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

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Abstract

Purpose: Diarrhea (with or without colitis) is an immune-related adverse event (irAE) associated with ipilimumab. A randomized, double-blind, placebo-controlled, multicenter, multinational phase II trial was conducted to determine whether prophylactic budesonide (Entocort EC), a nonabsorbed oral steroid, reduced the rate of grade ≥2 diarrhea in ipilimumab-treated patients with advanced melanoma.

Experimental Design: Previously treated and treatment-naïve patients (N = 115) with unresectable stage III or IV melanoma received open-label ipilimumab (10 mg/kg every 3 weeks for four doses) with daily blinded budesonide (group A) or placebo (group B) through week 16. The first scheduled tumor evaluation was at week 12; eligible patients received maintenance treatment starting at week 24. Diarrhea was assessed using Common Terminology Criteria for Adverse Events (CTCAE) 3.0. Patients kept a diary describing their bowel habits.

Results: Budesonide did not affect the rate of grade ≥2 diarrhea, which occurred in 32.7% and 35.0% of patients in groups A and B, respectively. There were no bowel perforations or treatment-related deaths. Best overall response rates were 12.1% in group A and 15.8% in group B, with a median overall survival of 17.7 and 19.3 months, respectively. Within each group, the disease control rate was higher in patients with grade 3 to 4 irAEs than in patients with grade 0 to 2 irAEs, although many patients with grade 1 to 2 irAEs experienced clinical benefit. Novel patterns of response to ipilimumab were observed.

Conclusions: Ipilimumab shows activity in advanced melanoma, with encouraging survival and manageable adverse events. Budesonide should not be used prophylactically for grade ≥2 diarrhea associated with ipilimumab therapy. (Clin Cancer Res 2009;15 (17):5591–8)

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Localized melanoma can be effectively treated by surgery (1), but new therapies for unresectable disease are urgently needed. Dacarbazine is the commonly used standard treatment for advanced melanoma (2, 3), but no systemic treatment has shown improved survival compared with dacarbazine in randomized clinical trials (4–7). Recent immunotherapy trials have shown median overall survival (OS) time of 11.4 months with high-dose interleukin 2 (8) and 11.7 months for tremelimumab (9). A recent meta-analysis of 42 phase II trials done by the cooperative groups between 1975 and 2005 in patients with metastatic melanoma documented a median survival time of 6.2 months, with a 25.5% 1-year survival rate (10).

Ipilimumab (Bristol-Myers Squibb and Medarex) is a fully human monoclonal antibody directed against CTL antigen-4 (CTLA-4; refs. 11–15). CTLA-4 is a key negative regulator of the T-cell immune response, and preclinical animal studies have shown that blocking CTLA-4 enhances adaptive immune responses and induces tumor regression (16, 17). In clinical trials,

Translational Relevance

In this article, we show that ipilimumab, an immunoregulatory molecule that blocks the CTL antigen-4 molecule on T cells, has clear antitumor activity against advanced melanoma, with an impressive overall survival whether given with oral budesonide, to try and prevent the diarrhea often associated with its use, or with placebo. The primary end point of the trial was a reduction in the incidence of diarrhea with ipilimumab, but budesonide did not achieve that. Nonetheless, this work adds to the phase II experience with ipilimumab at a dose of 10 mg/kg given every 3 weeks to promote the clinical utility of that dose and schedule. The data further support the notion that there is an association between the incidence of grade 3/4 immune-related adverse events and clinical benefit with this drug, suggesting that an understanding of the means by which tolerance is broken will help elucidate the mechanism of action of ipilimumab.

ipilimumab has shown activity against advanced melanoma, including encouraging survival rates; some patients have achieved durable responses and stable disease (SD) ongoing for >4 years (13, 18–26).

