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

Sandra P. D'Angelo,[1] James Larkin,[2] Jeffrey A. Sosman,[3] Celeste Lebbé,[4] Benjamin Brady,[5] Bart Neyns,[6] Henrik Schmidt,[7] Jessica C. Hassel,[8] F. Stephen Hodi,[9] Paul Lorigan,[10] Kerry J. Savage,[11] Wilson H. Miller, Jr,[12] Peter Mohr,[13] Ivan Marquez-Rodas,[14] Julie Charles,[15] Martin Kaatz,[16] Mario Sznol,[17] Jeffrey S. Weber,[18] Alexander N. Shoushtari,[1] Mary Ruisi,[19] Joel Jiang,[19] and Jedd D. Wolchok[1]

[1]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; [2]Royal Marsden Hospital, London, UK; [3]Vanderbilt University Medical Center, Nashville, TN; [4]AP-HP Dermatology CIC Departments, Saint-Louis Hospital, INSERM U976, Université Paris Diderot, Paris, France; [5]Cabrini Health, Melbourne, Victoria, Australia; [6]Universitair Ziekenhuis Brussel, Brussels, Belgium; [7]Århus University, Åarhus, Denmark; [8]University Hospital Heidelberg, Heidelberg, Germany; [9]Dana-Farber Cancer Institute, Boston, MA; [10]University of Manchester, Manchester, UK; [11]BC Cancer Agency, University of British Columbia, Vancouver, BC, Canada; [12]Lady Davis Institute and Jewish General Hospital, McGill University, Montreal, QC, Canada; [13]Elbe Kliniken Buxtehude, Buxtehude, Germany; [14]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [15]Grenoble University Hospital, Grenoble Alps University, Grenoble, France; [16]SRH Waldklinikum Gera, University Hospital Jena, Jena, Germany; [17]Yale University School of Medicine and Smilow Cancer Center, Yale-New Haven Hospital, New Haven, CT; [18]Moffitt Cancer Center, Tampa, FL; [19]Bristol-Myers Squibb, Princeton, NJ.

Corresponding author:
Sandra P. D'Angelo, M.D.
Assistant Attending Physician
Memorial Sloan Kettering Cancer Center
300 East 66th Street
New York, NY 10065
Phone: 646-888-4159
Fax: 646-888-4252
E-mail: dangelos@mskcc.org

Supported by Bristol-Myers Squibb Co. (Princeton, NJ).

Running head: Efficacy and safety of nivolumab in mucosal melanoma

Presented at the 12th International Congress of the Society for Melanoma Research, San Francisco, CA, November 18-21, 2015.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

ABSTRACT

Purpose: Mucosal melanoma is an aggressive malignancy with a poor response to conventional therapies. The efficacy and safety of nivolumab (a PD-1 checkpoint inhibitor), alone or combined with ipilimumab (a CTLA-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 (mPFS) 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. In studies of nivolumab combined with ipilimumab, mPFS 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 was 40.0% and 54.9% for combination therapy.

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

INTRODUCTION

Ipilimumab, which blocks cytotoxic T-lymphocyte antigen-4,[1] has demonstrated long-term survival in ~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 progressed on 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]

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 Caucasian populations, the primary sites of melanoma are cutaneous (82%), uveal (8%), acral (3%), and mucosal (2%), with ~5% being unknown.[7] Mucosal melanomas primarily occur in the head and neck region (eg, nasal and oral cavities), followed by the gastrointestinal 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 Caucasian 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 a very 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] Anatomical location often precludes complete surgical resection as 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] While typically of short duration, anti-tumor activity with KIT inhibitors such as imatinib has been observed in mucosal melanoma with certain KIT mutations.[14,15]

While 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.[16,17,18] 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 following 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 histological 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 progressed following 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 (n=313 from CheckMate 067, n=94 from CheckMate 069) had received nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks for up to 4 doses [and

following 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 4 doses).

Data Analyses

For comparisons of patient demographics between subtypes, *P* values were based on the Chi-square test for categorical variables and 2-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 (HRs) 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 dataset, with 95% CIs based on the Clopper and Pearson method. Kaplan-Meier methodology was used to calculate duration of response, defined as the time between the date of first documented objective response and the date of first subsequent disease progression or death, whichever occurred first. OS was not included in the analyses due to the lack of mature data for most of the studies. No formal comparisons were made between subtypes for any efficacy endpoint.

ORR and PFS were also evaluated in the pooled datasets according to PD-L1 status, which was evaluated with a verified immunohistochemical assay using a rabbit monoclonal antihuman antibody (clone 28-8) as described previously.[23] Each biopsied tissue sample was scored with a cutoff of ≥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 11-15% 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, across treatment groups, for age, ECOG performance status, and M stage (Table 1). However, relative to cutaneous melanoma, a higher percentage of patients with mucosal melanoma were female ($P = 0.0035$ for nivolumab monotherapy; $P = 0.0114$ for combination therapy) and a lower percentage had tumor PD-L1 expression ≥5% ($P = 0.0071$ for nivolumab monotherapy). While 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 c-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). In the combination group, a median of 4.0 doses (range, 1 to 28) of nivolumab and 4.0 doses (range, 1 to 4) 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]; ipilimumab, median of 4.0 doses [range, 1 to 4]). Patients treated with ipilimumab monotherapy, regardless of melanoma subtype, received a median of 4.0 doses (range, 1 to 4). In the three treatment groups, median follow-up times ranged from 6.2 to 8.6 months for mucosal melanoma and ranged from 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 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 was 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 Figure A1). In patients with mucosal melanoma, median reduction in tumor burden in the target lesions was -1.4% for nivolumab monotherapy, -34.2% for combination therapy, and +28.6% for ipilimumab monotherapy (Figure 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 (Figure 3). Moreover, there appeared to be longer PFS and higher ORR across patient subgroups for combination therapy compared to 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); 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 Figure 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 Figure 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% versus 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 were 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, nor 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 from ventricular arrhythmia 29 days after the last dose of 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. While 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 into 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 to 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, 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 to patients with cutaneous melanoma. While no formal comparisons were made between subtypes, efficacy outcomes appeared 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 biological differences among non-cutaneous melanomas and between cutaneous and non-cutaneous 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, while 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 biological characteristics of melanoma subtypes are likely to be explained, at least in part, by differences in genetic alterations.[25,26,27] *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 c-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 ≥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 ≥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.[16,17,18] While 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 very 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.

