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Phase II Trial of Tremelimumab (CP-675,206) in Patients with Advanced Refractory or Relapsed Melanoma

John M. Kirkwood[1], Paul Lorigan[2], Peter Hersey[3], Axel Hauschild[4], Caroline Robert[5], David McDermott[6], Margaret A. Marshall[7], Jesus Gomez-Navarro[7], Jane Q. Liang[7], and Cecile A. Bulanhagui[7]

Abstract

Purpose: This phase II study assessed the antitumor activity of tremelimumab, a fully human, anti–CTL-associated antigen 4 monoclonal antibody, in patients with melanoma.

Experimental Design: Patients with refractory/relapsed melanoma received 15 mg/kg tremelimumab every 90 days. After 4 doses, patients with tumor response or stable disease were eligible to receive ≤4 additional doses. Primary endpoint was best overall tumor response assessed by an independent endpoint review committee, and secondary endpoints included duration of response, overall survival, progression-free survival, and safety.

Results: Of 251 patients enrolled, 246 (241 response-evaluable) received tremelimumab. Objective response rate was 6.6% (16 partial responses); duration of response was 8.9 to 29.8 months. Eight (50%) objective responses occurred in patients with stage IV M_{1c} disease, and 11 (69%) were ongoing at last tumor assessment. Eight (3.3%) patients achieved responses in target lesions (Response Evaluation Criteria in Solid Tumors) despite progressive disease within the first cycle. All 8 survived for >20 months; 5 (63%) remained alive. Clinical benefit rate (overall response + stable disease) was 21% (16 partial responses and 35 stable disease), and median overall survival was 10.0 months. Progression-free survival at 6 months was 15%, and survival was 40.3% at 12 months and 22% at 24 months. Common treatment-related adverse events were generally mild to moderate, and grade 3/4 adverse events included diarrhea (n = 28, 11%), fatigue (n = 6, 2%), and colitis (n = 9, 4%). There were 2 (0.8%) treatment-related deaths.

Conclusions: Tremelimumab showed an objective response rate of 6.6%, with all responses being durable ≥170 days since enrollment, suggesting a potential role for tremelimumab in melanoma. *Clin Cancer Res; 16(3); 1042–8. ©2010 AACR.*

The only therapy that has yielded rare but reproducible and durable high-quality responses in patients with metastatic melanoma who can tolerate this therapy is interleukin-2 (IL-2), which has been approved by U.S. regulatory authorities. Chemotherapy with dacarbazine (DTIC) or its unapproved oral derivative, temozolomide, has been the standard palliative therapy of patients with metastatic melanoma, although no survival benefit of DTIC has been shown, and temozolomide has recently been shown to have no survival or progression interval benefits over DTIC (1). Response rates for single-agent chemotherapy are generally <8% to 15% and limited in durability (2–5). Although various biochemotherapy regimens have been shown to produce increased response rates in patients compared to DTIC, no improvements in survival have been observed (6, 7). Immunotherapy with high-dose IL-2 requiring inpatient administration produces responses in 6% to 16% of patients with advanced melanoma, and high-dose IFN-α2b has shown significant and durable relapse-free survival benefit in the adjuvant therapy of patients after surgery for high-risk stage IIB and III melanoma (8–13). However, toxicity has been an issue for both of these U.S. Food and Drug Administration–approved modalities, with flu-like symptoms, anorexia, and fatigue observed in the majority of patients (9, 12, 13). The small proportion of patients who respond to high-dose IL-2 is an obstacle to broader adoption of this immunotherapy, which is associated with severe, but generally reversible, toxicity (e.g., hemodynamic, cardiac, and renal complications) requiring hospitalization for administration in specialized or intensive care units (13). Therefore, there is an urgent need for new treatment options for patients with stage IV (metastatic) melanoma (4).

Authors' Affiliations: [1]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [2]Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; [3]University of Newcastle, Newcastle, New South Wales, Australia; [4]University of Kiel, Kiel, Germany; [5]Institute Gustave Roussy Dermatology Unit, Villejuif, France; [6]Beth Israel Deaconess Medical Center, Boston, Massachusetts; and [7]Pfizer Global Research & Development, New London, Connecticut

Note: Although now at the new address, J. Gomez-Navarro was affiliated with Pfizer during the conduct, analysis, and article development for this study.

