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Efficacy and Safety of Retreatment with Ipilimumab in Patients with Pretreated Advanced Melanoma Who Progressed after Initially Achieving Disease Control

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Abstract

Purpose: Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) that has been shown to improve survival in patients with pretreated, advanced melanoma in a phase III trial. Some patients in this study who initially responded to ipilimumab treatment but later progressed were eligible for retreatment with their original randomized regimen. Here, outcomes for these patients concerning baseline characteristics, best overall response, and disease control rate are assessed and considered with respect to the overall study population.

Experimental Design: In the phase III study, 676 pretreated patients were randomly allocated to treatment with ipilimumab 3 mg/kg plus gp100 vaccine, ipilimumab 3 mg/kg plus placebo, or gp100 vaccine alone. Of these patients, 32 had a partial or complete objective response or stable disease after treatment and met the eligibility criteria for retreatment, although a total of 40 patients were retreated.

Results: Best overall response rates (complete responses plus partial responses) for 31 retreatment-eligible patients in the ipilimumab plus gp100 and ipilimumab plus placebo groups were 3 of 23 (13.0%) and 3 of 8 (37.5%), respectively, and disease control rates were 65.2% and 75.0%. No new types of toxicities occurred during retreatment and most events were mild-to-moderate.

Conclusion: Ipilimumab provided durable objective responses and/or stable disease in qualifying patients who received retreatment upon disease progression with a similar toxicity profile to that seen during their original treatment regimen. *Clin Cancer Res; 19(8); 2232–9. ©2013 AACR.*

Introduction

Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4). In a phase III study of pretreated patients with advanced melanoma, intravenous ipilimumab (3 mg/kg every 3 weeks for 4 doses) with or without gp100 vaccine significantly improved survival compared with the gp100 vaccine control (HR for death: 0.66; $P = 0.003$ and 0.68; $P < 0.001$, respectively). Among patients treated with ipilimumab plus gp100, ipilimumab alone or gp100 alone, 43.6%, 45.6%, and 25.3% were alive at 1 year and 21.6%, 23.5% and 13.7% were alive at 2 years, respectively (1). The survival benefit conferred by ipilimumab was independent of negative prognostic factors at baseline including age, gender, lactate dehydrogenase levels, metastatic disease stage, or previous treatment with interleukin (IL)-2. The most common adverse events related to the study drugs were immune-related adverse events (irAE), which occurred

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Robert C, Hodi FS, O'Day S, et al. Efficacy and safety of ipilimumab re-induction in a phase III trial of patients with previously treated, advanced melanoma. Abstract P0023.

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Translational Relevance

Ipilimumab is an immunotherapeutic agent that modulates T-cell activity to enhance antitumor immune responses. Ipilimumab was approved in Europe for the treatment of adult patients with advanced (unresectable or metastatic) melanoma who have received prior therapy. Approval was based on the results of a phase III trial of ipilimumab with or without gp100 vaccine versus vaccine alone during which patients with advanced melanoma who met defined criteria could receive retreatment with their original treatment upon disease progression.

This article describes the rationale for retreatment with ipilimumab and provides resultant efficacy and safety outcomes for 40 qualifying patients who received retreatment. Durable objective responses and/or stable disease with a similar toxicity profile to that seen during the original treatment regimen were observed. Data support the prospective evaluation of retreatment with ipilimumab and provide further guidance regarding how and when ipilimumab should be administered in order to maximize patient outcomes.

in approximately 60% of patients treated with ipilimumab and 32% of patients treated with gp100 (1).

Unlike chemotherapeutic agents that kill tumor cells by direct cytotoxicity, the mechanism of ipilimumab in patients with melanoma is *indirect*. CTLA-4 is a negative regulator of T cells, which are known to play a critical role in the immunosurveillance and destruction of tumors (2–5). By blocking CTLA-4, ipilimumab therefore acts to potentiate T-cell–mediated antitumor immune responses (6, 7).

