Efficacy and Safety of Nivolumab in Patients With \textit{BRAF} V600 Mutant and \textit{BRAF} Wild-Type Advanced Melanoma

A Pooled Analysis of 4 Clinical Trials

James Larkin, MD, PhD; Christopher D. Lao, MD, MPH; Walter J. Urba, MD, PhD; David F. McDermott, MD; Christine Horak, PhD; Joel Jiang, PhD; Jedd D. Wolchok, MD, PhD

\textbf{IMPORTANCE} The anti–PD-1 therapeutic antibody, nivolumab, has demonstrated clinical activity in patients with advanced melanoma. The activity of nivolumab in subgroups of patients with tumors which have wild-type \textit{BRAF} kinase vs patients with tumors having mutant \textit{BRAF} has not systematically been explored in a large dataset.

\textbf{OBJECTIVE} To evaluate the efficacy and safety of nivolumab in patients with wild-type \textit{BRAF} and mutant \textit{BRAF} metastatic melanoma.

\textbf{DESIGN, SETTING, AND PARTICIPANTS} This was a retrospective analysis of data pooled from 4 clinical trials of nivolumab in 440 adult patients with unresectable stage III or stage IV melanoma, who had been tested for \textit{BRAF} mutational status while participating in one of the studies.

\textbf{INTERVENTION} The investigational drug, nivolumab, was administered intravenously to study participants over a 60-minute period, at doses of 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg every 2 weeks until disease progression, discontinuation owing to adverse events, withdrawal, or end of study. Most patients (83%) received nivolumab at a dosage of 3 mg/kg.

\textbf{MAIN OUTCOME AND MEASURE} Best overall response by modified World Health Organization or Response Evaluation Criteria in Solid Tumors criteria and safety profile.

\textbf{RESULTS} Of a total of 440 patients from 4 nivolumab clinical trials included in the analysis, 334 were \textit{BRAF} wild-type and 106 were positive for \textit{BRAF} V600 mutation. With the exception of prior \textit{BRAF} inhibitor therapy, the demographics were well balanced between the 2 cohorts. In patients evaluable for response, the objective response rates were 34.6% (95% CI, 28.3-41.3) for the 217 patients with wild-type \textit{BRAF} status and 29.7% (95% CI, 19.7-41.5) for the 74 with mutant \textit{BRAF} status. The objective response rates did not seem to be affected by prior \textit{BRAF} inhibitor therapy, prior ipilimumab therapy, or PD-L1 status of the tumor. The median duration of objective response was 14.8 months (95% CI, 11.1-24.0 months) for wild-type \textit{BRAF} and 11.2 months (95% CI, 7.3-22.9 months) for mutant \textit{BRAF}. Median time to objective response was 2.2 months in both patient groups. The incidence of treatment-related adverse events of any grade was 68.3% in the wild-type \textit{BRAF} group and 58.5% in the mutant \textit{BRAF} group, with grade 3 or 4 adverse events in 11.7% and 2.8% of patients, respectively. Treatment-related AEs of any grade that occurred in at least 5% of patients in either group were fatigue, pruritus, rash, and diarrhea.

\textbf{CONCLUSIONS AND RELEVANCE} The results of this retrospective analysis suggest that nivolumab has similar efficacy and safety outcomes in patients with wild-type or mutant \textit{BRAF}, regardless of prior \textit{BRAF} inhibitor or ipilimumab treatment.

Published online May 21, 2015. Corrected on November 17, 2016.
Several agents have been approved since 2011 for the treatment of unresectable or metastatic melanoma (MM). The first agent to demonstrate an improvement in overall survival (OS) in a randomized, controlled phase 3 trial was ipilimumab, which blocks the immune checkpoint molecule, cytotoxic T-lymphocyte antigen-4, to augment antitumor immunity. Subsequent approved therapies target mutant (Mut) BRAF kinase, which occurs in approximately 50% of all melanomas, or MEK, the downstream target of BRAF. The most common BRAF mutation is V600E, accounting for 70%-80% of BRAF mutations, with other mutations at the V600 position (eg, V600K) accounting for 5% to 15%. The BRAF inhibitor, vemurafenib, was approved in 2011 for the treatment of BRAF V600E Mut MM based on an improvement in OS in a phase 3 trial. In 2013, the BRAF inhibitor, dabrafenib, and the MEK inhibitor, trametinib, were approved for BRAF V600E Mut and BRAF V600E/V600K Mut MM, respectively, based on improvements in progression-free survival (PFS) in phase 3 trials. The combination of a BRAF inhibitor with a MEK inhibitor has demonstrated greater improvements in PFS and OS compared with a BRAF inhibitor alone in phase 3 trials of patients with BRAF V600 Mut MM.