Corresponding Author: John M. Kirkwood, Department of Medicine, University of Pittsburgh Cancer Institute, Hillman Cancer Center, Research Pavilion, Suite 1.32, 5117 Centre Avenue, Pittsburgh, PA 15213-2584. Phone: 412-623-7707; Fax: 412-623-7704; E-mail: kirkwoodjm@upmc.edu.

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Translational Relevance

Immunotherapy that can induce durable antitumor responses through modulation of the immune system is a promising treatment option for patients with advanced melanoma. This article describes the efficacy and safety of tremelimumab, a fully human monoclonal antibody specific for CTL-associated antigen 4, in a large phase II study in patients with advanced melanoma.

Immunotherapy that can induce durable antitumor responses through modulation of the immune system remains attractive for treatment of patients with advanced melanoma (14). CTL-associated antigen 4 (CTLA4) is an inhibitory receptor expressed on the surface of activated T cells and a fundamental regulator of immune function (14). When expressed on activated T cells, CTLA4 competes with CD28 for B7-1 (CD80) and B7-2 (CD86) ligands; binding of CTLA4 to these ligands provides a signal that downregulates T-cell activation. Thus, blocking the activity of CTLA4 may enhance T-cell activation, including that of tumor-specific T lymphocytes, and induce antitumor immune response. Anti-CTLA4 monoclonal antibodies can block the interaction of CTLA4 and B7 ligands (14), and murine tumor models showed that anti-CTLA4 monoclonal antibodies induce regression of established tumors (15–18). These findings supported the concept that blockade of CTLA4 with anti-CTLA4 monoclonal antibodies can mobilize or restore effective antitumor immune responses.

Tremelimumab (CP-675,206; Pfizer) is a fully human IgG2 anti-CTLA4 monoclonal antibody. The first-in-human phase I dose-escalation study indicated that tremelimumab can safely be administered at doses that generate antitumor responses in patients with advanced melanoma (19). A phase I/II trial was then conducted to evaluate safety and efficacy of multidose tremelimumab regimens. In the phase II portion of the study, patients (n = 89) received either 15 mg/kg administered every 90 days or 10 mg/kg every month. Both regimens induced tumor responses and had acceptable safety profiles. The 15 mg/kg every 90 days regimen was selected for further development based on the incidence of grade 3/4 adverse events (13% and 27% with 15 mg/kg every 90 days and 10 mg/kg every month, respectively) and serious adverse events (9% and 25%; ref. 20).

Materials and Methods

Patients. Adult patients with surgically incurable stage III or IV melanoma that was refractory or had relapsed after one or more cycle of prior systemic treatment for metastatic melanoma were eligible. The prior regimen(s) for metastatic disease must have contained at least one of the following: IL-2, dacarbazine, temozolomide, or IFN-α. Patients must have had one or more measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (21) and were required to have had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Patients must also have met the following baseline laboratory parameters: serum lactate dehydrogenase (LDH) level ≤2 × upper limit of normal (ULN) and adequate bone marrow, hepatic, and renal function determined within 14 days of enrollment (absolute neutrophil count ≥1.5 × 10^9 cells/L, platelets ≥100 × 10^9 cells/L, hemoglobin ≥10 g/dL, aspartate aminotransferase and alanine aminotransferase ≤2.5 or ≤5 × ULN with liver metastases, total bilirubin ≤2 × ULN, and serum creatinine ≤2.0 mg/dL). Additionally, patients were required to have recovered from all previous treatment-related toxicities to baseline status or to grade 0 or 1 according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (22). Patients were excluded if they had been treated with any CTLA4-inhibiting agent, any treatment for cancer within 1 month of enrollment, any vaccine therapy for melanoma within the preceding 6 months, a history of autoimmune disease (e.g., multiple sclerosis) or inflammatory bowel disease, or a potential requirement for systemic corticosteroids or concurrent immunosuppressive drugs. Patients with brain metastases (unless previously treated and no longer detectable) or a history of other malignancies (except for basal or squamous cell carcinoma or cervical carcinoma) were also excluded.

