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ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

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ABSTRACT

BACKGROUND

Nivolumab was associated with higher rates of objective response than chemotherapy in a phase 3 study involving patients with ipilimumab-refractory metastatic melanoma. The use of nivolumab in previously untreated patients with advanced melanoma has not been tested in a phase 3 controlled study.

METHODS

We randomly assigned 418 previously untreated patients who had metastatic melanoma without a *BRAF* mutation to receive nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks and dacarbazine-matched placebo every 3 weeks) or dacarbazine (at a dose of 1000 mg per square meter of body-surface area every 3 weeks and nivolumab-matched placebo every 2 weeks). The primary end point was overall survival.

RESULTS

At 1 year, the overall rate of survival was 72.9% (95% confidence interval [CI], 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (hazard ratio for death, 0.42; 99.79% CI, 0.25 to 0.73; P<0.001). The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1). Common adverse events associated with nivolumab included fatigue, pruritus, and nausea. Drug-related adverse events of grade 3 or 4 occurred in 11.7% of the patients treated with nivolumab and 17.6% of those treated with dacarbazine.

CONCLUSIONS

Nivolumab was associated with significant improvements in overall survival and progression-free survival, as compared with dacarbazine, among previously untreated patients who had metastatic melanoma without a *BRAF* mutation. (Funded by Bristol-Myers Squibb; CheckMate 066 ClinicalTrials.gov number, NCT01721772.)

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THE GLOBAL INCIDENCE OF MELANOMA continues to rise, and the mortality associated with unresectable or metastatic melanoma remains high.[1] Globally, 132,000 new cases of melanoma are diagnosed and an estimated 48,000 persons die from advanced melanoma each year.[2,3] Ipilimumab has been shown to improve the rate of survival at 2 years, as compared with a vaccine control, among previously treated patients with metastatic melanoma as well as among previously untreated patients who also received dacarbazine.[4,5] BRAF and MEK inhibitors are approved agents that, as monotherapy, have been associated with a survival advantage as compared with chemotherapy, with a median overall survival of 13 to 20 months.[6-8] Although the objective response rate is high with these agents (45 to 53%), the median duration of response is less than 1 year.[6-10]

Recently, a combination of anti-BRAF and anti-MEK agents has been associated with a higher response rate and longer duration of response, as compared with anti-BRAF monotherapies.[11,12] However, the use of these targeted agents, as monotherapy or in combination, is limited to the approximately 40% of patients who have melanoma with a *BRAF* V600 mutation. Dacarbazine is associated with a median overall survival of 5.6 to 7.8 months and remained until recently a commonly used therapy in patients with previously untreated melanoma without a *BRAF* mutation.[5,13] Despite new treatment options, there remains a substantial unmet need for treatments that extend survival and provide a better quality of life.

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2, disrupting the negative signal that regulates T-cell activation and proliferation.[14] In a phase 1 study, nivolumab was associated with promising antitumor activity and a favorable safety profile in patients with solid tumors, including advanced melanoma.[15,16] In an open-label, randomized, phase 3 study involving patients with ipilimumab-refractory melanoma, nivolumab was associated with a higher rate of objective response than chemotherapy (32% vs. 11%).[17] Recently, another anti–PD-1 antibody, pembrolizumab, has shown robust clinical activity and has been approved in the United States on the basis of an objective response rate of 24% among patients with advanced melanoma that progressed after ipilimumab, as well as treatment with a BRAF inhibitor if the patient had a *BRAF* V600 mutation.[18] Here, we report the results of a phase 3, randomized, double-blind study conducted to determine whether nivolumab, as compared with dacarbazine, improves overall survival among previously untreated patients who have advanced melanoma without a *BRAF* mutation.

METHODS

PATIENTS

Eligible patients had confirmed, unresectable, previously untreated stage III or IV melanoma without a *BRAF* mutation. Other eligibility criteria included an age of 18 years or more, an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and 1 indicating mild symptoms), and the availability of tumor tissue from a metastatic or unresectable site for PD-L1 biomarker analysis. Key exclusion criteria were active brain metastases, uveal melanoma, and a history of serious autoimmune disease. Patients who had received adjuvant therapy previously were not excluded.