The immune response against cancer occurs in 3 stages: elimination, equilibrium, and escape (8, 9). In the absence of complete elimination, persistent immune activation is required to sustain equilibrium between tumor growth and immunity, thus delaying or preventing disease relapse. However, persisting immune responses are also capable of altering the phenotype of the tumor via a process known as immunoediting or immunosculpting. For example, in patients with melanoma treated with NY-ESO-1 vaccine and immune adjuvant, histologic analysis of tumor samples from patients who relapsed following treatment showed a loss of NY-ESO-1 antigen and human leukocyte antigen expression necessary for immune activation (10, 11). This suggests immunoediting selects for tumor variants with little or no immunogenicity and may result in tumor responses to immunotherapies decreasing or reversing over time.

It is increasingly important, therefore, that immune-based treatment approaches are able to augment antitumor immune responses as well as overcome the immune-induced changes that allow tumors to evade destruction. Potential strategies include targeting multiple antigens to reduce selection for antigen-loss variants or disrupting the immunosuppressive tumor microenvironment (12). An alternative method, however, may be to restart immunotherapy after disease progression to reactivate the primed immune system to recognize and respond to any remaining tumor or tumor cells that have appeared during the tumor escape phase.

The aim of this retrospective analysis is to describe efficacy and safety data from the subgroup of patients included in the phase III study of ipilimumab with or without gp100 versus gp100 alone (1) who progressed after initially responding to treatment and subsequently restarted treatment with the same regimen they had initially received.

Materials and Methods

Full details of the study design, inclusion and exclusion criteria, treatment, response assessment, endpoints, and patient baseline characteristics for the whole study population have been published previously (1). In brief, 676 patients with unresectable stage III or IV melanoma were enrolled in the phase III study (MDX010-20; trial registration ID: NCT00094653). Patients were aged 18 years or older, had a life expectancy of at least 4 months, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Previous treatment was with one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or IL-2. Patients were randomized 3:1:1 to ipilimumab plus gp100 peptide vaccine ($n = 403$), ipilimumab alone ($n = 137$), or gp100 alone ($n = 136$). Ipilimumab at 3 mg/kg was administered every 3 weeks for up to 4 doses during the treatment phase (previously referred to as induction).

Patients who showed signs of clinical benefit from treatment (using modified World Health Organization criteria), that is, a confirmed objective response [OR; complete response (CR) or partial response (PR)] or stable disease (SD) lasting $\geq$3 months from week 12, were eligible for retreatment (previously referred to as re-induction) with their assigned treatment regimen upon disease progression providing they had not experienced a grade III non-skin irAE (except for endocrinopathies where clinical symptoms were controlled with appropriate hormone replacement therapy) or any grade IV toxicity during the treatment phase. Each retreatment cycle consisted of 4 doses of study drug given in an identical schedule to that used during the original treatment phase.

Results

Patients and treatment

From the original study population of 676 patients, 3 patients with signs of clinical benefit were ineligible for retreatment on the basis of the safety criteria. Forty patients (6%) were retreated, comprising 38 patients retreated with ipilimumab, either with gp100 ($n = 29$) or alone ($n = 9$) and 2 patients retreated with the gp100 vaccine alone (Table 1). All 40 retreated patients met the core safety criteria for retreatment; however, 8 retreated patients were ineligible for retreatment per protocol [3 (one per arm) were protocol

Table 1. Description of retreated patient populations contributing to safety and efficacy analyses

	Ipi + gp100	Ipi + placebo	gp100 + placebo	Total
	Patients, *n*			
Retreated patients (contributing to safety population)	29	9	2	40
Excluded from efficacy	6	1	1	8
Protocol violation	1	1	1	3
Week 24 BOR = PD	5	0	0	5
Retreated efficacy population	23	8	1	32
PD not reported in database	7	3	0	10
SD < 3 mo	1	1	0	2
Unknown BOR at week 24	1	0	0	1
Confirmed eligibility	14	4	1	19

NOTE: All retreated patients were eligible for safety analysis. Reasons for ineligibility in the efficacy cohort are reported for each arm of treatment.

Abbreviations: BOR, best OR (CR or PR according to modified World Health Organization criteria); Ipi, ipilimumab 3 mg/kg intravenously every 3 weeks for up to 4 doses.

violators and 5 patients in the ipilimumab plus gp100 arm had a best response of progressive disease (PD) during treatment and should not have received retreatment] and 2 patients were noncompliant with the retreatment protocol (one in the ipilimumab plus gp100 group and one in the ipilimumab alone group).