Authors' Disclosures of Potential Conflicts of Interest

Employment: Mary Ruisi, Bristol-Myers Squibb; Joel Jiang**,** Bristol-Myers Squibb. **Leadership Position:** None. **Stock Ownership:** Joel Jiang, Bristol-Myers Squibb; Wilson H. Miller, Jr, Bristol-Myers Squibb; Mary Ruisi, Bristol-Myers Squibb; Mario Sznol, Adaptive Biotechnologies, Amphivena Therapeutics, Intensity; Jeffrey S. Weber, Alder, cCAM, CytomX

Therapeutics, Gildex. **Honoraria**: Wilson H. Miller, Jr, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novartis, Roche; Peter Mohr, Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche; Jessica C. Hassel, Amgen, Bristol-Myers Squibb, GlaxoSmithKline, MSD, Novartis, Roche; Jeffrey A. Sosman, Array, Genentech, Merck, Novartis; Jeffrey S. Weber, Abbvie, Alkermes, AstraZeneca, Bristol-Myers Squibb, cCAM, Celldex, CytomX Therapeutics, Daiichi Sankyo, EMD Serono, Genentech, GlaxoSmithKline, Lion Biotechnologies, Merck, Nektar; Martin Kaatz, Bristol-Myers Squibb, Novartis, MSD, Roche; Celeste Lebbé, Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche; Paul Lorigan, Amgen, Bristol-Myers Squib, Merck, Novartis, Roche; Kerry J. Savage, Bristol-Myers Squibb, Celgene, Seattle Genetics. **Consultant or Advisory Role:** Wilson H. Miller, Jr, Bristol-Myers Squibb, Merck, Novartis, Roche; Ivan Marquez-Rodas, Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche; Bart Neyns, Bristol-Myers Squibb; Henrik Schmidt, Bristol-Myers Squibb, GlaxoSmithKline, MSD, Roche; Mario Sznol, Alexion, Adaptive Biotechnologies, Amphivena, Astra-Zeneca/Medimmune, Biodesix, Bristol-Myers Squibb, Genentech-Roche, Immune Design, Intensity, Janssen/Johnson and Johnson, Kyowa-Kirin, Lilly, Lion Biotechnologies, Merck, Nektar, Novartis, Pfizer, Pierre-Fabre, Prometheus, Symphogen, Theravance, Vaccinex; Peter Mohr, Bristol-Myers Squibb, MSD, Novartis, Roche; Sandra P. D'Angelo, Amgen, EMD Serono; Jessica C. Hassel, Amgen, MSD; F. Stephen Hodi, Bristol-Myers Squibb, EMD Serono, Genentech, Merck, Novartis, Synta; Jeffrey A. Sosman, Array, Genentech, Merck, Novartis; Jeffrey S. Weber, Abbvie, Alkermes, AstraZeneca, Bristol-Myers Squibb, cCAM, Celldex, CytomX, Daiichi Sankyo, EMD Serono, Genentech, GlaxoSmithKline, Lion Biotechnologies, Merck, Nektar; Martin Kaatz, Bristol-Myers Squibb, MSD, Novartis, Roche; Celeste Lebbé, Roche; Paul Lorigan, Amgen, Bristol-Myers Squib, Merck, Novartis, Roche; Benjamin Brady, Merck, Novartis; Jedd D.

Wolchok, Bristol-Myers Squibb, Genentech, MedImmune, Merck; Alexander N. Shoushtari, Castle Biosciences, Vaccinex; Kerry J. Savage, Bristol-Myers Squibb, Seattle Genetics. **Speakers' Bureau:** Bart Neyns, Bristol-Myers Squibb; Henrik Schmidt, Bristol-Myers Squibb, GlaxoSmithKline; Paul Lorigan, Bristol-Myers Squib, Merck, Novartis. **Research Funding:** Wilson H. Miller, Jr, Argos, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, MedImmune, Merck, Novartis, Roche; Peter Mohr, MSD; Jessica C. Hassel, Bristol-Myers Squibb; F. Stephen Hodi, Bristol-Myers Squibb; Jeffrey S. Weber, Acetylon, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, MacroGenics, Merck, Mirati; Celeste Lebbé, Roche; Jedd D. Wolchok, Bristol-Myers Squibb, Genentech, Merck, MedImmune, Merck; Alexander N. Shoushtari, Bristol-Myers Squibb; Kerry J. Savage, Roche. **Patents, Royalties, and Licenses**: F. Stephen Hodi, Patent pending to institution as per institutional policy. **Expert Testimony:** Martin Kaatz, Novartis, Roche. **Travel, Accommodations, Expenses:** Ivan Marquez-Rodas, Bristol-Myers Squibb, MSD; Bart Neyns, Bristol-Myers Squibb; Henrik Schmidt, Amgen, Bristol-Myers Squibb; Peter Mohr, Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche; Jessica C. Hassel, Amgen, Bristol-Myers Squibb, GlaxoSmithKline, MSD, Novartis, Roche; Julie Charles, Roche; Jeffrey S. Weber, Abbvie, Alkermes, AstraZeneca, Bristol-Myers Squibb, cCAM, Celldex, CytomX, Daiichi Sankyo, EMD Serono, Genentech, GlaxoSmithKline, Lion Biotechnologies, Merck, Nektar; Celeste Lebbé, Bristol-Myers Squibb, Roche; Paul Lorigan, Bristol-Myers Squib, Merck. Benjamin Brady, Bristol-Myers Squibb. **Other Relationships**: None.

Author Contributions

Conception and design: Sandra P. D'Angelo, Celeste Lebbé, Mary Ruisi, Jedd D. Wolchok

Collection and assembly of data: Sandra P. D'Angelo, Benjamin Brady, Jessica C. Hassel, F. Stephen Hodi, Martin Kaatz, Celeste Lebbé, Ivan Marquez-Rodas, Peter Mohr, Bart Neyns, Mary Ruisi, Kerry J. Savage, Mario Sznol, Jeffrey S. Weber

Data analysis and interpretation: Sandra P. D'Angelo, Julie Charles, F. Stephen Hodi, Joel Jiang, James Larkin, Celeste Lebbé, Paul Lorigan, Wilson H. Miller, Jr, Mary Ruisi, Kerry J. Savage, Henrik Schmidt, Alexander N. Shoushtari, Mario Sznol, Jeffrey A. Sosman, Mario Sznol, Jedd D. Wolchok

Provision of study materials or patients: Julie Charles, Jessica C. Hassel, Wilson H. Miller, Jr, Jeffrey A. Sosman, Jeffrey S. Weber

Manuscript writing: All authors

Final approval of manuscript: All authors

Acknowledgment

Dr. Larkin is supported by the Royal Marsden/Institute of Cancer Research Biomedical Research Centre for Cancer. Professional medical writing and editorial assistance were provided by Ward A. Pedersen, PhD, CMPP and Cara Hunsberger at StemScientific, an Ashfield Company, funded by Bristol-Myers Squibb.