Unlike the BRAF or MEK inhibitors, ipilimumab’s mechanism of action is independent of the BRAF signaling pathway because it targets the immune system rather than tumor cells. Tumors also exploit the immune checkpoint molecule, programmed death-1 (PD-1), to turn off the immune response by inactivating T cells at the tumor site. Nivolumab is an anti–PD-1 monoclonal antibody that is believed to break down tumor defenses either by preventing inactivation or by reactivating T-cell activity within the tumor microenvironment. In 2014, nivolumab was the first anti-PD-1 antibody to gain regulatory approval in Japan and was approved to treat patients with MM. Pembrolizumab and nivolumab were subsequently approved in the United States for the treatment of MM following progression on ipilimumab or a BRAF inhibitor.

To our knowledge, to date, there has not been any mechanistic evidence that BRAF mutations can have a direct impact on responses to immune checkpoint inhibitors. Retrospective analysis of data from an ipilimumab phase 2 study and observational data from US medical record review suggest that ipilimumab has similar activity in MM with wild-type (WT) BRAF kinase and Mut BRAF kinase. Evidence also exists that Mut BRAF does not substantially affect the antitumor activity of concurrent nivolumab and ipilimumab. Initial data from the phase 3 CheckMate 037 study suggest that nivolumab as monotherapy is an effective treatment for patients with advanced melanoma independent of BRAF mutation status. In this study, the objective response rate was 23% among patients who had tumors with BRAF Mut kinase and was 34% among those with BRAF WT kinase. To provide a broader data set to answer the question as to whether nivolumab activity is independent of BRAF Mut status in patients with advanced melanoma, we conducted a retrospective pooled analysis in nivolumab-treated patients with BRAF V600 Mut or WT tumors.

**At a Glance**
- Are there differences in the safety and efficacy of nivolumab in patients with wild-type (WT) and mutant (Mut) BRAF metastatic melanoma?
- Retrospective analysis of 4 clinical trials including 334 BRAF WT and 106 BRAF V600 Mut-positive patients with metastatic melanoma.
- The objective response rate was 34.6% for WT BRAF patients and 29.7% for Mut BRAF patients.
- The incidence of treatment-related adverse events was similar between the 2 groups.
- Results suggest that nivolumab has similar efficacy and safety outcomes regardless of BRAF mutation status.

**Methods**

**Patients**

Ongoing studies in which patients had received nivolumab monotherapy for unresectable stage III or stage IV melanoma following prior systemic therapy for advanced disease, and which enrolled patients with tumors unselected for BRAF mutational status, were included in the current data set (eTable 1 in the Supplement). Studies that contributed data to the current analysis included a dose-ranging phase 1 study (CA209-003 [NCT00730639]), a phase 1 biomarker study (CA209-038 [NCT01621490]), a phase 1 study of concurrent ipilimumab and nivolumab or ipilimumab sequenced with nivolumab (CA209-004 [NCT01024231]), and a phase 3 trial of nivolumab monotherapy vs chemotherapy (CA209-037 [CheckMate 037 [NCT01721746]]). Note that for study CA209-004, only cohorts 6 and 7, in which patients who had been previously treated with at least 3 doses of ipilimumab and received nivolumab monotherapy, were included. Other cohorts in study CA209-004 had received combination therapy with ipilimumab and nivolumab and were therefore excluded from the current analysis. Across studies, nivolumab was administered intravenously every 2 weeks at doses of 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg for up to 96 weeks; most patients (83%) had been treated at the 3.0 mg/kg dose.

