Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial

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Summary

Background A phase 2 trial suggested increased overall survival and increased incidence of treatment-related grade 3–4 adverse events with ipilimumab 10 mg/kg compared with ipilimumab 3 mg/kg in patients with advanced melanoma. We report a phase 3 trial comparing the benefit–risk profile of ipilimumab 10 mg/kg versus 3 mg/kg.

Methods This randomised, double-blind, multicentre, phase 3 trial was done in 87 centres in 21 countries worldwide. Patients with untreated or previously treated unresectable stage III or IV melanoma, without previous treatment with BRAF inhibitors or immune checkpoint inhibitors, were randomly assigned (1:1) with an interactive voice response system by the permuted block method using block size 4 to ipilimumab 10 mg/kg or 3 mg/kg, administered by intravenous infusion for 90 min every 3 weeks for four doses. Patients were stratified by metastasis stage, previous treatment for metastatic melanoma, and Eastern Cooperative Oncology Group performance status. The patients, investigators, and site staff were masked to treatment assignment. The primary endpoint was overall survival in the intention-to-treat population and safety was assessed in all patients who received at least one dose of study treatment. This study is completed and was registered with ClinicalTrials.gov, number NCT01515189.

Findings Between Feb 29, and July 9, 2012, 727 patients were enrolled and randomly assigned to ipilimumab 10 mg/kg (365 patients; 364 treated) or ipilimumab 3 mg/kg (362 patients; all treated). Median follow-up was 14·5 months (IQR 4·6–42·3) for the ipilimumab 10 mg/kg group and 11·2 months (4·9–29·4) for the ipilimumab 3 mg/kg group. Median overall survival was 15·7 months (95% CI 11·6–17·8) for ipilimumab 10 mg/kg compared with 11·5 months (9·9–13·3) for ipilimumab 3 mg/kg (hazard ratio 0·84, 95% CI 0·70–0·99; p=0·04). The most common grade 3–4 treatment-related adverse events were diarrhoea (37 [10%] of 364 patients in the 10 mg/kg group *vs* 21 [6%] of 362 patients in the 3 mg/kg group), colitis (19 [5%] *vs* nine [2%]), increased alanine aminotransferase (12 [3%] *vs* two [1%]), and hypophysitis (ten [3%] *vs* seven [2%]). Treatment-related serious adverse events were reported in 133 (37%) patients in the 10 mg/kg group and 66 (18%) patients in the 3 mg/kg group; four (1%) versus two (<1%) patients died from treatment-related adverse events.

Interpretation In patients with advanced melanoma, ipilimumab 10 mg/kg resulted in significantly longer overall survival than did ipilimumab 3 mg/kg, but with increased treatment-related adverse events. Although the treatment landscape for advanced melanoma has changed since this study was initiated, the clinical use of ipilimumab in refractory patients with unmet medical needs could warrant further assessment.

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Introduction

The enhancement of antitumour immunity through blockade of immune checkpoint molecules has led to a substantial survival advantage in patients with metastatic melanoma compared with patients given previously available treatments. Ipilimumab is a fully human immunoglobulin G1 monoclonal antibody designed to block CTLA-4.[1] Ipilimumab was the first therapy to show an improvement in overall survival of patients with metastatic melanoma in a randomised, controlled phase 3 trial. It has a manageable safety profile as monotherapy at both 3 mg/kg in previously treated patients[2] and 10 mg/kg in combination with dacarbazine in treatment-naive patients.[3] A 5-year survival benefit has been seen with ipilimumab 10 mg/kg plus dacarbazine in a phase 3 trial.[4] Additionally, a pooled analysis of prospective and retrospective trials in patients with advanced melanoma who were followed up for 10 years, which includes this 5-year dacarbazine trial, showed durable long-term survival in more than 20% of patients, with a plateau around year 3.[5] Ipilimumab at a dose of 3 mg/kg is approved in several countries for the treatment of unresectable or metastatic melanoma and a dose of 10 mg/kg is approved in the USA as an adjuvant treatment for resected stage III melanoma.

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Research in context

Evidence before this study

To identify other studies of ipilimumab in melanoma, we searched PubMed and congress abstracts from the annual meetings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the Society for Melanoma Research for articles published in English between Jan 1, 2010, and July 31, 2016. Our search terms included "ipilimumab", "anti-CTLA-4", "BMS-734016", "MDX-010", and "MDX-101". We focused on survival results in melanoma. Ipilimumab was the first drug to show a survival improvement in patients with metastatic melanoma in a randomised controlled phase 3 trial. Together, efficacy data across phase 2 and phase 3 studies show an overall survival benefit for both 3 mg/kg and 10 mg/kg doses of ipilimumab compared with controls. Additional data from a dose-ranging phase 2 study suggest longer survival with the 10 mg/kg dose than with lower doses. No studies done so far permit conclusive comparison of ipilimumab 10 mg/kg with ipilimumab 3 mg/kg.

Added value of this study

When the two doses of ipilimumab were directly compared in this study, overall survival was significantly improved with the 10 mg/kg dose compared with the 3 mg/kg dose, whereas the 3 mg/kg dose had a more favourable safety profile and a survival benefit consistent with that seen in other ipilimumab 3 mg/kg studies in advanced melanoma. Quality of life generally worsened during the ipilimumab induction phase treatment, and this worsening seemed to be more pronounced with 10 mg/kg compared with 3 mg/kg. However, insufficient duration of follow-up prevents conclusions to be drawn regarding the long-term effect of ipilimumab on quality of life.

Implications of all the available evidence

The treatment landscape for first-line treatment of patients with advanced melanoma has changed since this study was initiated, with ipilimumab being succeeded by newer treatments. However, the increased survival benefit of ipilimumab 10 mg/kg compared with 3 mg/kg suggests that the clinical utility of ipilimumab in refractory patients with high unmet medical need could warrant further assessment.

A randomised, phase 2, dose-ranging study of ipilimumab at 0·3 mg/kg, 3 mg/kg, and 10 mg/kg in patients with previously treated metastatic melanoma reported an improvement in best overall response with an increased ipilimumab dose, although with a higher frequency of immune-related adverse events.[6] The study was not designed to detect statistical differences in survival between the groups, but reported an improved median overall survival and 1-year overall survival at 10 mg/kg compared with lower doses, although crossover to 10 mg/kg was permitted for the lower doses.

Together, efficacy data across phase 2 and phase 3 studies show increased overall survival for patients treated with either 3 mg/kg or 10 mg/kg doses of ipilimumab compared with controls. However, no studies done so far permit conclusive comparison of these two doses. To further investigate the benefit of higher-dose ipilimumab in stage III unresectable or stage IV melanoma, we report survival outcomes from a comparison of ipilimumab 10 mg/kg with ipilimumab 3 mg/kg in a phase 3 trial.

Methods

Study design and patients

This was a randomised, double-blind, multicentre, phase 3 study done in 87 centres in 21 countries worldwide (appendix pp 13–14), with the largest proportion of participants from Europe. Eligible patients had treated or untreated histologically or cytologically confirmed unresectable stage III or IV melanoma (advanced melanoma) and no previous therapy with BRAF inhibitors, CTLA-4 or PD-1 antagonists, or PD-L1 or CD137 agonists. Other melanoma treatments were permitted with a washout period of 4 weeks for all previous anticancer therapy and at least 2 years for systemic immunosuppressive drugs, except for episodic low-dose corticosteroids. Disease progression was based on recommendation of the enrolling physician. Other eligibility criteria included an age of at least 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and measurable disease based on modified WHO criteria within 28 days of first dose. Laboratory testing required for study entry included baseline DNA samples from peripheral blood for testing of CD86 and CTLA-4 polymorphisms and genome-wide association analysis for immune-related adverse events, and testing for adequate haematological, renal, and hepatic function. Key exclusion criteria were the presence of brain metastases with symptoms or requiring treatment; a diagnosis of primary ocular melanoma; a history of autoimmune disease; uncontrolled infectious disease, any immunodeficiency disease, splenectomy, or splenic irradiation; or previous allogeneic stem cell transplantation.

