ORIGINAL ARTICLE

# Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

## ABSTRACT

### BACKGROUND

The immune checkpoint inhibitor ipilimumab is the standard-of-care treatment for patients with advanced melanoma. Pembrolizumab inhibits the programmed cell death 1 (PD-1) immune checkpoint and has antitumor activity in patients with advanced melanoma.

### METHODS

In this randomized, controlled, phase 3 study, we assigned 834 patients with advanced melanoma in a 1:1:1 ratio to receive pembrolizumab (at a dose of 10 mg per kilogram of body weight) every 2 weeks or every 3 weeks or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks. Primary end points were progression-free and overall survival.

### RESULTS

The estimated 6-month progression-free-survival rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (hazard ratio for disease progression, 0.58; P<0.001 for both pembrolizumab regimens versus ipilimumab; 95% confidence intervals [CIs], 0.46 to 0.72 and 0.47 to 0.72, respectively). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively (hazard ratio for death for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 to 0.83; P=0.0005; hazard ratio for pembrolizumab every 3 weeks, 0.69; 95% CI, 0.52 to 0.90; P=0.0036). The response rate was improved with pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (P<0.001 for both comparisons). Responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, respectively, after a median follow-up of 7.9 months. Efficacy was similar in the two pembrolizumab groups. Rates of treatment-related adverse events of grade 3 to 5 severity were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%).

### CONCLUSIONS

The anti–PD-1 antibody pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity than did ipilimumab in patients with advanced melanoma. (Funded by Merck Sharp & Dohme; KEYNOTE-006 ClinicalTrials.gov number, NCT01866319.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Robert at Gustave Roussy and Paris-Sud University, 114 Rue Edouard Vaillant, 94805 Villejuif Paris-Sud, France, or at caroline.robert@gustaveroussy.fr.

*A complete list of investigators in the KEYNOTE-006 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 19, 2015, at NEJM.org.

N Engl J Med 2015;372:2521-32.
DOI: 10.1056/NEJMoa1503093

Two therapeutic strategies have improved survival for patients with advanced melanoma in recent years: immunotherapy with checkpoint inhibitors and targeted therapies blocking BRAF and MEK.[1] BRAF and MEK inhibitors are indicated for the approximately 40 to 50% of patients with *BRAF* V600 mutations,[1] whereas immunotherapies are effective independently of *BRAF* mutational status.[2] Ipilimumab, which blocks cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), a coinhibitory molecule of the immune system,[3,4] is approved for treating advanced melanoma on the basis of its survival benefit.[5,6] However, grade 3 or 4 adverse events, mostly immune-related,[7] are observed in 23% of patients.[5,6]

When activated T cells reach tumors, they can then be functionally inactivated by engagement of programmed cell death 1 (PD-1) with its ligand PD-L1, which is expressed in peripheral tissues and cancers.[4,8,9] Therefore, PD-1 functions as a checkpoint of the effector stage of the immune system, which is distinct from the role of CTLA-4 in limiting T-cell activation.[10] Two monoclonal antibodies directed against PD-1, pembrolizumab and nivolumab, have shown clinical efficacy in patients with melanoma.[11-17] Pembrolizumab was first evaluated in the large, phase 1 KEYNOTE-001 study.[11-13] In a pooled analysis of 411 patients with advanced melanoma enrolled in KEYNOTE-001 and after a median follow-up duration of 18 months, the response rate was 34%, the response was maintained in 81% of those patients, and median overall survival was 25.9 months.[12] The KEYNOTE-002 study of pembrolizumab versus chemotherapy confirmed the benefit of pembrolizumab in patients who had disease progression during or after ipilimumab therapy.[14] Pembrolizumab was associated with toxic effects (mainly immune-related events) of grade 3 or 4 severity in 14% of patients.[12]

The anti–PD-1 monoclonal antibodies pembrolizumab and nivolumab are approved in the United States for use in patients who had disease progression after receiving ipilimumab and, in those with the *BRAF* V600 mutation, BRAF-targeted therapy. In this international, randomized, open-label phase 3 study of pembrolizumab versus ipilimumab, called KEYNOTE-006, we compared PD-1 inhibition with CTLA-4 blockade in a controlled, randomized trial involving patients with advanced melanoma.

## Methods

### Patients

Patients who were 18 years of age or older were eligible for enrollment if they had histologically confirmed, unresectable stage III or IV melanoma and had received no more than one previous systemic therapy for advanced disease. Known *BRAF* V600 mutational status was required; previous BRAF inhibitor therapy was not required for patients with normal lactate dehydrogenase levels and no clinically significant tumor-related symptoms or evidence of rapidly progressive disease. Other key eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability) and provision of a tumor sample adequate for assessing PD-L1 expression. Excluded from the study were patients who had received previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors and those who had ocular melanoma, active brain metastases, or a history of serious autoimmune disease.

### Study Design and Treatment

Patients were randomly assigned in a 1:1:1 ratio to receive pembrolizumab at a dose of 10 mg per kilogram of body weight either every 2 weeks or every 3 weeks or four cycles of ipilimumab at a dose of 3 mg per kilogram every 3 weeks. Randomization was stratified according to ECOG performance status (0 versus 1), line of therapy (first versus second), and PD-L1 expression (positive versus negative).

Pembrolizumab was administered intravenously during a 30-minute period and continued until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, withdrawal of patient consent, or 24 months of therapy. Patients with confirmed complete response who received pembrolizumab for at least 6 months could discontinue therapy after receiving at least two doses beyond the determination of complete response. Ipilimumab was administered intravenously during a 90-minute period and continued for four cycles or until disease progression, the onset of unacceptable side effects, an investigator's decision to discontinue treatment, or withdrawal of patient consent. After initial evidence of radiologic progression, patients whose condition was clinically stable could continue to receive study treatment until imaging

that was performed approximately 4 weeks later confirmed progression. (Details regarding the management of treatment decisions are provided in the protocol, available with the full text of this article at NEJM.org.)