Baseline characteristics of the 40 retreated patients are shown in Table 2. Patients in this subpopulation were similar to the overall study population in terms of mean age (53.4 vs. 56.2 years, respectively), although patients who received ipilimumab alone were slightly younger (mean age, 49.0 vs. 56.8 years; ref. 1). Compared with the overall study population, no patient with unresectable stage III melanoma was retreated, the proportion of patients with melanoma stage M1b was slightly higher in the 2 ipilimumab-containing arms whereas that of M1c was slightly lower and both patients in the gp100 plus placebo group had stage M1c disease. A higher percentage of patients retreated with an ipilimumab-containing regimen had received prior treatment with IL-2 compared with the study population as a whole (34.0% vs. 22.1% in the ipilimumab plus gp100 group and 33.0% vs. 23.4% in the ipilimumab plus placebo group, respectively; ref. 1).

Table 2. Baseline characteristics of retreated study subpopulation

Characteristic	Ipi + gp100 (*n* = 29) *n* (%)	Ipi + placebo (*n* = 9) *n* (%)	gp100 + placebo (*n* = 2) *n* (%)	Total (*N* = 40) *n* (%)
Age, y				
Mean	54.3	49.0	60.5	53.4
Gender				
Male	19 (66)	2 (22)	0 (0)	21 (52)
Female	10 (34)	7 (78)	2 (100)	19 (48)
M stage				
M1a	2 (7)	0 (0)	0 (0)	2 (5)
M1b	10 (34)	4 (44)	0 (0)	14 (35)
M1c	17 (59)	5 (56)	2 (100)	24 (60)
Prior IL-2				
Yes	10 (34)	3 (33)	0 (0)	13 (32)
No	19 (66)	6 (67)	2 (100)	27 (68)
ECOG PS				
0	22 (76)	5 (56)	1 (50)	28 (70)
1	7 (24)	4 (44)	1 (50)	12 (30)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; Ipi, ipilimumab 3 mg/kg intravenously every 3 weeks for up to 4 doses.

Most patients who started a first retreatment cycle received the target number of 4 doses (34 of 40; 85.0%). Of 7 patients who started a second retreatment cycle, 5 (71.4%) received all 4 doses. Only one patient started a third retreatment cycle, and this patient completed the cycle. Patients in the ipilimumab plus gp100, ipilimumab plus placebo, and gp100 plus placebo groups received a median number of retreatment doses of 4.0 (range, 2.0–4.0; $n = 29$), 4.0 (range, 2.0–4.0; $n = 9$), and 3.5 (range, 3.0–4.0; $n = 2$), respectively, for the first retreatment cycle and 3.5 (range, 2.0–4.0; $n = 4$) and 4.0 (range, 4.0–4.0; $n = 3$) for the second retreatment cycle (no patient in the gp100 plus placebo arm was retreated for a second time). Median time between the first treatment dose and first retreatment dose was 11.5 months (range, 6.0–48.7) for the 29 patients retreated with ipilimumab plus gp100; 8.9 months (range, 6.0–28.9) for the 9 patients retreated with ipilimumab and 10.1 months (range, 7.8–12.4) for the 2 patients retreated with gp100. The interval between the first and second retreatment cycle was 11.5 months (range, 6.7–12.6) for the 4 patients retreated with ipilimumab plus gp100 and 12.0 months (range, 8.5–14.0) for the 3 patients retreated with ipilimumab alone. For the one patient who started a third retreatment cycle with ipilimumab plus gp100, the interval between the second and third cycle was 7.3 months. Time to retreatment and follow-up status for each patient are shown in Fig. 1.

Of the 40 retreated patients, only the 32 patients considered eligible for retreatment per protocol qualified for inclusion in the efficacy analyses. These 32 patients included 10 patients with evidence of disease progression based solely on investigator assessment but for whom no formal PD assessment was documented; 2 patients who had confirmed SD as their best response at the week 24 assessment but for whom the documented period of SD was <3 months, and 1 patient whose week 24 best overall response was considered "unknown" by the investigator despite imaging (Table 1). However, these 13 patients were considered evaluable for efficacy.