Antibody inhibition of CTLA-4 can induce adverse events (AE) that are characteristically inflammatory in nature. These immune-related AEs (irAE) most commonly involve the gastrointestinal tract or the skin (11, 12, 27–31) without inducing generalized systemic autoimmunity (32). In melanoma patients treated with 10 mg/kg ipilimumab for four doses, reported irAEs ranged from generally well-tolerated grade 1/2 events in most patients to severe and life-threatening grade 3/4 events of colitis, hepatitis, and hypophysitis (30, 31). Management of higher-grade events included administration of high-dose steroids and interruption or cessation of anti–CTLA-4 therapy (30, 31, 33). In rare cases of steroid resistance, alternative immunosuppressive compounds such as infliximab (which blocks tumor necrosis factor) have been used successfully.

Diarrhea secondary to colitis is a clinically significant irAE. Prevention of grade ≥2 diarrhea while maintaining antitumor efficacy would improve the risk-benefit ratio for patients treated with ipilimumab. Budesonide (Entocort EC capsules, Astra-Zeneca) is a locally acting corticosteroid with low systemic bioavailability after oral administration because of extensive first-pass metabolism (34, 35).[11] We hypothesized that prophylactic oral budesonide could ameliorate the gastrointestinal side effects of ipilimumab without impairing its antitumor activity. To test that hypothesis, we performed a randomized, multicenter, double-blind, phase II trial of open-label ipilimumab administered with either prophylactic budesonide or placebo in patients with advanced melanoma(36).

[11] Entocort EC prescribing information. http://www.entocortec.com/c/pdf/Entocort_PI_rev_04-05.pdf.

Patients and Methods

Study end points. The primary study end point was the rate of grade ≥2 diarrhea during the first 24 wk of study in patients receiving i.v. ipilimumab with either prophylactic oral budesonide or placebo. Secondary end points included best overall response rate (BORR), defined per protocol as the best response of complete response (CR) or partial response (PR) per modified WHO criteria; disease control rate (DCR; proportion of patients with best response of CR or PR, or SD); OS; survival rate at 1 y; duration of response; proportion of patients with duration of response ≥24 wk; time to response; and AEs of the two regimens. Further secondary end points included potential predictors of response such as single nucleotide polymorphisms and histologic assessment of the overall effects on the gastrointestinal tract by endoscopic biopsies pre- and post-ipilimumab (37). An additional analysis was carried out to determine 18-mo survival rates.

Patient population. Patients with an age of ≥18 y with a histologic or cytologic diagnosis of unresectable and measurable stage III or IV melanoma (excluding ocular melanoma) were eligible. Patients could have had previous systemic therapy or were previously untreated. Other key inclusion criteria included life expectancy of at least 4 mo and Eastern Cooperative Oncology Group performance status of 0 or 1 (see Supplementary Appendix for additional inclusion and exclusion criteria).

Patients were excluded if with active untreated central nervous system metastases (those with stable brain metastases for 1 mo after therapy were eligible); other malignancies from which they had been disease-free for <5 y (except adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer, or *in situ* carcinoma of the cervix); autoimmune disease, including a history of inflammatory bowel disease; receipt of investigational drugs within 4 wk of starting protocol therapy; previous treatment with an anti–CTLA-4 antibody; or use of immunosuppression (unless on stable doses of corticosteroid replacement therapy for hypoadrenalism).

Trial design. During induction, patients were randomized 1:1 to receive concomitant oral budesonide (group A) or placebo (group B), with open-label ipilimumab administered at a dose of 10 mg/kg by 90-min i.v. infusion at weeks 1, 4, 7, and 10 (Supplementary Fig. S1). Randomization was stratified by previous immunotherapy. Blinded oral study medication was self-administered as 9 mg budesonide or placebo once daily until week 12, then tapered until discontinuation at week 16. Patients developing grade ≥2 diarrhea or other irAEs discontinued budesonide/placebo and commenced open-label budesonide/other steroids. Patients with grade 2 diarrhea lasting for 2 wk despite concomitant therapy or with grade 3 or 4 diarrhea discontinued ipilimumab.