### STUDY ASSESSMENTS

PD-L1 status was assessed in archival or newly obtained tumor samples by means of immunohistochemical analysis with the use of the 22C3 antibody (Merck) at a central laboratory before randomization. Positivity was defined as membranous PD-L1 staining in at least 1% of tumor cells. Response was assessed at week 12 and every 6 weeks thereafter according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[18] on the basis of central radiologic review and immune-related response criteria[19] by investigator review. RECIST was used for the primary assessment of efficacy, whereas immune-related response criteria were used for managing treatment. Survival was assessed every 3 months after the discontinuation of a study drug. Adverse events, laboratory values, and vital signs were assessed regularly and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

### END POINTS

Primary end points were progression-free survival (defined as the time from randomization to documented disease progression according to RECIST or death from any cause) and overall survival (defined as the time from randomization to death from any cause). Secondary end points included the objective response rate (defined as the percentage of patients with complete or partial response according to RECIST), the duration of response (defined as the time from the first documented response to radiologic progression according to RECIST), and safety. Efficacy was assessed in the intention-to-treat population, with all patients included in the treatment group to which they were randomly assigned. Safety was assessed in the as-treated population, which was defined as all patients who underwent randomization and who received at least one dose of a study drug.

### STUDY OVERSIGHT

The original protocol and all amendments were approved by the relevant institutional review board or independent ethics committee at each study center. The study was conducted in accordance with the protocol, Good Clinical Practice guidelines, and the provisions of the Declaration of Helsinki. All patients provided written informed consent.

KEYNOTE-006 was designed by representatives of the study sponsor, Merck Sharp & Dohme, a subsidiary of Merck, and the academic advisors. An external data and safety monitoring committee oversaw the study. (Members of the committee are listed in the Supplementary Appendix, available at NEJM.org.) All data were collected by investigators and associated site personnel, analyzed by statisticians employed by the sponsor, and interpreted by the authors, including those from the sponsor. The corresponding and senior authors wrote the first draft of the manuscript. Assistance in manuscript preparation was provided by a science writer paid by the sponsor. All authors participated in reviewing and editing the manuscript, approved the submitted draft, had full access to the data used to write the manuscript and vouch for their accuracy, and attest that the study was conducted in accordance with the protocol.

### STATISTICAL ANALYSIS

We used the Kaplan–Meier method to calculate estimates of progression-free and overall survival. Data for patients who did not have disease progression or who were lost to follow-up were censored at the time of last tumor assessment for progression-free survival. Treatment differences for progression-free and overall survival were assessed by means of the stratified log-rank test. Hazard ratios and associated 95% confidence intervals were assessed with the use of a stratified Cox proportional-hazards model with Efron's method of handling ties. We compared response rates in the study groups using the stratified Miettinen and Nurminen method.

The protocol specified the performance of two interim analyses (as summarized in Table S1 in the Supplementary Appendix). The first analysis was to be performed after at least 260 patients had disease progression or died in all study groups and all patients had been followed for at least 6 months. The primary objective of this analysis was to evaluate the superiority of either pembrolizumab regimen over ipilimumab for progression-free survival at a one-sided alpha level

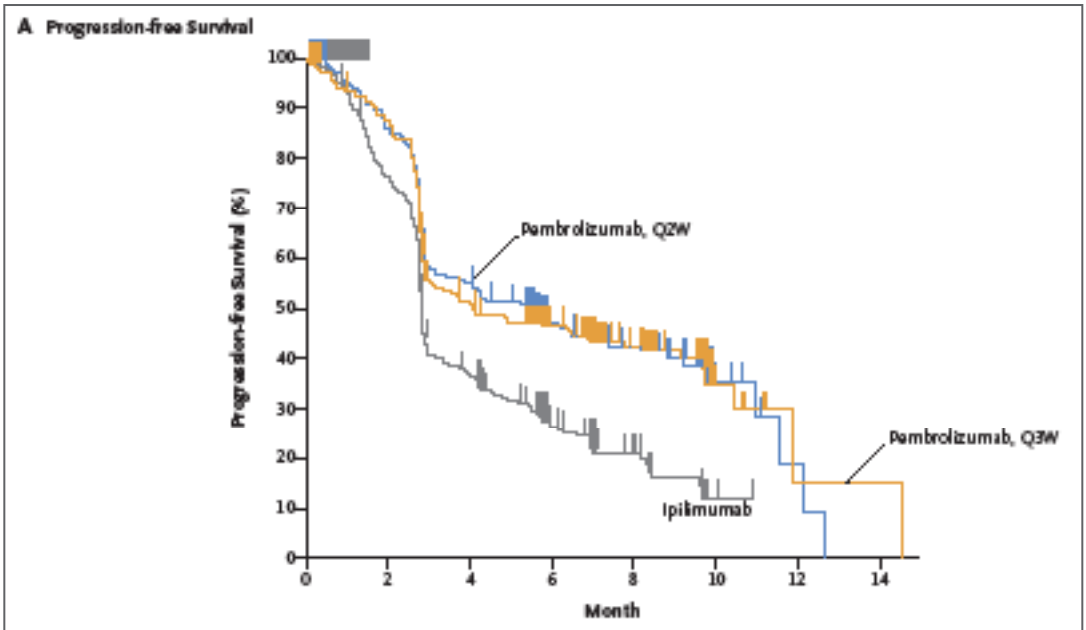
of 0.002. At the first interim analysis, overall survival was evaluated at a one-sided alpha level of 0.00002 to have a negligible effect on the overall type I error rate to preserve the alpha level for the second interim and final analyses. The second interim analysis, in which the primary objective was to evaluate the superiority of either pembrolizumab regimen over ipilimumab for overall survival at a one-sided alpha level of 0.005 with the use of the Hochberg step-up procedure, was to be performed after at least 290 patients had died in all the study groups and all patients had been followed for at least 9 months or when the minimum follow-up duration was 12 months, whichever occurred first.