Study design. This multicenter, phase II, single-arm study was designed to evaluate the objective response rate to tremelimumab using RECIST guidelines and to assess its safety profile and pharmacokinetics. Patients received intravenous 15 mg/kg tremelimumab every 90 days for up to four doses in a 12-month period. Each 3-month treatment cycle included a single dose (infusion) of tremelimumab. Therapy was to discontinue on disease progression or intolerable toxicity. However, patients with progressive disease at the first assessment could continue to receive tremelimumab if, in the investigators' judgment, there was no clinical progression. Patients who had objective response or stable disease at the end of four cycles were eligible to continue therapy with tremelimumab; patients with a complete response could receive up to two additional doses, and patients with a partial response or stable disease could receive up to four additional doses for a maximum of 24 months after enrollment. After each cycle, treatment with a subsequent dose was administered only if the patient had adequate performance status (ECOG ≤1), hepatic function (aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN or ≤5 × ULN if liver metastases), renal function (serum creatinine ≤2.0 mg/dL), and acceptable amylase and lipase levels (≤1.5 × ULN or baseline). Subsequent doses were only administered if treatment-related adverse events (except thyroiditis, rash, and vitiligo) had resolved to Common Terminology Criteria for Adverse Events grade 1

Table 1. Baseline demographics and disease characteristics

	Overall 15 mg/kg every 90 d (*n* = 251)	Objective responders (*n* = 16)
Median (range) age (y)	53 (18–89)	57 (43–72)
Patients ≥65, *n* (%)	61 (24)	4 (25)
Patients <65, *n* (%)	190 (76)	12 (75)
Male, *n* (%)	151 (60)	7 (44)
ECOG performance status, *n* (%)		
0	157 (63)	9 (56)
1	89 (35)	7 (44)
Not reported	5 (2)	
Melanoma stage, *n* (%)		
III	8 (3)	0 (0)
IV M_{1a}	27 (11)	4 (25)
IV M_{1b}	52 (21)	3 (19)
IV M_{1c}	164 (65)	9 (56)
Baseline LDH, *n* (%)		
<ULN	135 (54)	8 (50)
1-2 × ULN	81 (32)	7 (44)
>2 × ULN	14 (6)	0 (0)
Unknown	21 (8)	1 (6)

or baseline and were considered tolerable by the day of dosing.

This study was conducted in compliance with the Declaration of Helsinki and its amendments and relevant International Conference on Harmonization Good Clinical Practice guidelines and in agreement with the local institutional review board, independent ethics committee, or research ethics board. All study participants provided written informed consent before participating in the trial.

Assessments. The primary endpoint of this trial was best overall response as assessed by an independent endpoint review committee based on RECIST guidelines. Secondary endpoints included safety and tolerability, durable response rate, duration of tumor response, progression-free survival, and overall survival (OS). For each patient, tumor assessments were done at the end of each cycle and on day 60 of cycle 2. Based on preliminary data from a phase III trial of oblimersen plus DTIC versus DTIC alone, a tumor response present at ≥6 months (170 days) since enrollment was defined as a durable response. Safety assessments were done at the beginning of each month, with extra assessments during the first two cycles. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (22).

Pharmacokinetics of tremelimumab were characterized using specimens taken periodically after the first dose. Specimens from subsequent cycles were used to monitor for human anti-human antibody response.

Pharmacogenetic assessments included the collection of blood samples for analysis of polymorphisms in CTLA4, FcγRIIa, and IgG2 genes. Pharmacogenomic assessments included the collection of blood samples for analysis of RNA expression as it is related to tumor regression and toxicity. Optional blinded analysis of accessible blood and/or tumor samples (subject to patient consent) will be done separately.

Statistical analysis. The null hypothesis that the objective response rate in patients treated with tremelimumab does not exceed 10% was tested with a one-sided binomial test at 2.5% level of significance. A total of 194 patients evaluable for response were required to provide 80% power to reject the null hypothesis when the true response rate was 17%. To allow for up to 10% of patients to be nonevaluable for response, a total enrollment of at least 215 patients was planned.