The first scheduled tumor assessment was at week 12. Subsequent tumor assessments were scheduled at weeks 16, 20, and 24. Patients without progressive disease (PD) at week 24 with an Eastern Cooperative Oncology Group performance status of 0 or 1 and who did not experience toxicity requiring discontinuation of study therapy were eligible to receive maintenance ipilimumab at weeks 24, 36, and 48, and every 12 wk thereafter. Ipilimumab continued every 12 wk until PD, toxicity requiring discontinuation of study drug, withdrawal of consent, study closure, or start of alternative treatment. Tumor assessments were scheduled at weeks 30, 36, 42, and 48, and every 12 wk thereafter until PD or study closure.

The study was conducted in accordance with the ethical principles originating from the current Declaration of Helsinki and consistent with International Conference on Harmonization Good Clinical Practice. Institutional review board or independent ethics committee approval of the protocol was obtained before initiating the trial. All participating patients (or their legal representatives) gave written informed consent.

Study evaluations. Radiologic tumor assessments in all patients were confirmed by an independent review committee (IRC). A total of 39 (62%) of 63 patients were followed beyond PD. Novel efficacy

Table 1. Patient characteristics at baseline

	Ipilimumab + budesonide (group A; *n*= 58)	Ipilimumab + placebo (group B; *n*= 57)
Gender, *n* (%)		
Female	15 (26)	19 (33)
Male	43 (74)	38 (67)
Race, *n* (%)		
Caucasian	56 (97)	54 (95)
Asian	0	2 (4)
Black/African American	0	1 (1.8)
Other/unknown	2 (3)	0
Median age, y (range)	58 (30-82)	61 (26-86)
M stage at study entry, *n* (%)		
M_0	1 (2)	1 (2)
M_{1a} (soft tissue)	11 (19)	9 (16)
M_{1b} (lung)	18 (31)	18 (31)
M_{1c} (all viscera)	28 (48)	29 (51)
ECOG performance status, *n* (%)		
0	40 (69)	42 (74)
1	17 (29)	15 (26)
2	1 (2)	0
Disease stage at study entry, *n* (%)		
III	1 (2)	3 (5)
IV	57 (98)	54 (95)
Baseline lactate dehydrogenase, *n* (%)		
Within upper limit of normal	33 (57)	38 (67)
>Upper limit of normal	25 (43)	19 (33)
Previous systemic regimens, *n* (%)		
Any	50 (86)	41 (72)
1	22 (38)	18 (32)
2	13 (22)	14 (25)
3	12 (21)	7 (12)
4	2 (3)	0
≥5	1 (2)	2 (3)
Systemic therapy settings, *n* (%)		
Adjuvant therapy	20 (34)	26 (46)
Metastatic disease	38 (66)	25 (44)
Neoadjuvant therapy	1 (2)	0

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

criteria, applied to all on-study patients, were evolved from WHO and considered total tumor burden; that is, measurable index and new lesions as defined by the IRC (see Supplementary Appendix for additional information). Films that were obtained after WHO PD and before alternative anticancer therapy were only included in evaluations using the novel efficacy criteria.

AEs were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patients recorded

Table 2. Rate of grade ≥2 diarrhea in patients given ipilimumab with or without prophylactic budesonide

Patients with grade ≥2 diarrhea*	Ipilimumab + budesonide (group A; *n* = 58)	Ipilimumab + placebo (group B; *n* = 57)	Total (*N* = 115)
Grade 2, *n* (%)	11 (19.0)	10 (17.5)	21 (18.3)
Grade 3, *n* (%)	6 (10.3)	10 (17.5)	16 (13.9)
Grade 4, *n* (%)	2 (3.4)	0	2 (1.7)
Grade ≥2 diarrhea rate, *n* (%)	19/58 (32.7)	20/57 (35.0)	39/115 (33.9)
95% CI[†]	21.0-46.3	22.9-48.8	—
Difference in rate of grade ≥2 diarrhea, %[‡]	2.3		
95% CI[§]	-15.2 to 19.9		

*Patients reporting grade ≥2 diarrhea inflammatory events regardless of causality before week 24 or first maintenance treatment.
[†]Clopper and Pearson method.
[‡]Difference in rates between the budesonide arm and (minus) the placebo arm.
[§]Estimate and 95% CI for difference in rate of grade ≥2 diarrhea are computed using the Mantel-Haenszel method, stratified by previous use of immunotherapy (yes versus no) as recorded at randomization.

gastrointestinal symptoms in a diary. A data safety monitoring committee provided independent oversight of tolerability, study conduct, and risk-benefit ratio. Results of additional procedures, including flexible sigmoidoscopy and biopsies to examine gastrointestinal inflammation, are reported elsewhere (37).