The first interim analysis, with a data cutoff of September 3, 2014, was conducted by an independent statistician who was aware of study-group assignments. After the data and safety monitoring committee reviewed the results, they recommended continuing the study as planned and unblinding the results to select representatives of the study sponsor for regulatory purposes. The second interim analysis, with a data cutoff of March 3, 2015, was conducted in an unblinded manner by a statistician employed by the sponsor. After reviewing the results of the second interim analysis, the data and safety monitoring committee recommended that the study results be unblinded and pembrolizumab be made

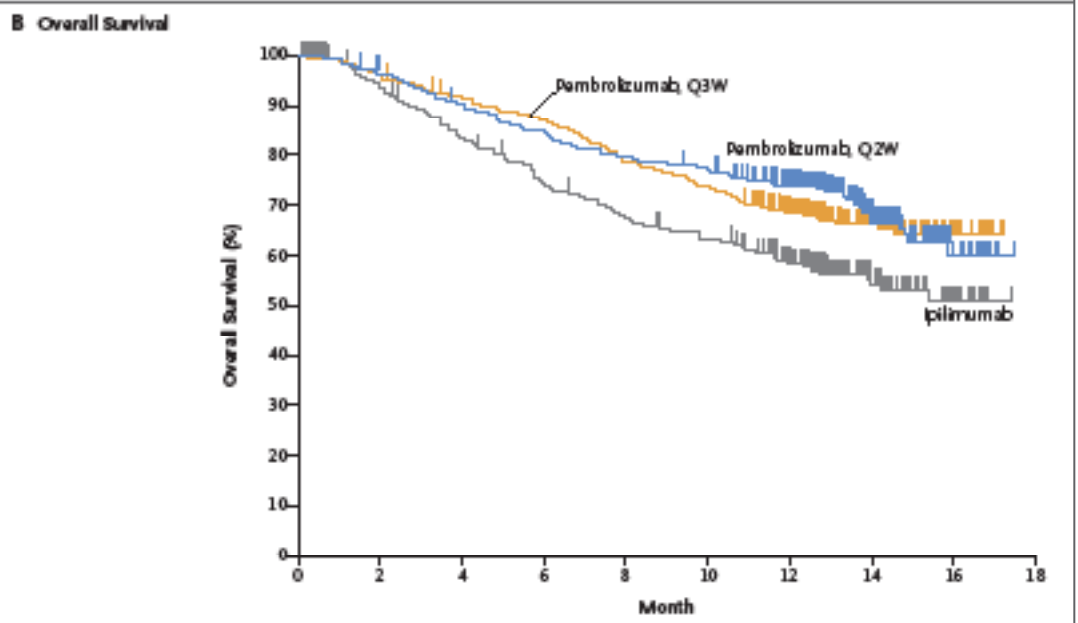
**Table 1. Demographic and Disease Characteristics of the Patients at Baseline (Intention-to-Treat Population).***

| Characteristic | Pembrolizumab Every 2 Wk (N=279) | Pembrolizumab Every 3 Wk (N=277) | Ipilimumab (N=278) |
|---|---|---|---|
| Median age (range) — yr | 61 (18–89) | 63 (22–89) | 62 (18–88) |
| Male sex — no. (%) | 161 (57.7) | 174 (62.8) | 162 (58.3) |
| ECOG performance status — no. (%) | | | |
| 0 | 196 (70.3) | 189 (68.2) | 188 (67.6) |
| 1 | 83 (29.7) | 88 (31.8) | 90 (32.4) |
| Elevated baseline LDH level — no. (%) | 81 (29.0) | 98 (35.4) | 91 (32.7) |
| Metastasis stage — no. (%)† | | | |
| M0 | 9 (3.2) | 9 (3.2) | 14 (5.0) |
| M1‡ | 6 (2.2) | 4 (1.4) | 5 (1.8) |
| M1a | 21 (7.5) | 34 (12.3) | 30 (10.8) |
| M1b | 64 (22.9) | 41 (14.8) | 52 (18.7) |
| M1c | 179 (64.2) | 189 (68.2) | 177 (63.7) |
| PD-L1–positive tumor — no. (%) | 225 (80.6) | 221 (79.8) | 225 (80.9) |
| *BRAF* V600 mutation — no. (%) | 98 (35.1) | 97 (35.0) | 107 (38.5) |
| Brain metastasis — no. (%) | 23 (8.2) | 27 (9.7) | 28 (10.1) |
| Line of previous systemic therapy — no. (%)§ | | | |
| 0 | 183 (65.6) | 185 (66.8) | 181 (65.1) |
| 1 | 96 (34.4) | 91 (32.9) | 97 (34.9) |
| Type of previous systemic therapy — no. (%)¶ | | | |
| Chemotherapy | 36 (12.9) | 41 (14.8) | 29 (10.4) |
| Immunotherapy | 8 (2.9) | 7 (2.5) | 12 (4.3) |
| BRAF or MEK inhibitor or both | 50 (17.9) | 45 (16.2) | 56 (20.1) |

* There were no significant differences among the groups. ECOG denotes Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, and PD-L1 programmed cell death 1 ligand 1.
† Details regarding metastasis stages in melanoma are provided in Table S3 in the Supplementary Appendix.
‡ Further classification of the metastasis stage was not provided.
§ One patient (0.4%) in the group receiving pembrolizumab every 3 weeks had received two previous systemic therapies.
¶ Only therapy administered for advanced or metastatic disease is listed.




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pembrolizumab, Q2W | 279 | 231 | 147 | 98 | 49 | 7 | 2 | 0 |
| Pembrolizumab, Q3W | 277 | 235 | 133 | 95 | 53 | 7 | 1 | 1 |
| Ipilimumab | 278 | 186 | 88 | 42 | 18 | 2 | 0 | 0 |




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab, Q2W | 279 | 266 | 248 | 233 | 219 | 212 | 177 | 67 | 19 | 0 |
| Pembrolizumab, Q3W | 277 | 266 | 251 | 238 | 215 | 202 | 158 | 71 | 18 | 0 |
| Ipilimumab | 278 | 242 | 212 | 188 | 169 | 157 | 117 | 51 | 17 | 0 |

**Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.**

Shown are rates of progression-free survival as of September 3, 2014 (Panel A), and overall survival as of March 3, 2015 (Panel B), in the intention-to-treat population among patients receiving pembrolizumab every 2 weeks (Q2W) or every 3 weeks (Q3W) or ipilimumab.