REFERENCES

1. Postow MA, Callahan MK, Wolchok JD: Immune checkpoint blockade in cancer therapy. J Clin Oncol 33:1974-1982, 2015
2. Schadendorf D, Hodi FS, Robert C, et al: Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 33:1889-1894, 2015
3. Robert C, Long GV, Brady B, et al: Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 372:320-330, 2015
4. Weber JS, D'Angelo SP, Minor D, et al: A randomised, controlled, open-label, phase 3 trial of nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 therapy (CheckMate 037). Lancet Oncol 16:375-384, 2015
5. Postow MA, Chesney J, Pavlick AC, et al: Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 372:2006-2017, 2015
6. Larkin J, Chiarion-Sileni V, Gonzalez R, et al: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373:23-34, 2015
7. Ahmad S, Qian W, Ellis S, et al: Ipilimumab in the real world: the UK expanded access programme experience in previously treated advanced melanoma patients. Melanoma Res 25:432-442, 2015
8. Tas F, Keskin S, Karadeniz A, et al: Noncutaneous melanoma have distinct features from each other and cutaneous melanoma. Oncology 81:353-358, 2011
9. Mihajlovic M, Vlajkovic S, Jovanovic P, Stefanovic V: Primary mucosal melanomas: a comprehensive review. Int J Clin Exp Pathol 5:739-753, 2012
10. DeMatos P, Tyler DS, Seigler HF: Malignant melanoma of the mucous membranes: a review of 119 cases. Ann Surg Oncol 5:733-742, 1998
11. Wang X, Si L, Guo J: Treatment algorithm of metastatic mucosal melanoma. Chin Clin Oncol 3:38, 2014
12. Bitas C, Shoushtari AN, Bluth MJ, et al: The Memorial Sloan Kettering Cancer Center (MSKCC) experience of systemic therapy in mucosal melanoma. J Clin Oncol 32, 2014 (suppl 5s; abstr 9073)

13. Yi JH, Yi SY, Lee HR, et al: Dacarbazine-based chemotherapy as first-line treatment in noncutaneous melanoma: multicenter, retrospective analysis in Asia. Melanoma Res 21:223-227, 2011
14. Carvajal RD, Antonescu CR, Wolchok JD, et al: KIT as a therapeutic target in metastatic melanoma. JAMA 305:2327-2334, 2011
15. Hodi FS, Corless CL, Giobbie-Hurder A, et al: Imatinib for melanomas harbouring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 31:3182-3190, 2013
16. Postow MA, Luke JJ, Bluth MJ, et al: Ipilimumab for patients with advanced mucosal melanoma. Oncologist 18:726-732, 2013
17. Alexander M, Mellor JD, McArthur G, Kee D: Ipilimumab in pretreated patients with unresectable or metastatic cutaneous, uveal and mucosal melanoma. Med J Aust 201:49-53, 2014
18. Del Vecchio M, Di Guardo L, Ascierto PA, et al: Efficacy and safety of ipilimumab 3 mg/kg in patients with pretreated, metastatic, mucosal melanoma. Eur J Cancer 50:121-127, 2014
19. Zimmer L, Eigentler TK, Kiecker F, et al: Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of metastatic melanoma. J Transl Med 13:351, 2015
20. Min L, Hodi FS. Anti-PD1 following ipilimumab for mucosal melanoma: durable tumor response associated with severe hypothyroidism and rhabdomyolysis. Cancer Immunol Res 2:15-18, 2014
21. Topalian SL, Sznol M, McDermott DF, et al: Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 32:1020-1030, 2014
22. Urba WJ, Martin-Algarra S, Callahan M, et al: Immunomodulatory activity of nivolumab monotherapy in patients with advanced melanoma. American Association for Cancer Research Annual Meeting, Philadelphia, PA, USA, April 18–22, 2015 (abstr 2855)
23. Wolchok JD, Kluger H, Callahan MK, et al: Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369:122-133, 2013
24. Del Prete V, Chaloupka K, Holzmann D, et al: Noncutaneous melanomas: A single-center analysis. Dermatology 232:22-29, 2016

25. Curtin JA, Fridlyand J, Kageshita T, et al: Distinct sets of genetic alterations in melanoma. N Engl J Med 353:2135-2147, 2005
26. Furney SJ, Turajlic S, Stamp G, et al: Genome sequencing of mucosal melanomas reveals that they are driven by distinct mechanisms from cutaneous melanoma. J Pathol 230:261-269, 2013
27. Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol 9:239-271, 2014
28. Larkin J, Lao CD, Urba WJ, et al: Efficacy and safety of nivolumab in patients with BRAF V600 mutant and BRAF wild-type advanced melanoma: A pooled analysis of 4 clinical trials. JAMA Oncol 1:433-440, 2015

Table 1. Baseline Characteristics of the Patients

	Nivolumab Monotherapy		Combination Therapy		Ipilimumab monotherapy	
	Mucosal (n=86)	**Cutaneous (n=665)**	**Mucosal (n=35)**	**Cutaneous (n=326)**	**Mucosal (n=36)**	**Cutaneous (n=269)**
Age, years						
Median (range)	61 (22–89)	60 (18–90)	65 (35–86)	62 (18–87)	61 (31–80)	62 (18–89)
Age category, No. (%)						
<65 years	49 (57.0)	412 (62.0)	17 (48.6)	191 (58.6)	24 (66.7)	150 (55.8)
≥65 and <75 years	23 (26.7)	167 (25.1)	8 (22.9)	106 (32.5)	9 (25.0)	81 (30.1)
≥75 years	14 (16.3)	86 (12.9)	10 (28.6)	29 (8.9)	3 (8.3)	38 (14.1)
Sex, No. (%)						
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, No. (%)						
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, No. (%)*						
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, No. (%)						
≤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)
≤2x ULN	69 (80.2)	576 (86.6)	28 (80.0)	295 (90.5)	31 (86.1)	249 (92.6)
>2x 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, No. (%)						
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, No. (%)						
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, No. (%)**						
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; ULN, upper limit of normal.