Statistical methods. The sample size was determined by an estimated rate of grade 2 to 3 diarrhea of 28% based on a trial in stage IV renal cancer patients receiving 3 mg/kg ipilimumab. With 50 patients in the ipilimumab plus placebo group, an anticipated grade 2 to 4 diarrhea rate of 30% to 40% would result in a maximum width of the estimated 95% confidence interval (95% CI) of 28%. With 50 patients in the ipilimumab plus budesonide group, an anticipated grade 2 to 4 diarrhea rate of 15% to 25% would result in a maximum estimated exact 95% CI width of 26%. The rate of grade ≥2 diarrhea was reported along with exact two-sided 95% CIs for groups A and B using the method of Clopper and Pearson (38), and a two-sided 95% CI for the difference was computed using the Mantel-Haenszel (39) weighting method. BORR and DCR were calculated together with the corresponding exact two-sided 95% CIs. OS was calculated using the Kaplan-Meier product-limit method to provide the median estimate, together with a two-sided 95% CI calculated using the method of Brookmeyer and Crowley (40). Two-sided 95% CI values for the survival rates were calculated using the bootstrap method.

Results

Patient characteristics. One hundred thirty-five patients were enrolled, and 115 randomized patients received at least one dose of ipilimumab and blinded oral therapy (Supplementary Fig. S1). Fifty-eight patients were randomized to group A (ipilimumab and budesonide) and 57 to group B (ipilimumab and placebo). All 115 patients received ipilimumab and blinded medication and were included in the efficacy as well as tolerability analyses. Baseline demographics and characteristics were generally similar between the two arms; however, in the budesonide arm, more patients received previous systemic therapy (Table 1). All patients had unresectable stage III or IV melanoma at study entry; 97% had stage IV disease.

More than half of patients received all four ipilimumab induction doses [32 (55%) of 58 in group A and 35 (61%) of

Table 3. Overall tolerability of ipilimumab with or without prophylactic budesonide

	Patients, *n* (%)	
	Ipilimumab + budesonide (group A; *n* = 58)	**Ipilimumab + placebo (group B; *n* = 57)**
AEs leading to discontinuation	15 (26)	18 (32)
Diarrhea*†	7 (12)	5 (9)
Colitis*†	2 (3)	3 (5)
Immune-related hepatitis†	2 (3)	3 (5)
Drug-related AEs		
Any grade	52 (90)	54 (95)
Grade 3	24 (41)	20 (35)
Grade 4	8 (14)	7 (12)
Serious adverse events		
All	34 (59)	31 (54)
Drug related	26 (45)	21 (37)
irAEs		
Overall irAEs		
Any grade	47 (81)	48 (84)
Grade 3	17 (29)	15 (26)
Grade 4	7 (12)	7 (12)
Gastrointestinal		
Any grade	28 (48)	26 (46)
Grade 3	10 (17)	11 (19)
Grade 4	4 (7)	2 (4)
Liver related		
Any grade	9 (16)	8 (14)
Grade 3	4 (6)	3 (5)
Grade 4	2 (3)	4 (7)
Endocrine		
Any grade	5 (9)	6 (11)
Grade 3	2 (3)	3 (5)
Grade 4	1 (2)	0
Skin		
Any grade	35 (60)	39 (68)
Grade 3	3 (5)	0
Grade 4	0	0
Other		
Any grade	2 (3)	2 (4)
Grade 3	1 (2)	0
Grade 4	0	1 (2)

*All events were considered drug related.
†Only AEs leading to discontinuation in ≥5% of patients in either group are listed; fatal on-study AEs in group A (disease progression in four, lobar pneumonia in one, and arrhythmia in one) and group B (disease progression in six, pneumonia aspiration in one, acute renal failure in one, cardiac arrest in one, and hepatic failure in one).