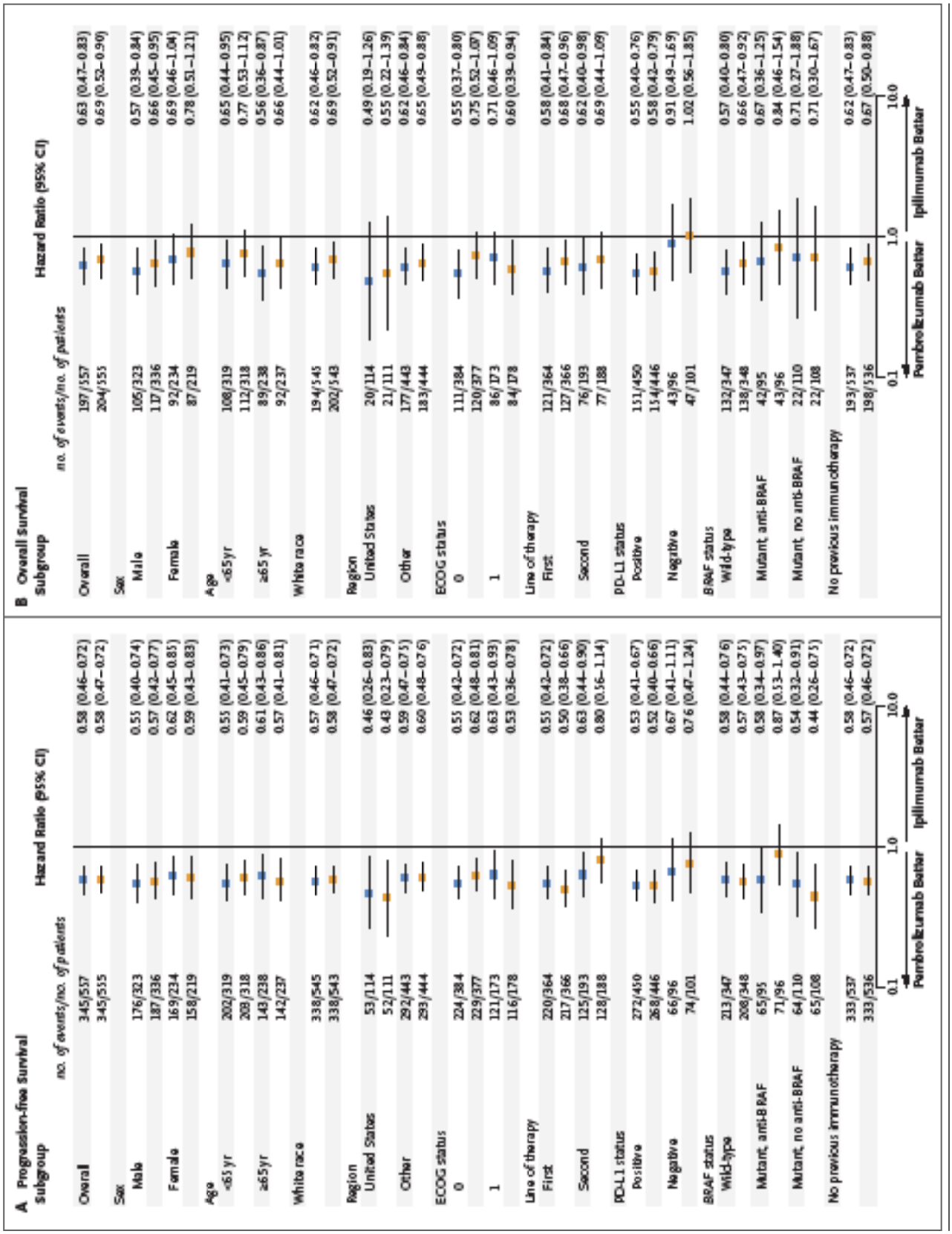


**Figure 2 (facing page). Prespecified Subgroup Analysis of Progression-free and Overall Survival, According to Pembrolizumab Regimen.**

Shown are hazard ratios for progression-free survival as of September 3, 2014 (Panel A), and overall survival as of March 3, 2015 (Panel B), among patients receiving pembrolizumab every 2 weeks (blue squares) or every 3 weeks (orange squares) versus ipilimumab. ECOG denotes Eastern Cooperative Oncology Group, and PD-L1 programmed cell death 1 ligand 1.

available to patients with disease progression in the ipilimumab group. Final overall survival analysis will be performed after at least 435 deaths have occurred in all the study groups or when all patients have been followed for at least 21 months. All data presented here are from the first interim analysis, except those for overall survival, which are from the second interim analysis.

## RESULTS

### PATIENTS AND TREATMENT

From September 18, 2013, to March 3, 2014, a total of 834 patients were enrolled in 16 countries; 279 were randomly assigned to receive pembrolizumab every 2 weeks, 277 to receive pembrolizumab every 3 weeks, and 278 to receive ipilimumab (Fig. S1 in the Supplementary Appendix). The characteristics of the patients at baseline were well balanced across the study groups (Table 1, and Table S2 in the Supplementary Appendix). Among enrolled patients, 65.8% had received no previous systemic treatment for advanced melanoma, 68.7% had an ECOG performance status of 0, 65.3% had stage M1c disease (see Table S3 in the Supplementary Appendix for characteristics of M1c disease), and 32.4% had elevated lactate dehydrogenase levels. *BRAF* V600 mutations were observed in 36.2% of patients, and of these, approximately 50% had received previous BRAF inhibitor treatment; 80.5% of patients had PD-L1–positive tissue samples. The median duration of follow-up at the time of data cutoff was 7.9 months (range, 6.1 to 11.5).