Summary statistics (e.g., means and medians) were used for continuous variables, and frequency and percentages were used for discrete variables. Survival, progression-free survival, and duration of response since enrollment were estimated using the Kaplan-Meier method (23).

Results

Patients. A total of 251 patients with stage III or IV refractory melanoma were enrolled between December 2005 and November 2006. These patients were predominantly male (60%), and 65% had stage IV M_{1c} melanoma (Table 1). Of the enrolled patients, 246 received at least one dose of

Table 2. Best overall responses per RECIST by the independent endpoint review committee (*n* = 241)

	15 mg/kg every 90 d, *n* (%)
Complete responses	0
Partial responses	16 (6.6)
Stable disease*	35 (14.5)
Clinical benefit (complete response + partial response + stable disease)	51 (21.1)
Durable responses†	16 (100)
Cycle of first response (*n* = 16)	
Cycle 1	3 (18.8)
Cycle 2	5 (31.3)
Cycle 3	6 (37.5)
Cycle 4	2 (12.5)

*Disease was considered stable if no disease progression was observed for ≥70 days.
†Responses were considered durable if they lasted ≥170 days since enrollment.

Table 3. Patients with response in target lesions but progressive disease in first cycle

Patient ID	Involved target lesions	Reason for progressive disease
10271004	Lung, lymph node	New lesions: adrenal, axillary lymph node, liver
10401005	Chest wall, iliac lymph node, mesenteric lymph node, periaortic lymph node, subcutaneous nodule	New lesions: abdominal wall, mesenteric lymph node
10521001	Abdominal wall, chest wall, lymph node, pelvis, subcutaneous soft-tissue lesion	Disease progression in nontarget lesions
10751001	Hilar lymph node, liver, lung	New lesions: abdominal wall, lymph node
10921001	Abdominal wall, ischioanal fossa, liver, lung	New lesions: axillary lymph node, brain, subcutaneous soft tissue
10361007	Liver, lung, lymph nodes (axillary, retroperitoneal), rectum	New lesions: lung, peritoneum
10581001	Liver, lung, lymph nodes (hilar and mediastinal), peritoneum	New lesions: liver, lung, and peritoneum
10601008	Breast, bone, lung, lymph nodes (axillary and retroperitoneal), ovary	Disease progression in nontarget lesions

tremelimumab. Median number of doses of tremelimumab administered to patients was 1 (range, 1-8 doses), and 109 patients (44%) received two or more doses of tremelimumab.

Efficacy. Sixteen of 241 (6.6%) evaluable patients had partial responses per RECIST according to the independent endpoint review committee, and 35 (14.5%) achieved stable disease for at least 70 days since first dose (Table 2). Only 3 (18.8%) responders achieved their response within the first cycle, and no complete responses were noted. Median time to response was 7.0 months (range, 2.7-12.0 months). Of the responders, 4 had stage IV M_{1a}, 3 had stage IV M_{1b}, and 9 had stage IV M_{1c} disease. All 16 objective responses met the criteria for a "durable response" [were sustained for at least 170 days since enrollment (range, 8.9-29.8 months)]. Responses for 11 (69%) patients were ongoing at the time of the last tumor assessment per independent endpoint review committee. One responding patient with an abnormal baseline electrocardiogram and a family history of sudden death died of an apparent cardiac event 321 days after enrollment; the patient was in response at the last known assessment. Although there was no autopsy or suggestion of an immune etiology, it could not be ruled out that this was a treatment-related event. The other 15 (94%) responding patients are alive, and their OS ranged from 20.1 to 34.1 months.

In addition to the objective responses per RECIST, 8 patients had ≥30% reduction in the sum of longest diameter of target lesions (partial response in target lesions per RECIST) but also had developed new lesions (6 patients) or progression of nontarget lesions (2 patients) during the first cycle (Table 3). The OS for these 8 patients ranged from 21.0 to 30.9 months, and 5 (63%) are still alive.