Table 4. BORR and DCR assessed by IRC

	Patients, *n* (%)	
	Ipilimumab + budesonide (group A; *n* = 58)	**Ipilimumab + placebo (group B; *n* = 57)**
BORR	7 (12)	9 (16)
95% CI*	5-23	8-28
CR	1 (2)	0
PR	6 (10)[†]	9 (16)[†]
SD	11 (19)	11 (19)
PD	34 (59)	29 (51)
Unknown	6 (10)[‡]	8 (14)[§]
DCR	18 (31)	20 (35)
95% CI*	20-45	23-49

*Two-sided, exact confidence interval (39).
[†]One additional patient in each group had an unconfirmed overall response of PR after a BORR of PD, as assessed by IRC.
[‡]Unknown; no postbaseline assessments (*n* = 4); no week 12 assessment (*n* = 2).
[§]Unknown; no postbaseline assessments (*n* = 6); no week 12 assessment (*n* = 2).

57 in group B]. The mean number of ipilimumab doses during induction was 3.3 in group A and 3.4 in group B. There were 7 (12%) of 58 patients in group A and 6 (11%) of 57 in group B who received ipilimumab in the maintenance period. Treatment was discontinued because of PD in 25 (43%) of 58 patients in group A and 30 (53%) of 57 in group B.

Safety and tolerability. The rate of grade ≥2 diarrhea was similar between treatment arms [group A, 19 (33%) of 58 patients; group B, 20 (35%) of 57 patients; Table 2]. A total of 16 (28%) of 58 patients in group A and 18 (32%) of 57 in group B had one event of grade ≥2 diarrhea; no patient experienced more than two events. Overall ipilimumab side effects were similar in the budesonide and placebo arms (Table 3). Drug-related AEs were in general medically manageable, tolerable, and reversible in most patients without known sequelae. There were no gastrointestinal or colonic perforations.

Drug-related AEs of any grade were reported for 52 (90%) of 58 patients in group A and 54 (95%) of 57 in group B (Table 3). The most common drug-related AEs of ≥10% across both arms and in decreasing order of frequency are shown in Table 3. Most drug-related AEs were consistent with immune-related events. Any grade irAEs were reported in 47 (81%) of 58 of patients in group A and 48 (84%) of 57 in group B, and involved the skin in 60% of patients in each group, the gastrointestinal tract in 45%, the liver in 14%, and the endocrine system in 8%. Systemic corticosteroids for the treatment of irAEs were used by 33 (57%) of 58 patients in group A and 25 (44%) of 57 in group B.

Grades 3 and 4 irAEs were seen in 17 (29%) of 58 and 7 (12%) of 58 patients in group A and in 15 (26%) of 57 and 7 (12%) of 57 patients in group B, respectively (Table 3). In decreasing order of frequency, diarrhea and autoimmune hepatitis were the most common (>5% across both arms). AEs leading to treatment discontinuation were reported for 15 (26%) of 58 patients in group A and 18 (32%) of 57 patients in group B (Table 3).

Efficacy. The BORR was 12.1% (7 of 58) in group A and 15.8% (9 of 57) in group B (Table 4), with one CR in the former. Responses in 15 of the 16 responders were ongoing at 24 weeks. There was an unconfirmed PR in a patient who initially was scored as having PD in group A and one in group B. SD was