### PRIMARY END POINTS

*Progression-free Survival*

On the basis of 502 events that were analyzed at the protocol-specified time point for the first interim analysis, the two pembrolizumab regimens significantly prolonged progression-free survival in the intention-to-treat population. The estimated 6-month progression-free survival rates were 47.3% for patients receiving pembrolizumab every 2 weeks, 46.4% for those receiving pembrolizumab every 3 weeks, and 26.5% for those receiving ipilimumab (Fig. 1A). Median estimates of progression-free survival were 5.5 months (95% confidence interval [CI], 3.4 to 6.9), 4.1 months (95% CI, 2.9 to 6.9), and 2.8 months (95% CI, 2.8 to 2.9), respectively. The hazard ratios for disease progression for pembrolizumab versus ipilimumab were 0.58 (95% CI, 0.46 to 0.72; P<0.001) for the 2-week regimen and 0.58 (95% CI, 0.47 to 0.72; P<0.001) for the 3-week regimen. The benefit for progression-free survival was evident in all prespecified subgroups for the two pembrolizumab groups (Fig. 2A). The benefit of pembrolizumab over ipilimumab was observed in both PD-L1–positive and PD-L1–negative subgroups, as compared with ipilimumab.

*Overall Survival*

At the time of data cutoff for the second interim analysis, which was driven by a minimum follow-up duration of 12 months for all patients, 289 deaths had occurred. One-year estimates of survival were 74.1% for patients receiving pembrolizumab every 2 weeks (hazard ratio for death as compared with the ipilimumab group, 0.63; 95% CI, 0.47 to 0.83; P<0.0005), 68.4% for those receiving pembrolizumab every 3 weeks (hazard ratio for death as compared with the ipilimumab group, 0.69; 95% CI, 0.52 to 0.90; P=0.0036), and 58.2% for those receiving ipilimumab (Fig. 1B). Because the overall survival results for the two pembrolizumab groups were superior to those for the ipilimumab group at the prespecified one-sided alpha level of 0.005 using the Hochberg step-up procedure, the independent data and safety monitoring committee recommended stopping the study early to allow patients in the ipilimumab group the option of receiving pembrolizumab. Median overall survival was not reached in any study group. The pembrolizumab benefit was observed across all subgroups and for the two regimens (Fig. 2B). The exception was for the 18% of patients with PD-L1–negative tumors, for whom the hazard ratios were 0.91 for those receiving pembrolizumab every 2 weeks and 1.02 for those receiving pembrolizumab every 3 weeks, as compared with ipilimumab. In

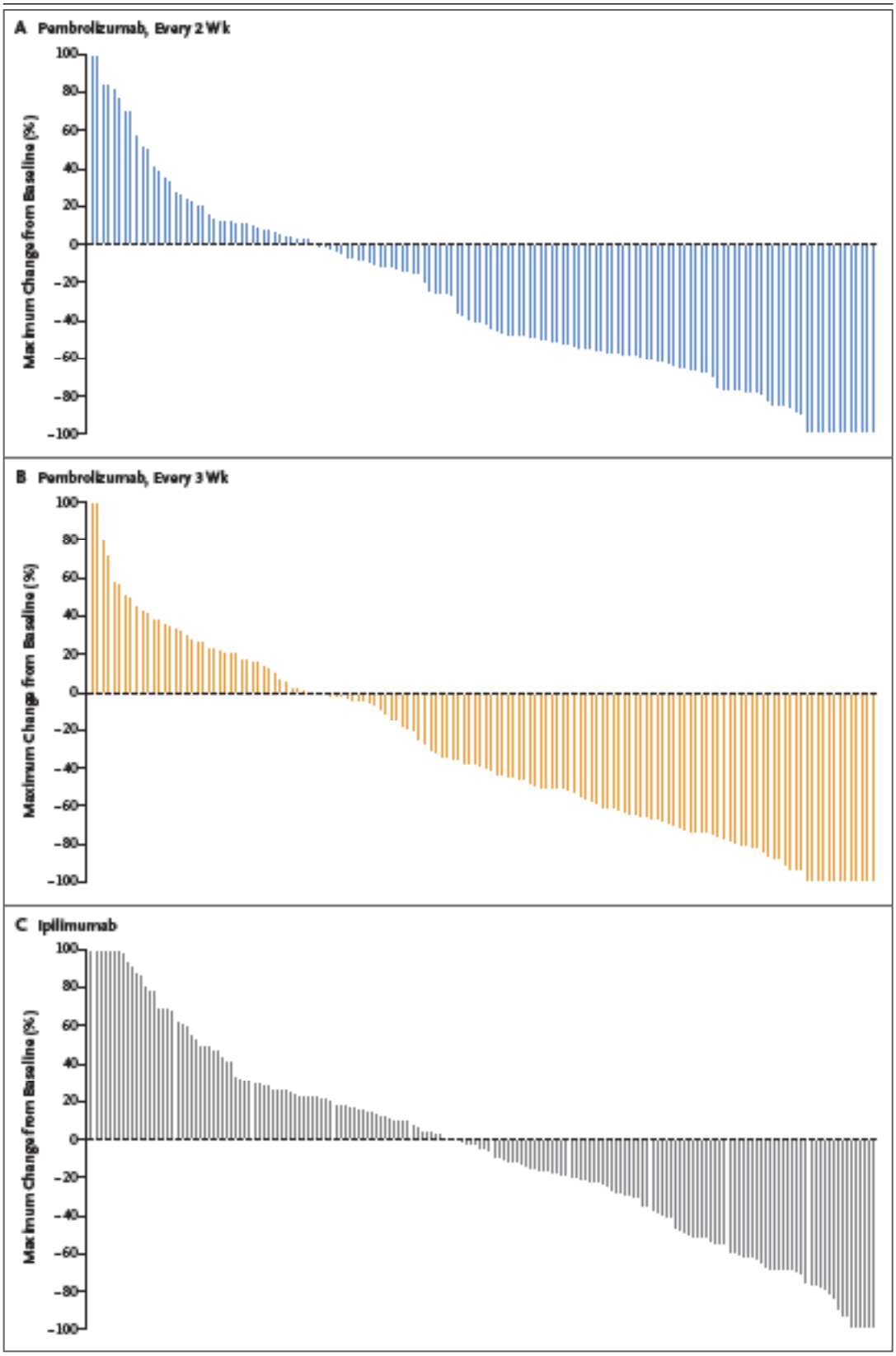


**Figure 3 (facing page). Maximum Percentage Change from Baseline in the Sum of the Longest Diameters of Target Lesions.**

Shown are maximum changes from baseline to September 3, 2014, for all patients receiving pembrolizumab every 2 weeks (Panel A), pembrolizumab every 3 weeks (Panel B), or ipilimumab (Panel C). In all panels, patients without centrally measurable disease according to Response Evaluation Criteria in Solid Tumors at baseline or who did not have a tumor assessment after baseline were excluded. Changes of more than 100% were truncated at 100%.

this subgroup, the sample sizes were small, and the confidence intervals were wide.

