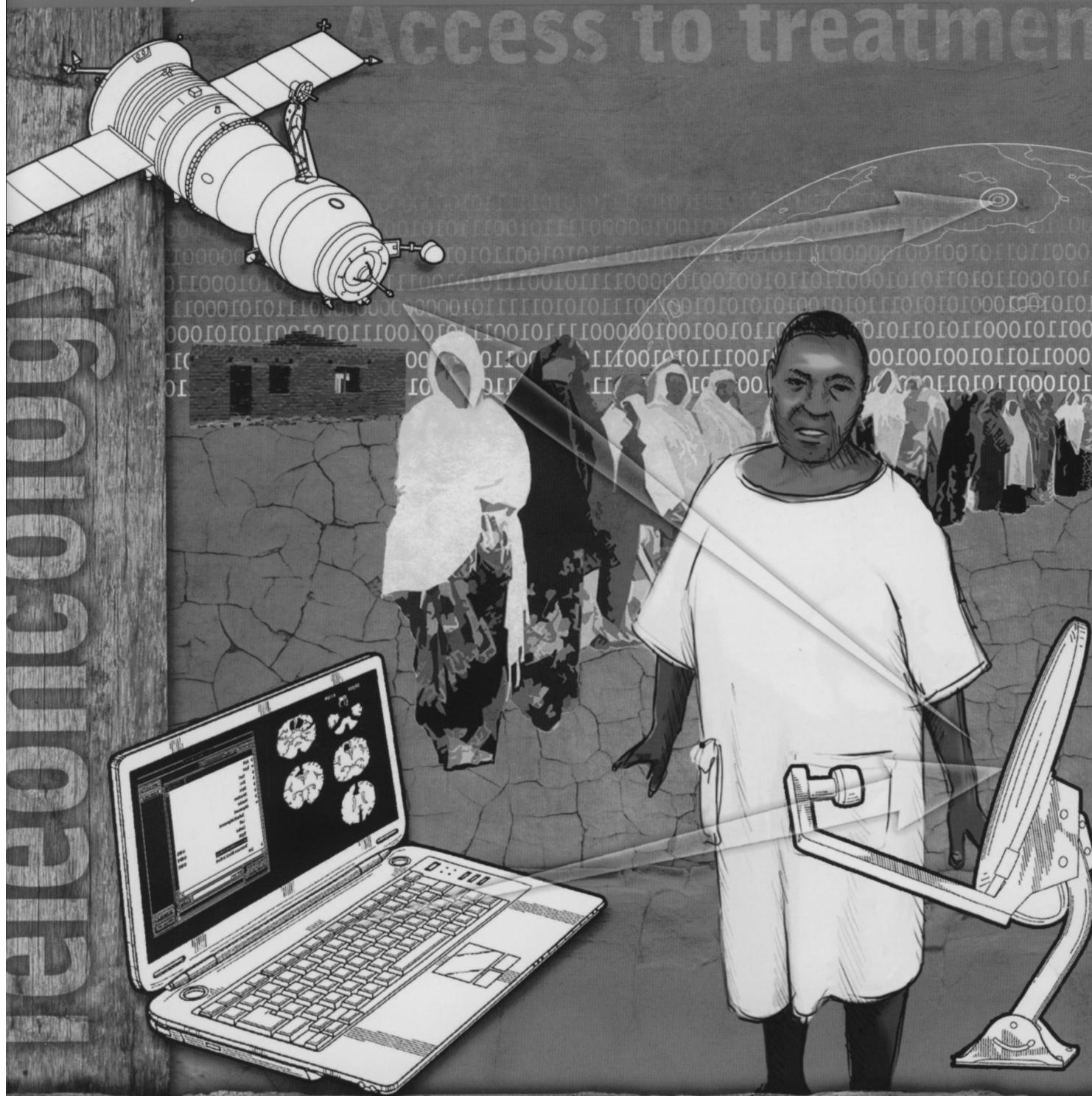


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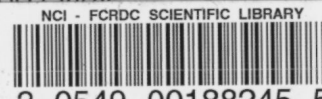
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Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study

Jedd D Wolchok, Bart Neyns, Gerald Linette, Sylvie Negrier, Jose Lutzky, Luc Thomas, William Waterfield, Dirk Schadendorf, Michael Smylie, Troy Guthrie Jr, Jean-Jacques Grob, Jason Chesney, Kevin Chin, Kun Chen, Axel Hoos, Steven J O'Day, Celeste Lebbé

Summary

Background Ipilimumab is a human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4 and has shown promising activity in advanced melanoma. We aimed to ascertain the antitumour efficacy of ipilimumab in patients with advanced melanoma.

Methods We undertook a randomised, double-blind, phase 2 trial in 66 centres from 12 countries. 217 patients with previously treated stage III (unresectable) or stage IV melanoma were randomly assigned a fixed dose of ipilimumab of either 10 mg/kg (n=73), 3 mg/kg (n=72), or 0·3 mg/kg (n=72) every 3 weeks for four cycles (induction) followed by maintenance therapy every 3 months. Randomisation was done with a permuted block procedure, stratified on the basis of type of previous treatment. The primary endpoint was best overall response rate (the proportion of patients with a complete or partial response, according to modified WHO criteria). Efficacy analyses were done by intention to treat, whereas safety analyses included patients who received at least one dose of ipilimumab. This study is registered with ClinicalTrials.gov, number NCT00289640.

Findings The best overall response rate was 11·1% (95% CI 4·9–20·7) for 10 mg/kg, 4·2% (0·9–11·7) for 3 mg/kg, and 0% (0·0–4·9) for 0·3 mg/kg ($p=0·0015$; trend test). Immune-related adverse events of any grade arose in 50 of 71, 46 of 71, and 19 of 72 patients at doses of 10 mg/kg, 3 mg/kg, and 0·3 mg/kg, respectively; the most common grade 3–4 adverse events were gastrointestinal immune-related events (11 in the 10 mg/kg group, two in the 3 mg/kg group, none in the 0·3 mg/kg group) and diarrhoea (ten in the 10 mg/kg group, one in the 3 mg/kg group, none in the 0·3 mg/kg group).

Interpretation Ipilimumab elicited a dose-dependent effect on efficacy and safety measures in pretreated patients with advanced melanoma, lending support to further studies at a dose of 10 mg/kg.

Funding Bristol-Myers Squibb.