**Assessments**

BRAF V600E testing was performed locally at the investigator sites for each study. Tumor assessments were done using modified World Health Organization criteria (CA209-004) or Response Evaluation Criteria in Solid Tumors, version 1.0 (CA209-003) or version 1.1 (CA209-037, CA209-038). Patients evaluable for response had a baseline tumor assessment and a confirmatory scan at least 4 weeks after the first documented response. Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 16.1 for studies CA209-037 and -038, and version 17.0 for studies CA209-003 and -004. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Select adverse events (ie, those defined as having the potential for an immunologic etiology) were analyzed by organ category. Adverse
events were reported between the first dose and 30 days after the last dose of study drug. To determine if PD-L1 status has an impact on responses to nivolumab within WT and Mut \( B_R_A_F \) groups, immunohistochemical assessment for tumor cell expression of PD-L1 was performed as described previously.\(^{24} \) Briefly, a tissue sample was scored as PD-L1-positive if at least 5% of tumor cells had cell-surface PD-L1 staining of any intensity in a section containing at least 100 evaluable tumor cells.

### Statistical Analysis

Objective response rates with 95% CIs were estimated using the Clopper-Pearson method. Medians for duration of objective response were calculated using the Kaplan-Meier method, with 95% CIs based on the Greenwood formula. Duration of response was defined as the time between the date of first documented objective response and the date of the first subsequent disease progression or death due to any cause, whichever occurred first. For patients whose disease progressed or who died, the duration of objective response was censored at the same time that they were censored for the primary definition of PFS.

### Results

A total of 440 nivolumab-treated patients from 4 clinical studies met the criteria for inclusion in the current analysis: 334 patients with \( B_R_A_F \) WT tumors and 106 patients with \( B_R_A_F \) V600 Mut tumors. Baseline characteristics of all patients included in the analysis are shown in Table 1. Patient characteristics were well balanced between the WT and Mut \( B_R_A_F \).
groups, including Eastern Cooperative Oncology Group performance status, lactate dehydrogenase levels, metastasis stage, presence of brain metastasis, and PD-L1 positivity. The study population was heavily pretreated, with about 75% of the patients having received more than 2 prior therapies for advanced melanoma. Among patients with known PD-L1 status using a 5% cutoff, a similar proportion in each group had positive tumor cell surface expression for PD-L1 (65 of 164 [39%] for WT BRAF and 21 of 54 [40%] for Mut BRAF). A total of 291 patients had at least 1 postbaseline tumor assessment, with a similar proportion in each group (217 of 334 patients [65%] for WT BRAF and 74 of 106 patients [70%] for Mut BRAF), and were included in the evaluation of response; 46 (62%) of the Mut BRAF patients had received a prior BRAF inhibitor, and 189 (65%) of all patients had been previously treated with ipilimumab.

A total of 253 patients (185 of 334 [55%] with WT BRAF and 68 of 106 [64%] with Mut BRAF) discontinued treatment during the study. The primary reason for discontinuing treatment was disease progression (143 of 185 WT BRAF patients [77%] and 56 of 68 Mut BRAF patients [82%]). Approximately 5% of patients in each group continued treatment owing to adverse events of the study drug.

**Objective Response**

Among 291 patients evaluated for response, the percentage with a complete or partial response was similar in the WT BRAF and Mut BRAF groups (Table 2). The objective response rate was 34.6% for the WT BRAF group (75 responses among 217 patients) and was 29.7% for the Mut BRAF group (22 responses among 74 patients) (Table 2). The median time to objective response was 2.2 months in both groups. The median duration of objective response was similar in the WT BRAF group (14.8 months; 95% CI, 11.1-24.0) and the Mut BRAF group (11.1 months; 95% CI, 7.3-22.9) (Table 2).