### RATES OF RESPONSE

Response rates were 33.7% for pembrolizumab every 2 weeks (P<0.001 vs. ipilimumab), 32.9% for pembrolizumab every 3 weeks (P<0.001), and 11.9% for ipilimumab (Table S4 in the Supplementary Appendix). Rates of complete response were 5.0%, 6.1%, and 1.4%, respectively. The median times to response were 86 days (range, 32 to 212), 85 days (range, 36 to 251), and 87 days (range, 80 to 250), respectively; and 89.4%, 96.7%, and 87.9% of responses, respectively, were ongoing at the time of this analysis, with the median duration of response not reached in any group (Table S4 in the Supplementary Appendix). The evaluation of the maximum change in tumor size that was conducted at the time of the first interim analysis supports the superiority of the two pembrolizumab regimens over ipilimumab (Fig. 3).

### ADVERSE EVENTS

The mean duration of exposure was 164 days among patients receiving pembrolizumab every 2 weeks, 151 days among those receiving pembrolizumab every 3 weeks, and 50 days for those receiving ipilimumab. Grade 3 to 5 adverse events that were attributed to a study drug by investigators occurred in 13.3%, 10.1%, and 19.9% of patients, respectively. The time until the onset of the first grade 3 to 5 adverse event, regardless of attribution, was longer in the pembrolizumab groups (Table S5 and Fig. S2 in the Supplementary Appendix). The rate of permanent discontinuation of a study drug because of treatment-related adverse events was lower in each pembrolizumab group than in the ipilimumab group (4.0%, 6.9%, and 9.4%, respectively). One death in the ipilimumab group was attributed to study treatment. The patient had a history of type 2 diabetes mellitus and died from cardiac arrest secondary to metabolic imbalances associated with ipilimumab-induced diarrhea.

The most common treatment-related adverse events of any grade occurring in the pembrolizumab groups were fatigue (20.9% in the 2-week group and 19.1% in the 3-week group), diarrhea (16.9% and 14.4%, respectively), rash (14.7% and 13.4%, respectively), and pruritus (14.4% and 14.1%, respectively) (Table 2, and Table S6 in the Supplementary Appendix); all events were of grade 3 to 4 severity in less than 1% of patients, except diarrhea (2.5% and 1.1%, respectively). For ipilimumab, the most frequent adverse events were pruritus (25.4%), diarrhea (22.7%), fatigue (15.2%), and rash (14.5%); these events were of grade 3 to 5 severity in less than 1% of patients, except for diarrhea (3.1%) and fatigue (1.2%).

The adverse events of special interest on the basis of the likely autoimmune or immune-related mechanism most frequently observed with pembrolizumab were hypothyroidism (10.1% in the 2-week group and 8.7% in the 3-week group) and hyperthyroidism (6.5% and 3.2%, respectively) (Table 2). Grade 3 to 4 events that were reported in more than 1% of pembrolizumab-treated patients were colitis (1.4% and 2.5%, respectively) and hepatitis (1.1% and 1.8%, respectively). In the ipilimumab group, the most common adverse event of special interest was colitis, which occurred in 8.2% of patients. Grade 3 to 4 events that were reported in more than 1% of ipilimumab-treated patients were colitis (7.0%) and inflammation of the pituitary gland (i.e., hypophysitis) (1.6%). Hypothyroidism and hyperthyroidism were more frequent in the pembrolizumab groups, whereas colitis and hypophysitis were more frequent in the ipilimumab group.

## DISCUSSION

In this randomized, controlled, phase 3 study, we found that two regimens of pembrolizumab, as compared with ipilimumab, improved both progression-free and overall survival in patients with advanced melanoma. The relative risk of progression or death was decreased by 42% with the two pembrolizumab regimens that were tested, and the relative risk of death was decreased by 31 to 37%. Because the overall survival results at the second interim analysis crossed the prespecified