Introduction

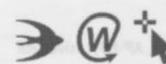
Malignant melanoma is one of the most aggressive cancers.¹ Adequate systemic treatments are needed because median overall survival for stage IV disease is only 6–9 months.² Both dacarbazine and high-dose interleukin 2 are approved in the USA, and fotemustine is approved within the European Union. Dacarbazine, a cytotoxic chemotherapeutic agent, yields low objective response rates; moreover, responses are short-lived, complete responses are rare, and the effect on overall survival is unclear.^{1,3} Interleukin 2 was approved on the basis of durable responses in 6% of patients, but predictive factors of response are not available, and toxic effects restrict use of this agent to carefully selected individuals and specialised treatment centres.⁴ Objective response rates have been enhanced by cytokines combined with chemotherapy, but this has not translated into an improvement in overall survival.⁵

A proposed immunotherapeutic approach for advanced melanoma entails targeting of cytotoxic T-lymphocyte antigen 4 (CTLA4),^{6–9} which is expressed on the surface of activated CD4+ and CD8+ T cells, to induce inhibitory

signals.¹⁰ Thus, CTLA4 blockade might increase the function of effector CD4+ and CD8+ T cells by removal of a key checkpoint mechanism.¹⁰ In murine models, antibody blockade of CTLA4 enhances immune responses resulting in tumour regression.^{11,12}

Ipilimumab is a human monoclonal antibody against CTLA4 currently in clinical development. Results of early studies in patients with advanced melanoma showed this agent's potential antitumour activity with various doses (0·1–20 mg/kg) and regimens (single or multiple doses, monotherapy, or in combination with dacarbazine, interleukin 2, or vaccines).^{13–19} In a phase 1/2 study, ipilimumab had antitumour activity in individuals with pretreated advanced melanoma, including patients who had failed previous treatment with interleukin 2 and biochemotherapy for metastatic disease.²⁰ Findings of a phase 2 study in treatment-naïve and previously treated individuals with advanced melanoma who received ipilimumab at 10 mg/kg, with or without prophylactic budesonide, showed 1-year survival of 55% or more.²¹

To date, no randomised clinical studies have assessed the dose-responsiveness of ipilimumab. Objective



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responses have been reported with ipilimumab at doses of 10 mg/kg or 3 mg/kg,¹³ and the possibility of clinical activity—ie, disease stabilisation—has been suggested with a dose of 0.3 mg/kg. In the current study, we aimed to assess the antitumour efficacy, pharmacokinetics, pharmacodynamics, overall survival, and safety of ipilimumab monotherapy at doses of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg in patients with previously treated stage III (unresectable) or stage IV melanoma.²² We chose 0.3 mg/kg to characterise fully the variables in the low range of the therapeutic window and to allow differences from the 10 mg/kg dose to be detected for many variables.

Methods

Patients

We undertook a multicentre, randomised, double-blind, parallel group study in 66 centres from 12 countries (study CA184-022). The first patient assessment was on April 6, 2006, and the last was on July 31, 2007. The study had four phases: screening, induction, maintenance, and follow-up. The database lock for the primary analysis took place on Nov 13, 2007.

We judged patients eligible for the study if they were aged at least 16 years old with a histological diagnosis of stage III (unresectable) or stage IV melanoma and measurable disease (by modified WHO criteria) and if they had: received at least one previous treatment with an antitumour regimen (except a CD137 agonist or CTLA4 modulator); and progressed after complete or partial response, or failed to show a complete or partial response within 12 weeks, or were unable to tolerate the regimen used. The webappendix contains additional details on inclusion and exclusion criteria.

We implemented this study in accordance with the Declaration of Helsinki and Good Clinical Practice as defined by the International Conference on Harmonization. The appropriate institutional review boards or independent ethics committees approved the protocol. All participating patients (or their legally acceptable representatives) gave written informed consent before enrolment.

Randomisation and masking

We randomly assigned patients in a 1:1:1 ratio to receive a fixed dose of ipilimumab (either 10 mg/kg, 3 mg/kg, or 0.3 mg/kg) by outpatient intravenous infusion (90 min duration) at weeks 1, 4, 7, and 10 (induction phase). We undertook randomisation with a permuted block procedure, stratified on the basis of type of previous treatment received (interleukin 2, dacarbazine, fotemustine, or temozolomide vs other treatments). After we obtained informed consent, investigators enrolled patients into the study by calling an interactive voice response system, which registered the enrolment and assigned a unique identification number to every individual. Once we had established eligibility, an

unmasked pharmacist called the interactive voice response system to obtain a treatment assignment. The system assigned the patient to one of the three treatment groups on the basis of a randomisation schedule generated and maintained by the randomisation group within Bristol-Myers Squibb.

Patients, treating doctors, and doctors' staff were unaware of the dose to which patients were assigned, whereas pharmacists were unmasked. The data monitoring committee was aware of treatment allocations to permit an ongoing overview assessment of safety and efficacy. One programmer and biostatistician were unmasked for compilation of the population pharmacokinetic analysis dataset. Summaries did not disclose treatment assignments of individual patients.

Procedures

The induction phase of the study ended at week 24 or on progressive disease, death, withdrawal of consent, or toxic effects requiring treatment discontinuation. Patients with progressive disease at any time were permitted, per protocol, to be followed up beyond progressive disease before non-ipilimumab anticancer agents were started. This step was allowed at the discretion of the investigator, since objective responses after initial progressive disease have been described with immunotherapy. After progressive disease, eligible patients remained unaware of their dose assignment and could crossover to a separate companion study (CA184-025)²³ to undergo reinduction with ipilimumab at 10 mg/kg.

The induction phase ended for every participant when all week-24 tumour assessments and other procedures were complete. On-treatment patients without progressive disease entered the maintenance phase beginning at week 24 and continued at their assigned ipilimumab dose every 12 weeks until progressive disease, death, toxic effects requiring treatment discontinuation, withdrawal of consent, or study closure. Two groups were eligible to enter the maintenance part of the trial. The first group consisted of individuals who did not progress during the induction phase and who had an Eastern Cooperative Oncology Group performance status of 0–1 at week 24, and those with no toxic effects requiring discontinuation. These patients continued to receive ipilimumab every 12 weeks until withdrawal of consent, progression (by WHO criteria), toxic effects requiring discontinuation of treatment, start of subsequent non-ipilimumab therapy, or discontinuation because of database lock. The second group contained individuals who did not progress during the induction phase but who had a poor performance status (>1), or toxic effects requiring discontinuation. These patients could continue with tumour assessment only until progressive disease.

We undertook CT or MRI of the chest, abdomen, and pelvis during the screening phase and at every tumour assessment. We did brain scans in the screening phase to rule out presence of brain metastases, and repeated these

See Online for webappendix

scans as clinically indicated to detect progressive disease. We noted visible cutaneous lesions with digital photography at every tumour assessment.

We did radiological and photographic tumour assessments in all patients at baseline and week 12; in those who did not progress, assessments continued at weeks 16, 20, and 24, and every 3 months thereafter. Individuals with progressive disease before week 12, but without rapid clinical deterioration, could continue treatment, and we labelled these people as non-progressors if the week-12 assessment showed stable disease or better compared with baseline. If we judged such patients to be progressors at week 12, we used the earlier date as the date of progression (an overall response assessment of progressive disease at or after week 12 precluded a subsequent designation of stable disease, complete response, or partial response). We characterised individuals with rapid progressive disease, who did not have a follow-up scan at week 12, as unknown (progressive disease by clinical observation only). All radiographic films obtained after progressive disease and before alternative anticancer treatment were included in the independent review committee assessment.