Similar percentage reductions in the magnitude of tumor burden were observed between WT BRAF (Figure 1A) and Mut BRAF (Figure 1B). Objective response rates with nivolumab treatment were not markedly different between WT and Mut BRAF across subgroups, including those defined by baseline lactate dehydrogenase levels, metastasis stage, or PD-L1 status (Figure 1C). Figure 2 depicts the time to first response and duration of response in both groups; 59 of 75 WT BRAF patients (78%) and 16 of 22 Mut BRAF patients (73%) remained in response. Among patients who discontinued treatment and remained in response, the median duration of response was 4.8 months for WT BRAF (n = 13 patients) and was 5.0 months for Mut BRAF (n = 2 patients).

**Prior BRAF Inhibitor Therapy**

An exploratory analysis was performed to assess whether prior BRAF inhibitor therapy in Mut BRAF patients had an impact on response to nivolumab. The objective response rate was 33.1% in Mut BRAF patients with no prior BRAF inhibitor therapy and was 24.5% in patients who had received a prior BRAF inhibitor (eTable 2 in the Supplement). Reductions in the magnitude of tumor burden in Mut BRAF patients were similar regardless of prior BRAF inhibitor therapy (eFigure 1 in the Supplement).

**Safety**

In the safety analysis, which included all patients, the overall incidence of treatment-related adverse events was similar in WT BRAF (and Mut BRAF groups (Table 3) (68.3% and 58.5% patients, respectively). Grade 3 or 4 adverse events occurred in 11.7% of WT BRAF patients and in 2.8% of Mut BRAF patients. The most common treatment-related adverse events of any grade (occurring in ≥10% of patients) were fatigue, pruritus, rash, and diarrhea. The rates of treatment-related select adverse events were similar between groups and were comparable with those in the total population: 46.1% of any grade for WT BRAF, 34% for Mut BRAF, and 43.2% for the total population; the rate of grade 3 or 4 adverse events was 3.6% in the WT BRAF group, 0% in the Mut BRAF group, and 2.7% in the total population (eTable 3 in the Supplement). Among the Mut BRAF patients, grade 3 or 4 adverse events occurred in 37% of patients who had received a prior BRAF inhibitor (n = 76) compared with 30% of patients who had not received a prior BRAF inhibitor (n = 30).

**Discussion**

The results of this retrospective analysis of pooled data from 4 clinical studies suggest that nivolumab has clinical activity with a manageable safety profile in patients with advanced melanoma, regardless of BRAF mutational status. The objective response rate, time to response, and duration of response seemed similar in patients with WT or Mut BRAF who received nivolumab. Our findings are consistent with the results of a recent study with the anti–PD-1 antibody, pembrolizumab, in which the objective response rate was 28% in 131 patients with WT BRAF MM and was 19% in 26 patients with...
Figure 1. Tumor Response and Subgroup Analyses of Objective Response Rate

The waterfall plots show the maximum change from baseline in the sum of diameters of the target lesion in patients with (A) wild-type (WT) BRAF or (B) mutant (Mut) BRAF following nivolumab treatment. Dashed lines indicate a 30% reduction in tumor burden in the target lesion by modified World Health Organization or Response Evaluation Criteria in Solid Tumors criteria. Analyses include all patients with a known response. C, Forest plot showing the treatment effect on objective response rate (ORR) across patient subgroups. n/N refers to the number of patients evaluated out of the total available for analysis in each subgroup. Patients with unknown PD-L1 status are excluded. Error bars indicate 95% CIs. IPI indicates ipilimumab; LDH, lactate dehydrogenase; ULN, upper limit of normal.
The results of our subgroup analyses further suggest a consistent objective response rate between both groups of patients. There were no substantial differences in subgroups defined by lactate dehydrogenase levels, M stage, PD-L1 status, or prior therapy with ipilimumab or a BRAF inhibitor. Although the patients had been heavily pretreated prior to nivolumab, many were still able to respond to the drug in both groups.

The current findings are consistent with the results of a recent phase 3 trial in previously untreated patients with WT BRAF, in which nivolumab at 3 mg/kg every 2 weeks produced an objective response rate of 40.0%. Because the current analysis was conducted on a data set from previously treated patients, we evaluated the impact of prior BRAF inhibitor therapy on the response to nivolumab. In Mut BRAF patients, the objective response rates were similar between the cohort that received a prior BRAF inhibitor and the cohort that had not received a prior BRAF inhibitor. There were no new safety signals in patients who received a BRAF inhibitor prior to nivolumab, and the incidence of grade 3 or 4 adverse events did not seem to be markedly affected by prior BRAF inhibitor therapy.