**Table 2. Adverse Events in the As-Treated Population.***

| Adverse Event | Pembrolizumab Every 2 Wk (N=278) | | Pembrolizumab Every 3 Wk (N=277) | | Ipilimumab (N=256) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3–5 | Any Grade | Grade 3–5 | Any Grade | Grade 3–5 |
| | *number of patients (percent)* | | | | | |
| Related to treatment* | | | | | | |
| Any | 221 (79.5) | 37 (13.3) | 202 (72.9) | 28 (10.1) | 187 (73.0) | 51 (19.9) |
| Occurring in ≥10% of patients in any study group | | | | | | |
| Fatigue | 58 (20.9) | 0 | 53 (19.1) | 1 (0.4) | 39 (15.2) | 3 (1.2) |
| Diarrhea | 47 (16.9) | 7 (2.5) | 40 (14.4) | 3 (1.1) | 58 (22.7) | 8 (3.1) |
| Rash | 41 (14.7) | 0 | 37 (13.4) | 0 | 37 (14.5) | 2 (0.8) |
| Pruritus | 40 (14.4) | 0 | 39 (14.1) | 0 | 65 (25.4) | 1 (0.4) |
| Asthenia | 32 (11.5) | 1 (0.4) | 31 (11.2) | 0 | 16 (6.3) | 2 (0.8) |
| Nausea | 28 (10.1) | 0 | 31 (11.2) | 1 (0.4) | 22 (8.6) | 1 (0.4) |
| Arthralgia | 26 (9.4) | 0 | 32 (11.6) | 1 (0.4) | 13 (5.1) | 2 (0.8) |
| Vitiligo | 25 (9.0) | 0 | 31 (11.2) | 0 | 4 (1.6) | 0 |
| Adverse event of special interest† | | | | | | |
| Hypothyroidism | 28 (10.1) | 1 (0.4) | 24 (8.7) | 0 | 5 (2.0) | 0 |
| Hyperthyroidism | 18 (6.5) | 0 | 9 (3.2) | 0 | 6 (2.3) | 1 (0.4) |
| Colitis | 5 (1.8) | 4 (1.4) | 10 (3.6) | 7 (2.5) | 21 (8.2) | 18 (7.0) |
| Hepatitis | 3 (1.1) | 3 (1.1) | 5 (1.8) | 5 (1.8) | 3 (1.2) | 1 (0.4) |
| Hypophysitis | 1 (0.4) | 1 (0.4) | 2 (0.7) | 1 (0.4) | 6 (2.3) | 4 (1.6) |
| Pneumonitis | 1 (0.4) | 0 | 5 (1.8) | 1 (0.4) | 1 (0.4) | 1 (0.4) |
| Type 1 diabetes mellitus | 1 (0.4) | 1 (0.4) | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Uveitis | 1 (0.4) | 0 | 3 (1.1) | 0 | 0 | 0 |
| Myositis | 0 | 0 | 2 (0.7) | 0 | 1 (0.4) | 0 |
| Nephritis | 0 | 0 | 1 (0.4) | 0 | 1 (0.4) | 1 (0.4) |

* The relationship between an adverse event and a study drug was attributed by the investigator. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks, except for hypothyroidism, hyperthyroidism, and colitis, which are reported as adverse events of special interest.

† The listed adverse events of special interest include related terms and are provided regardless of attribution to a study drug. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks.

efficacy boundary, the trial was stopped for efficacy and the results were unblinded. The study will continue safety and survival follow-up until the final analysis. Response rates, which significantly favored pembrolizumab, were in line with previous findings for both pembrolizumab[11-13] and ipilimumab.[5,6] Responses appeared to be durable in all groups, with ongoing responses in 93.0% of patients in the combined pembrolizumab groups and 87.8% of those in the ipilimumab group at the time of data cutoff.

There were no apparent differences in efficacy between the two pembrolizumab regimens tested in this study, neither of which is the dose that is approved in the United States (2 mg per kilogram every 3 weeks). The lack of a dose–response relationship is congruent with results of two randomized cohorts in KEYNOTE-001 and the randomized, controlled KEYNOTE-002 trial, in which the administration of pembrolizumab at doses ranging from 2 mg per kilogram every 3 weeks to 10 mg per kilogram every 2 weeks did not affect outcomes.[12-14,20]

Subgroup analyses showed that the progression-free and overall survival benefits provided by pembrolizumab extended to most subgroups that were assessed. Similar hazard ratios were observed for progression-free and overall sur-

vival with the two pembrolizumab regimens across all patient subgroups except for overall survival in patients with PD-L1–negative melanoma, a finding that reinforces the superiority of pembrolizumab over ipilimumab and the lack of an effect for pembrolizumab according to regimen. For PD-L1 expression, the sample size was too small (less than 20% of patients) to draw a definite conclusion on relative efficacy. Several factors add complexity when interpreting correlative analyses of PD-L1 expression with efficacy.[21-23] For example, various levels of expression can be found in different melanoma metastases originating from the same patients.[24] Furthermore, additional variables, such as the presence of preexisting intratumoral CD8+ T cells and tumor mutational load, may be important components to assess the potential for anti–PD-1 therapies.[25,26]

This study did not enroll patients with *BRAF* V600 mutations who did not receive previous anti-BRAF targeted therapy if they had high lactate dehydrogenase levels and symptomatic or rapidly progressive disease, because targeted anti-BRAF agents can have a rapid clinical benefit in this population of patients.[27] The treatment of patients with *BRAF* V600 mutations and, in particular, the most effective sequence of immunotherapy and BRAF or MEK inhibitors remains one of the most critical, yet unanswered, questions. Although this question cannot be addressed without randomized, controlled trials, *BRAF* V600 status did not seem to affect the benefit of pembrolizumab over ipilimumab in this study. Other important areas of clinical investigation include the role of combination immunotherapy and the treatment of patients who have minimal disease progression or mixed responses.

The safety profile of pembrolizumab was similar to that in previous studies,[11-14,20] with no unexpected safety concerns and few grade 3 to 5 treatment-related adverse events reported to date. Although exposure to treatment was approximately 3 times as long with pembrolizumab as with ipilimumab, which may account for an increase in the cumulative number of adverse events, the incidence of grade 3 to 5 events attributed to treatment was lower with pembrolizumab than with ipilimumab, as was the incidence of permanent discontinuation for an adverse event.

In conclusion, this randomized study comparing two immune checkpoint inhibitors showed that pembrolizumab, as compared with ipilimumab, significantly prolonged progression-free and overall survival with fewer high-grade toxic events in patients with advanced melanoma.

Supported by Merck Sharp & Dohme.