STUDY DESIGN AND TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive by means of intravenous infusion either 3 mg of nivolumab per kilogram of body weight every 2 weeks, plus a dacarbazine-matched placebo every 3 weeks, or 1000 mg of dacarbazine per square meter of body-surface area every 3 weeks, plus a nivolumab-matched placebo every 2 weeks. Randomization was stratified according to tumor PD-L1 status (positive vs. negative or indeterminate) and metastasis stage (M0, M1a, or M1b vs. M1c, defined according to the tumor–node–metastasis system of the American Joint Committee on Cancer and the International Union against Cancer). Treatment continued until there was disease progression, as assessed by the investigator, or an unacceptable level of toxic effects. Treatment after disease progression was permitted for patients who had a clinical benefit and did not have substantial adverse effects with the study drug, as determined by the investigator (Fig. S1 in the Supplementary

Appendix, available with the full text of this article at NEJM.org).

The primary end point was overall survival. Secondary end points included investigator-assessed progression-free survival, objective response rate, and PD-L1 expression in the tumor as a predictive biomarker of overall survival.

ASSESSMENT

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[19] at 9 weeks after randomization, every 6 weeks thereafter for the first year, and then every 12 weeks until disease progression or treatment discontinuation. Assessments for survival were performed every 3 months. Safety evaluations were performed for patients who received at least one dose of the study treatment, and the severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[20]

STUDY OVERSIGHT

The study protocol, available at NEJM.org with the most recent version of the statistical analysis plan, was approved by the institutional review board at each participating center. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All the patients provided written informed consent to participate in the study. Data were collected by the sponsor, Bristol-Myers Squibb, and analyzed in collaboration with the academic authors. All the authors vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the study to the protocol. The first draft of the manuscript was written by the first and last authors, with all the authors contributing to subsequent drafts. Medical-writing support, funded by the sponsor, was provided by StemScientific.

A data and safety monitoring committee was established to provide oversight of safety and efficacy considerations. On June 10, 2014, the monitoring committee reviewed an expedited report after noting a potential difference in overall survival during an earlier safety review. Data from the abbreviated report, which was based on an unplanned interim database lock, showed a significant difference in overall survival in favor of nivolumab. As a result, the monitoring committee recommended that the study be unblinded and amended to allow patients enrolled in the dacarbazine group to receive nivolumab. Reported here are the results from the double-blind portion of the study before the amendment (clinical data cutoff on June 24, 2014).

PD-L1 ASSESSMENT

Before randomization, the expression of PD-L1 on the surface of the tumor cells was assessed in a central laboratory with the use of an automated immunohistochemical assay (collaboratively developed by Bristol-Myers Squibb and Dako), as described previously.[21] PD-L1 positivity was defined as at least 5% of tumor cells showing cell-surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated. Indeterminate status was attributed to samples for which tumor cell–surface expression could not be discerned because of melanin content or strong cytoplasmic staining. PD-L1 status was prospectively determined, and the results were used to stratify randomization, which was performed by means of a fully automated interactive voice-response system. Statistical analyses were prespecified to assess the predictive value of PD-L1 expression.

STATISTICAL ANALYSIS

A sample of approximately 410 patients, randomly assigned in a 1:1 ratio to the two treatment groups, was planned. Overall survival and progression-free survival were compared between the two treatment groups with the use of a two-sided log-rank test stratified according to PD-L1 status (positive vs. negative or indeterminate) and metastasis stage (M0, M1a, or M1b vs. M1c). The hazard ratios for the nivolumab group, as compared with the dacarbazine group, and corresponding confidence intervals were estimated with the use of a stratified Cox proportional-hazards model. Survival curves for each treatment group were estimated with the use of the Kaplan–Meier product-limit method. Rates at fixed time points were derived from the Kaplan–Meier estimate, along with their corresponding log-log–transformed 95% confidence interval.

The objective response rate was compared between the two treatment groups with the use of a two-sided Cochran–Mantel–Haenszel test. The efficacy analyses were performed in the

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