Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial

F Stephen Hodi, Jason Chesney, Anna C Pavlick, Caroline Robert, Kenneth F Grossmann, David F McDermott, Gerald P Linette, Nicolas Meyer, Jeffrey K Giguere, Sanjiv S Agarwala, Montaser Shaheen, Marc S Ernstoff, David R Minor, April K Salama, Matthew H Taylor, Patrick A Ott, Christine Horak, Paul Gagnier, Joel Jiang, Jedd D Wolchok, Michael A Postow**

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*Contributed equally

Dana-Farber Cancer Institute, Boston, MA, USA (F S Hodi MD, P A Ott MD); **University of Louisville, Louisville, KY, USA** (Prof J Chesney MD); **New York University, New York, NY, USA** (A C Pavlick MD); **Gustave Roussy, INSERM U981, Paris, France** (Prof C Robert MD); **Huntsman Cancer Institute, Salt Lake City, UT, USA** (K F Grossmann MD); **Beth Israel Deaconess Medical Center, Boston, MA, USA** (D F McDermott MD); **Washington University School of Medicine, St Louis, MO, USA** (G P Linette MD); **Institut Universitaire du Cancer, Toulouse, France** (Prof N Meyer MD); **Greenville Health System Cancer Institute, Greenville, SC, USA** (J K Giguere MD); **St Luke's Cancer Center and Temple University, Bethlehem, PA, USA** (Prof S S Agarwala MD); **University of New Mexico, Albuquerque, NM, USA** (M Shaheen MD); **Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA** (Prof M S Ernstoff MD); **California Pacific Center for Melanoma Research, San Francisco, CA, USA** (D R Minor MD); **Duke University Medical Center, Durham, NC, USA** (A K Salama MD); **Oregon Health & Science University, Portland, OR, USA** (M H Taylor MD); **Bristol-Myers Squibb, Princeton, NJ, USA** (C Horak PhD, P Gagnier MD, J Jiang PhD); **and Memorial**

Summary

Background Results from phase 2 and 3 trials in patients with advanced melanoma have shown significant improvements in the proportion of patients achieving an objective response and prolonged progression-free survival with the combination of nivolumab (an anti-PD-1 antibody) plus ipilimumab (an anti-CTLA-4 antibody) compared with ipilimumab alone. We report 2-year overall survival data from a randomised controlled trial assessing this treatment in previously untreated advanced melanoma.

Methods In this multicentre, double-blind, randomised, controlled, phase 2 trial (CheckMate 069) we recruited patients from 19 specialist cancer centres in two countries (France and the USA). Eligible patients were aged 18 years or older with previously untreated, unresectable stage III or IV melanoma and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned 2:1 to receive an intravenous infusion of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg or ipilimumab 3 mg/kg plus placebo, every 3 weeks for four doses. Subsequently, patients assigned to nivolumab plus ipilimumab received nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity, whereas patients allocated to ipilimumab alone received placebo every 2 weeks during this phase. Randomisation was done via an interactive voice response system with a permuted block schedule (block size of six) and stratification by *BRAF* mutation status. The study funder, patients, investigators, and study site staff were masked to treatment assignment. The primary endpoint, which has been reported previously, was the proportion of patients with $BRAF^{V600}$ wild-type melanoma achieving an investigator-assessed objective response. Overall survival was an exploratory endpoint and is reported in this Article. Efficacy analyses were done on the intention-to-treat population, whereas safety was assessed in all treated patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01927419, and is ongoing but no longer enrolling patients.

Findings Between Sept 16, 2013, and Feb 6, 2014, we screened 179 patients and enrolled 142, randomly assigning 95 patients to nivolumab plus ipilimumab and 47 to ipilimumab alone. In each treatment group, one patient no longer met the study criteria following randomisation and thus did not receive study drug. At a median follow-up of 24·5 months (IQR 9·1–25·7), 2-year overall survival was 63·8% (95% CI 53·3–72·6) for those assigned to nivolumab plus ipilimumab and 53·6% (95% CI 38·1–66·8) for those assigned to ipilimumab alone; median overall survival had not been reached in either group (hazard ratio 0·74, 95% CI 0·43–1·26; p=0·26). Treatment-related grade 3–4 adverse events were reported in 51 (54%) of 94 patients who received nivolumab plus ipilimumab compared with nine (20%) of 46 patients who received ipilimumab alone. The most common treatment-related grade 3–4 adverse events were colitis (12 [13%] of 94 patients) and increased alanine aminotransferase (ten [11%]) in the combination group and diarrhoea (five [11%] of 46 patients) and hypophysitis (two [4%]) in the ipilimumab alone group. Serious grade 3–4 treatment-related adverse events were reported in 34 (36%) of 94 patients who received nivolumab plus ipilimumab (including colitis in ten [11%] of 94 patients, and diarrhoea in five [5%]) compared with four (9%) of 46 patients who received ipilimumab alone (including diarrhoea in two [4%] of 46 patients, colitis in one [2%], and hypophysitis in one [2%]). No new types of treatment-related adverse events or treatment-related deaths occurred in this updated analysis.

