (64.7)
Not reported	3 (3.5)	18 (2.7)	0	0	0	0
PD-L1 status†						
Positive (≥ 5%)	15 (17.4)	228 (34.3)	10 (28.6)	120 (36.8)	7 (19.4)	121 (45.0)
Negative/indeterminate (< 5%)	49 (57.0)	299 (45.0)	18 (51.4)	126 (38.7)	21 (58.3)	120 (44.6)
Not evaluable/not reported	22 (25.6)	138 (20.8)	7 (20.0)	80 (24.5)	8 (22.2)	28 (10.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.
*On the basis of cutaneous melanoma criteria.
†PD-L1 positivity was defined as ≥ 5% of tumor cells exhibiting cell-surface PD-L1 staining of any intensity in a section containing at least 100 evaluable tumor cells.

received nivolumab monotherapy, combination therapy, and ipilimumab monotherapy, respectively (Fig 1A). For patients with cutaneous melanoma, median PFS was 6.2 months (95% CI, 5.2 to 7.5 months), 11.7 months (95% CI, 8.9 to 16.7), and 3.9 months (95% CI, 2.9 to 4.4 months), respectively (Fig 1B). ORR was 23.3% (95% CI, 14.8% to 33.6%), 37.1% (95% CI, 21.5% to 55.1%), and 8.3% (95% CI, 1.8% to 22.5%) for mucosal melanoma, and 40.9% (95% CI, 37.1% to 44.7%), 60.4% (95% CI, 54.9% to 65.8%), and 21.2% (95% CI, 16.5% to 26.6%) for cutaneous melanoma, among those who received nivolumab, combination therapy, or ipilimumab, respectively (Table 2).

Median time to response was similar for both melanoma subtypes, regardless of treatment, and median duration of response was not reached in most groups (Table 2). There were ongoing responses in 85% of responders who received nivolumab alone or combination therapy (Appendix Fig A1, online only). In patients with mucosal melanoma, median reduction in tumor burden in the target lesions was −1.4% for nivolumab monotherapy, −34.2% for