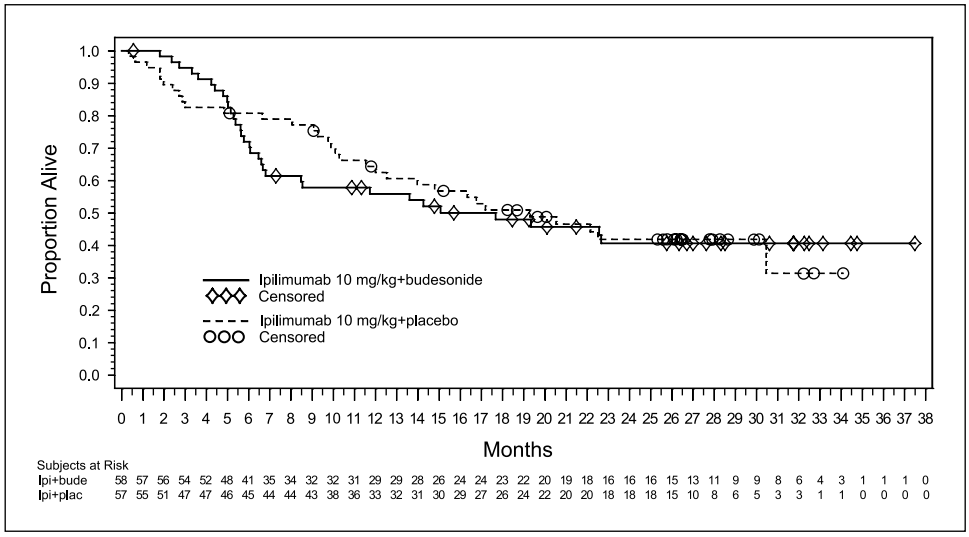

Fig. 1. Kaplan-Meier curves showing overall survival after ipilimumab with or without prophylactic budesonide.

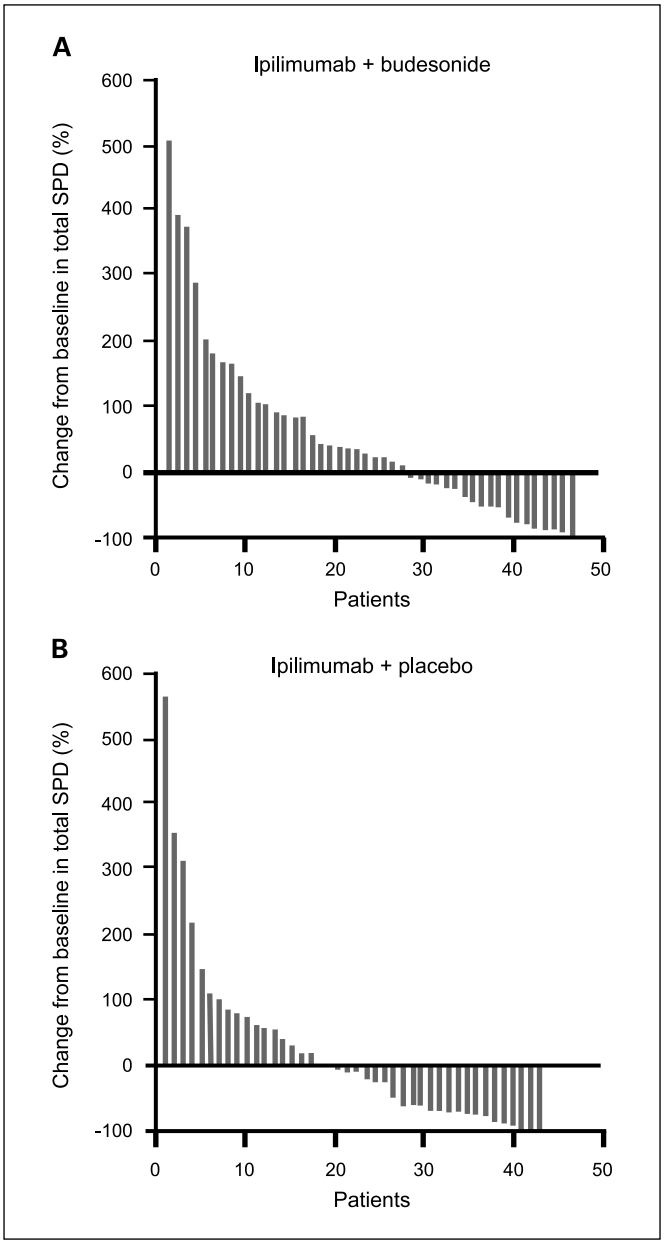

Fig. 2. Waterfall plots showing maximum percentage reduction in total tumor burden (index plus new lesions) with ipilimumab plus prophylactic budesonide (*A*) and ipilimumab plus placebo (*B*).