The study protocol and the statistical analysis plan are available in the appendix. The institutional review board at each study site approved the study protocol. The study was done in accordance with Good Clinical Practice, as defined by the International Conference on Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50. All patients provided informed written consent.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1) to treatment with ipilimumab at a dose of 10 mg/kg or 3 mg/kg by use of an interactive voice response system. To be enrolled in the system, the following information was required: date of birth, date of signed informed consent, sex, metastasis (M) substage, yes or no for previous treatment of metastatic melanoma, and ECOG performance status. Randomisation was done by the permutated block method using block size 4 and was stratified by M substage (M0/M1a/M1b *vs* M1c without brain metastases *vs* M1c with brain metastases), previous treatment for metastatic melanoma (yes *vs* no), and ECOG performance status (0 *vs* 1). After completion of all screening evaluations, an unmasked pharmacist called the interactive voice response system to obtain treatment assignment and an unmasked site monitor provided oversight of drug supply and other unmasked study documentation. The funder, patients, investigators, and site staff remained masked to treatment assignment. An independent data monitoring committee was unmasked to review emerging safety data.

Procedures

In both 10 mg/kg and 3 mg/kg dose groups, ipilimumab was administered by intravenous infusion for 90 min every 3 weeks for four doses. Treatment was continued for a maximum of four doses during the initial treatment phase until confirmed progression defined by immune-related response criteria,[7,8] unacceptable toxicity, or withdrawal of consent. In the absence of intolerable toxicity, patients who had stable disease for 3 months or more, or a partial or complete response after the last dose, and then progressed per immune-related response criteria, were eligible for retreatment with the study drug per the original randomisation and dose scheme. We assessed all response-based endpoints using modified WHO criteria, consistent with previous ipilimumab studies.[2,3] Tumour response was based on investigator assessment, which was done during the initial treatment phase at screening, at weeks 12, 16, and 24, and every 12 weeks thereafter, and was done for confirmation of response and progression, including new lesions. However, because ipilimumab can induce responses that occur after initial tumour volume increase or appearance of new lesions, discontinuation criteria were based on immune-related response criteria that address unconventional response patterns to ensure patients were not prematurely discontinued.[7,8]

We did safety evaluations in patients who had received at least one dose of study treatment, and graded severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[9] The funder provided guidelines for management of adverse events, which have been published.[10–12] We did not allow crossover or reduction of ipilimumab dose. Study dose could be delayed for non-skin-related, treatment-related adverse events that were higher than grade 2; grade 3 or higher laboratory abnormality; skin-related, any-cause adverse events that were grade 3 or higher; or an adverse event warranting delay by the judgment of the investigator. Laboratory monitoring included haematology, chemistry, C-reactive protein, endocrine, and pharmacokinetic or anti-drug antibody testing, and occurred at weeks 1, 4, 7, 10, 12, and 24 and at the end-of-treatment visit, except for endocrine testing, which occurred at weeks 1, 4, 7, 10, and 12. *BRAF* mutation testing was done locally per local regulations and standards.

We collected health-related quality-of-life (HRQoL) questionnaire data, as available, in all patients randomly assigned, at weeks 1, 4, 7, 10, and 12, and at the end-of-treatment visit. Assessment of HRQoL was done at each site with the appropriately translated and validated version

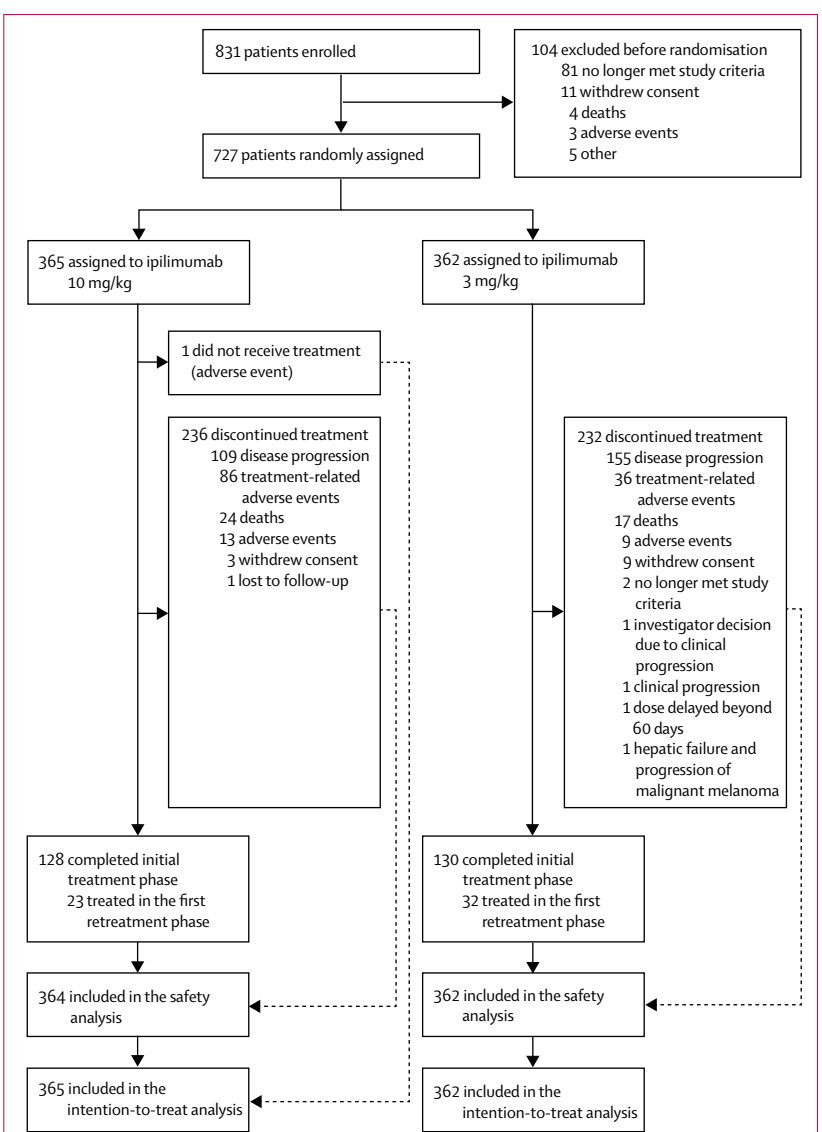

Figure 1: **Trial profile**

	Ipilimumab 10 mg/kg (n=365)	Ipilimumab 3 mg/kg (n=362)
Age (years)	62 (49–70)	62 (51–71)
<65	224 (61%)	208 (57%)
≥65	141 (39%)	154 (43%)
Sex		
Male	219 (60%)	231 (64%)
Female	146 (40%)	131 (36%)
Race		
White	361 (99%)	359 (99%)
Black or African American	1 (<1%)	1 (<1%)
Asian	2 (1%)	1 (<1%)
Other	1 (<1%)	1 (<1%)
ECOG PS		
0	262 (72%)	253 (70%)
1	103 (28%)	109 (30%)
M stage		
M0, M1a, or M1b	136 (37%)	142 (39%)
M1c without brain metastases	164 (45%)	158 (44%)
M1c with brain metastases	65 (18%)	62 (17%)
Previous treatment for melanoma		
Yes	205 (56%)	205 (57%)
No	160 (44%)	157 (43%)
Previous therapy		
Any previous systemic therapy*	206† (56%)	205 (57%)
Any previous radiotherapy	107 (29%)	96 (27%)
Any previous surgery	359 (98%)	346 (96%)
Lactate dehydrogenase		
≤ULN	222 (61%)	219 (60%)
>ULN	133 (36%)	136 (38%)
≤2 × ULN	321 (88%)	306 (85%)
>2 × ULN	34 (9%)	49 (14%)
Not reported	10 (3%)	7 (2%)
AJCC disease stage		
III	35 (10%)	35 (10%)
IV	330 (90%)	327 (90%)
BRAF status		
Mutation, V600	75 (21%)	75 (21%)
Mutation, other	5 (1%)	4 (1%)
No mutation	225 (62%)	237 (65%)
Unknown	60 (16%)	46 (13%)

Data are median (IQR) or n (%). ECOG PS=Eastern Cooperative Oncology Group performance status. ULN=upper limit of normal. AJCC=American Joint Committee on Cancer. *No patients received previous therapy with a BRAF inhibitor, CTLA-4 or PD-1 antagonists, or PD-L1 or CD137 agonists. †One patient had an unknown antineoplastic therapy with an unknown start date and missing end date on the survival follow-up case report form; we therefore listed the therapy as a previous systemic therapy (because we did not know that it was not a previous therapy), but not as a previous melanoma therapy (because it was not collected on the previous systemic therapy case report form).