Efficacy

Best overall response rates (CRs plus PRs) for the 31 retreatment-eligible patients in the ipilimumab plus gp100

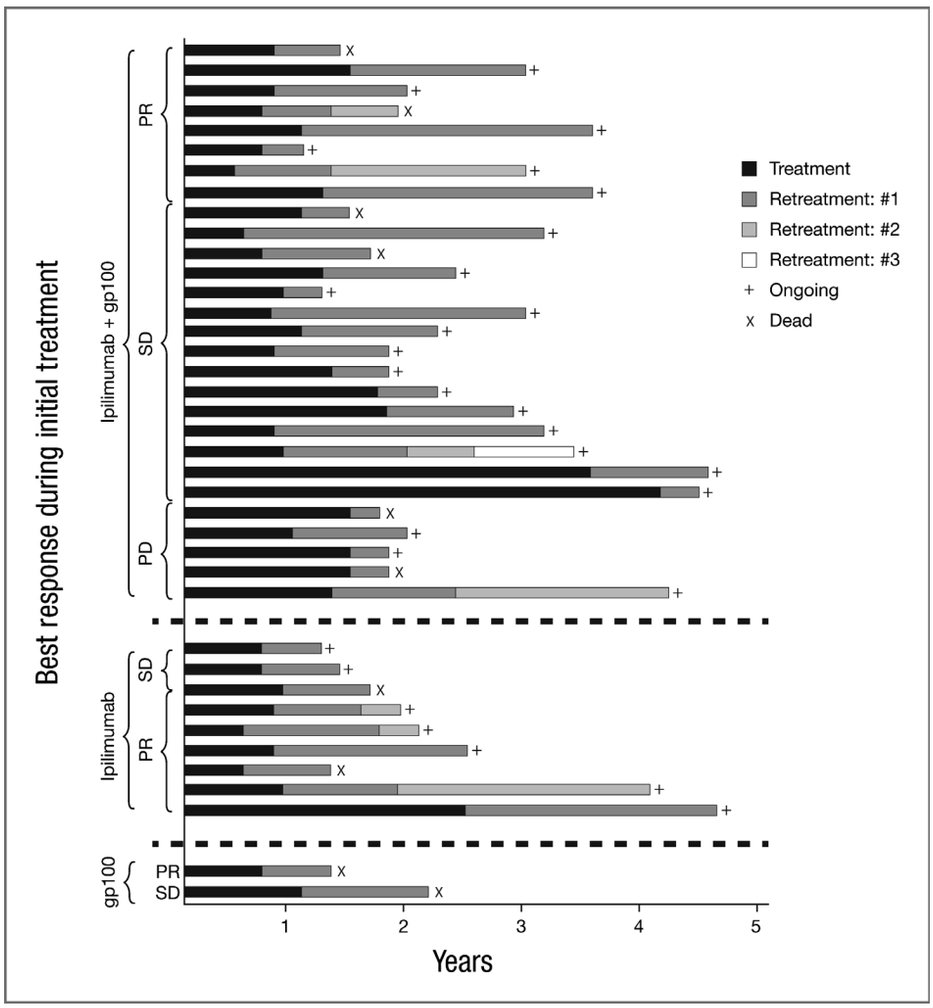

Figure 1. Time to retreatment and follow-up status in all retreated patients. For each patient (represented by individual lines), best response during their initial treatment regimen is provided, together with their follow-up status after 1 to 3 retreatments.

Table 3. Best overall response and survival outcomes for patients retreated with their original randomized regimen (per-protocol retreatment population; $N = 32$)

	Patients		
	Ipi + gp100 ($n = 23$)	**Ipi + placebo ($n = 8$)**	**gp100 + placebo ($n = 1$)**
	***n* (%)**	***n* (%)**	***n* (%)**
Best overall response during retreatment[a]			
CR	0 (0)	1 (12.5)	0 (0)
PR	3 (13.0)	2 (25.0)	0 (0)
SD	12 (52.2)	3 (37.5)	0 (0)
PD	8 (34.8)	2 (25.0)	1 (100.0)
No. alive >2 y from randomization	15 (65.2)	4 (50.0)	1 (100.0)
Survival range, mo	26.0–54.1+	24.6–55.1+	25.3

Abbreviation: Ipi, ipilimumab 3 mg/kg intravenously every 3 weeks for up to 4 doses.
[a]Measured by modified World Health Organization criteria.

and ipilimumab plus placebo groups were 3 of 23 (13.0%) and 3 of 8 (37.5%), respectively. The disease control rate among eligible patients retreated with ipilimumab was 65.2% and 75.0% in the ipilimumab plus gp100 and ipilimumab plus placebo groups, respectively, and 19 of 31 (61.3%) retreated patients who received ipilimumab survived >2 years from their initial randomization at study entry (Table 3).