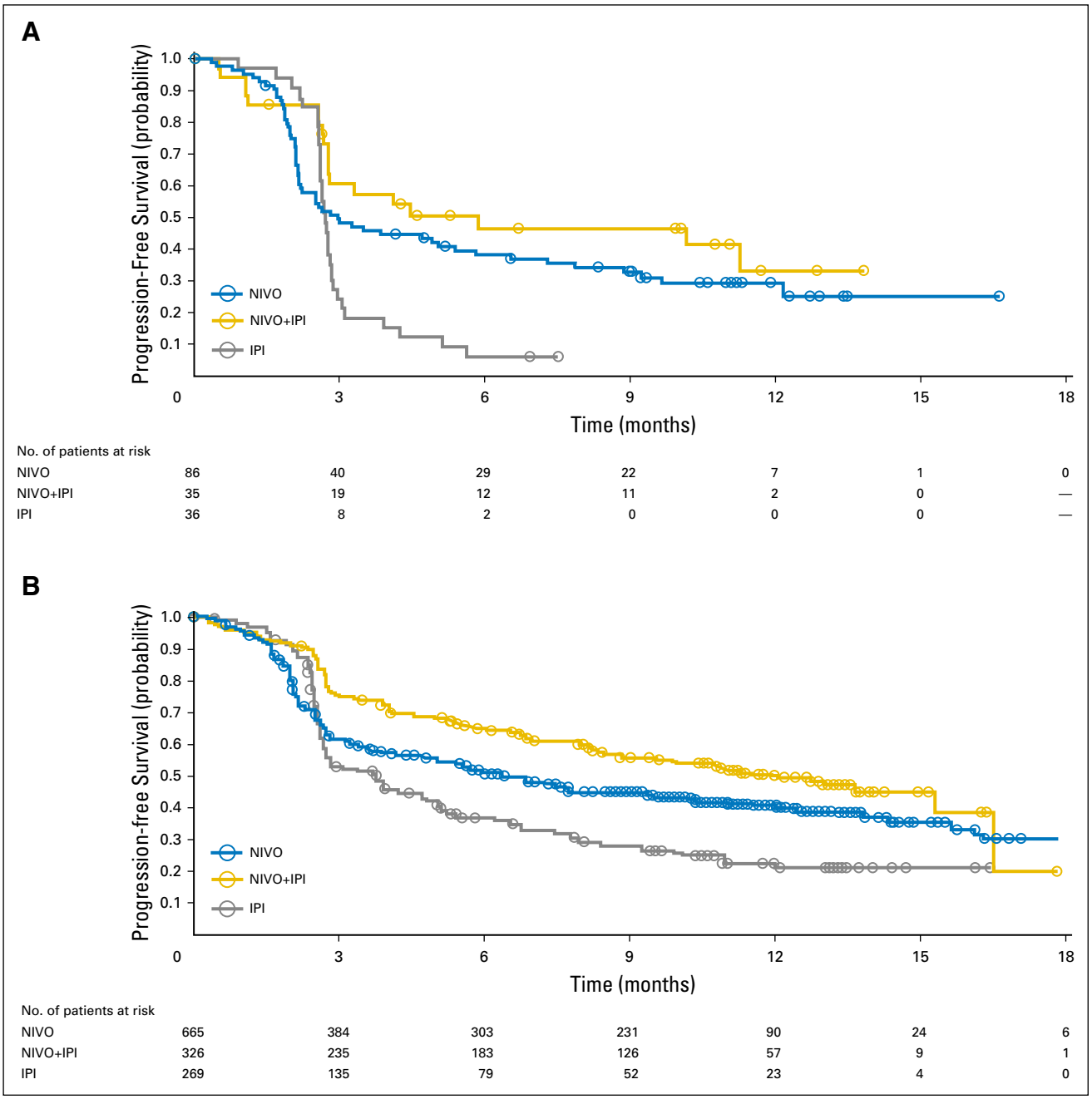

Fig 1. Progression-free survival in patients with (A) mucosal melanoma and (B) cutaneous melanoma who received nivolumab (NIVO) alone, combination therapy of NIVO plus ipilimumab (NIVO+IPI), or ipilimumab alone (IPI). Symbols indicate censored observations. Hazard ratios in (A): 0.61 (95% CI, 0.39 to 0.96; NIVO *v* IPI; $P = .116$); 0.42 (95% CI, 0.23 to 0.75; combination therapy versus ipilimumab; $P = .003$). Hazard ratios in (B): 0.73 (95% CI, 0.61 to 0.87; NIVO *v* IPI; $P = .04$); 0.49 (95% CI, 0.40 to 0.61; NIVO+IPI; $P < .0001$).

combination therapy, and +28.6% for ipilimumab monotherapy (Fig 2). Subgroup analyses in patients with mucosal melanoma suggested improved PFS and higher ORR with nivolumab monotherapy or combination therapy versus ipilimumab monotherapy across patient subgroups (Fig 3). Moreover, there seemed to be longer PFS and higher ORR across patient subgroups for combination therapy compared with nivolumab monotherapy.

Efficacy by PD-L1 status

In patients with mucosal melanoma and tumor PD-L1 expression ≥ 5% (n = 32), ORR was 53.3% (95% CI, 26.6% to 78.7%), 60.0% (95% CI, 26.2% to 87.8%), and 14.3% (95% CI, 0.4% to 57.9%) for nivolumab monotherapy, combination therapy, and ipilimumab monotherapy, respectively (Appendix Table A1, online only); among patients with PD-L1 expression < 5% (n = 88), ORR was 12.2% (95% CI, 4.6% to 24.8%), 33.3% (95% CI, 13.3% to 59.0%), and 9.5% (95% CI, 1.2% to 30.4%), respectively. The magnitude of differences in ORR between patients with PD-L1 expression ≥ 5% and those with PD-L1 expression < 5% were greater for mucosal melanoma than for cutaneous melanoma (Appendix Table A1). Median PFS among patients with mucosal melanoma and tumor PD-L1 expression ≥ 5% was 12.2 months (95% CI, 3.0 months to not reached) for nivolumab monotherapy, not reached for combination therapy, and 2.8 months (95% CI, 2.6 months to not reached) for ipilimumab monotherapy (Appendix Fig A2). Among patients with mucosal melanoma and tumor PD-L1 expression < 5%, median PFS ranged from 2.2 to 2.8 months across treatment groups (Appendix Fig A2).

Safety

Table 3 summarizes the AEs that were considered to be related to study drug treatment in at least 5% of patients. The types and frequencies of treatment-related AEs were generally similar among patients with mucosal and cutaneous melanoma. However, the frequencies of treatment-related grade 3 or 4 AEs were higher for patients with cutaneous melanoma, particularly for those who received combination therapy (54.9% *v* 40.0%). In patients with mucosal melanoma, the most common treatment-related grade 3 or 4 AEs were diarrhea and rash in those who received nivolumab monotherapy and increased lipase and diarrhea for those who received combination therapy. In mucosal and cutaneous melanoma, respectively, the rates of discontinuation due to treatment-related AEs of grade 3 or 4 were 2.3% and 3.9% for nivolumab monotherapy and 17.1% and 31.0% for combination therapy. There were no drug-related deaths in patients with mucosal or cutaneous melanoma who received nivolumab monotherapy or in patients with cutaneous melanoma who received combination therapy. One drug-related death (2.9%) was reported in a patient with mucosal melanoma who received combination therapy. This patient had a history of cardiac disease and died of ventricular arrhythmia 29 days after the last dose of the study drug.

DISCUSSION

To our knowledge, this pooled analysis represents the largest report to date of the efficacy and safety of an immune checkpoint inhibitor in mucosal melanoma. Although relatively small numbers of patients with mucosal melanoma were enrolled in individual nivolumab studies, this pooled analysis of data from six clinical studies has allowed for a more rigorous evaluation of anti–PD-1–based therapy in this subtype. The inclusion of these patients in the clinical trials and exclusion of other melanoma subtypes from most of the studies likely explains the higher incidence of mucosal melanoma in our analyses than is observed in the general population. Nivolumab combined with ipilimumab consistently showed a clinically meaningful improvement in PFS and ORR compared with either agent alone, with most tumor responses being durable. These results were observed across patient subgroups, including those with M1c disease and elevated LDH levels. Safety profiles were consistent with those observed in cutaneous melanoma.