Table 1: **Baseline characteristics**

of the questionnaires. Assessments were done using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire version 3[13] and the European Quality of Life 5 Dimensions (EQ-5D) summary index and visual analogue scale (VAS).[14]

EORTC QLQ-C30 is a 30-item, self-administered, multidimensional, cancer-specific HRQoL patient-reported outcome questionnaire.[13] A difference of 10 points on a 100-point scale was regarded as clinically significant, as is common in clinical trials in which sample size is not based on the HRQoL endpoint.[15]

The EQ-5D is a standardised measure of health status developed by the EuroQoL Group and provides a generic measure of health for clinical and economic appraisal.[14] The EQ-5D consists of a descriptive system comprising the five dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, and the EQ-5D VAS records the respondent's self-rated health on a vertical VAS. Score differences of 0·08 for the EQ-5D utility index score and 7 for the EQ-5D VAS were regarded as clinically significant.[16]

Outcomes

Overall survival was the primary endpoint, defined as the time between randomisation date and death, assessed at a minimum of every 12 weeks, censored at the last date the participant was known to be alive.

Secondary endpoints were progression-free survival defined as the time between randomisation date and the date of progression or death, whichever occurred first; objective response and disease control as per modified WHO criteria; duration of response and stable disease by modified WHO criteria; overall survival on a yearly basis for up to 5 years; and overall survival in the subset of patients with asymptomatic brain metastases. Additional secondary endpoints were evaluation of safety for both dose groups and HRQoL.

Statistical analysis

A study sample of 700 patients was planned for the primary endpoint of overall survival to obtain the 540 events necessary to detect an overall hazard ratio (HR) of 0·744 between the two randomised groups using a two-sided, log-rank test with an experiment-wise type I error of 0·05 with at least 90% power. An interim analysis for overall survival was originally planned at about 67% (360 deaths) of the total events. However, as a result of the faster than expected enrolment of less than 5 months, the projected interim analysis would have had a follow-up period of less than 18 months. Therefore, the protocol was amended on June 24, 2013, to remove the interim analysis and wait for the planned final analysis with a survival follow-up of at least 2 years.

For the primary endpoint (overall survival) and secondary endpoint (progression-free survival), a log-rank test compared randomised groups according to stratification factors, with HR and its associated 95% CI estimated using a stratified Cox model with randomised group as the only covariate. In both analyses, we estimated the event-free survival probabilities with the Kaplan-Meier

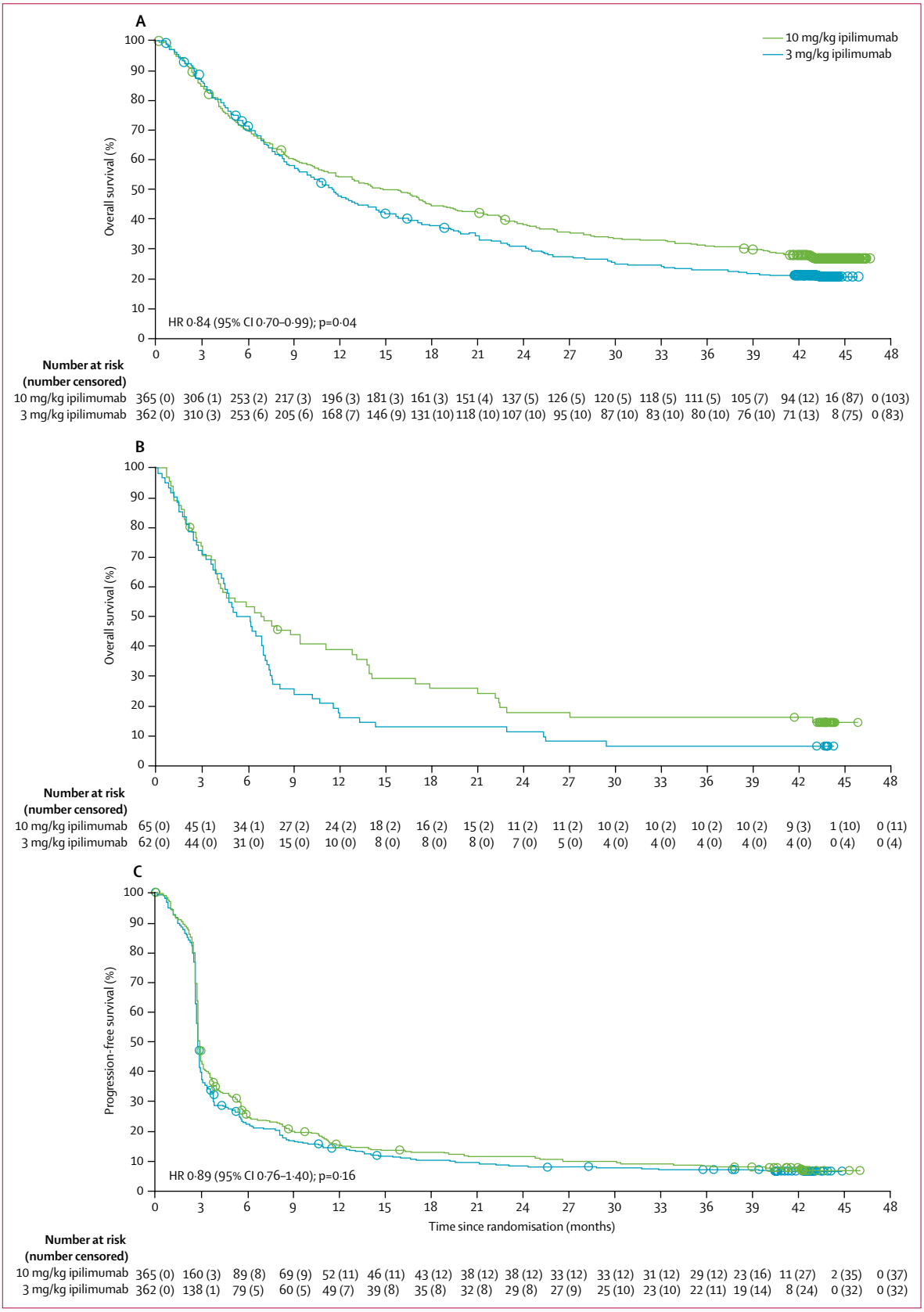

Figure 2: **Overall survival and progression-free survival**
(A) Overall survival in the intention-to-treat population. (B) Overall survival in patients with asymptomatic brain metastases at baseline. (C) Progression-free survival by modified WHO criteria in the intention-to-treat population. HR=hazard ratio.