The retrospective nature of this nonrandomized cohort analysis, with subgroups having small numbers of patients, is an important limitation of the analysis. We evaluated patients with MM harboring the BRAF V600E mutation, but the potential impact of other BRAF or MAPK variants on efficacy and safety outcomes with nivolumab cannot be ruled out. It is also important to note that the current data set includes patients who were eligible to receive additional treatment, particularly the
Mut BRAF patients who had prior BRAF inhibitor therapy. Thus, the patients in this analysis may have had a better prognosis than other Mut BRAF patients who may be too ill to be treated further. Survival follow-up of the patients may be presented in the future when data become more mature.

The current data suggest that some patients with Mut BRAF who receive BRAF inhibitor therapy will respond to subsequent immunotherapy with nivolumab. These findings may have implications for the sequencing of BRAF/MEK inhibitors with immune checkpoint inhibitors. Some treatment guidelines for advanced melanoma recommend the use of a BRAF inhibitor as the initial treatment of patients with BRAF Mut disease who have a poor performance status. However, the results of retrospective analyses suggest that better outcomes occur when ipilimumab is used prior to a BRAF inhibitor compared with the reverse treatment sequence. The results of the current analysis suggest that nivolumab has activity regardless of prior BRAF inhibitor or ipilimumab treatment, although the small numbers of patients limit the ability to make definitive conclusions on whether prior BRAF inhibitor therapy has a negative impact on the response to nivolumab. Further prospective studies will be required to determine the optimal treatment schedule for BRAF/MEK inhibitors and immune checkpoint inhibitors in advanced melanoma.

Conclusions

This pooled analysis represents the largest data set available to date to evaluate the efficacy and safety of nivolumab in WT and Mut BRAF patients with MM. Within the limitations of this retrospective analysis, the data suggest that nivolumab has activity in patients with WT BRAF and in patients with Mut BRAF, consistent with findings of previous retrospective analyses of ipilimumab monotherapy and a phase 1 study of concurrent nivolumab and ipilimumab. Moreover, nivolumab monotherapy may be an effective treatment for Mut BRAF patients regardless of whether they have previously received a BRAF inhibitor.

Table 3. Treatment-Related Adverse Events (AEs) Reported in ≥5% of Patients

<table>
<thead>
<tr>
<th>Patients Reporting AEs*</th>
<th>BRAF, No. (%)</th>
<th>Mutation, AE Grade (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wild-Type, AE Grade (n = 334)</td>
<td>Any</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td></td>
<td>228 (68.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>86 (25.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>55 (16.5)</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>40 (12.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>41 (12.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>31 (9.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td>20 (6.0)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td></td>
<td>18 (5.4)</td>
</tr>
<tr>
<td>Rash, maculopapular</td>
<td></td>
<td>18 (5.4)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td>16 (4.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>17 (5.1)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>20 (6.0)</td>
<td>13 (3.9)</td>
</tr>
</tbody>
</table>

* Patients may have had more than 1 AE.

Additional treatment-related grade 3–4 AEs in the WT BRAF group included anemia (3 [0.9%]), arthralgia (3 [0.9%]), colitis (3 [0.9%]), increased alanine aminotransferase level (3 [0.9%]), increased lipase level (3 [0.9%]), abdominal pain (2 [0.6%]), hyperglycemia (2 [0.6%]), hypotension (2 [0.6%]), increased aspartate aminotransferase level (2 [0.6%]), lymphopenia (2 [0.6%]; abnormal liver function test result (1 [0.3%]), adrenocortical insufficiency (1 [0.3%]), autoimmune neuropathy (1 [0.3%]), chronic myeloid leukemia (1 [0.3%]), decreased lymphocyte count (1 [0.3%]), decreased platelet count (1 [0.3%]), demyelination (1 [0.3%]), gait disturbance (1 [0.3%]), hepatitis (1 [0.3%]), herpes zoster infection (1 [0.3%]), hypertension (1 [0.3%]), hyperuricemia (1 [0.3%]), hypophosphatemia (1 [0.3%]), hypophysitis (1 [0.3%]), increased amylase level (1 [0.3%]), increased blood creatinine level (1 [0.3%]), increased blood creatine phosphokinase level (1 [0.3%]), infusion-related reaction (1 [0.3%]), musculoskeletal pain (1 [0.3%]), nephritis (1 [0.3%]), pancreatitis (1 [0.3%]), thrombocytopenia (1 [0.3%]), uveitis (1 [0.3%], and ventricular arrhythmia and vomiting (1 [0.3%]).