*Based on 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.

Table 2. Best Overall 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)
Duration of response (months)						
Median (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)

Abbreviations: CI, confidence interval; NR, not reached.
*Proportion of patients with a complete or partial response.

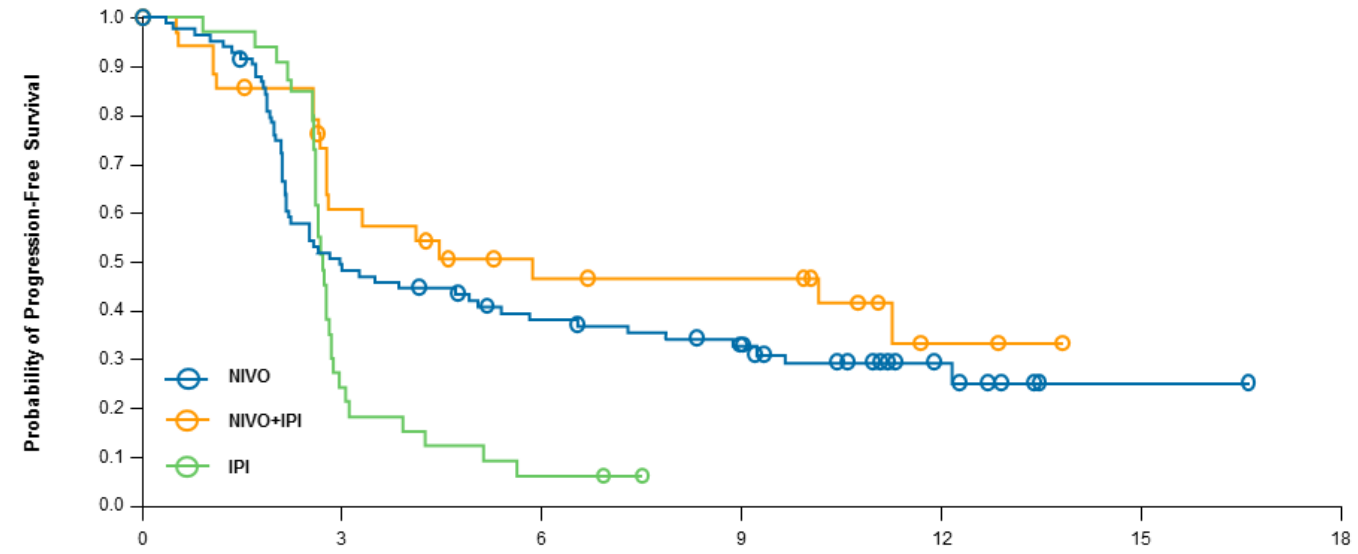
Table 3. Treatment-Related AEs That Occurred in at Least 5% of Patients

Adverse event, No. (%)*	Nivolumab Monotherapy				Combination Therapy			
	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)
Aspartate aminotransferase 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)
Alanine aminotransferase 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)
[a]Patients may have had more than one event.								

Figure 1. Progression-free survival in patients with (A) mucosal melanoma and (B) cutaneous melanoma who received nivolumab alone, combination therapy, or ipilimumab alone. Symbols indicate censored observations. Hazard ratios in (A): 0.61 (95% CI, 0.39 to 0.96; nivolumab versus ipilimumab; *P* = 0.116); 0.42 (95% CI, 0.23 to 0.75; combination therapy versus ipilimumab; *P* = 0.003). Hazard ratios in (B): 0.73 (95% CI, 0.61 to 0.87; nivolumab versus ipilimumab; *P* = 0.04); 0.49 (95% CI, 0.40 to 0.61; combination therapy versus ipilimumab; *P* <0.0001).

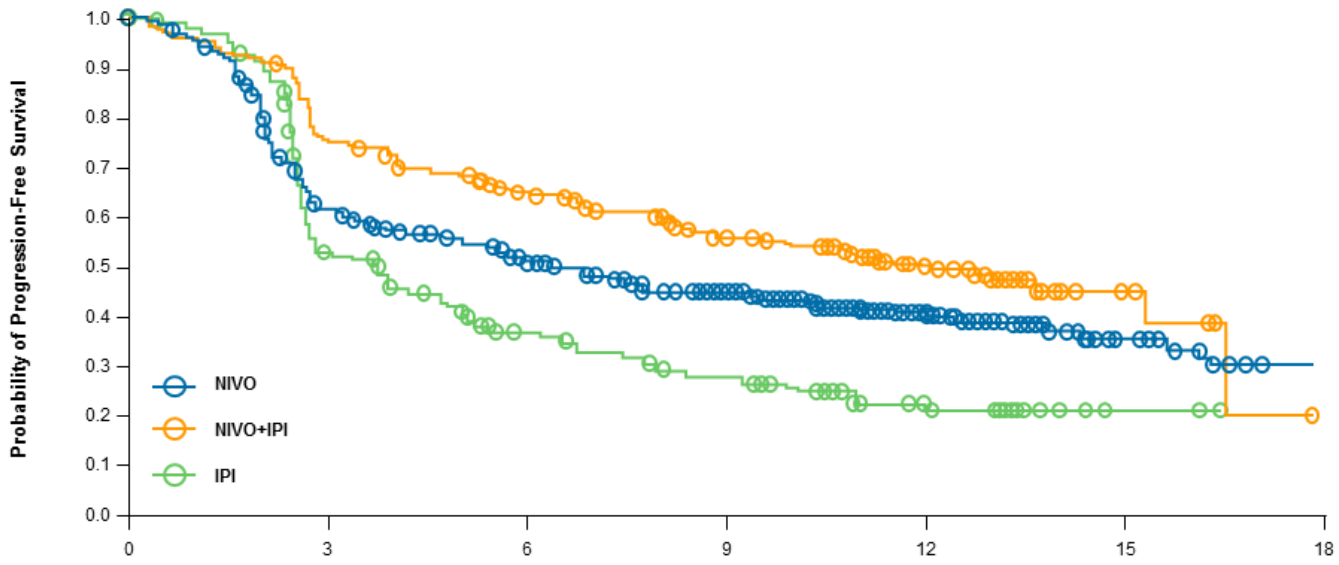
(A)