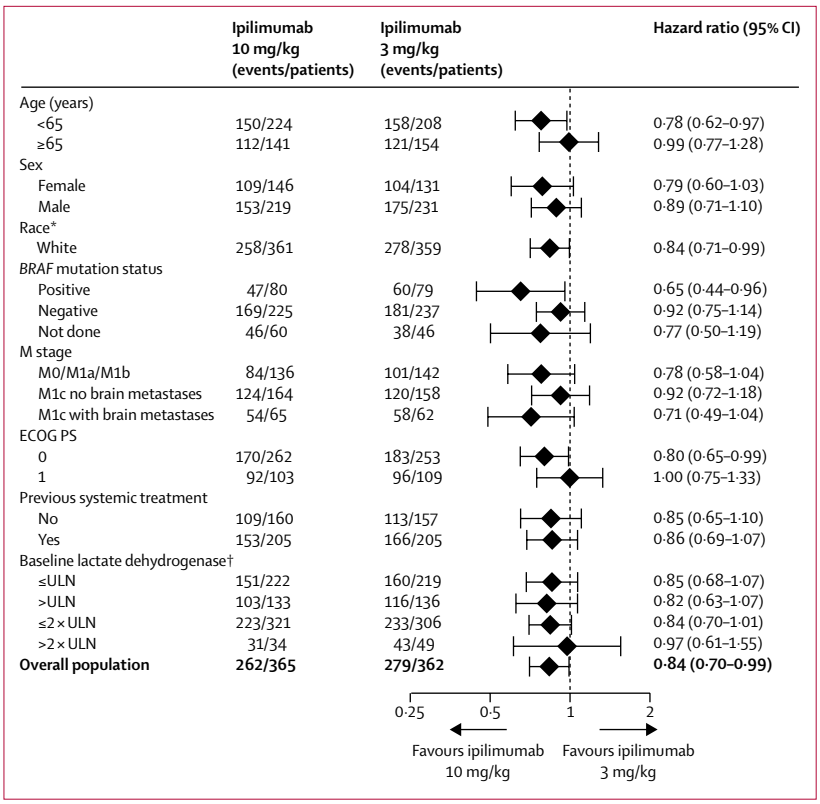

***Figure 3*: Subgroup analyses of overall survival**

Overall survival in prespecified subgroups of patients who received ipilimumab 10 mg/kg *vs* 3 mg/kg. ECOG PS=Eastern Cooperative Oncology Group performance status. ULN=upper limit of normal. *The number of non-white patients (two black or African American, three Asian, and three other) were too small to allow a clinically meaningful comparison. †Baseline lactate dehydrogenase was not reported in ten patients in the 10 mg/kg group (n=355) and seven patients in the 3 mg/kg group (n=355).

	Ipilimumab 10 mg/kg (n=365)	Ipilimumab 3 mg/kg (n=362)
Best overall response*		
Complete response	8 (2%)	9 (2%)
Partial response	48 (13%)	35 (10%)
Stable disease	59 (16%)	57 (16%)
Progressive disease	170 (47%)	189 (52%)
Not evaluable†	69 (19%)	60 (17%)
Not reported	11 (3%)	12 (3%)
Objective response‡		
Number of patients (% [95% CI])	56 (15% [11·8–19·5])	44 (12% [9·0–16·0])
Median duration of response, months (95% CI)	16·3 (6·0–24·0)	15·9 (10·4–NR)
Disease control§		
Number of patients (% [95% CI])	115 (32% [26·8–36·5])	101 (28% [23·3–32·8])

Data are n (%) unless stated otherwise. NR=not reached. *Best overall response was assessed by the investigator with the use of modified WHO criteria; responses are based only on assessments taken during the initial treatment phase and first progression follow-up phase. †Includes death before disease assessment (47 [13%] *vs* 43 [12%]), early discontinuation due to toxicity (eight [2%] *vs* three [1%]), never treated (one [<1%] *vs* 0), and other (13 [4%] *vs* 14 [4%]). ‡Data include patients with a complete response or partial response. §Data include patients with a complete response, partial response, or stable disease.

***Table 2*: Response to treatment**

method and calculated estimates of median and corresponding 95% CI with the Brookmeyer and Crowley method.[17] We based yearly rates for overall survival on Kaplan-Meier estimates along with corresponding log–log transformed 95% CI.[18] We did two sensitivity analyses for overall survival: one as an unstratified analysis and one in which we censored for subsequent cancer therapy. Additionally, we did subgroup analyses for overall survival including the prespecified subgroups of age, race, sex, M stage, ECOG performance status, previous treatment for melanoma, and baseline lactate dehydrogenase, as well as *BRAF* mutation status, which, although not a prespecified subgroup in the protocol, was generated before database lock. We analysed descriptive statistics for HRQoL endpoints at baseline for all patients with baseline measurements, and for change from baseline for all patients with both baseline and on-study assessment for a particular timepoint; mean change from baseline and 95% CI for each timepoint were plotted for each scale.

To preserve a type I error rate of 5%, a hierarchical testing approach was applied in the following order: overall survival, progression-free survival, objective response, and disease control. A superiority claim could be made for a given endpoint only if all preceding endpoint comparisons in the hierarchy were shown to be statistically significant.

Efficacy, response, and HRQoL analyses were based on the randomised, intention-to-treat population. We did safety assessments for all patients who received at least one dose of study treatment. In general, missing values were not imputed, except for EORTC QLQ-C30, in which missing values for missing items were imputed by assuming that the missing items had values equal to the average of the items that were present for any scale in which at least half of the items were completed (method from the scoring manual). Irrespective of missing data, all participants contributed to the calculation of the following tumour response endpoints: best overall response or disease control (by inclusion in the denominators), and the Kaplan-Meier analyses of duration of response, duration of stable disease, and progression-free survival (by censoring, as appropriate). A data and safety monitoring committee was established to provide general oversight. All statistical analyses were done with SAS version 9.3 and 9.4.

This study is registered with ClinicalTrials.gov number, NCT01515189.

Role of the funding source

This study was designed by the funder. Data were collected by the investigators and analysed by the funder in collaboration with all authors. Data were interpreted jointly by the funder and the authors. Writing and editorial support were funded by the funder of the study.

All authors had access to the data and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Feb 29, and July 9, 2012, we enrolled 831 patients. 727 patients were randomly assigned to treatment and included in the intention-to-treat population for efficacy: 365 to the 10 mg/kg group and 362 to the 3 mg/kg group (figure 1). One patient in the 10 mg/kg group was not treated due to an adverse event and therefore the safety analysis consisted of 364 patients for the 10 mg/kg group and 362 patients for the 3 mg/kg group. Baseline characteristics were balanced between the two dose groups (table 1). Baseline characteristics were also generally balanced between the 80 (22%) patients in the 10 mg/kg group and the 79 (22%) patients in the 3 mg/kg group with *BRAF* mutation-positive tumours (appendix p 2).

The database lock occurred on March 18, 2016, after trial completion. At a minimum follow-up of 43 months, the median number of doses of ipilimumab received per patient in the initial treatment phase was 4·0 (IQR 3·0–4·0) in the 10 mg/kg group, with 212 (58%) of 364 patients completing all four doses, and 4·0 (3·0–4·0) in the 3 mg/kg group, with 241 (67%) of 362 patients completing all four doses. At database lock, 23 (6%) of 364 patients in the 10 mg/kg group and 32 (9%) of 362 patients in the 3 mg/kg group entered the first retreatment phase. In the initial treatment phase, the most common reason for discontinuation in both groups was disease progression, followed by treatment-related adverse events. Discontinuation due to disease progression was lower in the 10 mg/kg group (109 [30%] of 364 patients) than in the 3 mg/kg group (155 [43%] of 362 patients), whereas discontinuation due to treatment-related adverse events was higher in the 10 mg/kg group (86 [24%] of 364 patients) than in the 3 mg/kg group (36 [10%] of 362 patients; figure 1, appendix p 3).

