ORIGINAL ARTICLE

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

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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 response criteria).[12] The overall response rate was defined as the number of patients with a complete or partial response divided by the total number of patients who had measurable disease at baseline and received at least one treatment dose. The overall response rate and exact two-sided 95% confidence interval were calculated. Toxic effects were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[13] Descriptive statistics were provided for the pharmacokinetic analysis of trough and peak samples according to treatment cohort.

## RESULTS

### Baseline Characteristics of the Patients

Between December 1, 2011, and September 6, 2012, a total of 135 patients with advanced melanoma were enrolled in this multi-institutional, international, phase 1 expansion study. Initially, patients were enrolled in a cohort that received lambrolizumab at a dose of 10 mg per kilogram every 2 weeks. Subsequently, additional patients were enrolled in concurrent (not randomized) cohorts that received lambrolizumab at 10 mg per kilogram or 2 mg per kilogram every 3 weeks. A distinction was made between patients who had received prior treatment with ipilimumab (48 patients) and those who had not (87 patients) to provide preliminary data on the safety and antitumor activity of lambrolizumab on the basis of prior or no prior treatment with ipilimumab. The median time between the last dose of ipilimumab and the initiation of lambrolizumab was 23 weeks (range, 6 to 83). The majority of patients (38 of 48) were enrolled more than 12 weeks after the last dose of ipilimumab, and 90% (43 of 48) had received three or more infusions of ipilimumab. The baseline characteristics of the patients were similar across all the treatment groups (Table 1). Overall, more than 50% of the patients had visceral metastases (stage M1c), approximately 25% had an elevated lactate dehydrogenase level, and close to 9% had a history of brain metastases — all of which are recognized as poor prognostic factors in patients with advanced melanoma.

**TABLE 1**

Baseline Characteristics of the Patients, According to Cohort.

### Safety

Table 2 shows the adverse events that were considered to be related to lambrolizumab therapy. Table S2 in the Supplementary Appendix provides further details of drug-related toxic effects according to the dosing cohort, and Table S3 in the Supplementary Appendix describes all adverse events regardless of the cause, according to the dosing cohort. Of the 135 patients who received at least one dose of lambrolizumab, 79% reported drug-related adverse events of any grade, and 13% reported grade 3 or 4 drug-related adverse events. Generalized symptoms, including fatigue and asthenia, fever and chills, myalgias, and headaches, were reported frequently but were of low grade in more than 95% of the cases. In addition to the data shown in the tables, there was one case of grade 1 infusion reaction. Rashes and pruritus were reported in 21% of the patients; grade 3 or 4 pruritus was reported in 1% of the patients, and grade 3 or 4 rash in 2%. Vitiligo was attributed to lambrolizumab in 9% of the patients. The highest incidence of overall treatment-related adverse events was seen among the patients who received 10 mg of lambrolizumab per kilogram every 2 weeks, as compared with the patients receiving 10 mg per kilogram every 3 weeks and those receiving 2 mg per kilogram every 3 weeks (23%, vs. 4% and 9%, respectively) (Table S2 in the Supplementary Appendix).

**TABLE 2**

Drug-Related Adverse Events.

Adverse events of particular interest were of an inflammatory or autoimmune nature. Treatment-related pneumonitis was reported in 4% of the patients; none of the cases were grade 3 or 4. One patient, a 96-year-old man, died during the course of the study. Initial asymptomatic pneumonitis was identified on a scan, and lambrolizumab was discontinued. Subsequently, after shortness of breath developed, the patient received glucocorticoids. The clinical course was complicated when acute bronchopneumonia and pneumothorax due to bronchoscopy and biopsies were diagnosed. Although the pulmonary infiltrates were reduced with glucocorticoids, the patient died from a myocardial infarction and bronchopneumonia. Grade 3 or 4 elevations of aminotransferase levels were reported in 1% of the patients. Two cases of grade 3 renal failure were reported. Both cases were potentially immune-mediated, and the patients' renal function improved with glucocorticoid therapy along with the discontinuation of lambrolizumab. Although diarrhea was reported in 20% of the patients, a single case of grade 3 treatment-related diarrhea was reported. This case was managed with treatment of the symptoms, and the patient recovered promptly without glucocorticoid treatment. Hypothyroidism was reported in 8% of the patients and was effectively managed with thyroid-replacement therapy. In addition to the data shown in the tables, grade 3 hyperthyroidism and grade 2 adrenal insufficiency developed in one patient; these were managed with standard measures, and the patient continued in the study with a durable response. No other endocrinopathies were recorded.

### Pharmacokinetics

Serum concentrations of lambrolizumab in samples obtained before and after administration of the drug were lower by a factor of approximately 5 in patients receiving 2 mg per kilogram every 3 weeks than in those receiving 10 mg per kilogram every 3 weeks; steady-state trough concentrations were 20% greater in the patients receiving 10 mg per kilogram every 2 weeks than in those receiving the same dose every 3 weeks (Table S4 in the Supplementary Appendix). The increase in trough serum concentrations over time is consistent with the half-life of lambrolizumab of about 2 to 3 weeks.[10]

