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# Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

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## ABSTRACT

### BACKGROUND

An improvement in overall survival among patients with metastatic melanoma has been an elusive goal. In this phase 3 study, ipilimumab — which blocks cytotoxic T-lymphocyte–associated antigen 4 to potentiate an antitumor T-cell response — administered with or without a glycoprotein 100 (gp100) peptide vaccine was compared with gp100 alone in patients with previously treated metastatic melanoma.

### METHODS

A total of 676 HLA-A*0201–positive patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus gp100 (403 patients), ipilimumab alone (137), or gp100 alone (136). Ipilimumab, at a dose of 3 mg per kilogram of body weight, was administered with or without gp100 every 3 weeks for up to four treatments (induction). Eligible patients could receive reinduction therapy. The primary end point was overall survival.

### RESULTS

The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio for death, 0.68; P<0.001). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; P=0.003). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; P=0.76). Grade 3 or 4 immune-related adverse events occurred in 10 to 15% of patients treated with ipilimumab and in 3% treated with gp100 alone. There were 14 deaths related to the study drugs (2.1%), and 7 were associated with immune-related adverse events.

### CONCLUSIONS

Ipilimumab, with or without a gp100 peptide vaccine, as compared with gp100 alone, improved overall survival in patients with previously treated metastatic melanoma. Adverse events can be severe, long-lasting, or both, but most are reversible with appropriate treatment. (Funded by Medarex and Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00094653.)

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The incidence of metastatic melanoma has increased over the past three decades,[1,2] and the death rate continues to rise faster than the rate with most cancers.[3] The World Health Organization (WHO) estimates that worldwide there are 66,000 deaths annually from skin cancer, with approximately 80% due to melanoma.[4] In the United States alone, an estimated 8600 persons died from melanoma in 2009.[1] The median survival of patients with melanoma who have distant metastases (American Joint Committee on Cancer stage IV) is less than 1 year.[5,6] No therapy is approved beyond the first-line therapy for metastatic melanoma, and enrollment in a clinical trial is the standard of care. No therapy has been shown in a phase 3, randomized, controlled trial to improve overall survival in patients with metastatic melanoma.[6-9]

Regulatory pathways that limit the immune response to cancer are becoming increasingly well characterized. Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is an immune checkpoint molecule that down-regulates pathways of T-cell activation.[10] Ipilimumab, a fully human monoclonal antibody (IgG1) that blocks CTLA-4 to promote antitumor immunity,[11-14] has shown activity in patients with metastatic melanoma when it has been used as monotherapy in phase 2 studies.[15-17] Ipilimumab has also shown activity when combined with other agents,[18,19] including cancer vaccines.[20,21] One well-studied cancer vaccine comprises HLA-A*0201–restricted peptides derived from the melanosomal protein, glycoprotein 100 (gp100). Monotherapy with this vaccine induces immune responses but has limited antitumor activity.[22] However, the results of a recent study suggest that gp100 may improve the efficacy of high-dose interleukin-2 in patients with metastatic melanoma.[23] With no accepted standard of care, gp100 was used as an active control for our phase 3 study, which evaluated whether ipilimumab with or without gp100 improves overall survival, as compared with gp100 alone, among patients with metastatic melanoma who had undergone previous treatment.

## Methods

### Patients

Patients were eligible for inclusion in the study if they had a diagnosis of unresectable stage III or IV melanoma and had received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2. Other inclusion criteria were age of at least 18 years; life expectancy of at least 4 months; Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active, able to carry on all predisease performance without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work)[24]; positive status for HLA-A*0201; normal hematologic, hepatic, and renal function; and no systemic treatment in the previous 28 days. Exclusion criteria were any other cancer from which the patient had been disease-free for less than 5 years (except treated and cured basal-cell or squamous-cell skin cancer, superficial bladder cancer, or treated carcinoma in situ of the cervix, breast, or bladder); primary ocular melanoma; previous receipt of anti–CTLA-4 antibody or cancer vaccine; autoimmune disease; active, untreated metastases in the central nervous system; pregnancy or lactation; concomitant treatment with any nonstudy anticancer therapy or immunosuppressive agent; or long-term use of systemic corticosteroids.