Subsequent systemic therapy was received by 131 (36%) of 365 patients in the 10 mg/kg group (including subsequent immunotherapy in 57 [16%] and subsequent targeted therapy in 37 [10%]) and by 136 (38%) of 362 patients in the 3 mg/kg group (including subsequent immunotherapy in 51 [14%] patients and subsequent targeted therapy in 47 [13%]; appendix p 4). A similar proportion of patients with *BRAF* mutation-positive tumours received subsequent therapy in both dose groups (43 [54%] of 80 patients in the 10 mg/kg group *vs* 47 [59%] of 79 patients in the 3 mg/kg group), although more patients in the 10 mg/kg group than in the 3 mg/kg group received subsequent anti-PD-1 therapy (15 [19%] *vs* eight [10%]; appendix p 5). Median time from randomisation to first subsequent therapy was 216 days (IQR 141–371) for the 10 mg/kg group and 190 days (134–360) for the 3 mg/kg group.

For overall survival, median follow-up was 14·5 months (IQR 4·6–42·3) for the 10 mg/kg group and 11·2 months

	Ipilimumab 10 mg/kg (n=364)			Ipilimumab 3 mg/kg (n=362)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	162 (45%)	99 (27%)	25 (7%)	162 (45%)	57 (16%)	9 (2%)
Rash	90 (25%)	5 (1%)	0	48 (13%)	2 (1%)	0
Pruritus	80 (22%)	2 (1%)	0	79 (22%)	2 (1%)	0
Pruritic rash	5 (1%)	0	0	3 (1%)	1 (<1%)	0
Maculopapular rash	3 (1%)	1 (<1%)	0	4 (1%)	0	0
Erythema nodosum	0	0	0	0	1 (<1%)	0
Toxic skin eruption	1 (<1%)	0	0	0	1 (<1%)	0
Diarrhoea	99 (27%)	36 (10%)	1 (<1%)	63 (17%)	21 (6%)	0
Colitis	16 (4%)	18 (5%)	1 (<1%)	10 (3%)	9 (2%)	0
Nausea	19 (5%)	1 (<1%)	0	25 (7%)	0	0
Vomiting	14 (4%)	2 (1%)	0	11 (3%)	0	0
Abdominal pain	12 (3%)	1 (<1%)	0	9 (2%)	0	0
Autoimmune colitis	0	3 (1%)	0	1 (<1%)	3 (1%)	1 (<1%)
Constipation	1 (<1%)	0	0	4 (1%)	1 (<1%)	0
Rectal haemorrhage	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0
Lower abdominal pain	0	0	0	0	1 (<1%)	0
Ulcerative colitis	0	2 (1%)	0	0	0	0
Gastrointestinal pain	0	1 (<1%)	0	0	0	0
Gastrointestinal perforation	0	0	0	0	0	1 (<1%)
Large intestine perforation	0	1 (<1%)	0	0	0	0
Small intestinal perforation	0	0	0	0	0	1 (<1%)
Small intestinal obstruction	0	1 (<1%)	0	0	0	0
Fatigue	38 (10%)	3 (1%)	0	30 (8%)	3 (1%)	0
Asthenia	27 (7%)	4 (1%)	0	17 (5%)	1 (<1%)	0
Pyrexia	22 (6%)	1 (<1%)	0	18 (5%)	0	0
General physical health deterioration	0	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)
Influenza-like illness	1 (<1%)	1 (<1%)	0	3 (1%)	0	0
Increased alanine aminotransferase	15 (4%)	9 (2%)	3 (1%)	2 (1%)	1 (<1%)	1 (<1%)
Increased aspartate aminotransferase	16 (4%)	6 (2%)	2 (1%)	2 (1%)	1 (<1%)	0
Decreased weight	11 (3%)	1 (<1%)	0	5 (1%)	0	0
Increased transaminases	2 (1%)	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	0
Increased gamma-glutamyltransferase	2 (1%)	2 (1%)	0	1 (<1%)	1 (<1%)	1 (<1%)
Increased blood alkaline phosphatase	2 (1%)	0	0	1 (<1%)	1 (<1%)	0
Increased hepatic enzyme	2 (1%)	1 (<1%)	0	0	0	0
Abnormal liver function test	0	1 (<1%)	1 (<1%)	0	0	0
Abnormal alanine aminotransferase	0	1 (<1%)	0	0	0	0
Increased amylase	0	1 (<1%)	0	0	0	0
Abnormal gamma-glutamyltransferase	0	1 (<1%)	0	0	0	0
Increased lipase	0	0	1 (<1%)	0	0	0
Decreased neutrophil count	0	0	1 (<1%)	0	0	0
Hypophysitis	14 (4%)	9 (2%)	1 (<1%)	5 (1%)	4 (1%)	3 (1%)
Hypopituitarism	4 (1%)	4 (1%)	0	3 (1%)	1 (<1%)	0
Hypothyroidism	7 (2%)	1 (<1%)	0	7 (2%)	0	0
Thyroiditis	4 (1%)	1 (<1%)	0	2 (1%)	0	0
Adrenal insufficiency	1 (<1%)	1 (<1%)	0	5 (1%)	0	0

(Table 3 continues on next page)

	Ipilimumab 10 mg/kg (n=364)			Ipilimumab 3 mg/kg (n=362)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Adrenocorticotropic hormone deficiency	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0
Acute adrenocortical insufficiency	0	1 (<1%)	0	0	0	1 (<1%)
Lymphocytic hypophysitis	0	1 (<1%)	0	1 (<1%)	0	0
Thyrotoxic crisis	0	0	0	0	0	1 (<1%)
Hypothalamo-pituitary disorder	0	0	0	0	1 (<1%)	0
Headache	17 (5%)	3 (1%)	1 (<1%)	16 (4%)	0	0
Guillain-Barré syndrome	0	2 (1%)	0	0	0	0
Peripheral sensory neuropathy	0	2 (1%)	0	0	0	0
Peripheral motor neuropathy	0	1 (<1%)	0	0	0	0
VIIth nerve paralysis	0	1 (<1%)	0	0	0	0
Decreased appetite	11 (3%)	3 (1%)	0	14 (4%)	1 (<1%)	0
Dehydration	2 (1%)	3 (1%)	0	1 (<1%)	0	0
Hyperglycaemia	0	1 (<1%)	0	0	0	0
Hyperlipasaemia	0	0	1 (<1%)	0	0	0
Hyponatraemia	0	0	1 (<1%)	0	2 (1%)	0
Hypophosphataemia	0	1 (<1%)	0	0	0	0
Arthralgia	8 (2%)	0	0	5 (1%)	2 (1%)	0
Polymyalgia rheumatica	0	0	0	1 (<1%)	1 (<1%)	0
Uveitis	0	0	0	0	1 (<1%)	0
Cytomegalovirus colitis	0	0	0	0	1 (<1%)	0
Erysipelas	0	0	0	0	1 (<1%)	0
Peritonitis	0	0	0	0	0	1 (<1%)
Hepatitis	0	4 (1%)	1 (<1%)	0	2 (1%)	0
Hepatocellular injury	1 (<1%)	2 (1%)	2 (1%)	1 (<1%)	0	0
Autoimmune hepatitis	0	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)	0
Hepatotoxicity	0	2 (1%)	1 (<1%)	0	2 (1%)	0
Hyperbilirubinaemia	0	0	0	0	1 (<1%)	0
Acute hepatic failure	0	0	1 (<1%)	0	0	0
Acute hepatitis	0	0	1 (<1%)	0	0	0
Hypersensitivity	10 (3%)	3 (1%)	0	1 (<1%)	0	0
Infection	0	1 (<1%)	0	0	0	0
Dyspnoea	2 (1%)	2 (1%)	0	0	0	0
Pneumonitis	0	3 (1%)	1 (<1%)	0	0	0
Hypertension	0	1 (<1%)	0	0	0	0
Anaemia	1 (<1%)	1 (<1%)	0	3 (1%)	2 (1%)	0
Febrile neutropenia	0	1 (<1%)	1 (<1%)	0	0	0
Bicytopenia	0	1 (<1%)	0	0	0	0
Pancytopenia	0	1 (<1%)	0	0	0	0
Thrombocytopenia	0	0	1 (<1%)	0	0	0
Renal failure	1 (<1%)	0	1 (<1%)	0	0	0
Cardiac arrest	0	0	1 (<1%)	0	0	0
Pericarditis	0	1 (<1%)	0	0	0	0