achieved in 11 (19%) of 58 patients in group A and 11 (19%) of 57 in group B. The DCR (CR + PR + SD) was 31.0% (18 of 58) and 35.1% (20 of 57), respectively (Table 4), with 8 (14%) of 58 and 4 (7%) of 57 patients having disease control ≥24 weeks.

For groups A and B, respectively, 1-year survival rates (95% CI) were 55.9% (42.7-68.8) and 62.4% (49.4-75.1); 24-month survival rates were 40.5% (27.12-54.37) and 41.7% (28.30-55.46). With a median follow-up in months (95% CI) of 12.6 (5.6-22.1) and 16.3 (9.1-21.4) for groups A and B, respectively, the median OS (95% CI) was 17.7 months (6.8, not reached) and 19.3 months (12.0, not reached; Fig. 1).

Two new patterns of clinical activity were observed: reduction in total tumor burden after the appearance of new lesions and/or response after initial increase in total tumor burden (Supplementary Fig. S2). Novel immune-related response criteria were used (41), which defined response as a change from baseline in total tumor burden (defined as index plus measurable new lesions, when present) in the following categories: irCR, decrease by 100%; irPR, decrease by ≥50%; irPD, increase ≥25%; and irSD, all other settings. Thirty-nine of 63 patients were followed beyond WHO PD; of these, 8 had evidence of clinical activity using immune-related response criteria. The waterfall plot of peak change in total tumor burden in all evaluable patients is shown in Fig. 2.

Association of response with irAEs. Eleven (46%) of 24 patients in group A and 13 (59%) of 22 patients in group B who experienced grade 3 to 4 irAEs had disease control. For patients experiencing grade 1 to 2 irAEs, 6 (26%) of 23 in group A and 7 (27%) of 26 in group B had disease control. There were no objective responses among the 20 patients that did not experience an irAE, although one patient in group A without an irAE had SD. There was a statistically significant difference between the DCR in patients with grade 0 to 2 irAEs and the DCR in patients with grade 3 to 4 irAEs (for group A, $P = 0.0495$; for group B, $P = 0.0042$ by two-sided Fisher's exact test).

Discussion

Prophylactic budesonide did not alter the rate of grade ≥2 diarrhea or improve general tolerability in patients treated with ipilimumab. Possible explanations for the absence of an effect could include an inability of budesonide to suppress inflammation, delivery of budesonide primarily to the small bowel and proximal colon, or insufficient absorption (42). The results from the present study suggest that budesonide should not be used for the prevention of grade ≥2 diarrhea. However, treatment guidelines developed from ipilimumab clinical trials recommend the use of budesonide for grade 2 diarrhea and high-dose steroids for grade 3 to 4 diarrhea (30). For grade 1 to 2 diarrhea, budesonide, Lomotil, and Imodium have been used by a number of investigators therapeutically to control symptoms induced by ipilimumab. Prompt attention to irAEs and the use of these treatment guidelines seem to be effective in preventing serious complications from diarrhea/colitis; that is, gastrointestinal perforation (30).

The overall AE profile of ipilimumab was consistent with other studies at the same dose. The incidence of grade 3 to 4 irAEs in our trial was ~40% [46 of 115 patients; 32 of grade 3 (28%) and 14 (12%) of grade 4] compared with rates of 25% and 22% in other studies using the same dosing regimen (20, 23). Most drug-related AEs were medically manageable and reversible, and there were no drug-related deaths. As well as having no effect on the incidence of grade ≥2 diarrhea, prophylactic budesonide had no detectable effect on the incidence of any AE.