We defined measurable disease as lesions with a diameter of 20 mm or greater (in at least one place) and a perpendicular dimension of 10 mm or greater (or 10×10 mm for spiral CT). We characterised the area as the product of the largest diameter with its perpendicular. Non-measurable (assessable) disease consisted of all

other tumours, including measurable disease in one dimension only and small lesions with a diameter of less than 20 mm. We selected as index lesions all measurable tumours (up to a maximum of five per organ, including the skin, and 15 in total). We designated measurable tumours not regarded as index lesions, and all sites of non-measurable disease, as non-index lesions.

We used WHO criteria to ascertain overall response, according to combined assessments of index and non-index lesions. For index lesions, we defined complete response as full disappearance of all designated tumours; partial response as a decrease by at least 50% of the sum of the products of the two largest perpendicular diameters of all index lesions relative to baseline; stable disease as disease not meeting criteria for complete or partial response in the absence of progressive disease; and progressive disease as a 25% or greater increase in the sum of the products of all index lesions relative to nadir, the appearance of any new tumours, or both. For non-index lesions, we defined complete response as full disappearance of all tumours; stable disease or partial response as no change or any change with persistence of one or more non-index lesions; and progressive disease as appearance of any new tumour, unequivocal progression of non-index lesions, or both.

We applied novel immune-related response criteria to all on-study patients; these measures evolved from those of WHO to incorporate both conventional and novel patterns of response not seen previously with chemotherapy.²⁴ They

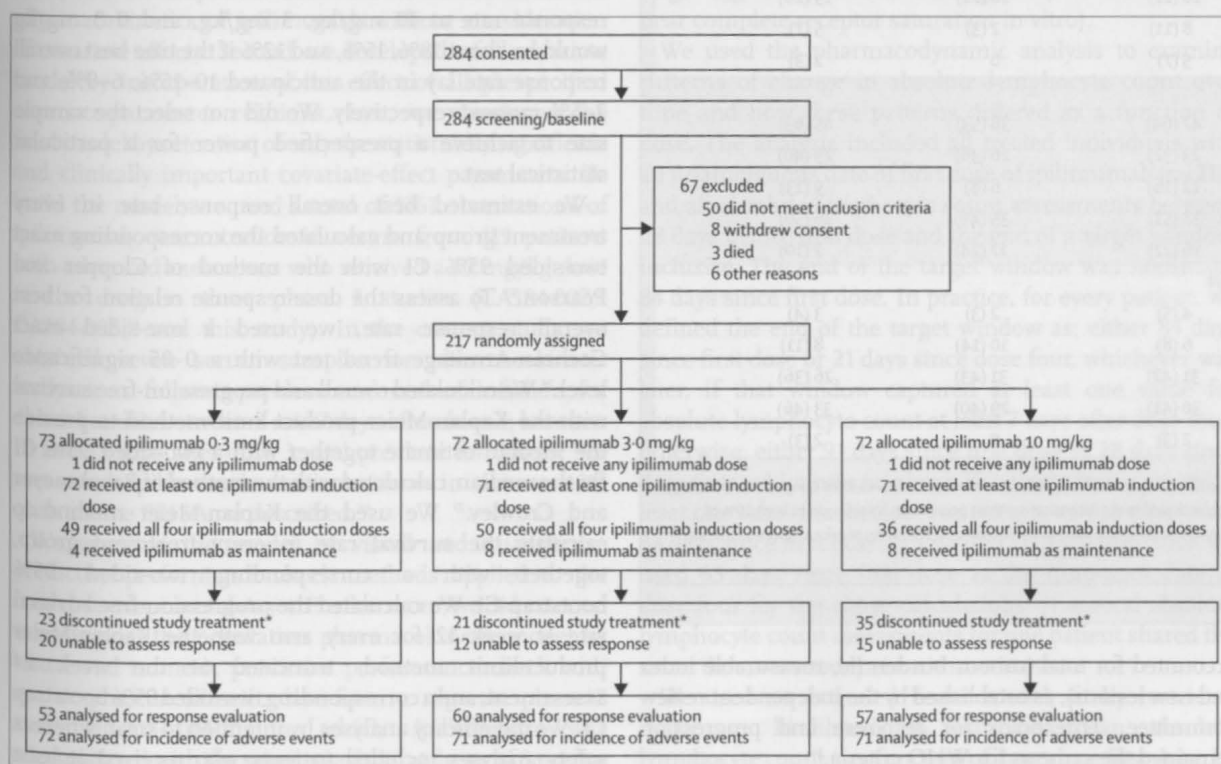


Figure 1: Trial profile

*Received fewer than four induction doses.

	Ipilimumab 0.3 mg/kg (n=73)	Ipilimumab 3 mg/kg (n=72)	Ipilimumab 10 mg/kg (n=72)
Sex (male)	52 (71)	48 (67)	44 (61)
Ethnic origin (white)	72 (99)	72 (100)	70 (97)
Age (years)	59 (25–85)	59 (29–78)	56 (19–83)
Lactate dehydrogenase			
Within ULN	38 (52)	40 (56)	33 (46)
>ULN	35 (48)	32 (44)	39 (54)
M-stage at study entry			
M0	5 (7)	4 (6)	3 (4)
M1a	10 (14)	11 (15)	17 (24)
M1b	13 (18)	21 (29)	15 (21)
M1c	45 (62)	36 (50)	37 (51)
ECOG performance status			
0	46 (63)	44 (61)	41 (57)
1	26 (36)	28 (39)	31 (43)
2	1 (1)*	0	0
Sites of commonest index lesion†			
Lymph nodes	41 (56)	42 (58)	41 (57)
Liver	27 (37)	25 (35)	30 (42)
Lung	26 (36)	24 (33)	24 (33)
Skin	11 (15)	6 (8)	12 (17)
Chest wall	11 (15)	2 (3)	5 (7)
Adrenal gland	9 (12)	4 (6)	2 (3)
Spleen	8 (11)	1 (1)	4 (6)
Previous systemic treatment regimens			
1	23 (32)	22 (31)	27 (38)
2	21 (29)	32 (44)	19 (26)
3	16 (22)	16 (22)	19 (26)
4	8 (11)	2 (3)	5 (7)
≥5	5 (7)	0	2 (3)
Previous systemic treatment			
Dacarbazine	47 (64)	38 (53)	45 (63)
Temozolomide	23 (32)	26 (36)	29 (40)
Fotemustine	12 (16)	6 (8)	9 (13)
Other chemotherapeutic agent	38 (51)	35 (49)	36 (50)
Interleukin 2	16 (22)	17 (24)	7 (10)
Best response to previous therapy‡			
Complete response	4 (5)	2 (3)	3 (4)
Partial response	6 (8)	10 (14)	8 (11)
Stable disease	31 (42)	31 (43)	26 (36)
Progressive disease	30 (41)	29 (40)	33 (46)
Unable to ascertain	2 (3)	0	2 (3)

Data are number of patients (%) or median (range). ULN=upper limit of normal. ECOG=Eastern Cooperative Oncology Group. *This patient was inadvertently included in the intention-to-treat population. †Arising in at least 10% of patients in any treatment group; patients could have lesions in more than one site. ‡Any previous systemic therapy including adjuvant treatment.