Primary mucosal melanomas can arise from virtually any mucosal membrane, with the female genital tract being a common site of origin.[8,9] In our study population, there was a higher percentage of females among patients with mucosal melanoma,

Table 2. Best Overall Response

Response	Nivolumab Monotherapy		Combination Therapy		Ipilimumab Monotherapy	
	Mucosal (n = 86)	Cutaneous (n = 665)	Mucosal (n = 35)	Cutaneous (n = 326)	Mucosal (n = 36)	Cutaneous (n = 269)
Best overall response, No. (%)						
Complete response	5 (5.8)	46 (6.9)	1 (2.9)	44 (13.5)	0	7 (2.6)
Partial response	15 (17.4)	226 (34.0)	12 (34.3)	153 (46.9)	3 (8.3)	50 (18.6)
Stable disease	19 (22.1)	112 (16.8)	7 (20.0)	41 (12.6)	3 (8.3)	67 (24.9)
Progressive disease	40 (46.5)	245 (36.8)	11 (31.4)	66 (20.2)	27 (75.0)	120 (44.6)
Not evaluable	7 (8.1)	36 (5.4)	4 (11.4)	22 (6.7)	3 (8.3)	25 (9.3)
Objective response rate, % (95% CI)*	23.3 (14.8 to 33.6)	40.9 (37.1 to 44.7)	37.1 (21.5 to 55.1)	60.4 (54.9 to 65.8)	8.3 (1.8 to 22.5)	21.2 (16.5 to 26.6)
Time to objective response, months						
No. of responders	20	272	13	197	3	57
Median (range)	2.3 (1.6 to 6.9)	2.6 (1.2 to 12.5)	2.9 (1.9 to 9.9)	2.8 (1.1 to 11.6)	2.6 (2.5 to 6.6)	2.8 (2.5 to 12.4)
Median duration of response, months (95% CI)	NR	22.0 (22.0 to NR)	NR (7.6 to NR)	NR (13.1 to NR)	2.4 (1.8 to 3.0)	NR (8.8 to NR)

Abbreviation: NR, not reached.
*Proportion of patients with a complete or partial response.

