Broad Applicability of Nivolumab in Melanoma
Regardless of BRAF Mutation Status

Tara C. Gangadhar, MD; Lynn M. Schuchter, MD

Advances in immune therapy for the treatment of melanoma have resulted in unprecedented responses and survival rates for patients with unresectable and metastatic disease. The recent regulatory approvals of the PD-1 blocking agents nivolumab and pembrolizumab represent the great potential of immunologically directed therapy to have an impact on the care of patients with advanced cancer.

Given the availability of several new active therapies, the identification of subsets of patients who may be more or less likely to benefit from any agent or class of agents is important for clinical decision making. In this issue of JAMA Oncology, Larkin et al1 examine the activity of nivolumab in the subsets of patients with and without a BRAF V600-activating mutation. In a retrospective analysis of 4 clinical trials including 334 patients with BRAF wild-type melanoma and 106 who were positive for the BRAF V600 mutation, the authors suggest that there are no differences in adverse events, objective response rates, time to response, or duration of responses to nivolumab in patients with advanced melanoma, with or without the BRAF mutation. The objective response rate was 34.6% for patients with wild-type BRAF melanoma and 29.7% for those with mutant BRAF melanoma, suggesting that nivolumab had similar efficacy and safety outcomes regardless of BRAF mutation status in the study population.

This retrospective analysis included 440 patients who received treatment with nivolumab as a single agent while enrolled in 1 of 4 clinical trials. Most of the patients included in the analysis (approximately 75%) did not have an activating BRAF V600 mutation, whereas the incidence of BRAF V600 mutant melanoma is approximately 50% in the overall population of patients with advanced melanoma. The smaller proportion of patients with BRAF mutant melanoma in the study is likely owing in part to the availability of competing BRAF-directed clinical trials and treatment options for these patients.

In addition, most of the study patients with BRAF-mutant melanoma had received prior BRAF inhibitor therapy; therefore, the BRAF-mutant patients included in the analysis were limited to those patients who remained eligible, with a good performance status and organ function, following prior BRAF-directed therapy. Therefore, trial eligibility criteria possibly also account for the smaller percentage of BRAF-mutant patients included. That is, it is possible that patients treated with prior BRAF inhibitor therapy may have developed a clinical decline owing to disease progression and therefore were not eligible for the clinical trials of nivolumab included in this analysis.

Apart from the lower percentage of patients with BRAF-mutant melanoma, the patient population was representative of the overall population of patients with advanced melanoma, with balanced demographics between the BRAF-mutant and nonmutant comparison groups. Both groups had a majority of patients who had received prior ipilimumab and who had stage M1C disease.

The results suggest a similar rate of adverse events in patients with and without BRAF-mutant melanoma treated with nivolumab; 6.0% and 11.3% of patients discontinued nivolumab therapy owing to any grade of treatment-related adverse events in those with BRAF nonmutant and BRAF-mutant melanoma, respectively. Overall, nivolumab is very well tolerated by all patients, with a very small incidence of grade 3 to 4 treatment-related adverse events observed across all single-agent studies to date.

Objective response rates were similar among the BRAF-mutant and nonmutant patient comparison groups, with complete responses observed in both groups. Furthermore, although based on a much smaller number of patients, there was no clear difference in response rates among patients with BRAF-mutant melanoma who had received a prior BRAF inhibitor (11 of 37 patients [29.7%]) vs those patients with BRAF-mutant melanoma who had not received a prior BRAF inhibitor (5 of 17 patients [29.4%]) among the overall study population included in this analysis.

Of note, 1 of the 4 studies included, the randomized phase 3 study of nivolumab vs chemotherapy (the CheckMate 037 trial), which comprised approximately 60% of the patients included in the analysis, required all patients with a BRAF mutation to have received prior BRAF inhibitor therapy. An exploratory analysis of response by BRAF mutation status in that study alone identified an objective response rate of 34% in non-BRAF-mutant patients vs 23.1% in BRAF-mutant patients treated with nivolumab, all of whom would have received prior BRAF therapy as well. Given that all of the patients with BRAF-mutant melanoma in that study were uniformly required to have received prior BRAF inhibitor therapy, it is possible that there may be a small effect of prior treatment with BRAF inhibition (as opposed to BRAF mut-
tation status) on objective response rates with nivolumab, although this difference was not observed in the overall data analysis reported by Larkin et al.\(^1\) Furthermore, while there are data to suggest synergy between BRAF-directed therapy and PD-1 blockade (an area of active investigation, although not approved for clinical use), current data do not support clear differences in clinical response rates to PD-1 blockade that can be related to the drug mechanism of action of prior BRAF inhibitor therapy. However, factors associated with prior BRAF inhibition, such as an increased baseline tumor size after prior therapy, may have an impact on response rates to PD-1 blockade, as previously described.\(^2\)

Overall, the results do suggest a similar response rate to PD-1 blockade in patients with and without BRAF mutant melanoma in this retrospective data analysis including a heterogeneous study population. The results are also consistent with those of prior studies of immune therapy with ipilimumab\(^3\) in which BRAF mutation status does not have an impact on objective response rates and are also consistent with a prior report of PD-1 blockade with pembrolizumab in which response rates were similar in the BRAF-mutant and nonmutant patients enrolled in a large clinical trial.\(^4\) A prospective randomized clinical study in a uniform study population would be required to confirm that response rates are truly equal in patients with or without BRAF-mutant melanoma, and in patients with and without prior BRAF inhibitor therapy among the BRAF-mutant patients.

The results are applicable to patients similar to those eligible for the clinical trials included in the analysis; that is, patients with a good performance status and normal organ function can be considered for treatment with PD-1 blockade with nivolumab regardless of BRAF mutation status. However, clinicians should exercise caution in applying these results to patients who would not meet the trial eligibility criteria of the study population—for example, patients with a poor performance status, because response rates to nivolumab may not be similar in patients with and without BRAF mutations in a nontrial population. BRAF-directed therapy may offer a higher chance of response and clinical benefit in some patients with BRAF-mutant melanoma and should be considered in all patients with BRAF-mutant melanoma.

It is clear that patients both with and without BRAF-activating mutations gain benefit from PD-1 blockade, with durable responses observed in both subsets of patients, regardless of prior therapies. Ongoing studies will further define the role of sequencing of BRAF-targeted therapy and PD-1 or CTLA-4 blockade on clinical outcomes. Clinical trials that include PD-1 blockade as well as novel immune therapy combination studies or targeted therapy combination studies can be considered among the first line of therapy options for all patients with advanced melanoma.