Table 1: Baseline characteristics

accounted for total tumour burden (ie, measurable index and new lesions), as established by the independent review committee. Thresholds for response and progression remained the same as for WHO criteria.²⁴

We graded adverse events with the National Cancer Institute's common terminology criteria for adverse

events version 3.0, and we based safety analyses on frequency and severity of all adverse events for all patients receiving at least one dose of ipilimumab. We recorded adverse events from the date of first dose up to and including 70 days after the final dose (corresponding to five half-lives).

We based all efficacy endpoints (except survival) on assessments made by a central independent review committee. The primary endpoint was best overall response rate, defined (per protocol) as the proportion of patients with complete or partial responses (by WHO criteria). We confirmed any complete or partial response at a second assessment done at least 4 weeks after criteria for response were first met. We measured best overall response rate at the end of the primary observation period, which ended after the last randomised patient had completed the tumour assessment at week 24.

Secondary objectives included an assessment of disease control rate (proportion of complete and partial responses plus stable disease), median overall survival, and survival rate at 1 year. We also established the safety profile of ipilimumab at every dose level. Additional analyses included progression-free survival rate at week 24. We assessed survival throughout the observation period and about every 6 months thereafter.

Statistical analysis

We calculated that 70 patients should be randomly allocated to every treatment group, whereby the maximum width of the exact 95% CI for best overall response rate at 10 mg/kg, 3 mg/kg, and 0.3 mg/kg would be about 18%, 15%, and 12% if the true best overall response rate lay in the anticipated 10–15%, 6–9%, and 2–5% ranges, respectively. We did not select the sample size to achieve a prespecified power for a particular statistical test.

We estimated best overall response rate in every treatment group and calculated the corresponding exact two-sided 95% CI with the method of Clopper and Pearson.²⁵ To assess the dose-response relation for best overall response rate, we used a one-sided exact Cochran-Armitage trend test with a 0.05 significance level.²⁶ We calculated overall and progression-free survival with the Kaplan-Meier product-limit method to provide the median estimate together with a two-sided 95% CI for the median, calculated with the method of Brookmeyer and Crowley.²⁷ We used the Kaplan-Meier method to calculate the survival rate in every treatment group, together with a corresponding two-sided 95% bootstrap CI. We calculated the progression-free survival rate at week 12 for every arm with the Kaplan-Meier product-limit method, truncated at the week 24 assessment, and a corresponding two-sided 95% bootstrap CI. We did efficacy analyses by intention to treat, whereas safety analyses included patients who received at least one dose of ipilimumab. We did statistical analyses with SAS version 8.2 (SAS Institute, Cary, NC, USA).

	Ipilimumab 0.3 mg/kg (n=73)	Ipilimumab 3 mg/kg (n=72)	Ipilimumab 10 mg/kg (n=72)
Best overall response			
Complete response	0	0	2
Partial response	0	3	6
Stable disease	10	16	13
Progressive disease	43	41	36
Unknown (progressive disease by clinical observation only)	20	12	15
Best overall response rate*	0% (0.0-4.9)	4.2% (0.9-11.7)	11.1% (4.9-20.7)
Disease control rate†	13.7% (6.8-23.8)	26.4% (16.7-38.1)	29.2% (19.0-41.1)
Number (%) with disease control ≥24 weeks (complete or partial response or stable disease) [95% CI]	0 (0%) [0.0-4.9]	2 (3%) [0.3-9.7]	5 (7%) [2.3-15.5]
Median (95% CI) overall survival (months)	8.6 (7.7-12.7)	8.7 (6.9-12.1)	11.4 (6.9-16.1)
Survival at 1 year	39.6% (28.2-51.2)	39.3% (28.0-50.9)	48.6% (36.8-60.4)
Survival at 18 months	23.0% (13.4-33.6)	30.2% (19.8-41.4)	34.5% (23.4-46.2)
Survival at 24 months	18.4% (9.6-28.2)	24.2% (14.4-34.8)	29.8% (19.1-41.1)
Median (IQR) survival follow-up (months)	8.3 (3.5-15.3)	8.7 (4.0-22.3)	10.7 (3.6-23.3)
Progression-free survival at 24 weeks‡	2.7% (0.0-7.3)	12.9% (0.0-25.9)	18.9% (7.9-28.9)

Data are number of patients (%) or rate (95% CI), unless otherwise indicated. *Number of patients with complete or partial response/N. †Number of patients with complete or partial response, or stable disease/N. ‡Calculated with the Kaplan-Meier product-limit method for all patients, which includes censoring, and therefore the rates for progression-free survival are different from disease control rates.

Table 2: Summary of efficacy results

For population pharmacokinetic analyses of ipilimumab, we used non-linear mixed-effects compartmental modelling with the NONMEM software program version VI (level 1.1). We developed this model in three stages. First, we developed a base model to describe the pharmacokinetics of ipilimumab without consideration of covariate effects. Second, we developed a full-covariate model by incorporation of the effect of all prespecified covariate-parameter relations. Last, we developed the final model by retention of only the statistically significant and clinically important covariate-effect parameters. To build the model, we used a total of 1761 observations of ipilimumab concentration in serum from 419 patients with advanced melanoma who received a 10 mg/kg dose of the drug in three phase 2 studies (CA184-007,²¹ CA184-008,¹⁴ and this study). In the current study, we obtained seven serum samples for pharmacokinetic analyses as follows: pre-dose and end of infusion for doses 1 and 3; between 3 and 7 days after dose 3; between 10 and 15 days after dose 3; and pre-dose for dose 4. We measured ipilimumab concentrations in serum with quantitative ELISA, as described.²⁰

We assessed the model by visual and quantitative predictive performance check methods applied to the model development dataset. Furthermore, we did external validation of the population pharmacokinetic model by visual and numeric predictive performance check with sparse pharmacokinetic data from a separate phase 2 study (CA184-004),²⁸ in which ipilimumab was administered with the same schedule, at doses of 3 mg/kg and 10 mg/kg. Finally, we applied the population pharmacokinetic model to simulate distributions of

ipilimumab steady-state trough concentration (C_{min}) before the fourth (and last) induction dose, to assess the extent to which patients receiving ipilimumab induction doses of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg achieved the target C_{min} concentration of 20 µg/mL (which resulted in near complete receptor saturation in vitro).

We used the pharmacodynamic analysis to examine patterns of change in absolute lymphocyte count over time and how these patterns differed as a function of dose. The analysis included all treated individuals with an unambiguous date of first dose of ipilimumab (n=213) and all absolute lymphocyte count assessments between 28 days before first dose and the end of a target window, inclusive. The end of the target window was nominally 84 days since first dose. In practice, for every patient, we defined the end of the target window as: either 84 days since first dose or 21 days since dose four, whichever was later, if that window captured at least one value for absolute lymphocyte count at least 7 days after dose four; otherwise, either 91 days since first dose or 28 days since dose four, whichever was later, if that window captured at least one value for absolute lymphocyte count; otherwise, 84 days since first dose. If a patient skipped dose four, we used 63 days since first dose as the (imputed) date of dose four for the above calculations. If several absolute lymphocyte count assessments for one patient shared the same date, we used their arithmetic mean.