(Table 3 continues on next page)

(4·9–29·4) for the 3 mg/kg group. In the intention-to-treat population, 541 patients died during the study (262 [72%] of 365 patients in the 10 mg/kg group *vs* 279 [77%] of 362 in the 3 mg/kg group). Median overall survival was 15·7 months (95% CI 11·6–17·8) in the ipilimumab 10 mg/kg group and 11·5 months (9·9–13·3) in the 3 mg/kg group (HR 0·84, 95% CI 0·70–0·99; p=0·04; figure 2A). 1-year overall survival was 54·3% (95% CI 49·0–59·3) in the 10 mg/kg group versus 47·6% (42·4–52·7) in the 3 mg/kg group; 2-year overall survival was 38·5% (33·4–43·5) versus 31·0% (26·2–35·8) and 3-year overall survival was 31·2% (26·4–36·0) versus 23·2% (18·9–27·7). For patients with asymptomatic brain metastases at baseline (65 patients in the 10 mg/kg group, 62 patients in the 3 mg/kg group), median overall survival was 7·0 months (95% CI 4·0–12·8) in the 10 mg/kg group (54 deaths) and 5·7 months (4·2–7·0) in the 3 mg/kg group (58 deaths; HR 0·71, 95% CI 0·49–1·04; figure 2B). Overall survival results in prespecified subgroups were consistent with the overall result (figure 3). Sensitivity analyses for overall survival using an unstratified analysis and censoring for subsequent therapy did not show differences between the 10 mg/kg and 3 mg/kg groups (appendix pp 6, 11). Post-hoc analyses of overall survival by subsequent systemic therapy are shown in the appendix (p 12).

During the study, 328 patients had a progression event in the 10 mg/kg group and 330 patients had an event in the 3 mg/kg group. Median progression-free survival was 2·8 months (95% CI 2·8–3·0) in the 10 mg/kg group and 2·8 months (2·8–2·8) in the 3 mg/kg group (figure 2C). A similar proportion of patients in the 10 mg/kg group and 3 mg/kg group had an objective response and achieved disease control (table 2). Because of the prespecified hierarchical testing procedure, the non-significant p value for progression-free survival meant that statistical significance for objective response and disease control was not formally tested. Median duration of response was similar between the dose groups (table 2); median duration of stable disease was 5·6 months (95% CI 3·0–8·0) in the 10 mg/kg group and 3·2 months (2·7–5·6) in the 3 mg/kg group.

286 (79%) of 364 patients in the 10 mg/kg group and 228 (63%) of 362 patients in the 3 mg/kg group had a treatment-related adverse event of any grade (table 3). The most common grade 3–4 treatment-related adverse events were diarrhoea (37 [10%] patients in the 10 mg/kg group *vs* 21 [6%] patients in the 3 mg/kg group), colitis (19 [5%] *vs* nine [2%]), increased alanine aminotransferase (12 [3%] *vs* two [1%]), and hypophysitis (ten [3%] *vs* seven [2%]). Treatment-related serious adverse events were reported in 133 (37%) of 364 patients in the 10 mg/kg group; the most common were diarrhoea in 39 (11%) patients, colitis in 29 (8%), and hypophysitis in 16 (4%). In the 3 mg/kg group, treatment-related serious adverse events were reported in 66 (18%) of 362 patients; the most common were diarrhoea in 20 (6%) patients and colitis in 11 (3%).

Adverse events leading to discontinuation were more frequent in the 10 mg/kg group than in the 3 mg/kg group, both for any-grade events (114 [31%] *vs* 68 [19%]) and grade 3–4 events (87 [24%] *vs* 44 [12%]). Events leading

to discontinuation in more than 1% of patients in either the 10 mg/kg or 3 mg/kg group included diarrhoea (24 [7%] *vs* 14 [4%]), colitis (14 [4%] *vs* nine [2%]), malignant neoplasm progression (five [1%] *vs* two [1%]), general health deterioration (one [<1%] *vs* five [1%]), hypophysitis (five [1%] *vs* four [1%]), increased alanine aminotransferase (six [2%] *vs* one [<1%]), increased aspartate aminotransferase (six [2%] *vs* one [<1%]), and dyspnoea (five [1%] *vs* one [<1%]).

Immune-related adverse events (ie, those consistent with an immune-mediated mechanism and identified by the investigator as treatment related) occurred in 269 (74%) of 364 patients in the 10 mg/kg group (110 [30%] were grade 3–4) and 197 (54%) of 362 patients in the 3 mg/kg group (50 [14%] were grade 3–4; appendix pp 7–9). The most common immune-related adverse events in the 10 mg/kg group versus the 3 mg/kg group were diarrhoea (136 [37%] *vs* 84 [23%]), rash (95 [26%] *vs* 50 [14%]), and pruritus (82 [23%] *vs* 81 [22%]). During the induction phase, one patient in the 3 mg/kg group died due to an immune-related adverse event (large intestine perforation). Median time to onset and resolution of immune-related adverse events are shown in the appendix (p 10).

In the safety population, 239 (66%) of 364 patients in the 10 mg/kg group died due to disease progression versus 257 (71%) of 362 in the 3 mg/kg group. Six patients died because of treatment-related adverse events (four [1%] in the 10 mg/kg group: diarrhoea leading to general deterioration, fulminant colitis, multiorgan failure, and bowel perforation *vs* two [1%] in the 3 mg/kg group: multifocal colon perforation, and myocardial infarction from complications of diarrhoea and colitis). The remaining deaths in the 10 mg/kg and 3 mg/kg groups were reported as unknown (12 [3%] *vs* 12 [3%]) and other (six [2%; one each of pulmonary embolism, retroperitoneal bleeding, hypercalcaemia and alteration of general status, pneumonia, Alzheimer's disease, and ventricular haemorrhage] *vs* eight [3%; one each of chronic myeloid leukaemia, pulmonary embolism, bronchial adenocarcinoma, sepsis, pneumonia and acute cardiovascular failure associated with pneumonia, left hemiparesis, necrotising faciitis, and suicide]).

The EORTC QLQ-C30 global health status questionnaire was completed by 321 (88%) of 365 patients in the 10 mg/kg group and 317 (88%) of 362 patients in the 3 mg/kg group. Missing data for this assessment seems to have occurred randomly because the percentage of patients completing the questionnaire was similar in each treatment group at all timepoints (figure 4). The EQ-5D index was completed by 333 (91%) of 365 patients in the 10 mg/kg group versus 331 (91%) of 362 in the 3 mg/kg group; the EQ-5D VAS was completed by 331 (91%) patients versus 328 (91%) patients. Clinically significant declines in EORTC QLQ-C30 global health status were seen with both ipilimumab doses from baseline to end of treatment and also for ipilimumab 10 mg/kg from baseline to week 10 and to week 12 (figure 4A). Mean change from baseline to week 12 for the 10 mg/kg group was –13·26 (95% CI –17·57 to –8·95) and for the 3 mg/kg was –8·07 (–11·46 to –4·68). By contrast, clinically significant declines were only seen in the 10 mg/kg group for the EQ-5D index and EQ-5D VAS mean scores from baseline to week 12 and from baseline to end of treatment (figure 4B, C). Mean change in EQ-5D index from baseline to week 12 for the 10 mg/kg group was –0·09 (95% CI –0·12 to –0·06) and for the 3 mg/kg group was –0·05 (–0·08 to –0·02). Mean change in EQ-5D VAS from baseline to week 12 for the 10 mg/kg group was –8·54 (95% CI –12·86 to –4·22) and for the 3 mg/kg group was –2·11 (–6·28 to 2·06). The long-term effect of both ipilimumab doses on quality of life cannot be determined because patients were not followed up beyond the end of treatment.