### Clinical Activity

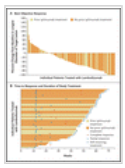
We evaluated the response to therapy using two different criteria: investigator-assessed immune-related response criteria, which were designed to analyze the response to immunotherapy agents[11]; and RECIST,[12] as assessed by independent, central radiologic review, which is used routinely to

assess responses to cytotoxic agents for cancer. The overall response rate during receipt of therapy, across all doses, on the basis of assessment by the investigator according to immune-related response criteria was 37%. The confirmed response rate across all doses, as assessed by central review according to RECIST, was 38% (44 of 117 patients). There were an additional 8 unconfirmed responses. Six of these unconfirmed responses were in patients who had not yet undergone confirmatory scanning at the time of the data cutoff. Since then, 1 of these patients has been confirmed as having an objective response. The response rate, including confirmed and unconfirmed responses, across all doses was 44% (44 confirmed and 8 unconfirmed). The confirmed response rate, as assessed by central review according to RECIST, ranged from 25% in the cohort that received 2 mg per kilogram every 3 weeks to 52% in the cohort that received 10 mg per kilogram every 2 weeks. As shown in Figure 1A, 77% of the patients had a reduction in the tumor burden during the study, including 8 patients who were confirmed by central review as having stable disease for longer than 24 weeks. Responses did not vary according to prior exposure to ipilimumab (Table 3 and Figure 1A).

Figure 1B shows the time to response and the treatment duration in the 52 patients who had an objective response (confirmed or unconfirmed) on the basis of central radiologic review according to RECIST. The majority of responses were seen at the time the first imaging was performed at 12 weeks. An additional 17 patients who had stable disease at an early assessment showed durable objective response with continued treatment, with 1 patient achieving a partial response according to RECIST after 48 weeks of treatment. The median duration of response had not been reached at the time of the analysis, at a median follow-up time of 11 months. A total of 81% of the patients who had a response were still receiving the study treatment at the time of the analysis in March 2013. Of the 52 patients with a response, 5 discontinued treatment owing to disease progression, and 5 discontinued treatment for other reasons (most commonly adverse events). The median progression-free survival among the 135 patients, as estimated with the use of a Kaplan–Meier analysis, was more than 7 months. The estimated median overall survival had not been reached.

Biopsied specimens of regressing lesions were densely infiltrated by CD8+ cytotoxic T lymphocytes (Figure 2A and 2B), a finding that is consistent with the mechanism of action of lambrolizumab. As shown in Figure 2C and 2D, some patients may have had delayed responses after an initial period in which the tumor burden increased, a process consistent with an immune-related response.

**FIGURE 1**

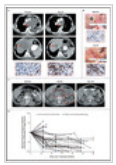


Antitumor Activity of Lambrolizumab.

**TABLE 3**

Objective Response Rate, According to Dosing Regimen and Status with Respect to Prior Therapy with Ipilimumab, as Assessed According to Two Criteria.

**FIGURE 2**



Tumor Responses with Lambrolizumab.

## DISCUSSION

Immunotherapeutic agents, including high-dose interleukin-2, interferon alfa, and anti–CTLA-4 antibodies, have shown activity in patients with advanced melanoma; however, this is an infrequent event that is seen in 10 to 15% of patients.[6,14] This study provides evidence of a high response rate with lambrolizumab in patients with advanced melanoma. Most responses to lambrolizumab were durable — similar to the pattern of response with other immunotherapies[1,2,15,16] — and the majority of responses were ongoing at the time of the current analysis. The cohort with the maximum administered dose of lambrolizumab (10 mg per kilogram every 2 weeks) showed the highest response rate of 52%. This cohort also showed the highest rate of drug-related adverse events, although that may be due in part to a longer duration of therapy (Table S5 in the Supplementary Appendix). It is also possible that these nonrandomized cohorts had unmeasured confounders that could have led to different outcomes — although this is not readily apparent from an analysis of the baseline characteristics of the patients. Therefore, an additional randomized expansion of the cohort is ongoing to investigate the higher response rate observed in the cohort receiving 10 mg per kilogram every 2 weeks as compared with every 3 weeks.

Although cross-study comparisons of adverse-event rates should be viewed with caution, it seems that in comparison with anti–CTLA-4 therapy, lambrolizumab therapy was associated with a lower incidence and a different spectrum of immune-related adverse events, possibly owing to a distinct mechanism of action with a more targeted effect on tumor-specific T cells.[6]

Prior exposure to other immunotherapy strategies, most notably the use of the anti–CTLA-4 antibody ipilimumab or interleukin-2, did not have a major effect on the benefit from lambrolizumab treatment. Furthermore, the rate of immune-mediated or other toxic effects was not increased in patients who had received prior treatment with ipilimumab. In addition, a response to lambrolizumab was documented in patients who had previously had disease progression while receiving other forms of immunotherapy, chemotherapy, or BRAF-targeted therapy. The striking anticancer activity observed with lambrolizumab requires confirmation in larger studies. A randomized clinical trial involving patients who have ipilimumab-refractory disease (and if positive for the *BRAF V600* mutation have received treatment with an approved BRAF or MEK inhibitor) has commenced.

The ability to induce immune responses against cancer by abrogating an immune-system checkpoint that limits the antitumor activity of preexisting tumor-specific cytotoxic T cells points to the importance of focusing on immune regulatory events for cancer therapy. As first described with anti–CTLA-4 antibodies in preclinical studies[17] and in patients,[1,2,16] this study confirms the importance of releasing inhibitory immune regulation by PD-1 for effective antitumor immunity.[6]

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