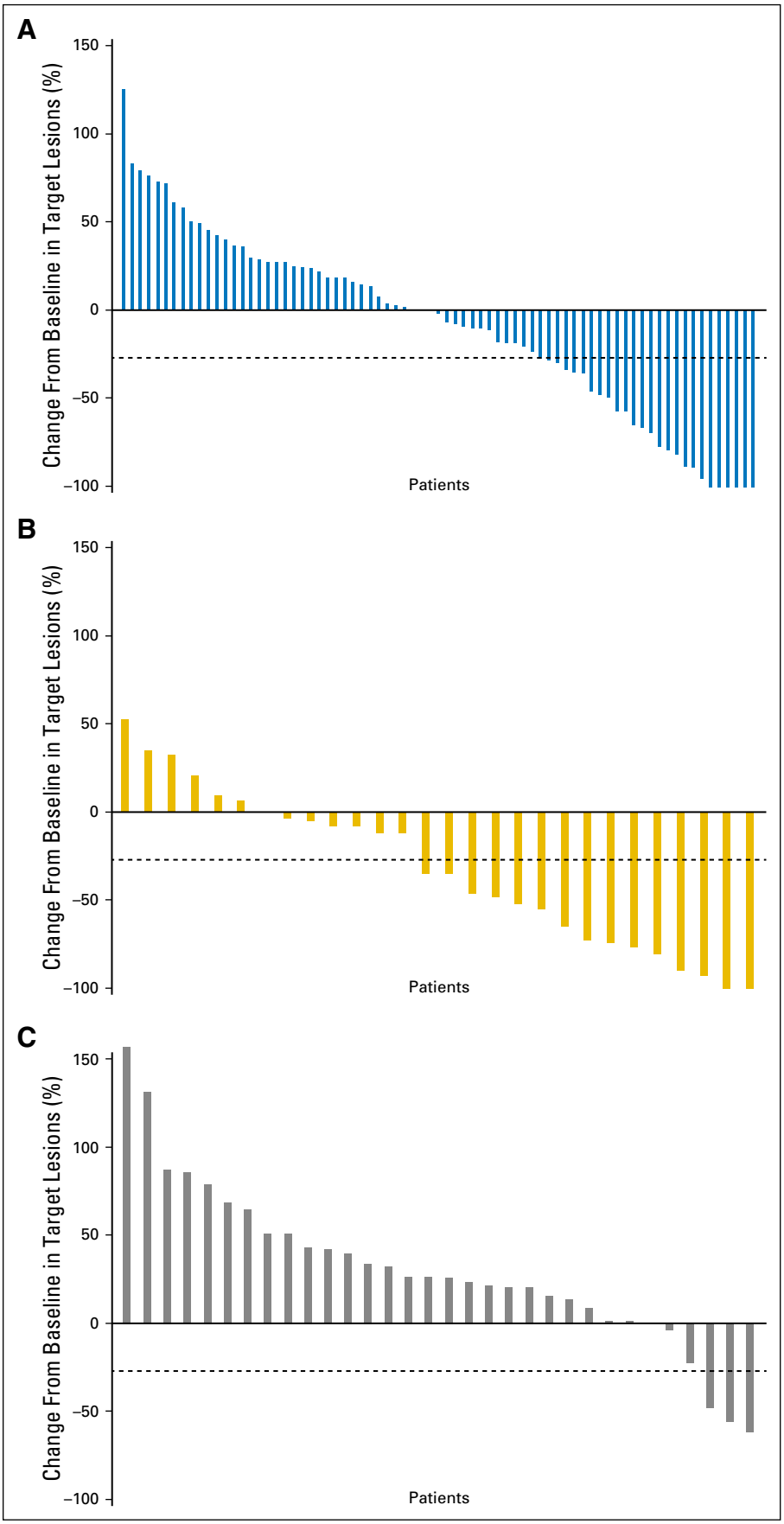

Fig 2. Waterfall plots showing tumor burden change from baseline in patients with mucosal melanoma who received (A) nivolumab alone (n = 75; median change, −1.4%); (B) combination therapy (n = 28; median change, −34.2%); and (C) ipilimumab alone (n = 32; median change, +28.6%). Dashed lines indicate a 30% reduction in tumor burden.

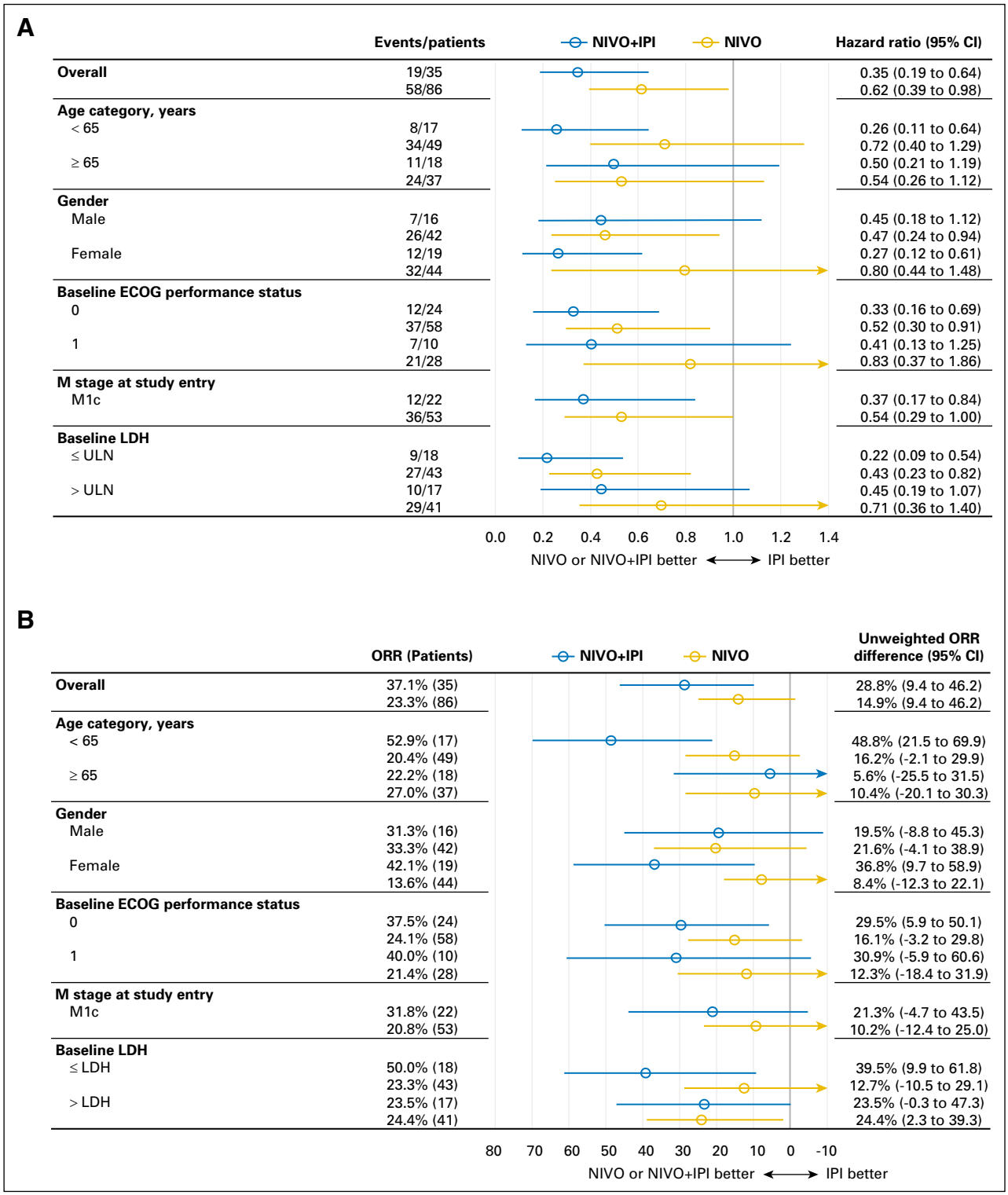

Fig 3. Subgroup analyses of (A) progression-free survival and (B) objective response rate (ORR) for patients with mucosal melanoma. Horizontal bars indicate 95% CIs. ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab alone; LDH, lactate dehydrogenase; NIVO, nivolumab alone, NIVO+IPI, combination therapy.