We used an extended linear model, fit by restricted maximum likelihood, to estimate mean absolute lymphocyte count as a function of days since first dose, by treatment group, and the corresponding pointwise two-sided 95% CI. The model had fixed effects of

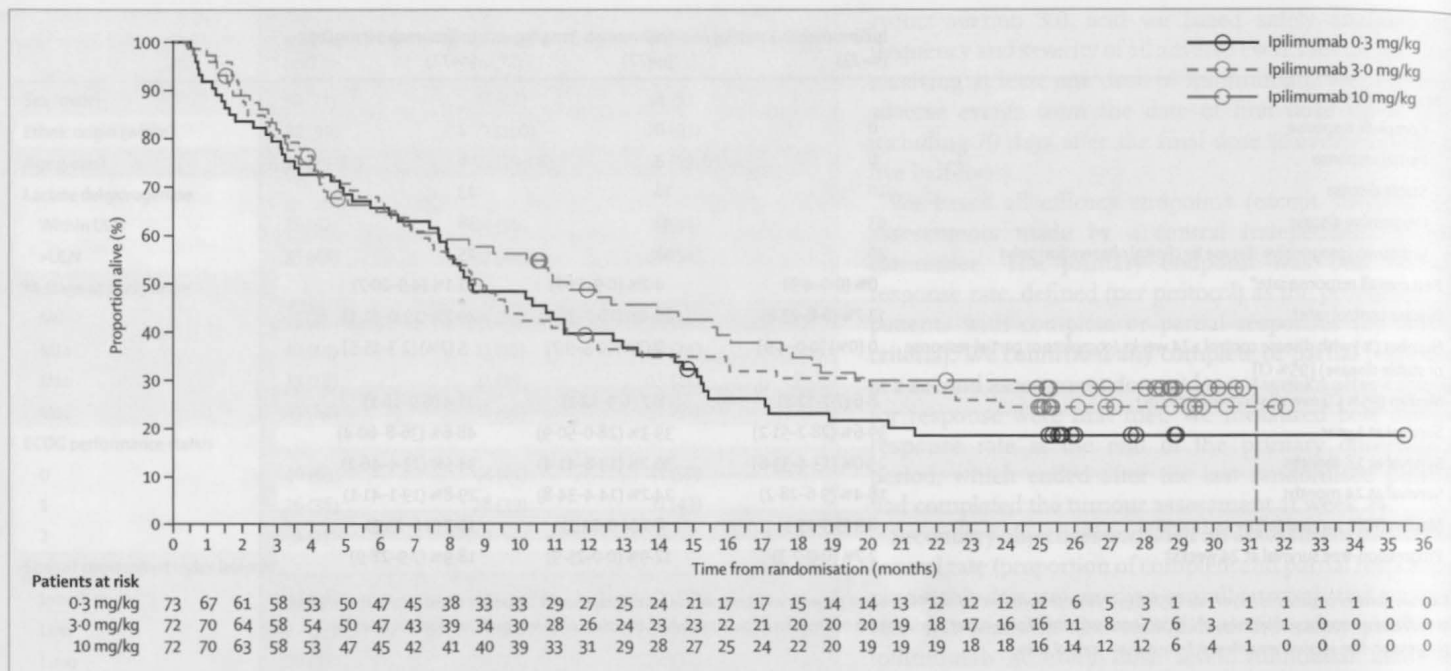


Figure 2: Kaplan-Meier estimate for overall survival, by treatment arm

	Ipilimumab 0.3 mg/kg (n=72)	Ipilimumab 3 mg/kg (n=71)	Ipilimumab 10 mg/kg (n=71)
Overall serious adverse events			
Total	26	35	38
Grade 5	15	14	15
Drug-related	6	13	19
Drug-related (grade 5)	0	0*	0
Adverse events leading to discontinuation			
Total	9	7	19
Drug-related (any grade)	2	5	11
Drug-related (grade 3-4)	2	4	9
Most frequent treatment-related adverse events†			
Diarrhoea			
Any grade	12	18	28
Grade 3-4	0	1	10
Nausea			
Any grade	11	13	17
Grade 3-4	0	0	1
Vomiting			
Any grade	6	5	10
Grade 3-4	0	1	0
Pruritus			
Any grade	2	15	23
Grade 3-4	0	1	2
Rash			
Any grade	3	17	16
Grade 3-4	0	1	0
Fatigue			
Any grade	16	12	16

(Continues on next page)

treatment (as a three-level factor) and days since first dose. We modelled the effect of days since first dose by linear splines with, for every patient, a knot at the day of every induction dose and interaction between treatment and the splines. For a skipped dose, we used the nominal days since first dose value (0, 21, 42, or 63) for placing a knot. We modelled within-individual correlations with a spatial exponential structure with Euclidean distance, and within-individual variances inversely proportional to the number of absolute lymphocyte counts on a given day. We did pharmacodynamic analyses and plotting with S-Plus 70.6 for Unix/Linux.

This study is registered with ClinicalTrials.gov, number NCT00289640.

Role of the funding source

This work was undertaken as part of a clinical trial programme for which Bristol-Myers Squibb served as the study sponsor and provided funding support. AH (Bristol-Myers Squibb) contributed to study design. KChin, KChen, and AH (Bristol-Myers Squibb) contributed to analysis and interpretation of data and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

284 patients were enrolled into the current study, and 217 were randomly allocated treatment between April 6, 2006 and Jan 24, 2007 (figure 1). The most frequent reason for screening failure was presence of a brain metastasis (32/67). Demographics and baseline

characteristics were consistent across treatment groups (table 1). All 217 patients who underwent random allocation had received previous systemic therapy, 213 in the metastatic setting. 90% (196/217) had received interleukin 2, dacarbazine, temozolomide, fotemustine, or a combination. 118 (54%) patients had received previous immunotherapy, including interferon (n=61; 28%), interleukin 2 (40; 18%), or an investigational immunotherapy (20; 9%).

Three individuals who underwent randomisation were not treated because they no longer met study criteria (n=2) or because they withdrew due to progressive disease (n=1). Thus, 214 patients were treated with ipilimumab (figure 1). In the induction phase, 36 of 71, 50 of 71, and 49 of 72 treated individuals received all four ipilimumab doses (10 mg/kg, 3 mg/kg, and 0.3 mg/kg, respectively). 20 of 214 patients received maintenance therapy during the current study (CA184-022); nine who did not receive maintenance dosing went directly into the maintenance phase in the separate companion study (CA184-025). 17 of 72, 26 of 72, and 23 of 73 patients from the 10 mg/kg, 3 mg/kg, and 0.3 mg/kg groups, respectively, progressed during this study and crossed over to the companion study for reinduction dosing at 10 mg/kg. Median follow-up was for 10.7 (IQR 3.6–20.4), 8.7 (4.0–20.4), and 8.3 (3.5–15.3) months for 10 mg/kg, 3 mg/kg, and 0.3 mg/kg groups, respectively.