Number of Patients at Risk

NIVO	86	40	29	22	7	1	0
NIVO+IPI	35	19	12	11	2	0	--
IPI	36	8	2	0	0	0	--

(B)

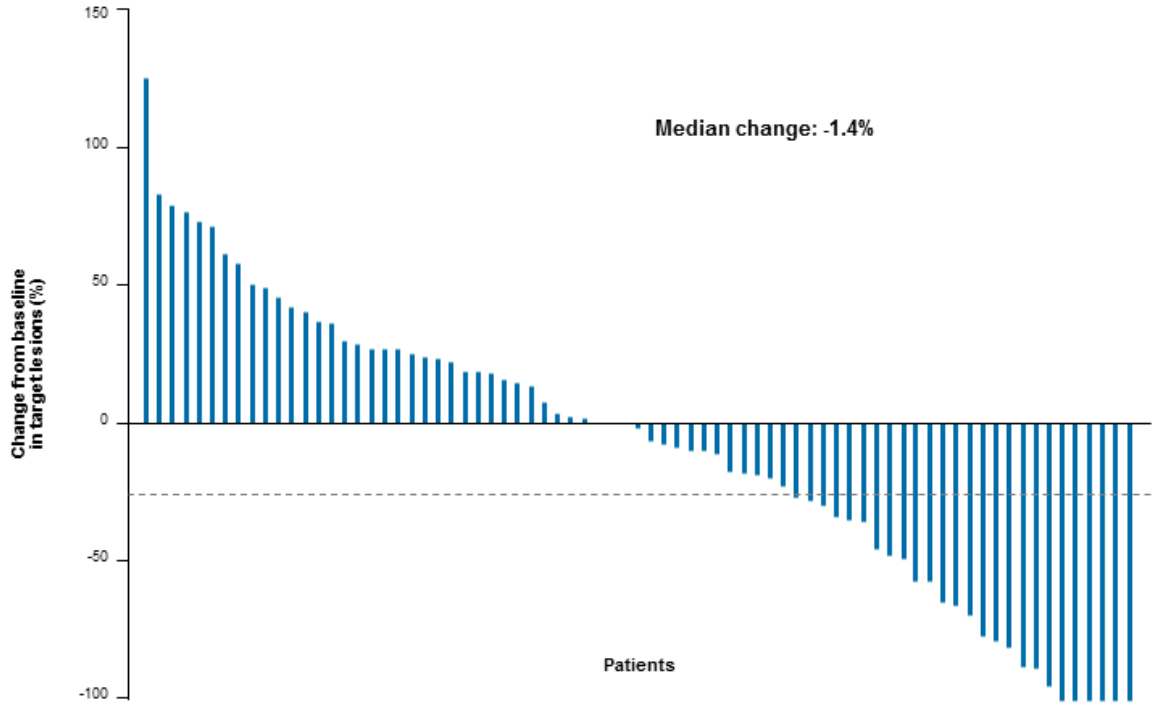


Number of Patients at Risk

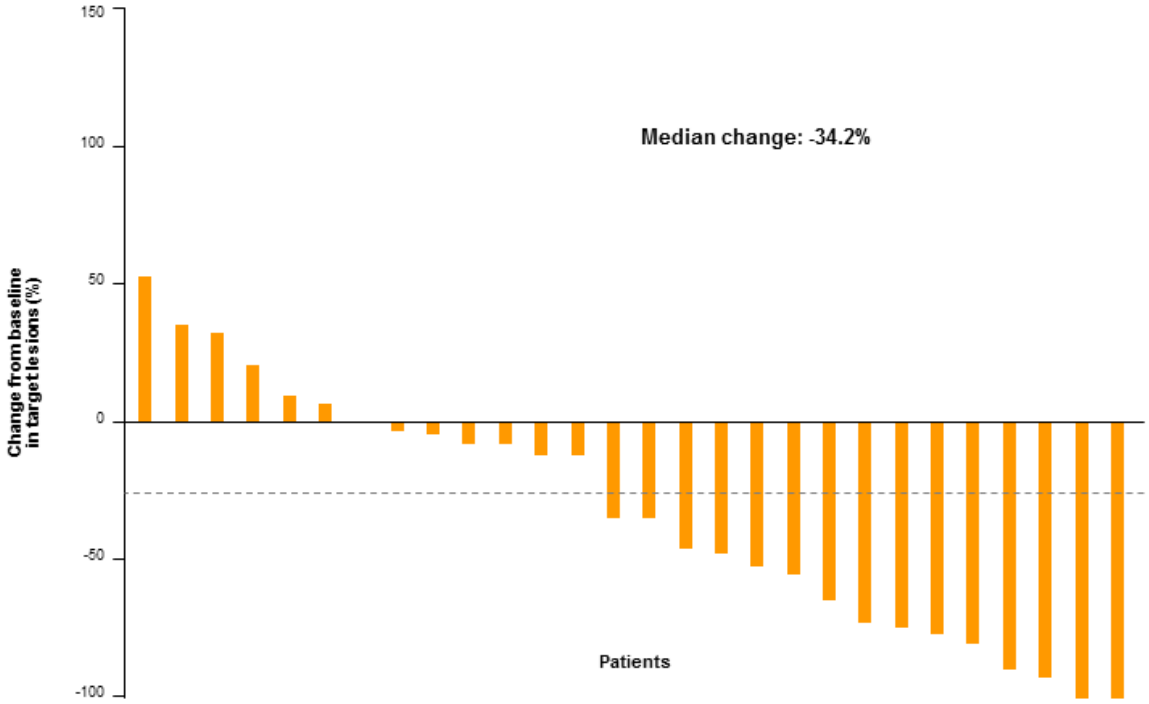
NIVO	665	384	303	231	90	24	6
NIVO+IPI	326	235	183	126	57	9	1
IPI	269	135	79	52	23	4	0

Figure 2. Waterfall plots showing tumor burden change from baseline in patients with mucosal melanoma who received (A) nivolumab alone (n=75), (B) combination therapy (n=28), and (C) ipilimumab alone (n=32). Dotted lines indicate a 30% reduction in tumor burden.