The protocol was approved by the institutional review board at each participating institution and was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization. All patients (or their legal representatives) gave written informed consent before enrollment.

### Study Design and Treatment

In this randomized, double-blind, phase 3 study, we enrolled patients at 125 centers in 13 countries in North America, South America, Europe, and Africa. Between September 2004 and August 2008, patients were randomly assigned to one of three study groups, with stratification according to baseline metastasis stage (M0, M1a, or M1b vs. M1c, classified according to the tumor–node–metastasis [TNM] categorization for melanoma of the American Joint Committee on Cancer), and receipt or nonreceipt of previous interleukin-2 therapy. The full original protocol, a list of amendments, and the final protocol, as well as the statistical analysis plan, are available with the full text of this article at NEJM.org.

Patients were randomly assigned, in a 3:1:1 ratio, to treatment with an induction course of ipilimumab, at a dose of 3 mg per kilogram of body weight, plus a gp100 peptide vaccine; ipilimumab plus gp100 placebo; or gp100 plus ipilimumab placebo — all administered once every 3 weeks for four treatments. In the vaccine groups, patients received two modified HLA-A*0201–restricted peptides, injected subcutaneously as an emulsion with incomplete Freund's adjuvant (Montanide ISA-51): a gp100:209-217(210M) peptide, 1 mg injected in the right anterior thigh, and a gp100:280-288(288V) peptide, 1 mg injected in the left anterior thigh. Peptide injections were given immediately after a 90-minute intravenous infusion of ipilimumab or placebo. Treatment began on day 1 of week 1, and if there were no toxic effects that could not be tolerated, no rapidly progressive disease, and no significant decline in performance status, patients received an additional treatment during weeks 4, 7, and 10. Patients in whom new lesions developed or baseline lesions grew were allowed to receive additional treatments to complete induction. Patients with stable disease for 3 months' duration after week 12 or a confirmed partial or complete response were offered additional courses of therapy (reinduction) with their assigned treatment regimen if they had disease progression.

The original primary end point was the best overall response rate (i.e., the proportion of patients with a partial or complete response). The primary end point was amended to overall survival (with the amendment formally approved on January 15, 2009) in the ongoing blinded study, on the basis of phase 2 data and in alignment with another ongoing phase 3 trial of ipilimumab involving patients with metastatic melanoma.[25] The primary comparison in overall survival was between the ipilimumab-plus-gp100 group and the gp100-alone group. Prespecified secondary end points included a comparison of overall survival between the ipilimumab-alone and the gp100-alone groups and between the two ipilimumab groups, the best overall response rate, the duration of response, and progression-free survival. Subgroup comparisons of overall survival were performed across five prespecified categories: metastasis stage (M0, M1a, or M1b vs. M1c), receipt or nonreceipt of previous interleukin-2 therapy, baseline levels of serum lactate dehydrogenase (less than or equal to the upper limit of the normal range vs. higher than the upper limit of the normal range), age (<65 years vs. ≥65 years), and sex.

The trial was designed jointly by the senior academic authors and the sponsors, Medarex and Bristol-Myers Squibb. Data were collected by the sponsors and analyzed in collaboration with the senior academic authors, who vouch for the completeness and accuracy of the data and analyses and for the conformance of this report to the protocol, as amended. An initial draft of the manuscript was prepared by six of the academic authors in collaboration with the sponsor and a professional medical writer paid by the sponsor. All the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. All the authors signed a confidentiality disclosure agreement with the sponsor.

### ASSESSMENTS

For the assessment of a patient's eligibility, each patient's HLA-A*0201 status was determined at a central laboratory. Patients who met the study criteria were assigned to receive treatment within 35 days after HLA typing and within 28 days after diagnostic imaging. Computed tomography with contrast material or magnetic resonance imaging of the brain, chest, abdomen, pelvis, and other anatomical regions, as clinically indicated, was performed. Cutaneous lesions were photographed. Tumor assessments were performed at baseline, and all patients who did not have documented early disease progression and who had stable disease or better at week 12 had confirmatory scans at weeks 16 and 24 and every 3 months thereafter. Tumor responses were determined by the investigators with the use of modified WHO criteria to evaluate bidimensionally measurable lesions.[26]