versus a higher percentage of males in patients with cutaneous melanoma. Mucosal melanomas are considered to be the most aggressive of all melanoma subtypes.[11] A higher percentage of patients with mucosal melanoma in our study had elevated LDH compared with patients with cutaneous melanoma. Although no formal comparisons were made between subtypes, efficacy outcomes seemed to be poorer in mucosal melanoma than in cutaneous melanoma. The exact reasons for the apparent differences in response to treatment between these subtypes remain unclear, yet studies have shown distinct biologic differences among noncutaneous melanomas and

Table 3. Treatment-Related AEs That Occurred in at Least 5% of Patients

AE	Nivolumab Monotherapy, No. (%)*				Combination Therapy, No. (%)*			
	Mucosal (n = 86)		Cutaneous (n = 665)		Mucosal (n = 35)		Cutaneous (n = 326)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any treatment-related AE	57 (66.3)	7 (8.1)	508 (76.4)	83 (12.5)	34 (97.1)	14 (40.0)	306 (93.9)	179 (54.9)
Fatigue	22 (25.6)	1 (1.2)	188 (28.3)	4 (0.6)	13 (37.1)	1 (2.9)	118 (36.2)	17 (5.2)
Diarrhea	13 (15.1)	2 (2.3)	102 (15.3)	7 (1.1)	10 (28.6)	3 (8.6)	144 (44.2)	27 (8.3)
Rash	8 (9.3)	2 (2.3)	106 (15.9)	0	9 (25.7)	1 (2.9)	101 (31.0)	11 (3.4)
Pruritus	9 (10.5)	0	121 (18.2)	1 (0.2)	8 (22.9)	1 (2.9)	117 (35.9)	6 (1.8)
Nausea	7 (8.1)	0	84 (12.6)	0	8 (22.9)	0	81 (24.8)	7 (2.1)
Lipase increased	1 (1.2)	0	26 (3.9)	16 (2.4)	6 (17.1)	5 (14.3)	34 (10.4)	26 (8.0)
Hypothyroidism	4 (4.7)	0	45 (6.8)	0	6 (17.1)	0	50 (15.3)	1 (0.3)
Hyperthyroidism	3 (3.5)	0	19 (2.9)	1 (0.2)	5 (14.3)	1 (2.9)	26 (8.0)	2 (0.6)
Decreased appetite	7 (8.1)	0	51 (7.7)	0	5 (14.3)	1 (2.9)	53 (16.3)	3 (0.9)
Pyrexia	1 (1.2)	0	36 (5.4)	0	5 (14.3)	1 (2.9)	65 (19.9)	4 (1.2)
Thyroiditis	0	0	0	0	4 (11.4)	0	10 (3.1)	1 (0.3)
Colitis	7 (1.1)	4 (0.6)	1 (1.2)	1 (1.2)	3 (8.6)	2 (5.7)	46 (14.1)	32 (9.8)
AST increased	1 (1.2)	0	26 (3.9)	5 (0.8)	3 (8.6)	2 (5.7)	55 (16.9)	18 (5.5)
Maculopapular rash	5 (5.8)	0	28 (4.2)	2 (0.3)	3 (8.6)	1 (2.9)	45 (13.8)	8 (2.5)
Dyspnea	2 (2.3)	0	23 (3.5)	1 (0.2)	3 (8.6)	1 (2.9)	31 (9.5)	3 (0.9)
Vitiligo	4 (4.7)	0	57 (8.6)	1 (0.2)	3 (8.6)	0	26 (8.0)	0
Headache	3 (3.5)	0	36 (5.4)	0	3 (8.6)	0	35 (10.7)	3 (0.9)
ALT increased	0	0	23 (3.5)	8 (1.2)	3 (8.6)	0	61 (18.7)	27 (8.3)
Asthenia	8 (9.3)	0	48 (7.2)	1 (0.2)	3 (8.6)	0	32 (9.8)	1 (0.3)
Constipation	7 (8.1)	0	39 (5.9)	0	3 (8.6)	0	16 (4.9)	1 (0.3)
Vomiting	2 (2.3)	0	39 (5.9)	2 (0.3)	3 (8.6)	0	48 (14.7)	8 (2.5)
Amylase increased	0	0	16 (2.4)	5 (0.8)	2 (5.7)	2 (5.7)	20 (6.1)	8 (2.5)
Pneumonitis	1 (1.2)	0	12 (1.8)	1 (0.2)	2 (5.7)	1 (2.9)	23 (7.1)	4 (1.2)
Anemia	3 (3.5)	0	21 (3.2)	1 (0.2)	2 (5.7)	0	12 (3.7)	2 (0.6)
Arthralgia	1 (1.2)	0	53 (8.0)	0	2 (5.7)	0	37 (11.3)	1 (0.3)
Dizziness	1 (1.2)	0	14 (2.1)	0	2 (5.7)	0	19 (5.8)	1 (0.3)
Hyperhidrosis	3 (3.5)	0	0	0	2 (5.7)	0	10 (3.1)	0
Chills	0	0	19 (2.9)	0	2 (5.7)	0	27 (8.3)	0
Pain	0	0	0	0	2 (5.7)	0	5 (1.5)	0
Vision blurred	3 (3.5)	0	8 (1.2)	0	2 (5.7)	0	8 (2.5)	0
Dry mouth	1 (1.2)	0	22 (3.3)	0	1 (2.9)	0	17 (5.2)	0
Hypophysitis	1 (1.2)	0	0	0	1 (2.9)	0	29 (8.9)	5 (1.5)
Cough	1 (1.2)	0	29 (4.4)	1 (0.2)	1 (2.9)	0	26 (8.0)	0
Weight decreased	3 (3.5)	0	8 (1.2)	1 (0.2)	1 (2.9)	0	20 (6.1)	0
Myalgia	2 (2.3)	0	24 (3.6)	0	1 (2.9)	0	19 (5.8)	0
Abdominal pain	3 (3.5)	0	27 (4.1)	1 (0.2)	0	0	29 (8.9)	1 (0.3)
Treatment-related AEs leading to discontinuation	4 (4.7)	2 (2.3)	36 (5.4)	26 (3.9)	9 (25.7)	6 (17.1)	124 (38.0)	101 (31.0)