Median OS for all enrolled patients was 10.0 months [95% confidence interval (95% CI), 7.9-11.7 months; Fig. 1]. Kaplan-Meier estimated survival at 1 and 2 years was 40% (95% CI, 34-46%) and 22% (95% CI, 17-27%), respectively. Median progression-free survival per independent endpoint review committee was 2.8 months

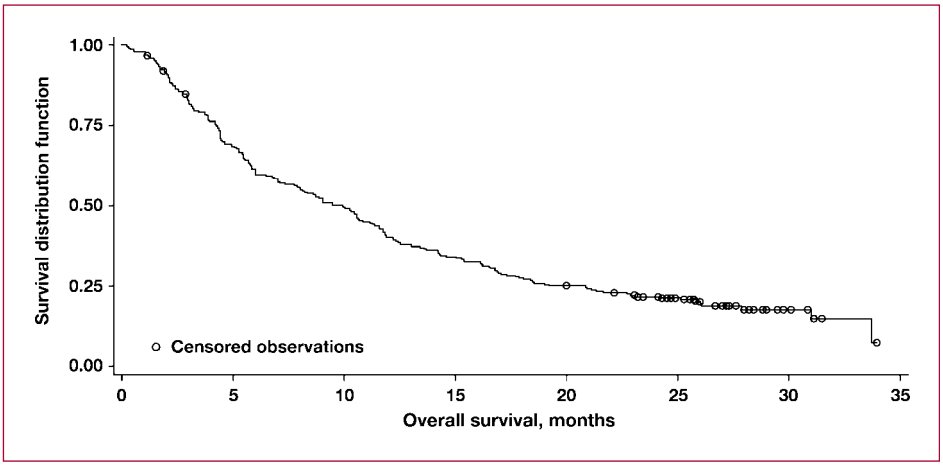

Fig. 1. Kaplan-Meier plot of OS of patients as enrolled.

(95% CI, 2.7-2.8 months), and 6-month progression-free survival was 15%. Baseline ECOG performance status was the strongest prognostic indicator for survival; the median OS was 11.67 months for ECOG of 0 and 5.59 months for ECOG of 1, with nonoverlapping 95% CIs. As expected, patients with elevated LDH or more advanced stage did not live as long as patients with normal LDH or less advanced stage, although the 95% CIs for these smaller subsets overlapped. Age and sex did not appear to strongly influence survival (Table 4).

Retrospective analysis of an earlier study indicated a statistically significant shorter time to progression and survival in patients treated with tremelimumab who had received prior immunotherapy with IL-2 compared with those who had not (24). In contrast, there was no association with prior therapy with IFN and survival or time to progression (24). In this study, there was no difference in OS between patients who received prior IFN ($n = 119$) compared with no prior IFN (9.1 versus 10.4 months; $P = 0.8584$) or prior IL-2 ($n = 74$) compared with no prior IL-2 (10.3 versus 10.0; $P = 0.9428$). There was also no difference observed in progression-free survival between patients who received prior IFN compared with no prior IFN (2.76 versus 2.83 months; $P = 0.15557$) or prior IL-2 compared with no prior IL-2 (2.76 versus 2.79 months; $P = 0.1545$).

Safety. Although the majority (77%) of patients ($n = 190$) developed treatment-related adverse events of any grade, most were mild to moderate (grade 1 or 2). Only 51 (21%) patients developed adverse events grade >2, and 47 (19%) had serious adverse events. Common adverse events included diarrhea, pruritus, rash, nausea, fatigue, and vomiting (Table 5). Thirteen (5%) patients discontinued because of treatment-related adverse events, and there were 2 (0.8%) treatment-related deaths (sudden death and diverticular perforation). Most common adverse events grade ≥3 included diarrhea ($n = 28$, 11%) and fatigue ($n = 6$, 2%). In addition, colitis was observed in 9 (4%) patients, and 6 of these patients developed grade ≥2 colitis. Endocrine adverse events occurred in 9 (4%) patients, including 8 patients with thyroid disorders (hyperthyroidism, hypothyroidism, autoimmune thyroiditis, or Basedow's disease) and 1 patient with hypophysitis and pituitary insufficiency. All thyroid and pituitary adverse events were attributed to tremelimumab.