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. An immune-related adverse event was defined as an adverse event that was associated with exposure to the study drug and that was consistent with an immune phenomenon. Protocol guidelines for the management of immune-related adverse events included the administration of corticosteroids (orally or intravenously), a delay in a scheduled dose, or discontinuation of therapy.[15-17] Assigned doses were delayed in the case of nondermatologic immune-related adverse events of grade 2 or higher until the event im-

proved to grade 1 or lower; if the event did not improve to grade 1 or lower, treatment was discontinued permanently. Monitoring of adverse events continued for at least 70 days after the last dose of study drugs had been administered or until any ongoing event resolved or stabilized. All patients, including those with low-grade changes in bowel frequency or stool consistency, were followed closely. A data and safety monitoring committee provided independent oversight of safety and the risk–benefit ratio.

During the study enrollment, the following stopping rule was in place: if 10% or more of the patients in any study treatment group, evaluated cumulatively every 3 months, had a nondermatologic-related toxic adverse event of grade 3 or higher that was attributable to the investigational agents and that could not be alleviated or controlled by appropriate care or corticosteroid therapy within 14 days after the initiation of supportive care or corticosteroid therapy, assignment of patients to that study group would be suspended until the sponsor and the data and safety monitoring committee had reviewed the events and determined the appropriate course of action.

### STATISTICAL ANALYSIS

The original study sample size of 750 patients was determined on the basis of the primary end point of best overall response rate but was revised with the new primary end point of overall survival. We estimated that with 385 events (deaths) among a total of 500 patients randomly assigned to the ipilimumab-plus-gp100 and the gp100-alone groups, the study would have at least 90% power to detect a difference in overall survival, at a two-sided alpha level of 0.05, with the use of a log-rank test. A total of 481 events were required in all three groups (assuming that the events were distributed in a 3:1:1 ratio in the ipilimumab-plus-gp100, ipilimumab-alone, and gp100-alone groups, respectively). Therefore, all patients who were randomly assigned in the study were to be followed until at least 481 events had occurred in the study. Enrollment was completed on July 25, 2008, when more than 650 patients had been enrolled. A post hoc power analysis showed that the 219 events observed among a total of 273 patients randomly assigned to the ipilimumab-alone and gp100-alone groups provided at least 80% power to detect a difference in overall survival between the two groups, at a two-sided alpha level of 0.05, with the assumption that ipilimumab alone has the same treatment effect as the combination regimen of ipilimumab plus gp100.

Survival was defined as the time from randomization to death from any cause, and progression-free survival as the time from randomization to documented disease progression or death. Event-time distributions were estimated with the use of the Kaplan–Meier method. Cox proportional-hazards models, stratified according to metastasis status and receipt or nonreceipt of previous interleukin therapy, were used to estimate hazard ratios and to test for significance of the timing of events. All reported P values are two-sided, and confidence intervals are at the 95% level. Survival rates were based on Kaplan–Meier estimation, and confidence intervals were calculated with the use of the bootstrap method. Descriptive statistics were used for adverse events.

## RESULTS

### PATIENTS AND TREATMENT

Among 676 patients enrolled in the study, 403 were randomly assigned to receive ipilimumab plus gp100, 137 to receive ipilimumab alone, and 136 to receive gp100 alone (control group) (Fig. 1 in the Supplementary Appendix, available at NEJM.org). Included among these patients were 82 patients who had metastases in the central nervous system at baseline, of whom 77 received the study drug. The baseline characteristics of the patients are shown in Table 1. Efficacy analyses were performed on the intention-to-treat population, which included all patients who had undergone randomization (676 patients). The safety population included all patients who had undergone randomization and who had received any amount of study drug (643 patients). A total of 242 of 403 patients in the ipilimumab-plus-gp100 group (60.0%), 88 of 137 in the ipilimumab-alone group (64.2%), and 78 of 136 in the gp100-alone group (57.4%) received all four ipilimumab doses or placebo infusions. The most frequent reason for discontinuation of therapy was disease progression.

### EFFICACY

All the analyses of the efficacy end points reported here were prespecified as per protocol.

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