	Ipilimumab 10 mg/kg (n=364)			Ipilimumab 3 mg/kg (n=362)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Infusion-related reaction	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Confusional state	0	1 (<1%)	0	0	1 (<1%)	0
Lung disorder	0	0	0	0	1 (<1%)	0
Acute kidney injury	0	0	0	0	0	1 (<1%)
Prostatitis	0	0	0	0	1 (<1%)	0

Data are n (%). The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Table 3: **Treatment-related adverse events (safety population, initial treatment phase)**

Discussion

In this randomised, double-blind, multicentre, phase 3 trial of patients with advanced melanoma, treatment with ipilimumab 10 mg/kg resulted in a significant improvement in overall survival compared with ipilimumab 3 mg/kg. The improvement in overall survival with the higher ipilimumab dose supports previous results from a phase 2 dose-ranging study, which showed a median overall survival of 11·4 months (95% CI 6·9–16·1) in patients treated with ipilimumab 10 mg/kg versus 8·7 months (6·9–12·1) in patients treated with ipilimumab 3 mg/kg.[6] However, no differences were seen in the present analysis between ipilimumab dose groups regarding the secondary endpoints of progression-free survival, objective response, or disease control, which is also consistent with previous studies. Consistent with the original dose-finding study, an increase in treatment-related adverse events was seen with ipilimumab 10 mg/kg compared with 3 mg/kg in the present study.

Median overall survival was 15·7 months in the 10 mg/kg group and 11·5 months in the 3 mg/kg group, with 3-year overall survival of 31% versus 23%. Although direct comparisons cannot be made because of trial differences,

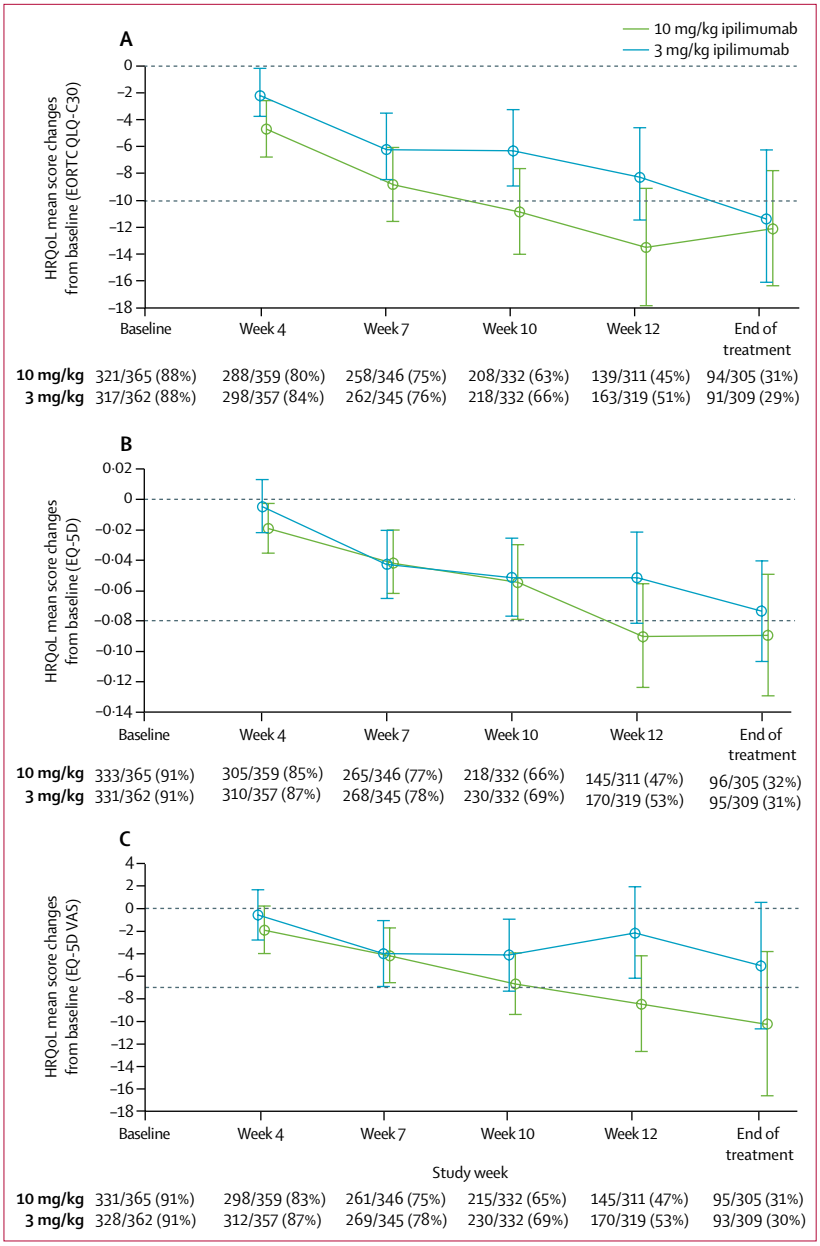

Figure 4: **Quality-of-life outcomes by ipilimumab dose**
Mean change from baseline in patients who received ipilimumab 10 mg/kg and 3 mg/kg for EORTC QLQ-C30 global health status (A), EQ-5D summary index (B), and EQ-5D VAS (C). Completion proportions are expressed as number of patients who completed the assessment over the number of eligible patients. Error bars are 95% CIs. Median baseline values for EORTC QLQ-C30 were 66·7 for both 10 mg/kg and 3 mg/kg groups, for the EQ-5D summary index were 0·83 for both dose groups, and for the EQ-5D VAS were 70·0 for both dose groups. Clinical significance (denoted by the horizontal dashed line at these points) is determined by the MID value for each test, which is 10 points for EORTC QLQ-C30, 0·8 points for EQ-5D, and 7 points for EQ-VAS. HRQoL=health-related quality of life. EORTC=European Organisation for Research and Treatment of Cancer. EQ-5D=European Quality of Life-5 Dimensions. VAS=visual analogue scale. MID=minimal important difference.

the results for the 3 mg/kg group are consistent with a pooled analysis of overall survival data from multiple ipilimumab studies (with monotherapy doses ranging from 0·3 mg/kg to 10 mg/kg) in which median overall survival was 11·4 months and the 3-year survival rate was 22%.[5] Again, although direct cross-trial comparisons cannot be made, the survival results of the 10 mg/kg group seem to improve on those results. However, our results should be interpreted in the context of the changing treatment landscape, in which ipilimumab monotherapy is no longer used in the first-line setting for melanoma in most countries where improved drugs that result in increased survival have become available. Keeping in mind the caveats of cross-trial comparison, the overall survival benefit of ipilimumab 10 mg/kg compared with ipilimumab 3 mg/kg was not favourable compared with nivolumab[11,19] and pembrolizumab[20,21] monotherapies, both of which also show increased tumour response and improved tolerability. Additionally, BRAF and MEK inhibitor combinations of dabrafenib plus trametinib increase survival in treatment-naive patients with *BRAF*^{V600E}-mutant or *BRAF*^{V600K}-mutant metastatic melanoma compared with controls.[22,23] Ipilimumab at 3 mg/kg also shows increased benefit when used in combination with nivolumab compared with ipilimumab monotherapy, as seen in the CheckMate 067 study,[24] in which progression-free survival was 11·5 months (95% CI 8·9–16·7) with the combination versus 2·9 months (2·8–3·4) with ipilimumab 3 mg/kg alone, and objective response was achieved in 181 (58%) of 314 patients versus 60 (19%) of 315 patients.