The results of this trial provide further evidence that ipilimumab is clinically active in patients with metastatic melanoma, with a BORR of 12.1% and 15.8% and DCR of 31.0% and 35.1% in the presence or absence of budesonide, respectively. Median OS with ipilimumab in groups A and B (with a median follow-up of over 12 months) was 17.7 and 19.3 months. The 1-year survival rates were estimated as 55.9% with ipilimumab plus budesonide and 62.4% with ipilimumab plus placebo compared with rates of 25% to 44% from other studies with chemotherapy and immunotherapy

(5–10). The 2-year survivals of 40.5 and 41.7 months, respectively, were also noteworthy. This study included patients who had not received previous systemic therapy as well as patients who were previously treated for metastatic disease (including previous immunotherapy). Because there was no cap on baseline serum lactate dehydrogenase levels, ipilimumab efficacy was obtained in a patient cohort that included many with poor prognostic factors; that is, high lactate dehydrogenase levels.

DCR was higher in patients who developed grade 3 to 4 irAEs compared with patients who had no irAEs/grade 1 to 2 irAEs, with a statistically significant difference having been obtained despite small sample sizes. These results are consistent with previous findings of an association between irAEs and objective response rates in patients receiving ipilimumab (12, 27). However, patients with grade 1 to 2 irAEs and patients who not develop an irAE may still experience a clinical benefit with ipilimumab.

Systemic steroids, principally administered by mouth, but also i.v., were used to treat irAEs in 57% of patients in the prophylactic budesonide group and 44% in the placebo group. There was no evidence that systemic steroids altered ipilimumab activity. These data are supported by a preclinical study in which corticosteroids did not affect the antitumor activity achieved by CTLA-4 inhibition (43). Although glucocorticoids profoundly inhibit naïve T cells, they do not seem to impair the antitumor activity of activated T cells (44). Indeed, evidence from clinical studies indicates that steroid treatment for irAEs does not affect the antitumor efficacy of ipilimumab (18, 27).

Patterns of response to ipilimumab differ from those seen with chemotherapy (19, 45). New lesions can appear or existing lesions may grow before tumor regression, which may lead to an assessment of PD using WHO criteria (41). In this study, four patterns of response were observed: (*a*) response in baseline lesions, (*b*) a slow steady decline in total tumor burden, (*c*) response after initial increase in total tumor burden, and (*d*) response in index and new lesions after the appearance of new lesions. These findings suggest that the appearance of new lesions or the growth of index lesions may not always indicate treatment failure in patients receiving ipilimumab. We suggest that PD in ipilimumab-treated patients be confirmed radiologically at least 4 weeks later. New efficacy criteria such as those discussed by Hodi et al. (41) may be required to more accurately describe the clinical benefit of ipilimumab. Similar findings have been reported from other ipilimumab trials (20, 23, 46).

Ipilimumab is clinically active in metastatic melanoma with an acceptable toxicity profile and encouraging median OS, and the new response patterns are consistent with those observed by other investigators. The findings from this study do not support the routine prophylactic use of budesonide for the prevention of grade ≥2 diarrhea at the dose and schedule investigated, although it is still considered for the management of low-grade diarrhea and early colitis associated with ipilimumab. Importantly, budesonide did not seem to affect the development of an antitumor response to ipilimumab. Ongoing studies are evaluating the efficacy of ipilimumab at 10 mg/kg in patients with metastatic melanoma and whether high-dose steroids affect its clinical benefit.

Disclosure of Potential Conflicts of Interest

J.A. Thompson, S.J. O'Day, and J. Weber received commercial research grants from Bristol-Myers Squibb; O. Hamid received other commercial research support; S.J. O'Day, O. Hamid, and J. Weber received honoraria from the Bristol-Myers Squibb speakers bureau; S.J. O'Day, O. Hamid, and J. Weber are members of a Bristol-Myers Squibb advisory board. J. Weber and USC share a patent with Medarex on CT2A-4 antibodies.

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