Dr. Robert reports receiving fees for serving on advisory boards from Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Amgen, Merck, and Roche; Dr. Long, receiving honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Merck, Provectus, and Roche and consulting fees from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novartis, Provectus, and Roche; Dr. Arance, receiving fees for lectures and for serving on advisory boards for Bristol-Myers Squibb, Roche, and GlaxoSmithKline and grant support from Roche; Dr. Grob, receiving fees for serving on advisory boards from Merck, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Novartis, and Amgen and lecture fees from Bristol-Myers Squibb, Roche, and GlaxoSmithKline; Dr. Mortier, receiving fees for serving on an advisory board from Merck; Dr. Carlino, receiving honoraria and fees for lectures and for serving on advisory boards from Merck Sharp & Dohme and Bristol-Myers Squibb; Dr. McNeil, serving on an advisory board for and receiving travel support from Merck Sharp & Dohme; Dr. Lotem, receiving fees for serving on an advisory board from Bristol-Myers Squibb; Dr. Lorigan, receiving consulting fees and travel support from Merck; Dr. Neyns, receiving lecture and consulting fees from Merck Sharp & Dohme, Bristol-Myers Squibb, and Novartis/GlaxoSmithKline and grant support from Pfizer and Novartis/GlaxoSmithKline; Dr. Blank, receiving consulting fees from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, and GlaxoSmithKline and grant support from Novartis; Dr. Hamid, receiving consulting fees and grant support from Bristol-Myers Squibb, Genentech, and Merck; Dr. Zhou, being an employee of Merck; Dr. Ibrahim, having an equity interest in GlaxoSmithKline and Merck; Dr. Ebbinghaus, being an employee of Merck and having an equity interest in the company; and Dr. Ribas, receiving consulting fees and honoraria from Amgen, Compugen, Flexus, GlaxoSmithKline, Genentech, Novartis, and Merck and having an equity interest in Kite Pharma. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their families and caregivers for participating in the study, as well as all site investigators and personnel; Melanie Leiby, Ph.D. (APO Group, Yardley, PA), for assistance with preparation of the manuscript; Margaret Hodgson, R.N., B.S.N., M.B.A. (Merck), for logistic and administrative support; Lamar Eaton, B.S., and Maureen Bucci, B.S.N. (Merck), for collection of data; Keaven Anderson, Ph.D., and Cong Chen, Ph.D. (Merck), for statistical expertise and critical review of the manuscript; and Roger Dansey, M.D., and Eric Rubin, M.D. (Merck), for leadership of the study group and critical review of the manuscript.

## APPENDIX

The authors' affiliations are as follows: Gustave Roussy Département de Médecine Oncologique, Service de Dermatologie, F-94805, Villejuif, and Université Paris-Sud, Faculté de Médecine, F-94270 Le Kremlin-Bicêtre (C.R., C. Mateus), Hôpital de la Timone, Marseille (J.J.G.), and Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille (L.M.) — all in France; Ella Lemelbaum Institute for Melanoma, Sheba Medical Center, Tel Hashomer (J.S., R.S.-F.), and Sharett Institute of Oncology, Hadassah Hebrew University Medical Center, Jerusalem (M.L.) — both in Israel; Melanoma Institute Australia, the University of Sydney, and the Mater Hospital

(G.V.L.) and Westmead and Blacktown Hospitals, Melanoma Institute Australia and the University of Sydney (M.C.S.), Sydney, and the Chris O'Brien Lifehouse, Royal Prince Alfred Hospital, and Melanoma Institute Australia, Camperdown, NSW (C. McNeil) — all in Australia; the Department of Medical Oncology, Hospital Clinic and Translational Genomics and Targeted Therapeutics in Solid Tumors, Barcelona (A.A.); the University of California, San Francisco, San Francisco (A.D.); the Royal Marsden Hospital, London (J.L.), and the University of Manchester and the Christie NHS Foundation Trust, Manchester (P.L.) — both in the United Kingdom; Universitair Ziekenhuis Brussel, Brussels (B.N.); the Netherlands Cancer Institute, Amsterdam (C.U.B.); the Angeles Clinic and Research Institute (O.H.) and the University of California, Los Angeles (A.R.), Los Angeles; and Merck, Kenilworth, NJ (M.K., H.Z., N.I., S.E.).

## REFERENCES

**1.** McArthur GA, Ribas A. Targeting oncogenic drivers and the immune system in melanoma. J Clin Oncol 2013;31:499-506.
**2.** Ascierto PA, Simeone E, Sileni VC, et al. Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort. J Transl Med 2014;12:116.
**3.** Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734-6.
**4.** Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
**5.** Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
**6.** Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-26.
**7.** Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691-7.
**8.** Blank C, Brown I, Peterson AC, et al. PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res 2004;64:1140-5.
**9.** Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19:813-24.
**10.** Ribas A. Tumor immunotherapy directed at PD-1. N Engl J Med 2012;366:2517-9.
**11.** Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti–PD-1) in melanoma. N Engl J Med 2013;369:134-44.
**12.** Ribas A, Wolchok JD, Robert C, et al. Updated clinical efficacy of the anti-PD-1 monoclonal antibody pembrolizumab in 411 patients with melanoma. Pigment Cell Melanoma Res 2014;27:1223. abstract.
**13.** Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384:1109-17.
**14.** Ribas A, Puzanov I, Drummer R, et al. A randomized controlled comparison of pembrolizumab and chemotherapy in patients with ipilimumab-refractory melanoma. Presented at the Society for Melanoma Research 2014 International Congress, Zurich, Switzerland, November 13–16, 2014.
**15.** Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-33.
**16.** Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014;32:1020-30.
**17.** Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. N Engl J Med 2015;372:320-30.
**18.** Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
**19.** Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412-20.
**20.** Robert C, Joshua AM, Weber JS, et al. Pembrolizumab (pembro; MK-3475) for advanced melanoma: randomized comparison of two dosing schedules. Ann Oncol 2014;25:Suppl 4:LBA34. abstract.
**21.** Liu J, Hamrouni A, Wolowiec D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-$\gamma$ and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood 2007;110:296-304.
**22.** Kondo A, Yamashita T, Tamura H, et al. Interferon-$\gamma$ and tumor necrosis factor-$\alpha$ induce an immunoinhibitory molecule, B7-H1, via nuclear factor-kappaB activation in blasts in myelodysplastic syndromes. Blood 2010;116:1124-31.
**23.** Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739-45.
**24.** Madore J, Vilain RE, Menzies AM, et al. PD-L1 expression in melanoma shows marked heterogeneity within and between patients: implications for anti-PD-1/PD-L1 clinical trials. Pigment Cell Melanoma Res 2014 December 5 (Epub ahead of print).
**25.** Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014;515:568-71.
**26.** Rizvi NA, Hellmann MD, Snyder A, et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
**27.** Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.