Reanalysis of data including all 38 retreated patients who received ipilimumab plus gp100 or ipilimumab alone, irrespective of eligibility, gave corresponding overall response rates of 4 of 29 (13.8%) and 3 of 9 (33.3%), respectively, and the disease control rate ranged from 51.7% to 66.7%. Six patients achieved a better response after retreatment than after their original treatment, including PR to CR in 1 patient retreated with ipilimumab alone, SD to PR in 2 patients retreated with ipilimumab plus gp100 and 1 patient retreated with ipilimumab alone, and SD in 2 patients retreated with ipilimumab plus gp100 who had evidence of PD, or whose status was unknown, following treatment (Table 4). Of 7 patients retreated with ipilimumab despite not meeting protocol-defined eligibility criteria, one patient survived >2 years from randomization.

Considering all 40 retreated patients, 4 patients in the ipilimumab plus gp100 arm had a PR after retreatment lasting 57, 78, 113, and 814 days, respectively, although one

Table 4. Best overall response among patients retreated with their original randomized regimen (total retreatment population; $N = 40$)

		Patients		
Best overall response[a]		**Ipi + gp100 ($n = 29$)**	**Ipi + placebo ($n = 9$)**	**gp100 + placebo ($n = 2$)**
At treatment	After retreatment	*n* (%)	*n* (%)	*n* (%)
PR	CR	0 (0)	1 (11.1)	0 (0)
	PR	3[b] (10.3)	0 (0)	0 (0)
	SD	3 (10.3)	1 (11.1)	0 (0)
	PD	2 (6.9)	1[b] (11.1)	1 (100.0)
SD	CR	0 (0)	0 (0)	0 (0)
	PR	1 (3.4)	2 (22.2)	0 (0)
	SD	8 (27.6)	2 (22.2)	0 (0)
	PD	6 (20.7)	2 (22.2)	1[b] (100.0)
PD[c]	SD	1 (3.4)	0 (0)	0 (0)
	PD	4 (13.8)	0 (0)	0 (0)
Unknown[c]	SD	1 (3.4)	0 (0)	0 (0)

Abbreviation: Ipi, ipilimumab 3 mg/kg intravenously every 3 weeks for up to 4 doses.
[a]Measured by modified World Health Organization criteria.
[b]Includes 1 patient in each arm with protocol violation.
[c]Patients ($n = 6$) did not meet the protocol-defined eligibility criteria for retreatment.

had received prior treatment with a cancer vaccine before study entry and therefore violated the protocol (Table 4). In the ipilimumab plus placebo arm, there were 3 responders: 1 patient had a CR for 162 days followed by a PR for a further 30 days and the other 2 patients had a PR for 85 and 95 days, respectively. There were no responders among patients retreated with gp100 plus placebo.

Safety

The frequencies of irAEs observed during retreatment were similar to those observed during treatment, with no new types of toxicities. Furthermore, toxicities observed during initial treatment did not predispose to retreatment toxicity. Overall, drug-related adverse events were reported in 25 patients (86.2%), 7 patients (77.8%), and 2 patients (100%) in the ipilimumab plus gp100, ipilimumab plus placebo, and gp100 plus placebo arms, respectively. The most common adverse events were irAEs, occurring in 15 patients (51.7%), 7 patients (77.8%), and 1 patient (50.0%) in the respective groups. Most irAEs affected the skin and gastrointestinal tract and were grade I/II in severity. Grade III irAEs occurred in 2 of 29 patients (6.9%; colitis and diarrhea in 1 patient each) in the ipilimumab plus gp100 group and in 2 of 9 patients (22.2%; eosinophilia and rash in 1 patient each) in the ipilimumab plus placebo group (Table 5). There were no grade IV or V irAEs in any patient during retreatment.