Analyses of prespecified subgroups showed an overall survival benefit that generally favoured the ipilimumab 10 mg/kg dose. However, it is important to keep in mind that this study was not powered for these subgroup analyses. Baseline characteristics were generally similar between dose groups for patients with *BRAF* mutations, although more patients in the ipilimumab 10 mg/kg group were younger than 65 years, had normal lactate dehydrogenase concentrations, or had M0, M1a, or M1b stage disease when compared with patients in the 3 mg/kg group. Additionally, subsequent systemic therapy was received by more than a third of patients in each dose group. Post-hoc analyses assessing the effect of subsequent systemic therapies on overall survival for all patients show the longest overall survival for both dose groups in patients who received subsequent immunotherapy (primarily anti-PD-1), compared with those who recevied BRAF and MEK inhibitors or chemotherapy. Although the analysis is exploratory and the results might be biased by patient selection, the finding is interesting in view of the present debate on sequencing of BRAF and MEK inhibition versus immunotherapy in patients with a *BRAF* mutation.

The results seen in this study showing a difference in survival without a difference in the proportion of patients with an objective response or progression-free survival are not unexpected in view of previous studies with ipilimumab, in which a difference was seen for survival but not necessarily for response.[2,3] Additionally, although previous trials have shown that ipilimumab reduces the number of patients who progress compared with control groups, the median values for progression-free survival

with both 3 mg/kg and 10 mg/kg doses of ipilimumab were consistent with that seen in the present trial.[2,3] One possible explanation for increased overall survival without response benefit is the immunological memory provided by ipilimumab treatment, which is increased in the 10 mg/kg dose group.[6] The survival benefit with ipilimumab might be obtained from unconventional response patterns or stable disease.

Consistent with the phase 2 dose-ranging ipilimumab study,[6] the proportion of patients with treatment-related adverse events in the present study was higher with ipilimumab 10 mg/kg than with 3 mg/kg, as was the proportion of patients with adverse events leading to discontinuation. The frequency and types of adverse events were consistent with those reported in previous phase 3 trials of ipilimumab in advanced melanoma, with immune-related adverse events being the most commonly reported.[2,3] Most adverse events resolved in both dose groups with established management algorithms. Additionally, time to onset, resolution frequency, and time to resolution were similar between the dose groups. Finally, during the induction phase, clinically significant reductions in the quality-of-life scales were seen more frequently and earlier for the 10 mg/kg group compared with the 3 mg/kg dose group; however, conclusions cannot be made about the long-term effect of either ipilimumab dose on quality of life because of the limited duration of follow-up for this endpoint.

In view of the present treatment landscape in advanced melanoma, the most substantial limitation of this study was the outdated nature of the exclusion criteria, which required patients to have no previous therapy with BRAF or immune checkpoint inhibitors. Additionally, quality of life data were collected only during the induction phase of the study, which limited the long-term assessment of these patients. Longer quality-of-life follow-up of these patients could have contributed to the assessment of the benefit–risk ratio of the regimen.

In conclusion, treatment with ipilimumab at 10 mg/kg led to a significant improvement in overall survival compared with ipilimumab at 3 mg/kg in patients with advanced melanoma who had not received a previous BRAF inhibitor or immune checkpoint inhibitor, but was associated with a higher frequency of treatment-related adverse events and adverse events leading to discontinuation. The clinical relevance of the improved overall survival with 10 mg/kg compared with 3 mg/kg of ipilimumab must be assessed in the context of several factors: the magnitude of effect seen; the attenuation of effect seen in the sensitivity analyses; the relative safety profile of each dose; and the changes in the treatment landscape since this study was initiated. Although the therapeutic landscape for first-line treatment of advanced melanoma has changed, the clinical use of ipilimumab 10 mg/kg monotherapy in patients with PD-1 refractory disease might warrant further assessment; for example, in patients with unmet medical need.

Contributors

PAA, MDV, CR, AM, VC-S, AA, CLe, LB, OH, PR, CM, CG, CLo, BD, LT, J-JG, GL, MN, RG, JP, FG, CH, VF, MS, DS, LM, IMS, and MM contributed to patients' treatment, data acquisition, data interpretation, and writing of the manuscript. DH is the lead statistician for the study and AQ is the medical monitor of the study. All authors approved the final version of the manuscript. All authors vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the study to the protocol. The first draft of the manuscript was written by the lead author (PAA), and all authors contributed to subsequent drafts and made the decision to submit the manuscript for publication.

Declaration of interests

PAA reports a paid consulting role with Bristol-Myers Squibb, Roche-Genentech, Merck Sharp & Dohme, and GlaxoSmithKline; honoraria from Bristol-Myers Squibb, Roche-Genentech, and GlaxoSmithKline; consulting roles with Ventena, Novartis, and Amgen; and institutional research funding from Bristol-Myers Squibb, Roche-Genentech, and Ventena. MDV reports honoraria from Bristol-Myers Squibb, Roche-Genentech, and GlaxoSmithKline; has served on an advisory board for Roche-Genentech; and has received research funding from Roche-Genentech. CR has had a paid consulting role with Bristol-Myers Squibb, Merck, Roche-Genentech, and Amgen; and has received honoraria from Bristol-Myers Squibb, Merck, Roche-Genentech, Amgen, GlaxoSmithKline, and Novartis. VC-S reports a paid consulting or speakers' bureau role with Bristol-Myers Squibb, Roche-Genentech, and GlaxoSmithKline; travel funding from Bristol-Myers Squibb, Roche-Genentech, and GlaxoSmithKline; and a paid consulting role with Merck Sharp & Dohme as well as travel funding from Merck Sharp & Dohme. AA had a paid consulting and speakers' bureau role with GlaxoSmithKline and Roche-Genentech, and a paid speakers' bureau role with Bristol-Myers Squibb as well as travel funding from Bristol-Myers Squibb. CLe has served on advisory boards for Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Roche-Genentech. LB has served on advisory boards for Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, and Roche-Genentech. OH reports a paid consulting role for Amgen, Novartis, Roche-Genentech, Bristol-Myers Squibb, Merck, Merck Serono, Pfizer, and Genentech and a paid speaker role for Bristol-Myers Squibb, Genentech, and Novartis. PR reports honoraria and institutional research funding from Bristol-Myers Squibb as well as a paid consulting role for Bristol-Myers Squibb; a paid consulting role and honoraria from Roche-Genentech; honoraria and travel funding from Novartis as well as a paid speakers' bureau role with Novartis; paid consulting and speakers' bureau roles with Merck Sharp & Dohme as well as honoraria from Merck Sharp & Dohme; honoraria from GlaxoSmithKline; a paid consulting role with Amgen; and a paid speakers' bureau role with Pfizer. CM has received personal fees and travel funding from Bristol-Myers Squibb. CG has had a paid consulting role with Bristol-Myers Squibb, Roche, and Novartis; has received an honoraria, research funding, and travel funding from Bristol-Myers Squibb, Roche, and Novartis; has had a paid consulting role with Merck Sharp & Dohme and Amgen; and has received an honoraria and travel funding from Merck Sharp & Dohme and Amgen. CLo has been a paid consultant and a speakers' bureau member with Bristol-Myers Squibb, Roche, and Merck Sharp & Dohme; has received travel funding from Bristol-Myers Squibb, Roche, and Merck Sharp & Dohme; and has been a paid consultant with Amgen. BD has received research funding from Bristol-Myers Squibb. J-JG has had a paid consulting role with Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Roche, Merck, and Amgen; has been on a speakers' bureau for Bristol-Myers Squibb, GlaxoSmithKline, and Roche; has received research funding from Bristol-Myers Squibb and Roche; and has received travel funding from Roche. RG reports study documentation fees for this study and also reports honoraria for lectures and advisory board participation from Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, Amgen, Roche, Almirall, GlaxoSmithKline, Merck Serono, Galderma, Janssen, Boehringer Ingelheim, LEO, and Pierre Fabre as well as research grants from Pfizer and Johnson&Johnson. CH reports honoraria and research funding from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, and GlaxoSmithKline; honoraria from Amgen; and a paid consulting role with Bristol-Myers Squibb, Merck Sharp & Dohme,

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