Table 2 shows efficacy data for every treatment group. As the dose of ipilimumab increased, best overall response rate rose (p=0.0015, trend test). Survival data are presented in table 2 and figure 2. Hazard ratios for comparisons of median overall survival between groups were as follows: 10 mg/kg versus 0.3 mg/kg, 0.770 (95% CI 0.525–1.130); 10 mg/kg versus 3 mg/kg, 0.875 (0.593–1.291); and 3 mg/kg versus 0.3 mg/kg, 0.879 (0.604–1.279). Subgroup analyses of best overall response rate and overall survival, according to stratification criteria, were consistent with the main analyses (data not shown).

The webfigure shows a waterfall plot of peak change in total tumour burden, tracked by immune-related response criteria, by dose. Two patients allocated 10 mg/kg ipilimumab achieved a partial response (one confirmed) at week 15 after initial progressive disease (by WHO criteria) at week 12; these responses were not included in the estimation of the primary endpoint. One patient in the 3 mg/kg group achieved a reduction in total tumour burden after progressive disease. Stable disease followed by a slow steady decline in total tumour burden was noted in all three treatment groups.

Ipilimumab had a manageable safety profile at all three doses (table 3). The most frequently reported adverse events were immune-related; most of these were grade 1–2 and mainly affected the skin and gastrointestinal tract. The frequency of immune-related adverse events of any grade rose with increasing dose of ipilimumab. No grade 4 immune-related adverse events were recorded in any group and no grade 3–4 events were seen in patients

	Ipilimumab 0.3 mg/kg (n=72)	Ipilimumab 3 mg/kg (n=71)	Ipilimumab 10 mg/kg (n=71)
(Continued from previous page)			
Grade 3–4	1	1	2
Colitis			
Any grade	0	4	4
Grade 3–4	0	1	2
Immune-related adverse events†			
Any grade	19	46	50
Grade 3–4	0	5	18
Immune-related adverse events by area			
Gastrointestinal			
Any grade	12	23	28
Grade 3–4	0	2	11
Liver			
Any grade	0	0	2
Grade 3–4	0	0	2
Endocrine			
Any grade	0	4	3
Grade 3–4	0	2	1
Skin			
Any grade	9	32	33
Grade 3–4	0	1	3
Other			
Any grade	1	1	5
Grade 3–4	0	0	2‡

*One patient died because of grade 3 respiratory infection on day 51, within 30 days of last dose date. This event of death was not captured as a drug-related death in the clinical database before database lock (Nov 13, 2007); however, analysis of the internal safety database indicated the death and, according to the investigator, the event was possibly related to the study drug. †Present at 10% or higher at any grade for non-immune-related adverse events or 5% or higher at any grade for immune-related adverse events (diarrhoea, pruritus, rash, and colitis). ‡Scleritis (n=1) and pneumonitis (n=1).

Table 3: Safety results

allocated the 0.3 mg/kg dose. Overall, the incidence of serious immune-related adverse events was 5% or lower in all treatment groups, except for gastrointestinal immune-related adverse events in patients assigned the 10 mg/kg dose.

The most frequent reason for treatment discontinuation or death in all three groups was progressive disease. Table 3 shows the number of patients with drug-related adverse events leading to discontinuation. In the 0.3 mg/kg group, individuals who discontinued reported asthenia and bone pain (grade 3). In the 3 mg/kg group, enteritis (grade 2) and hypopituitarism, hydrocephalus, confusion, respiratory-tract infection, and diarrhoea (grade 3) were noted as reasons for stopping treatment. The most frequent (≥5%) drug-related adverse event leading to discontinuation with the 10 mg/kg dose was grade 3 diarrhoea (in six of nine patients).

One possible treatment-related death was recorded in the 3 mg/kg group (respiratory infection on day 51). No gastrointestinal perforation was reported, although one patient assigned the 10 mg/kg dose developed immune

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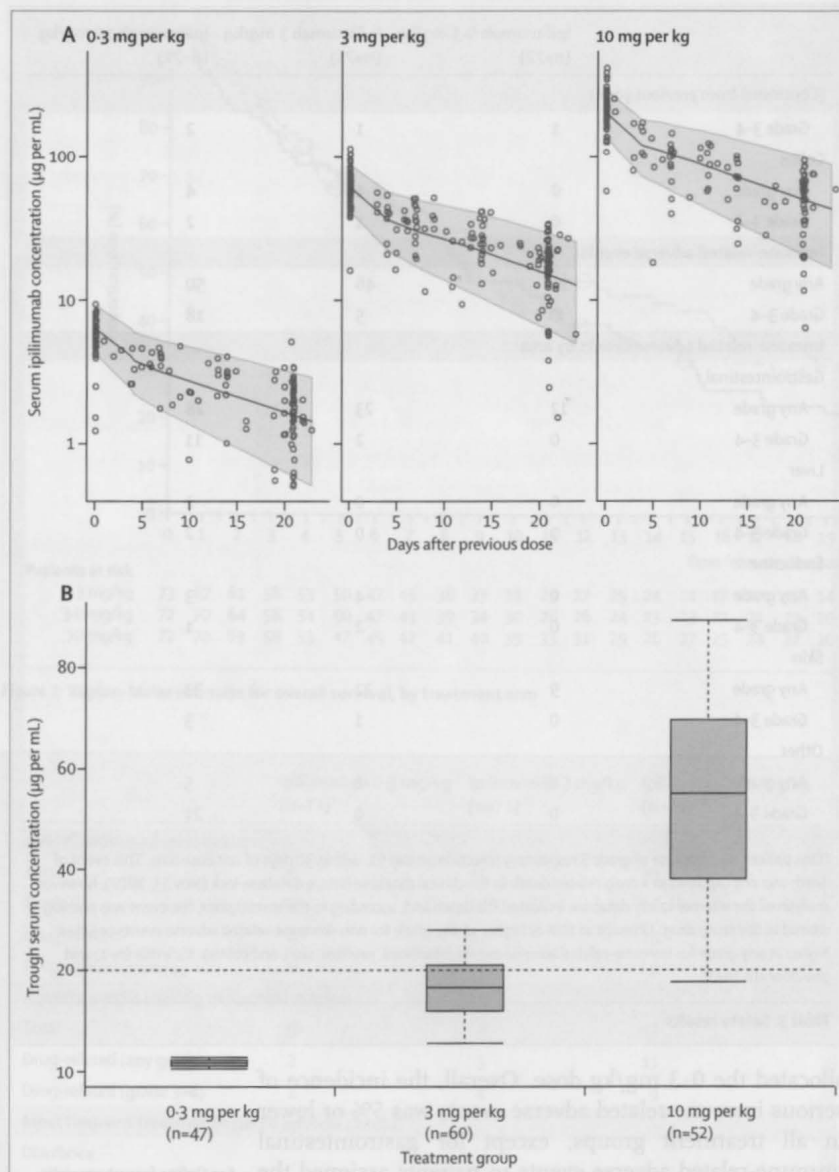


Figure 3: Concentrations of ipilimumab in serum, by treatment group

(A) Observed (circles) and predicted concentrations of ipilimumab versus time. Red line=median. Green shaded region=90% prediction interval. (B) Distribution of model-predicted C_{min} . Dashed line=target trough concentration. Box=median and interquartile range. Whiskers=5th and 95th percentiles. Analyses pertain to concentrations in the dose interval prior to the last induction dose.

colitis with gastrointestinal bleeding requiring colectomy. Diarrhoea and colitis (confirmed on biopsy) were, in general, managed effectively with oral or systemic steroids. Patients maintained their response to ipilimumab when treated with steroids, as reported in other studies.²⁹ In the 10 mg/kg group, grade 3–4 diarrhoea resolved or improved (to grade 1 or lower, or baseline grade) after a median of 4.4 weeks (95% CI 1.0–6.0) in all ten patients. Grade 3–4 immune-related adverse events of the liver (managed with steroids) and of the endocrine system (managed with steroids, hormone replacement therapy, or both) resolved or improved within 30 days of the last ipilimumab dose.

