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ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

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ABSTRACT

BACKGROUND

The programmed death 1 (PD-1) receptor is a negative regulator of T-cell effector mechanisms that limits immune responses against cancer. We tested the anti–PD-1 antibody lambrolizumab (previously known as MK-3475) in patients with advanced melanoma.

METHODS

We administered lambrolizumab intravenously at a dose of 10 mg per kilogram of body weight every 2 or 3 weeks or 2 mg per kilogram every 3 weeks in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not. Tumor responses were assessed every 12 weeks.

RESULTS

A total of 135 patients with advanced melanoma were treated. Common adverse events attributed to treatment were fatigue, rash, pruritus, and diarrhea; most of the adverse events were low grade. The confirmed response rate across all dose cohorts, evaluated by central radiologic review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, was 38% (95% confidence interval [CI], 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg per kilogram every 2 weeks (52%; 95% CI, 38 to 66). The response rate did not differ significantly between patients who had received prior ipilimumab treatment and those who had not (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively). Responses were durable in the majority of patients (median follow-up, 11 months among patients who had a response); 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median progression-free survival among the 135 patients was longer than 7 months.

CONCLUSIONS

In patients with advanced melanoma, including those who had had disease progression while they had been receiving ipilimumab, treatment with lambrolizumab resulted in a high rate of sustained tumor regression, with mainly grade 1 or 2 toxic effects. (Funded by Merck Sharp and Dohme; ClinicalTrials.gov number, NCT01295827.)

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Cancer evolves to exploit multiple mechanisms in order to avoid immune-cell recognition and antitumor effector functions, thereby limiting the clinical benefits of immunotherapy strategies. Antibodies that block the inhibitory receptor cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), such as ipilimumab, have been shown to release one of these negative immune regulatory pathways, leading to durable responses in a subgroup of patients with metastatic melanoma and an overall survival benefit in patients with metastatic melanoma.[1,2] The programmed cell death 1 (PD-1) receptor is another inhibitory receptor expressed by T cells preferentially with long-term exposure to antigens. Its primary ligand, PD-L1 (also known as B7-H1 or CD274), is frequently expressed within the tumor microenvironment, including cancer cells and tumor-infiltrating macrophages. The PD-1 receptor has a second ligand, PD-L2 (also known as B7-DC or CD273), that is preferentially expressed by antigen-presenting cells.[3] In tumor models, PD-1 negatively regulates the effector phase of T-cell responses after ligation of PD-L1 expressed within the tumor.[4] It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systemic toxic effects than those that are seen with other immune checkpoint inhibitors.[3,5,6]

Two large, dose-escalation, phase 1 clinical trials evaluating the safety of the anti–PD-1 antibody nivolumab (formerly known as BMS936558) and the anti–PD-L1 antibody BMS936559 showed significant antitumor activity in patients with advanced melanoma, lung carcinoma, and renal-cell carcinoma, among other cancers, thus validating the PD-1–PD-L1 axis as a therapeutic target.[7-9] Most tumor responses were durable beyond 1 year.[8,9] Toxic effects were generally of low grade.

Lambrolizumab (previously known as MK-3475) is a highly selective, humanized monoclonal IgG4–kappa isotype antibody against PD-1 that is designed to block the negative immune regulatory signaling of the PD-1 receptor expressed by T cells. The variable region sequences of a very-high-affinity mouse antihuman PD-1 antibody (dissociation constant, 28 pM) were grafted into a human IgG4 immunoglobulin with a stabilizing S228P Fc alteration. The IgG4 immunoglobulin subtype does not engage Fc receptors or activate complement, thus avoiding cytotoxic effects of the antibody when it binds to the T cells that it is intended to activate. In T-cell activation assays that used human donor blood cells, the 50% effective concentration was in the range of 0.1 to 0.3 nM (unpublished data). The first dose-escalation phase 1 study involving patients with solid tumors showed that lambrolizumab was safe at the dose levels tested (1 mg per kilogram of body weight, 3 mg per kilogram, and 10 mg per kilogram, administered every 2 weeks) without reaching a maximum tolerated dose. In addition, clinical responses were observed at all the dose levels.[10] We report here the safety and antitumor activity of three dosing regimens of lambrolizumab that we evaluated in patients with advanced melanoma.