Abbreviation: AE, adverse event.
*Patients may have had more than one event.

between cutaneous and noncutaneous melanomas.[8,11,24] These differences include higher ratios of metastasis at diagnosis for mucosal and unknown primary melanomas,[8] and a different pattern of metastasis for mucosal melanomas compared with other subtypes.[24] Furthermore, although we did not collect information on the primary site of mucosal melanomas in our patient population, it is possible that response to treatment may have differed depending on anatomic location.

The distinct biologic characteristics of melanoma subtypes are likely to be explained, at least in part, by differences in genetic alterations.[25-27] *BRAF* gene mutations occur at a much lower rate in mucosal melanomas than in cutaneous melanomas without chronic sun damage.[25] Conversely, gene copy number and structural variations (eg, in *KIT*) are much more common in mucosal melanoma than in cutaneous melanoma.[26] Patients were not selected for mutational status in our analyses; however, the results suggest that nivolumab may be effective in mucosal melanoma regardless of the tumor molecular profile, similar to the demonstrated efficacy of nivolumab in cutaneous melanoma regardless of *BRAF* mutation status.[28]

In our study population, it is interesting to note that more patients with cutaneous melanoma had tumor PD-L1 expression $\geq$ 5% than patients with mucosal melanoma. The reasons for this finding remain unclear, but one hypothesis is that mucosal melanomas may be less immunogenic due to a lower mutational burden.[26] Despite differences in the proportion of patients with tumor PD-L1 expression $\geq$ 5%, ORR was similar between subtypes for nivolumab monotherapy and combination therapy. In contrast, lower activity in mucosal melanoma was observed across treatment groups for patients with tumor PD-L1 expression $<$ 5%. However, an ORR of 33.3% with nivolumab plus ipilimumab in patients with mucosal melanoma and tumor PD-L1 expression $<$ 5% suggests clinical activity of the combination regardless of PD-L1 status. The role of PD-L1 as a biomarker for nivolumab alone or in combination with ipilimumab remains unclear in any melanoma subtype, but the availability of mature OS data may help answer this question.

Poor outcomes have been reported with conventional therapies for mucosal melanoma, and there remains a high unmet need for effective systemic treatments for this subtype.[12] Due to its rarity, mucosal melanoma has not been studied in large, randomized clinical trials. Thus, data supporting the efficacy of new systemic therapies is mostly based on anecdotal evidence and small retrospective analyses. Imatinib has demonstrated efficacy in patients with mucosal melanoma, but treatment is limited to the subset of patients with *KIT* mutations.[14,15] The results of our current analyses support prior reports showing an ORR with ipilimumab of 7% to 12% and a median PFS of 2.3 to 4.3 months in patients with mucosal melanoma.[16-18] Although there are no studies directly comparing agents, the median PFS of 5.9 months and ORR of 37.1% with nivolumab plus ipilimumab suggest that this combination may provide a greater outcome in patients with mucosal melanoma than previously reported with other therapies.

In summary, this large, pooled analysis of data from six clinical studies provides evidence for the efficacy and safety of anti–PD-1–based therapy in an aggressive melanoma subtype with a poor prognosis. Patients may benefit from anti–PD-1–based therapy regardless of the presence of poor prognostic factors, tumor PD-L1 expression, and prior therapy. The results of our analyses, pending mature OS data, suggest that nivolumab alone and in combination with ipilimumab are promising treatment options for mucosal melanoma.