The population pharmacokinetic analysis of ipilimumab was characterised by a two-compartment model with zero-order intravenous infusion and first-order elimination. Parameters in the model were clearance, volume of central compartment, inter-compartmental clearance, and volume of peripheral compartment. Interindividual variability in clearance and volume of central compartment was represented by lognormal distributions and the residual error by a combined model (additive and proportional error). Analysis of covariate effects indicated that clearance rose with increase in baseline bodyweight and concentration of lactate dehydrogenase in serum, and volume of central compartment grew with increase in bodyweight. Other demographic and clinical covariates tested were not significant.

The final population pharmacokinetic analysis provided an adequate description of ipilimumab serum concentration–time profiles (figure 3A). Model-based simulation to assess achievement of the target trough concentration of 20 µg/mL before the fourth (and last) dose in the induction phase indicated that the target concentration was expected to be exceeded by about 95% of patients in the 10 mg/kg group, but by only 30% and 0% in the 3 mg/kg and 0.3 mg/kg groups, respectively (figure 3B). Moreover, ipilimumab at 10 mg/kg induced a greater mean rate of increase in absolute lymphocyte count than did the lower doses (figure 4).

Discussion

In the current study, ipilimumab monotherapy showed a dose-dependent effect on pharmacokinetic, biological, and clinical variables in patients with advanced melanoma. The primary endpoint (best overall response rate) was associated significantly with increasing dose of ipilimumab. This study was not designed to detect differences in survival between groups; however, favourable non-significant results were noted with the 10 mg/kg dose for both overall and progression-free survival, despite about a third of patients in the lower dosing groups crossing over to the 10 mg/kg group in the separate companion study (around 3 months after randomisation). Indeed, this crossover might have confounded survival differences between groups. Overall, our pharmacokinetic and pharmacodynamic data lend support to our clinical observations of superior CTLA4 target inhibition and lymphocyte activation at the highest ipilimumab dose and suggest that administration of ipilimumab at 10 mg/kg could be beneficial in an induction-maintenance regimen for patients with pretreated advanced melanoma.

The results of the current study are consistent with those of a single-arm phase 2 trial of 155 pretreated patients with advanced melanoma who were administered ipilimumab at 10 mg/kg. They showed a 1-year survival of 47.2% (95% CI 39.5–55.1) and a median overall survival of 10.2 months (7.6–16.3).¹⁴ The survival data

from both these trials are especially noteworthy in view of the poor outlook of the patients (eg, >50% had M1c stage disease) and since a raised lactate dehydrogenase concentration at baseline was not an exclusion criterion, as it is in many other studies. As a benchmark for ongoing and future studies, a meta-analysis of 42 phase 2 trials (which included 2100 untreated and pretreated patients with stage IV melanoma) recorded a median overall survival of 6.2 months and a 1-year survival of 25.5%;³⁰ multivariate analyses showed that Eastern Cooperative Oncology Group performance status, presence of visceral disease, sex, and brain metastases were significant prognostic factors for overall survival.³⁰ Our study excluded individuals with brain metastases, and all patients in the 10 mg/kg group had a performance status of 0 or 1; however, more than 60% were men and many had visceral disease, both of which are associated with short overall survival.³⁰ Overall, the results of our study support further investigations to establish if ipilimumab can extend survival in patients with advanced melanoma, both in those with good and poor prognostic factors.

New response patterns have been noted consistently in clinical studies with ipilimumab, which are captured by the immune-related response criteria, as shown by exploratory analyses of data from study CA184-008 and this current study.²⁴ These patterns include a response in the presence of new lesions and a decline in total tumour burden after progressive disease, as characterised by modified WHO criteria.²⁴ Stable disease is also commonly observed with ipilimumab therapy, which in some patients is followed by a slow, steady decline in total tumour burden.^{13,20,24} Most importantly, patients who achieve stable disease have a favourable survival outcome similar to individuals who achieve an objective response.²⁴ Stable disease was recorded in all three treatment groups in the current study, although the number of patients achieving clinical activity per immune-related response criteria were few. Capturing such responses might have been limited by the small size of the study and incomplete follow-up after progressive disease.

The overall adverse event profile of ipilimumab in this study is consistent with previous findings and with the drug's immune-based mechanism of action.¹³ Immune-related adverse events differ from adverse events typically reported with cytotoxic agents, and grade 3–4 immune-related events need swift medical attention to prevent life-threatening outcomes. A dose-dependent increase in immune-related adverse events of any grade was seen with increasing dose of ipilimumab; grade 3–4 events affected a quarter of patients in the 10 mg/kg group. Although no grade 3–4 immune-related adverse events were reported in the 0.3 mg/kg group, the appearance of mild-to-moderate immune-related events suggests a biological effect of ipilimumab that was sufficient to cause mild effects but insufficient to translate into an objective response.

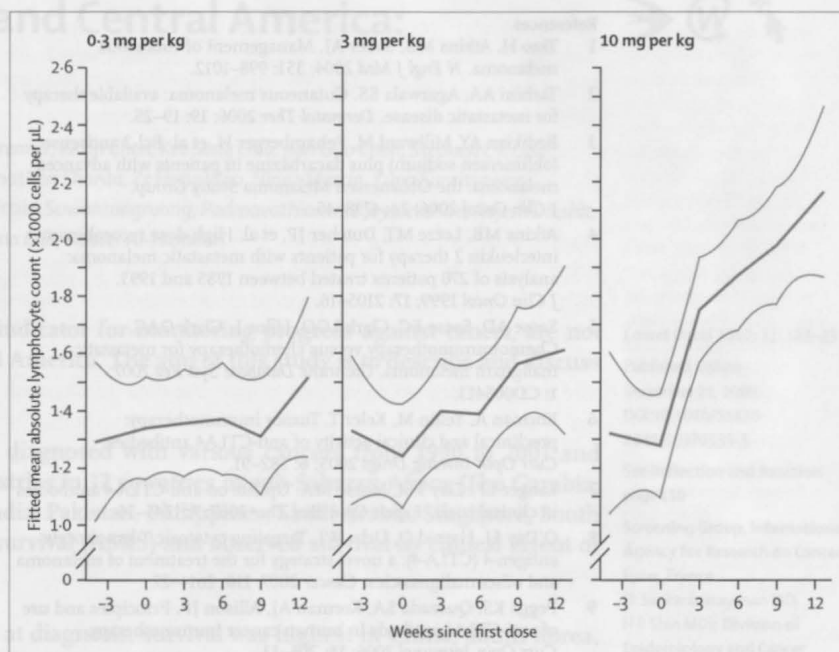


Figure 4: Fitted mean absolute lymphocyte count versus weeks since first dose, by treatment group. Datapoints include 4 weeks before baseline to the end of the induction dosing period. Thick curves=fitted means. Thin curves=pointwise two-sided 95% CI.