Discussion

Among 676 patients enrolled in this phase III trial, 40 (6%) were retreated with their original treatment regimen following disease progression. Our analysis has some limitations, most obviously the small patient numbers which precluded a rigorous statistical analysis. Only 19 of 32 evaluable patients had their response status confirmed in the study database (Table 1), but it is likely that the investigators' clinical judgment was accurate in most cases. Although the sample size is small, durable ORs and/or SD were achieved in some patients retreated with ipilimumab, with additional restoration of disease control with a second or, in the case of one patient, third retreatment schedule.

Most patients tolerated one full cycle of ipilimumab retreatment, and several tolerated a full second cycle of retreatment. The frequencies of irAEs observed during retreatment were similar to those observed during treatment, with no new types of toxicities, and most events were mild-to-moderate. Although patient numbers were substantially smaller, retrospective analysis showed that best overall response rates for protocol-compliant, eligible patients were higher than those for the overall phase III study population at 13% (ν 6%) and 38% (ν 11%) for patients in the ipilimumab plus vaccine and ipilimumab monotherapy groups, respectively. Disease control rates in retreated patients were also higher than for the overall population, with 65% and 75% of patients in the ipilimumab plus vaccine and ipilimumab monotherapy groups, respectively, achieving disease control after retreatment compared with 20% and 29% of patients in those groups for the whole study (1). These findings are perhaps unsurprising as only patients who had responded to ipilimumab treatment therapy were eligible for retreatment, and these individuals presumably had responsive tumors and/or

Table 5. Incidence of irAEs by type and severity grade

	Patients					
	Ipi + gp100 ($n = 29$)		Ipi + placebo ($n = 9$)		gp100 + placebo ($n = 2$)	
	n (%)		*n* (%)		*n* (%)	
	All	Grade III[b]	All	Grade III[b]	All	Grade III[b]
irAE type						
Dermatologic	12 (41)	0 (0)	6 (67)	1 (11)	0 (0)	0 (0)
Gastrointestinal	5 (17)	2 (7)	3 (33)	0 (0)	0 (0)	0 (0)
Blood and lymphatic	0 (0)	0 (0)	1 (11)	1 (11)	0 (0)	0 (0)
Endocrine	1 (3)	0 (0)	1 (11)	0 (0)	0 (0)	0 (0)
Hepatic	0 (0)	0 (0)	1 (11)	0 (0)	1 (50)	0 (0)
Investigations[a]	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
irAE occurrence (all grades)						
Treatment only	6 (21)		2 (22)		1 (50)	
Retreatment only	10 (34)		2 (22)		—	
Treatment and retreatment	5 (17)		5 (56)		1 (50)	
No irAEs	8 (28)		—		—	

NOTE: Details on when irAEs occurred during therapy (initial treatment vs. retreatment or both) are also provided.
Abbreviation: Ipi, ipilimumab 3 mg/kg intravenously every 3 weeks for up to 4 doses.
[a]Increased lipase.
[b]No grade IV AEs reported.

immune systems (13). The majority of responding patients had SD as their best overall response, possibly reflecting ipilimumab maintaining the cancer in its equilibrium phase (8, 9, 14). SD, when associated with clinical benefit (such as improved survival), is a meaningful outcome for melanoma patients (15).

Two analyses were conducted, one including data from only those patients eligible for retreatment per protocol and the other including all patients actually retreated. To avoid premature assumption of treatment failure, the study protocol required that PD was confirmed at least 4 weeks after its first observation. Among the 40 retreated patients, 6 patients were retreated despite not qualifying according to the protocol: 2 of these (1 who did not respond to their initial treatment regimen and 1 whose response was unknown) subsequently achieved SD. The other 4 patients, with a best response of PD after their initial treatment, did not respond to retreatment with ipilimumab. This suggests that the criterion for retreatment should remain disease control after treatment, before subsequent progression.