METHODS

STUDY OVERSIGHT

This study was sponsored by Merck Sharp and Dohme, which provided the study drug and worked jointly with the senior academic authors to design the study, collect the data, and interpret the study results. The data were analyzed by a statistician employed by the sponsor and by the senior academic authors. All the authors made the decision to submit the manuscript for publication, vouch for the accuracy and completeness of the data, and attest that the study was conducted as specified in the protocol, which is available with the full text of this article at NEJM.org. The protocol and its amendments were approved by the relevant institutional review boards or ethics committees, and all participants provided written informed consent. All drafts of the manuscript were written by the corresponding author with input from the other authors. The sponsor provided assistance with the preparation of the manuscript. Aside from the authors and those listed in the acknowledgments, no others contributed to the preparation of the manuscript.

STUDY DESIGN

The primary objective of this study was to evaluate the safety profile of lambrolizumab. The secondary end point was a preliminary analysis of the antitumor activity of lambrolizumab, both in patients who had received prior treatment with ipilimumab and in those who had not. After dose escalation of lambrolizumab to a maximum

administered dose of 10 mg per kilogram every 2 weeks,[10] an expansion cohort (Part B of the study) was initiated, with eligibility restricted to patients with advanced melanoma. In Part B of the study, which we report on here, the initial cohort of patients who were enrolled received lambrolizumab as a 30-minute intravenous infusion, every 2 weeks at a dose of 10 mg per kilogram; patients enrolled in additional cohorts in Part B received lambrolizumab as a 30-minute intravenous infusion every 3 weeks at a dose of 2 mg per kilogram or 10 mg per kilogram in sequential or concurrent cohorts without randomization. The study therapy was continued until disease progression was confirmed, unacceptable toxic effects developed, or consent was withdrawn. Patients in whom a scheduled scan showed initial disease progression were allowed to continue receiving treatment until a confirmatory scan was obtained at least 1 month later. Patients underwent a mandatory baseline biopsy and optional biopsies during the course of the trial for biomarker studies. Safety evaluations (clinical and laboratory) were performed at baseline and before each dose of lambrolizumab was administered. No premedications were administered before lambrolizumab infusions. The first scheduled assessment of tumor response was performed 12 weeks after the first dose of lambrolizumab and every 12 weeks thereafter. The evaluation of tumor response was made by investigators at the study site and by a central imaging vendor (Perceptive Informatics).

PATIENTS

Patients were eligible for participation in Part B of the study if they were 18 years of age or older, had measurable metastatic or locally advanced unresectable melanoma, and had adequate performance status and organ function (according to criteria listed in the protocol). The cohorts of patients who had not received prior treatment with ipilimumab were restricted to patients who had received no more than two prior regimens of systemic therapy. The cohorts of patients who had received prior therapy with ipilimumab included only patients who had full resolution of ipilimumab-related adverse events and no history of severe immune-related adverse events associated with ipilimumab therapy. Patients were allowed to enter the trial 6 weeks after the last dose of ipilimumab was administered. The protocol did not require patients who were asymptomatic to undergo screening brain imaging; however, patients with previously treated brain metastases were required to undergo baseline imaging by means of computed tomographic scanning or magnetic resonance imaging and to have had no evidence of central nervous system progression for 8 weeks. Major exclusion criteria were a melanoma of ocular origin, prior therapy with a PD-1 or PD-L1 blocking agent, current systemic immunosuppressive therapy, or active infections or autoimmune diseases.

PHARMACOKINETIC ANALYSIS

Peak-level and trough-level blood samples for pharmacokinetic analysis were obtained from patients at the initiation of treatment. Trough samples were also obtained approximately every 12 weeks for the first 12 months of the study and every 6 months thereafter. The serum concentration of lambrolizumab was quantified with the use of a validated electrochemiluminescent assay with a lower limit of quantification of 10 ng per milliliter.

STATISTICAL ANALYSIS

Data from 135 patients with melanoma who were enrolled and treated according to protocol amendments 02, 03, and 04 were used for the analysis of adverse events. Of the 135 patients, 117 had radiographically measurable disease as assessed by means of central radiologic review and were included in the efficacy analysis of responses according to central review. All other efficacy analyses (an analysis of response on the basis of assessment by the investigator, progression-free survival, and overall survival) were based on data from all 135 patients. Patients were included in the analysis if they received a first dose of study medication by September 6, 2012. Efficacy and safety data that were available as of February 1, 2013, were included in all the analyses. The efficacy analysis included two end points: overall responses derived from investigator-reported data, with assessment according to immune-related response criteria (135 patients)[11]; and overall responses derived from independent, central, blinded radiologic review, with assessment according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (117 patients) (see Table S1 in the Supplementary Appendix, available at NEJM.org, for re-

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