Most high-grade events could be managed medically with treatment guidelines included in the trial protocol, and they resolved or improved within about 4 weeks.³¹

Our results indicate that treatment with ipilimumab monotherapy at 10 mg/kg showed activity in heavily pretreated patients with advanced melanoma, with high-grade immune-related adverse events well managed with specific treatment guidelines. Further investigations of ipilimumab efficacy and safety at 10 mg/kg in patients with advanced melanoma are warranted. Ongoing studies include a phase 3 trial of ipilimumab (at 10 mg/kg) in combination with dacarbazine (at standard dosing) in treatment-naïve patients with unresectable stage III or IV melanoma.

Contributors

JDW, AH, and SO'D designed the study. BN, GL, JL, DS, MS, JC, KChin, KChen, AH, SO'D, and CL contributed to either analysis or interpretation of data, or both. All authors collected data and helped to write the report.

Conflicts of interest

All study sites and institutions received funding from Bristol-Myers Squibb to cover the expenses of the investigators for undertaking this trial. KChin, KChen, and AH are employed by Bristol-Myers Squibb and declare stock ownership in the company. JDW, JL, DS, MS, J-JG, SO'D, and CL have served as consultants for, acted on advisory boards, served on speakers bureau, or received honoraria from Bristol-Myers Squibb. JDW has acted as a consultant for Medarex. All other authors declared no conflicts of interest.

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References

- 1 Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med* 2004; **351**: 998–1012.
- 2 Tarhini AA, Agarwala SS. Cutaneous melanoma: available therapy for metastatic disease. *Dermatol Ther* 2006; **19**: 19–25.
- 3 Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; **24**: 4738–45.
- 4 Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999; **17**: 2105–16.
- 5 Sasse AD, Sasse EC, Clark LGO, Ulloa L, Clark OAC. Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma. *Cochrane Database Syst Rev* 2007; **1**: CD005413.
- 6 Korman A, Yellin M, Keler T. Tumor immunotherapy: preclinical and clinical activity of anti-CTLA4 antibodies. *Curr Opin Investig Drugs* 2005; **6**: 582–91.
- 7 Langer LF, Clay TM, Morse MA. Update on anti-CTLA-4 antibodies in clinical trials. *Expert Opin Biol Ther* 2007; **7**: 1245–56.
- 8 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.
- 9 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.
- 10 Fong L, Small EJ. Anti-cytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. *J Clin Oncol* 2008; **26**: 5275–83.
- 11 Kwon ED, Hurwitz AA, Foster BA, et al. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. *Proc Natl Acad Sci USA* 1997; **94**: 8099–103.
- 12 Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 1996; **271**: 1734–36.
- 13 Weber J. Ipilimumab: controversies in its development, utility and autoimmune adverse events. *Cancer Immunol Immunother* 2009; **58**: 823–30.
- 14 O'Day SJ, Ibrahim R, DePril V, et al. Efficacy and safety of ipilimumab induction and maintenance dosing in patients with advanced melanoma who progressed on one or more prior therapies. 2008 ASCO Annual Meeting; Chicago, IL, USA; May 30–June 3, 2008. Abstract 9021.
- 15 Hersh EM, Weber JS, Powderly JD, et al. Disease control and long-term survival in chemotherapy-naïve patients with advanced melanoma treated with ipilimumab (MDX-010) with or without dacarbazine. 2008 ASCO Annual Meeting; Chicago, IL, USA; May 30–June 3, 2008. Abstract 9022.
- 16 Downey SG, Klapper JA, Smith FO, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. *Clin Cancer Res* 2007; **13**: 6681–88.
- 17 Maker AV, Phan GQ, Attia P, et al. Tumor regression and autoimmunity in patients treated with cytotoxic T lymphocyte-associated antigen 4 blockade and interleukin 2: a phase I/II study. *Ann Surg Oncol* 2005; **12**: 1005–16.
- 18 Hodi FS, Mihm MC, Soiffer RJ, et al. Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastatic melanoma and ovarian carcinoma patients. *Proc Natl Acad Sci USA* 2003; **100**: 4712–17.
- 19 Phan GQ, Yang JC, Sherry RM, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. *Proc Natl Acad Sci USA* 2003; **100**: 8372–77.
- 20 Weber JS, O'Day S, Urba W, et al. Phase I/II study of ipilimumab for patients with metastatic melanoma. *J Clin Oncol* 2008; **26**: 5950–56.
- 21 Weber J, Thompson JA, Hamid O, 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**: 5591–98.
- 22 ClinicalTrials.gov. Study of ipilimumab (MDX-010) monotherapy in patients with previously treated unresectable stage III or IV melanoma. <http://clinicaltrials.gov/ct2/show/NCT00289640> (accessed Oct 23, 2009).
- 23 ClinicalTrials.gov. A companion study for patients enrolled in prior/parent ipilimumab studies. <http://clinicaltrials.gov/show/NCT00162123> (accessed Oct 23, 2009).
- 24 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related Response Criteria. *Clin Cancer Res* 2009; **15**: 7412–20.
- 25 Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934; **26**: 404–13.
- 26 Corcoran CD, Mehta CR. Exact level and power of permutation, bootstrap and asymptotic tests of trend. *J Mod Appl Stat Meth* 2002; **1**: 42–51.
- 27 Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics* 1982; **38**: 29–41.
- 28 ClinicalTrials.gov. Phase II study to determine predictive markers of response to BMS-734016 (MDX-010). <http://clinicaltrials.gov/show/NCT00261365> (accessed Nov 24, 2009).
- 29 Amin A, DePril V, Hamid O, et al. Evaluation of the effect of systemic corticosteroids for the treatment of immune-related adverse events (irAEs) on the development or maintenance of ipilimumab clinical activity. 2009 ASCO Annual Meeting; Orlando, FL, USA; May 29–June 2, 2009. Abstract 9037.
- 30 Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol* 2008; **26**: 527–34.
- 31 Lin R, Yellin MJ, Lowy I, Safferman A, Chin K, Ibrahim R. An analysis of the effectiveness of specific guidelines for the management of ipilimumab-mediated diarrhea/colitis: prevention of gastrointestinal perforation and/or colectomy. 2008 ASCO Annual Meeting; Chicago, IL, USA; May 30–June 3, 2008. Abstract 9063.