(A)



(B)


150
100
50
0
-50
-100
Change from baseline in target lesions (%)
Median change: -34.2%
Patients

(C)

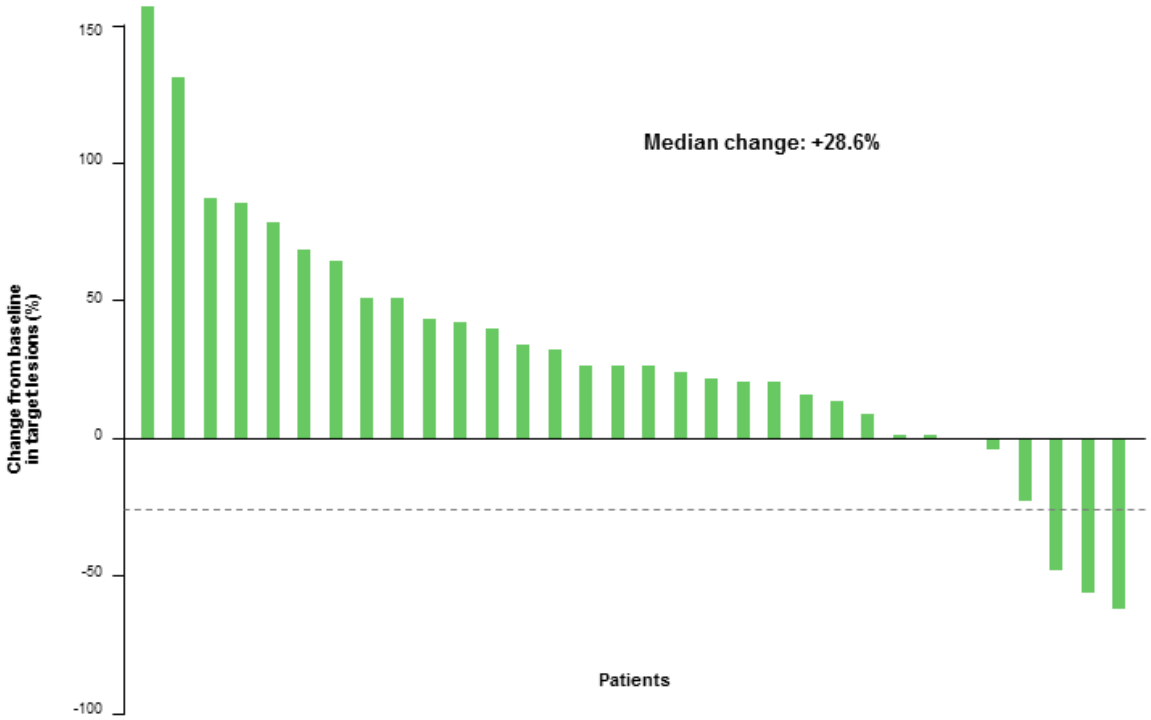
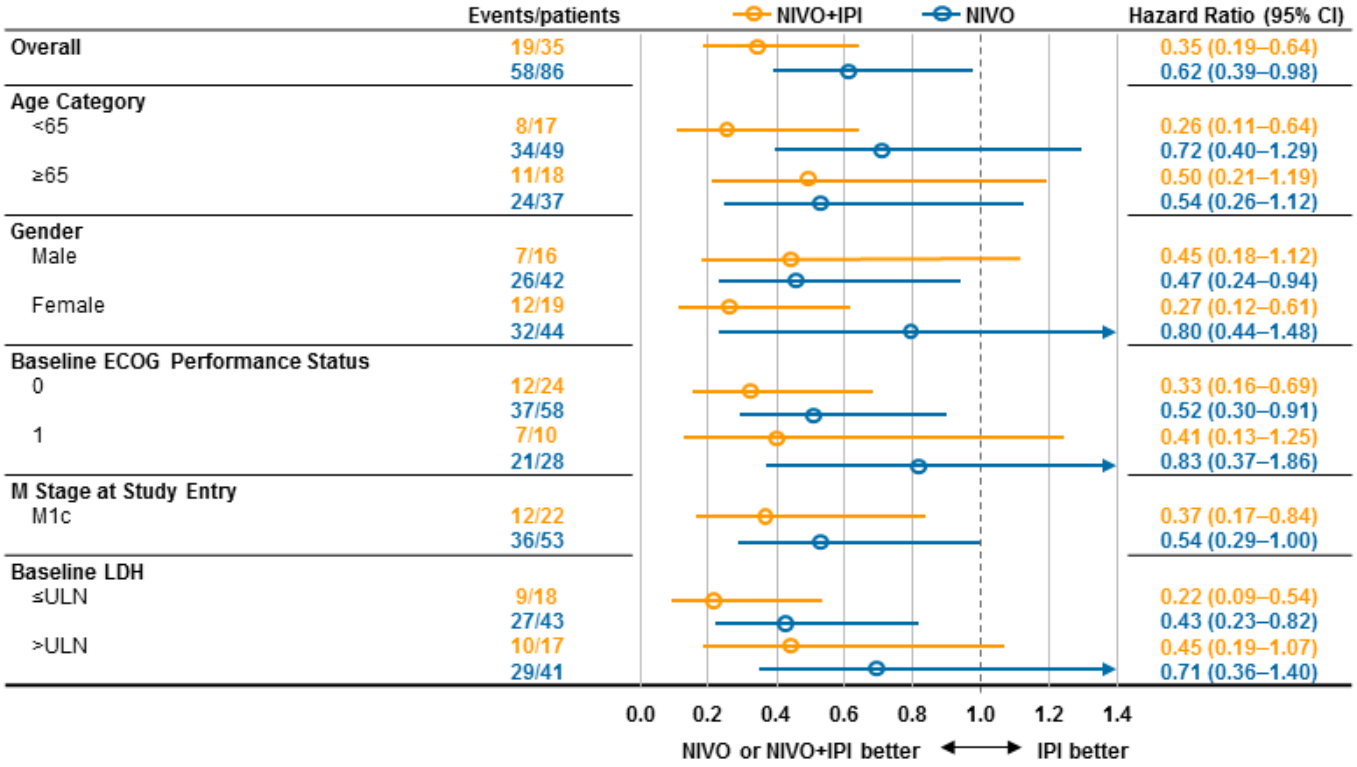
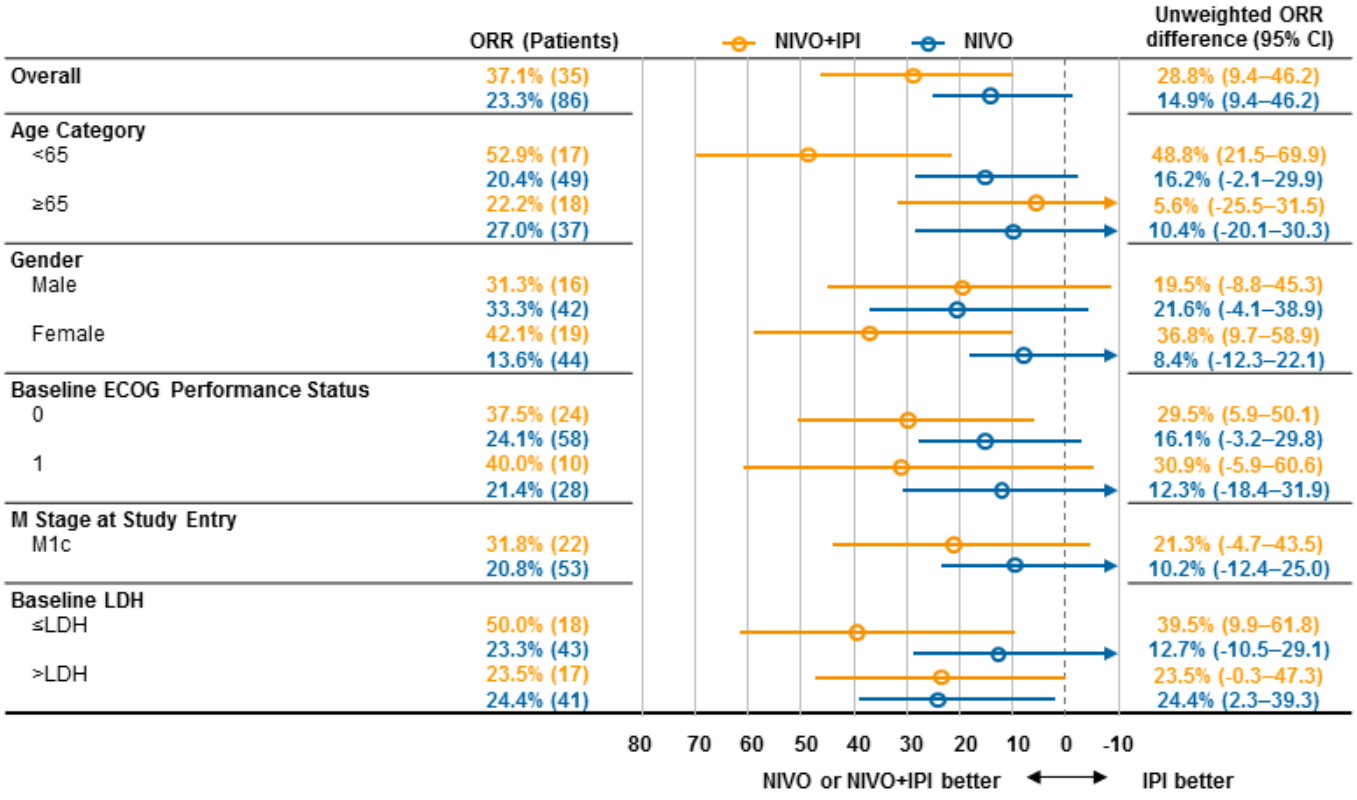