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Efficacy and Safety of Nivolumab Alone or in Combination With Ipilimumab in Patients With Mucosal Melanoma: A Pooled Analysis

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Appendix

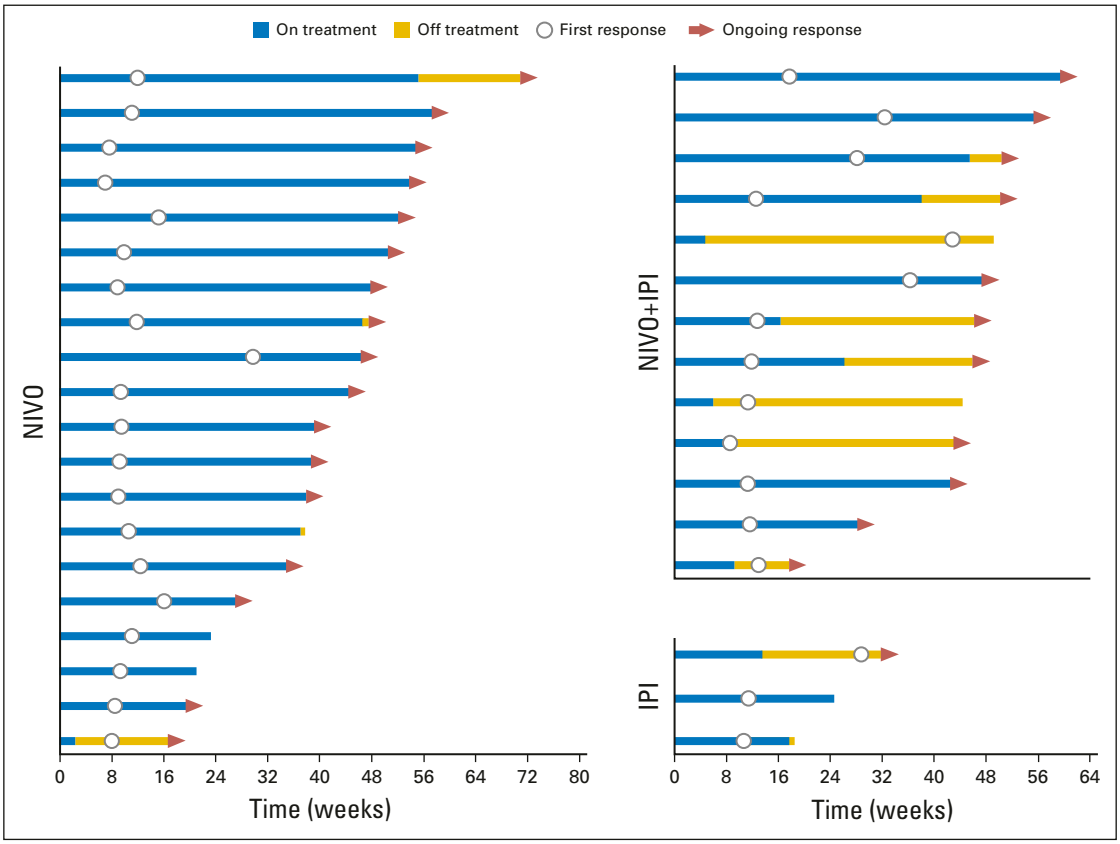

Fig A1. Time to and duration of response in patients with mucosal melanoma. IPI, ipilimumab alone; NIVO, nivolumab alone, NIVO+IPI, combination therapy.