Additional treatment-related grade 3–4 adverse events in the WT BRAF group included increased lipase level (2 [1.9%]) and increased amylase level (1 [0.9%]).

ARTICLE INFORMATION

Accepted for Publication: April 2, 2015.
Correction: This article was corrected on November 17, 2016, to add the information about open access.
Published Online: May 21, 2015. doi:10.1001/jamaoncol.2015.1184
Open Access: This article is published under JAMA Oncology’s open access model and is free to read on the day of publication.

Author Affiliations: Department of Medical Oncology, Royal Marsden Hospital, London, England (Larkin); Department of Internal Medicine, University of Michigan, Ann Arbor (Lao); Department of Dermatology, University of Michigan, Ann Arbor (Lao); Earle A. Chiles Research Institute at Providence Cancer Center, Portland, Oregon (Urba); Department of Hematology/Oncology, Beth Israel Deaconess Medical Center, Boston, Massachusetts (McDermott); Bristol-Myers Squibb Co, Princeton, New Jersey (Horak); Bristol-Myers Squibb Co, Hopewell, New Jersey (Jiang); Weill-Cornell Medical College, New York, New York (Larkin); Memorial Sloan Kettering Cancer Center, New York, New York (Wolchok); Weill-Cornell Medical College, New York, New York (Wolchok).

Author Contributions: Drs Larkin and Wolchok had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Larkin, Urba, Horak.
Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Larkin, Urba, Horak, Wolchok.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Jiang.

Administrative, technical, or material support: McDermott, Horak.

Study supervision: Larkin, Urba, Wolchok.

Conflict of Interest Disclosures: Dr Larkin has received research funding from Novartis and Pfizer and has been a consultant (nonremunerated since 2012) for Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pfizer, and Roche/Genentech. Dr Urba has served as an advisor and has participated in a speakers’ bureau for Bristol-Myers Squibb, his institution has a sponsored research agreement with Bristol-Myers Squibb. Dr McDermott has participated in advisory boards for Bristol-Myers Squibb, Merck, Pfizer, and Roche. Dr Horak is currently employed by Bristol-Myers Squibb and is a stock holder in the company. Dr Wolchok reports receiving grants, personal fees, and nonfinancial support from Bristol-Myers Squibb; grants and personal fees from Medimmune and Merck; and personal fees from Jounce, Polaris, Polynoma, Potenza, and Ziopharm. No other disclosures are reported.

Funding/Support: Funding for this work was provided by Bristol-Myers Squibb. Dr Larkin is supported by the NIH/NIHR Royal Marsden Hospital/Institute of Cancer Research Biomedical Research Centre for Cancer.

Role of the Funder/Sponsor: The design and conduct of the study, as well as collection, management, analysis, and interpretation of the data, were done by the sponsor in collaboration with the academic authors. Preparation, review, and approval of the manuscript was done by all authors and by Ward A. Pedersen, PhD, at StemScientific, an Ashfield Company.

Additional Contributions: Professional medical writing and editorial assistance were provided by Ward A. Pedersen, PhD, at StemScientific, an Ashfield Company, and were funded by Bristol-Myers Squibb.

REFERENCES


28. Ascierto PA, Margolin K. Ipilimumab before BRAF inhibitor treatment may be more beneficial than vice versa for the majority of patients with advanced melanoma. Cancer. 2014;120(11):1671-1679.