Table 4. Baseline factors associated with OS

Subgroup	*n**	Median (95% CI) OS (mo)
Whole population	251	10.00 (7.92-11.67)
ECOG 0	161	11.67 (9.53-13.51)
ECOG 1	89	5.59 (3.98-7.95)
LDH ≤ ULN	143	11.80 (9.53-14.66)
ULN < LDH ≤2 × ULN	85	7.46 (5.06-10.55)
Age <65 y	190	10.09 (7.92-11.80)
Age ≥65 y	61	9.53 (5.92-13.08)
Stage III	8	11.75 (5.52-NA)
Stage M_{1a}	27	11.67 (9.53-26.49)
Stage M_{1b}	52	9.10 (6.84-14.66)
Stage M_{1c}	164	8.74 (5.95-11.21)
Male	151	10.09 (7.92-11.90)
Female	100	8.28 (5.88-12.49)

Abbreviation: NA, not available.
*As enrolled.

Table 5. Treatment-related adverse events occurring in percentage of patients treated with tremelimumab ($n = 246$)

	Adverse events of any grade, *n* (%)	Adverse events grade ≥3, *n* (%)
Diarrhea	99 (40)	28 (11)
Pruritus	56 (23)	0
Rash	55 (22)	3 (1)
Nausea	53 (22)	3 (1)
Fatigue	41 (17)	6 (2)
Vomiting	36 (15)	3 (1)
Anorexia	28 (11)	2 (1)
Abdominal pain, upper and lower	17 (7)	1 (<1)
Headache	17 (7)	0
Asthenia	14 (6)	1 (<1)
Pyrexia	14 (6)	1 (<1)
Weight loss	14 (6)	3 (1)

Pharmacokinetics. Pharmacokinetics data were evaluated for 150 patients. Mean maximal concentration was 329 μg/mL, and a biphasic pharmacokinetic profile was observed. Mean clearance rate of tremelimumab (0.152 mL/h/kg) and volume of distribution (85 mL/kg) were low, and half-life was 19.2 ± 5.9 days.

Pharmacogenetics and pharmacogenomics. A preliminary study was done to investigate whether genetic variation in CTLA4 is associated with efficacy or occurrence of autoimmune reactions. The CTLA4 gene is polymorphic, and several single nucleotide polymorphisms have been identified across the gene. Some of these single nucleotide polymorphisms are reported to alter gene function/expression and some are associated with increased susceptibility to a range of autoimmune disorders (25, 26). Three single nucleotide polymorphisms have been extensively studied: the CT60 polymorphism (rs3087243) within the 3′-untranslated region, a +49G (rs231775) within exon 1, and the C-318T polymorphism (rs5742909) within the promoter (27). In contrast to a recent study that showed an association between rs231775 and response to another anti-CTLA4 therapy in a population of 152 Caucasian melanoma patients, this pharmacogenetic analysis indicated no major influence of genetic variation in CTLA4 (28). In addition, no genetically defined subpopulation of patients that could be targeted for efficacy or safety was identifiable based on these analyses.

Discussion

The objective response rate among patients with relapsed/refractory metastatic melanoma treated with tremelimumab (15 mg/kg every 90 days) was 6.6% and did not exceed the 10% threshold with 97.5% confidence sought in this study. Responses to tremelimumab were characteristically durable, and all 16 patients with objective response sustained their response for ≥170 days after enrollment. The majority (69%) were ongoing at last known tumor assessment, with duration of response ranging from 8.9 to 29.8 months. In contrast to historic experience with high-dose IL-2, where nonvisceral sites are more likely to respond to therapy, tremelimumab responders included 8 (53%) patients with stage IV M_{1c} disease, 7 of whom had visceral sites of disease at baseline (including adrenal, bone, and liver metastases). Tremelimumab thus shows durable clinical activity in second-line treatment of patients with disease that is not limited to lymph node, lung, or skin sites. In addition, 7 (47%) responders had elevated baseline LDH levels. Thus, these data suggest that elevation of LDH does not bias against response as has been suggested for chemotherapy with DTIC and other agents (29). Therefore, recent trends to exclude patients from trials based on elevations of LDH do not appear to be appropriate for studies of biologic agents such as the CTLA4-blocking antibody tremelimumab. Future studies of tremelimumab may more reasonably enroll patients without restrictions in relation to baseline LDH levels, perhaps with stratification to evaluate whether patients with elevated LDH (>2 × ULN) benefit from tremelimumab.