In the patient with PD who went on to develop SD on retreatment, it may be that the immune response was still building, and tumor regression (or in this case, stabilization) occurred only after retreatment. However, it is also possible that the observed disease progression initially recorded in this patient was not a function of tumor growth but of T-cell infiltration and inflammation following ipilimumab-induced T-cell potentiation (16, 17). Had this patient been analyzed using proposed immune-related response criteria (irRC), which allow for disease progression before response (18), they may have been deemed as having disease control rather than PD. Some evaluable patients also had better responses after retreatment than they obtained initially, which may also be a reflection of a gradually building immune response to the tumor and is consistent with the frequently reported instances of evolving and unusual responses to ipilimumab (1, 18–23). Alternatively, one further possible mechanism to explain the phenomenon is that the blockade of CTLA-4 activity is reset in the absence of continued treatment but can be reactivated upon subsequent retreatment.

It is possible that in patients responding to ipilimumab therapy, T cells that recognize antigens expressed by the tumor undergo clonal expansion and are potentiated by ipilimumab, producing a reduction in lesion size. Selective pressure from these activated, antigen-specific T cells may result in a shift in the antigen repertoire of the cancer, and new lesions develop that are antigenically different, and therefore no longer responsive to the expanded, activated T-cell clones (12). This process manifests as disease progression and, as discussed, is part of the "escape" phase of tumor development. Upon retreatment with ipilimumab, the newly arising lesions begin to respond and disease control is regained as clones from the tumor-infiltrating T-cell population–specific for the altered tumor antigenic repertoire expand and become activated by ipilimumab. Such "immune adaptation" to shifts in tumor antigen expression has been recorded even in the absence of immunotherapy (24). In nonresponders to retreatment, this immune adaptation may not occur, allowing the tumor to escape further immune potentiation. Multiple tumor immune escape mechanisms have been hypothesized to be responsible for this; however, further studies are required to provide definitive answers (8, 9, 25).

Safety after retreatment was comparable to safety in the overall study population. IrAEs were well described and could generally be managed using established treatment algorithms (26–28). Most irAEs affected the skin and gastrointestinal tract, consistent with data reported from other studies (29). Importantly, toxicity during the first treatment regimen did not predispose patients to toxicity during retreatment. Among the 18 patients with an irAE during their initial treatment, only 10 had an irAE upon retreatment. The majority of eligible patients who received retreatment with ipilimumab completed a full retreatment cycle.

A retreatment response rate of 38% and disease control rate of 75% after ipilimumab monotherapy are encouraging, and merit further study. Of note, alternative posttreatment protocols have been investigated in clinical trials of ipilimumab. For example, in the phase III trial evaluating ipilimumab plus dacarbazine compared with dacarbazine alone (30), patients with SD or an OR and no dose-limiting toxic effects were eligible to receive maintenance therapy with ipilimumab or placebo every 12 weeks. Further investigation is required to determine how and when ipilimumab should be provided posttreatment to maximize patient outcomes.

In conclusion, retreatment with ipilimumab in patients who respond to treatment and then progress is a feasible proposition with encouraging efficacy and tolerability. The majority of retreated patients achieved durable disease control lasting longer than 2 years from randomization and toxicity was not cumulative between treatment phases. These data suggest that if patients meet defined criteria, retreatment with ipilimumab can translate into clinical benefit with no deleterious morbidity and strongly support the further evaluation of retreatment protocols.

Disclosure of Potential Conflicts of Interest

C. Robert is a consultant/advisory board member of Bristol-Myers Squibb, Roche, GlaxoSmithKline, and Merck. D. Schadendorf has honoraria from speakers' bureau from Bristol-Myers Squibb and is a consultant/advisory board member of Bristol-Myers Squibb, Roche, Novartis, GlaxoSmithKline, and Amgen. F.S. Hodi has commercial research support and is a consultant/advisory board member of Bristol-Myers Squibb. S. O'Day has a commercial research grant, honoraria from speakers' bureau, and is a consultant/advisory board member of Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other author.