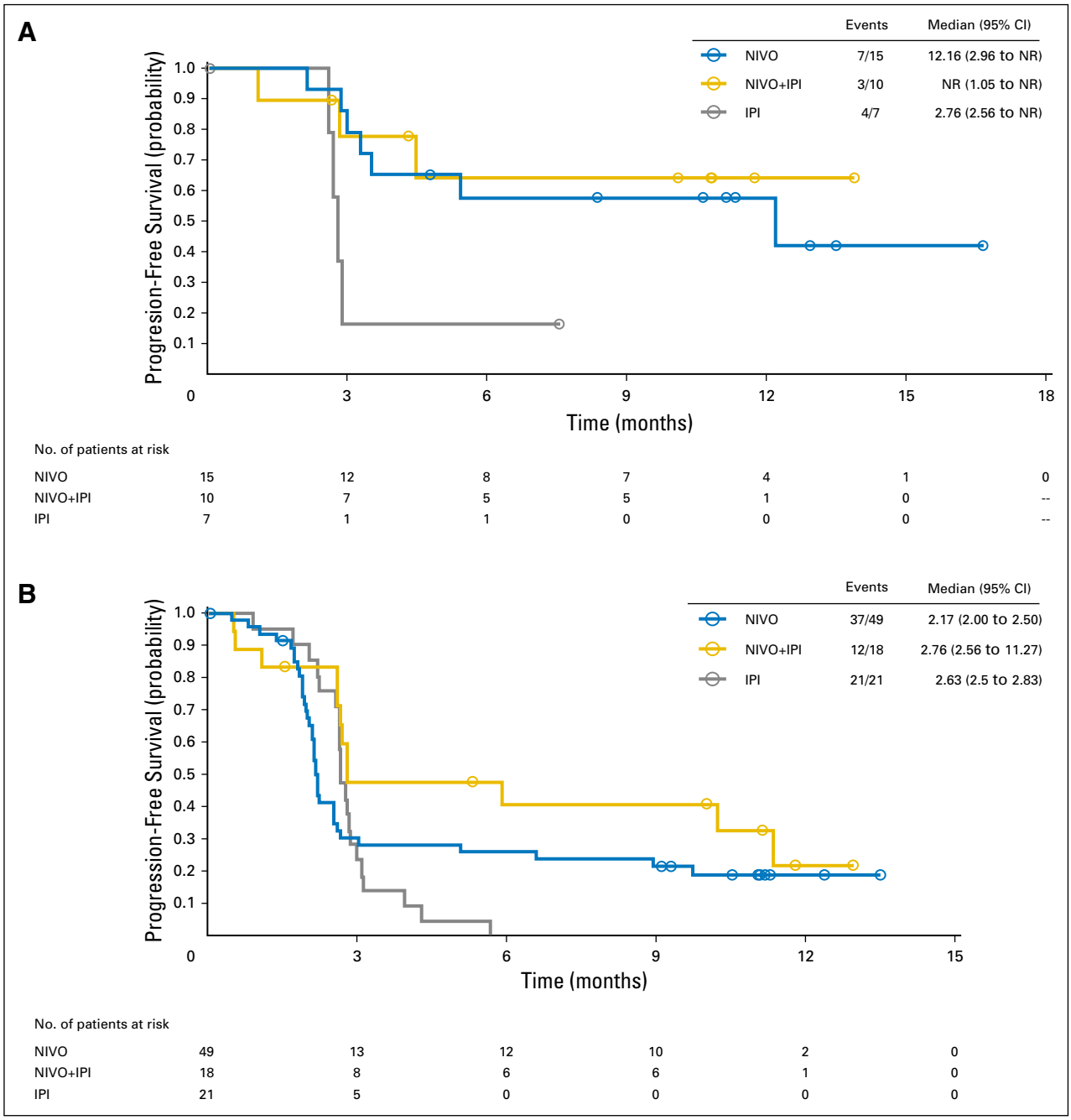

Fig A2. Progression-free survival by programmed death-1 receptor ligand 1 (PD-L1) status in patients with mucosal melanoma. (A) PD-L1 expression ≥ 5%; (B) PD-L1 expression < 5%. IPI, ipilimumab alone; NIVO, nivolumab alone, NIVO+IPI, combination therapy.

Table A1. Best Overall Response by PD-L1 Status

Response	Nivolumab Monotherapy		Combination Therapy		Ipilimumab Monotherapy	
	Mucosal	Cutaneous	Mucosal	Cutaneous	Mucosal	Cutaneous
PD-L1 expression ≥ 5%						
Best overall response, No. (%)	n = 15	n = 228	n = 10	n = 120	n = 7	n = 121
Complete response	2 (13.3)	29 (12.7)	1 (10.0)	12 (10.0)	0	6 (5.0)
Partial response	6 (40.0)	98 (43.0)	5 (50.0)	70 (58.3)	1 (14.3)	24 (19.8)
Stable disease	4 (26.7)	27 (11.8)	2 (20.0)	9 (7.5)	0	37 (30.6)
Progressive disease	3 (20.0)	64 (28.1)	2 (20.0)	25 (20.8)	5 (71.4)	46 (38.0)
Not evaluable	0	10 (4.4)	0	4 (3.3)	1 (14.3)	8 (6.6)
Objective response rate, % (95% CI)*	53.3 (26.6 to 78.7)	55.7 (49.0 to 62.3)	60.0 (26.2 to 87.8)	68.3 (59.2 to 76.5)	14.3 (0.4 to 57.9)	24.8 (17.4 to 33.5)
PD-L1 expression < 5%						
Best overall response, No. (%)	n = 49	n = 299	n = 18	n = 126	n = 21	n = 120
Complete response	1 (2.0)	12 (4.0)	0	17 (13.5)	0	1 (0.8)
Partial response	5 (10.2)	93 (31.1)	6 (33.3)	49 (38.9)	2 (9.5)	22 (18.3)
Stable disease	6 (12.2)	48 (16.1)	3 (16.7)	20 (15.9)	1 (4.8)	22 (18.3)
Progressive disease	30 (61.2)	121 (40.5)	7 (38.9)	30 (23.8)	18 (85.7)	61 (50.8)
Not evaluable	7 (14.3)	25 (8.4)	2 (11.1)	10 (7.9)	0	14 (11.7)
Objective response rate, % (95% CI)*	12.2 (4.6 to 24.8)	35.1 (29.7 to 40.8)	33.3 (13.3 to 59.0)	52.4 (43.3 to 61.3)	9.5 (1.2 to 30.4)	19.2 (12.6 to 27.4)

Abbreviation: PD-L1, programmed death-ligand 1.
*Proportion of patients with a complete or partial response.