The majority of patients received only a single dose of tremelimumab. A similar study of second-line therapy with another investigational anti-CTLA4 monoclonal antibody showed a very similar response rate (5.8%), although patients (n = 155) in that phase II study received antibody once every 3 weeks for four cycles followed by maintenance dosing once every 12 weeks (30). This suggests that more frequent dosing may not have produced a higher response rate. Analysis of antitumor responses in patients in this trial does not show that antitumor effects of tremelimumab are greater in patients with normal LDH compared with patients with LDH 1 to 2 × ULN or in patients with baseline ECOG of 0 compared with patients who have baseline ECOG of 1 as has been speculated for other immunotherapy (31). These findings do not support the common assumption that immunotherapy can only benefit the healthiest patients and those with minimal disease burden.

In this trial for patients with refractory advanced disease, median OS of 10.1 months compares favorably with median survival of 6.2 months recently reported from a retrospective analysis of phase II trials conducted over the past 35 years (32). This analysis is complicated by the exclusion of patients with baseline serum LDH ≥2 × ULN in the present trial, as this criterion was not a component of any of the historic trials included in the prior collective analysis. The OS in this trial is similar to that in a recently reported phase III trial of sorafenib plus carboplatin/paclitaxel compared with placebo plus carboplatin/paclitaxel in patients (n = 270; PRISM trial) with melanoma who had progressed on prior chemotherapy; in that study, OS was 9.6 months in each arm (33).

It has been noted that some patients appear to benefit from tremelimumab in spite of early (first cycle, following a single dose) assessments of progressive disease, and it has been postulated that this early progression following CTLA4 blockade may be attributed to the delayed effect of this immunotherapy (34) or possibly to an increase in apparent lesion size due to inflammatory infiltration (tumor flare). Because of this observation, a post hoc analysis was done using a "non-RECIST" endpoint, defined as patients with ≥30% reduction in sum of target lesions but appearance of new lesions or progression of a nontarget lesion within the first cycle. Eight patients who met these objective criteria were identified. The fact that 5 of these 8 patients remain alive with survival times of 24.7 to 30.9 months suggests that modified endpoints of response allowing early progression may identify patients who also derive benefit from this immunotherapy and may be of use in future trials.

It is now of paramount importance to identify the patient population that responds to tremelimumab and determine early indicators of later response to therapy. The discovery of such markers would improve the therapeutic index and allow consideration of other agents or combinations for those who lack the ability to respond to tremelimumab. Given the posited mechanism of action for anti–CTLA4-blocking antibodies, combinations of these antibodies with other immunotherapies will be of interest, and studies evaluating combinations of tremelimumab with vaccines and with IFN-α are in progress (35, 36).

Disclosure of Potential Conflicts of Interest

M.A. Marshall, C.A. Bulanhagui, J.Q. Liang, and J. Gomez-Navarro were employed by Pfizer during this study. J.M. Kirkwood received a commercial research grant from Intrexon, has received speaker's bureau honoraria from Schering, and has received funding as an advisor to Pfizer, Vical, Bristol-Myers Squibb, Glaxo, Schering, and Eisai. D. McDermott has received speaker's bureau honoraria from Wyeth and Novartis and has received funding as a consultant/advisor for Wyeth, Novartis, Genentech, and Glaxo. P. Lorigan has received funding as an advisor for Pfizer. C. Robert has received funding as a consultant/advisor for Johnson & Johnson and AstraZeneca. M.A. Marshall and J. Gomez-Navarro have ownership interests in Pfizer.

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