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):
Study supervision: C. Robert

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References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.
2. Ishikawa T, Fujita T, Suzuki Y, Okabe S, Yuasa Y, Iwai T, et al. Tumor-specific immunological recognition of frameshift-mutated peptides in colon cancer with microsatellite instability. Cancer Res 2003;63: 5564–72.
3. Nagorsen D, Scheibenbogen C, Marincola FM, Letsch A, Keilholz U. Natural T cell immunity against cancer. Clin Cancer Res 2003;9:4296–303.
4. Pagès F, Berger A, Camus M, Sanchez-Cabo F, Costes A, Molidor R, et al. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med 2005;353:2654–66.
5. Sato E, Olson SH, Ahn J, Bundy B, Nishikawa H, Qian F, et al. Intraepithelial $CD8^+$ tumor-infiltrating lymphocytes and a high $CD8^+$ /regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci U S A 2005;102:18538–43.
6. Peggs KS, Quezada SA, Korman AJ, Allison JP. Principles and use of anti-CTLA4 antibody in human cancer immunotherapy. Curr Opin Immunol 2006;18:206–13.
7. Robert C, Ghiringhelli F. What is the role of cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma? Oncologist 2009;14:848–61.
8. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329–60.
9. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest 2007;117:1137–46.
10. Nicholaou T, Chen W, Davis ID, Jackson HM, Dimopoulos N, Barrow C, et al. Immunoediting and persistence of antigen-specific immunity in patients who have previously been vaccinated with NY-ESO-1 protein formulated in ISCOMATRIX. Cancer Immunol Immunother 2011;60: 1625–37.
11. Yuan J, Ginsberg B, Page D, Li Y, Rasalan T, Gallardo HF, et al. CTLA-4 blockade increases antigen-specific $CD8^+$ T cells in prevaccinated patients with melanoma: three cases. Cancer Immunol Immunother 2011;60:1137–46.
12. Reiman JM, Kmieciak M, Manjili MH, Knutson KL. Tumor immunoediting and immunosculpting pathways to cancer progression. Semin Cancer Biol 2007;17:275–87.
13. Wang E, Panelli MC, Marincola FM. Understanding the response to immunotherapy in humans. Springer Semin Immunopathol 2005;27: 105–17.
14. Agarwala SS. Novel immunotherapies as potential therapeutic partners for traditional or targeted agents: cytotoxic T-lymphocyte antigen-4 blockade in advanced melanoma. Melanoma Res 2010;20:1–10.
15. Tolcher AW. Stable disease is a valid end point in clinical trials. Cancer J 2009;15:374–8.
16. Hodi FS, Butler M, Oble DA, Seiden MV, Haluska FG, Kruse A, et al. Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients. Proc Natl Acad Sci U S A 2008;105:3005–10.
17. Ribas A, Chmielowski B, Glaspy JA. Do we need a different set of response assessment criteria for tumor immunotherapy? Clin Cancer Res 2009;15:7116–8.
18. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15: 7412–20.
19. Hersh EM, O'Day SJ, Powderly J, Khan KD, Pavlick AC, Cranmer LD, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naive patients with advanced melanoma. Invest New Drugs 2011;29:489–98.
20. O'Day SJ, Maio M, Chiarion-Sileni V, Gajewski TF, Pehamberger H, Bondarenko IN, et al. Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study. Ann Oncol 2010;21:1712–7.
21. Weber J, Thompson JA, Hamid O, Minor D, Amin A, Ron I, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 2009;15: 5591–8.
22. Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. Cancer Immunol Immunother 2009;58: 823–30.
23. Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010;11:155–64.
24. Yamshchikov GV, Mullins DW, Chang CC, Ogino T, Thompson L, Presley J, et al. Sequential immune escape and shifting of T cell responses in a long-term survivor of melanoma. J Immunol 2005; 174:6863–71.
25. Whiteside TL. The tumor microenvironment and its role in promoting tumor growth. Oncogene 2008;27:5904–12.
26. Kaehler KC, Piel S, Livingstone E, Schilling B, Hauschild A, Schadendorf D. Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns, immune-related adverse events, and their management. Semin Oncol 2010;37:485–98.
27. Kähler KC, Hauschild A. Treatment and side effect management of CTLA-4 antibody therapy in metastatic melanoma. J Dtsch Dermatol Ges 2011;9:277–86.
28. O'Day SJ, Hamid O, Urba WJ. Targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4): a novel strategy for the treatment of melanoma and other malignancies. Cancer 2007;110:2614–27.
29. Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. Semin Oncol 2010;37:499–507.
30. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26.