Median change: +28.6%
Change from baseline in target lesions (%)
150
100
50
0
-50
-100
Patients

Figure 3. Subgroup analyses of PFS (A) and ORR (B) for patients with mucosal melanoma. Horizontal bars indicate 95% CIs.

(A) Progression-free survival



(B) Objective response rate



Appendix

Table A1. Best Overall Response by PD-L1 Status

	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: CI, confidence interval.
*Proportion of patients with a complete or partial response.

Figure A1. Time to and duration of response in patients with mucosal melanoma.

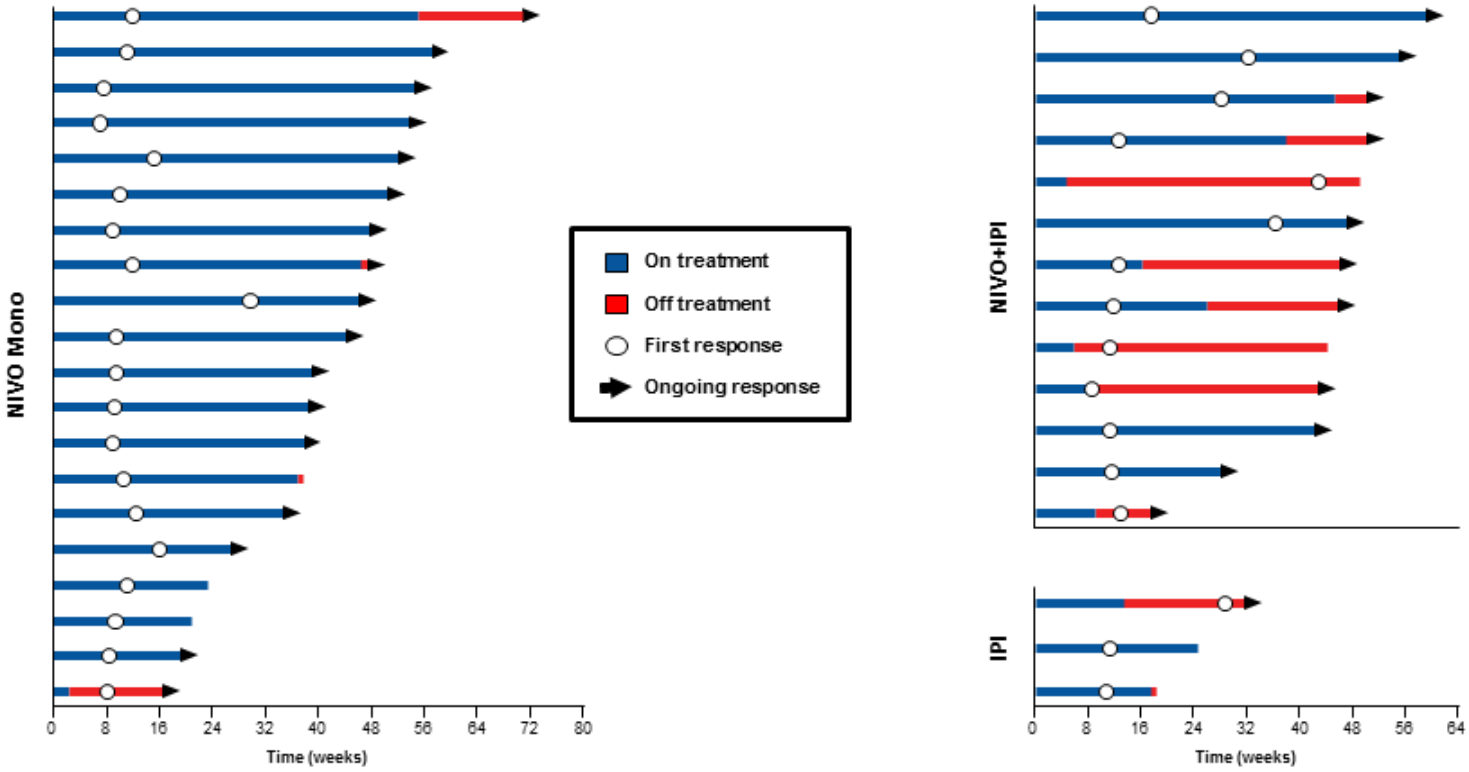
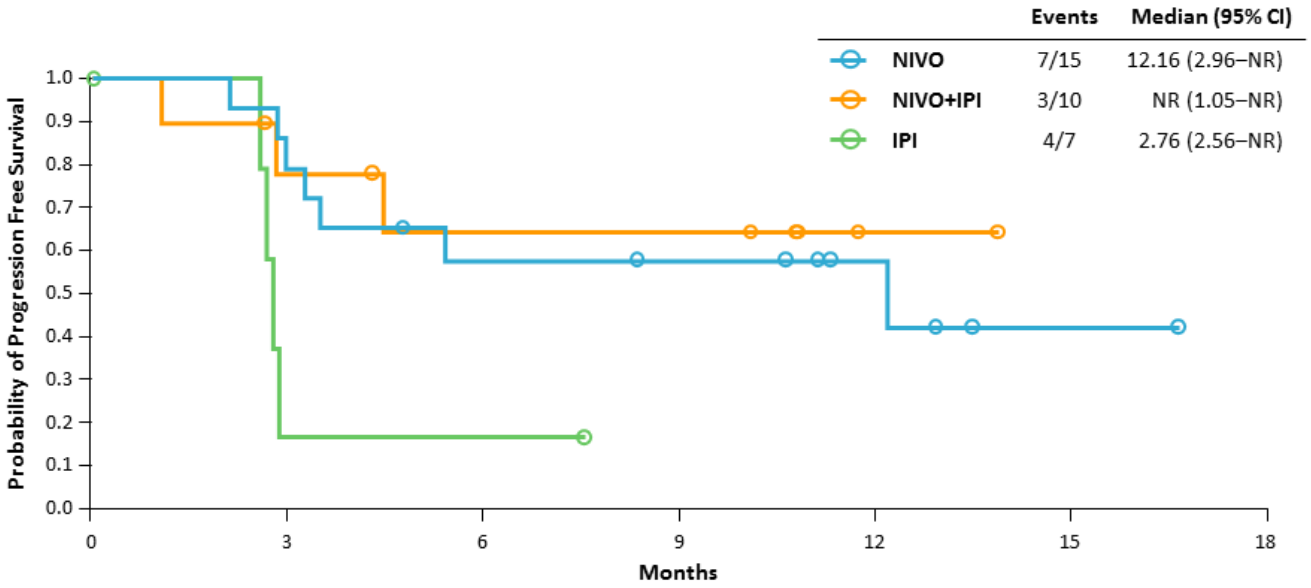


Figure A2. Progression-free survival by PD-L1 status in patients with mucosal melanoma.

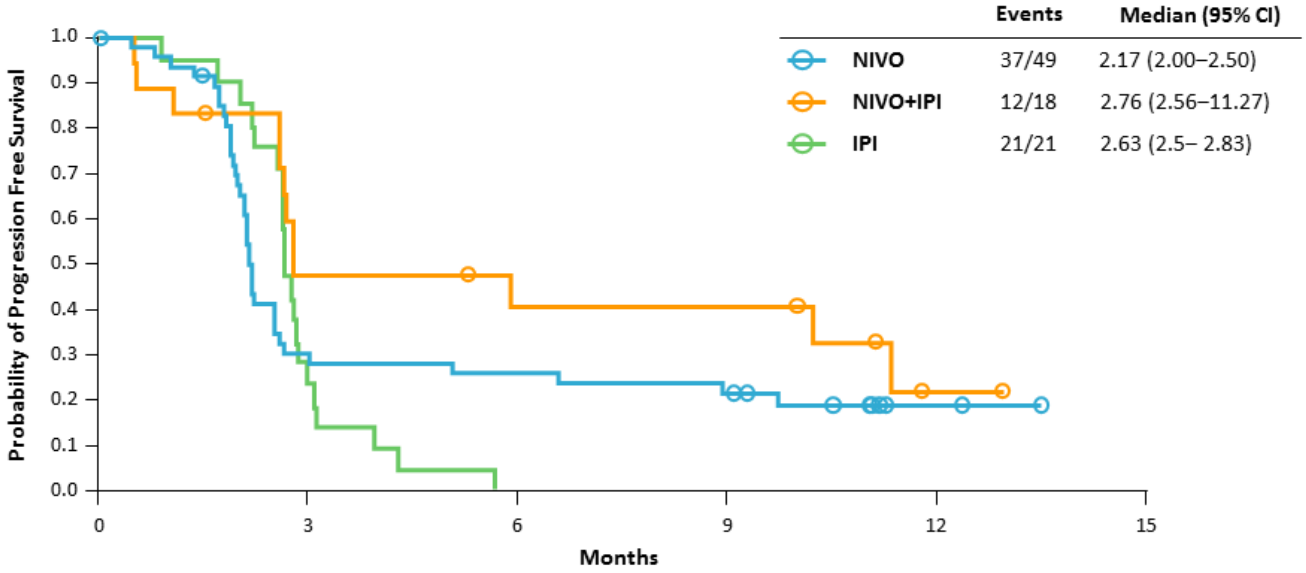
(A) PD-L1 Expression ≥5%



Number of Patients at Risk

NIVO	15	12	8	7	4	1	0
NIVO+IPI	10	7	5	5	1	0	--
IPI	7	1	1	0	0	0	--

(B) PD-L1 Expression <5%



Number of Patients at Risk

NIVO	49	13	12	10	2	0
NIVO+IPI	18	8	6	6	1	0
IPI	21	5	0	0	0	0