Interpretation Although follow-up of the patients in this study is ongoing, the results of this analysis suggest that the combination of first-line nivolumab plus ipilimumab might lead to improved outcomes compared with first-line ipilimumab alone in patients with advanced melanoma. The results suggest encouraging survival outcomes with immunotherapy in this population of patients.

Funding Bristol-Myers Squibb.

Research in context

Evidence before this study

We searched PubMed and congress abstracts from the annual meetings of the American Society of Clinical Oncology, the European Society of Medical Oncology/European Cancer Congress, and the Society for Melanoma Research, to identify all studies that assessed combinations of immune checkpoint inhibitors in patients with melanoma, focusing on studies that included overall survival as either a primary, secondary, or exploratory endpoint. We searched for studies published between Jan 1, 2012, and March 1, 2016, using the search terms "PD-1","PD-L1", "nivolumab", "MK-3475", "pembrolizumab", "lambrolizumab", "MPDL3280A", "MEDI4736", AND "ipilimumab"; each search term AND "combination" with or without "overall survival"; "immune checkpoint inhibitor" AND "combination" with or without "overall survival". Our search identified several ongoing studies of combinations of immune checkpoint inhibitors, most of which are early phase clinical trials without long-term follow-up of the patients for overall survival. Before our present study, the longest survival follow-up duration for patients with advanced melanoma who received nivolumab plus ipilimumab was from a phase 1, dose-escalation study (CA209-004). In this relatively small study of untreated and previously treated patients, 3-year overall survival of 68% was reported.

Added value of this study

To the best of our knowledge, the present study is the first to report overall survival data from a randomised, controlled trial investigating the combination of nivolumab and ipilimumab as a first-line treatment for advanced melanoma.

Implications of all the available evidence

Combination therapy is emerging as an effective treatment option for advanced melanoma. Our survival data further support the combination of nivolumab plus ipilimumab as an effective first-line treatment option for patients with advanced melanoma, irrespective of *BRAF* mutation status.
The combination of these immune checkpoint inhibitors was approved for the treatment of unresectable or metastatic melanoma in the USA in January, 2016, and in the European Union in May, 2016.

Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA
(Prof J D Wolchok MD, M A Postow MD)

Correspondence to:
Dr F Stephen Hodi, Dana-Farber Cancer Institute, Boston, MA 02115, USA
stephen_hodi@dfci.harvard.edu

Introduction

Survival outcomes for patients with advanced melanoma have, historically, been very poor, with a median overall survival of about 8 months and 5-year overall survival from a diagnosis of metastatic disease of roughly 10%.[1] Ipilimumab, which blocks CTLA-4, was the first agent to improve overall survival in a randomised controlled, phase 3 trial of patients with advanced melanoma.[2] In this phase 3 trial, 2-year overall survival in ipilimumab-treated patients was 25%.[3] A pooled analysis of data from 12 clinical trials of advanced melanoma, in which some ipilimumab-treated patients were followed up for up to 10 years, showed durable long-term overall survival, with 3-year overall survival of 22%.[4] Newer immune checkpoint inhibitors, which block PD-1, include nivolumab and pembrolizumab. In a phase 3 trial (CheckMate 066),[5] nivolumab monotherapy was shown to improve overall survival versus dacarbazine in previously untreated patients with *BRAF* wild-type tumours. Follow-up of patients in CheckMate 066 has shown 2-year overall survival of 58% with nivolumab and 27% with dacarbazine.[6]

Both nivolumab and pembrolizumab monotherapy have been shown to have superior efficacy outcomes compared with ipilimumab alone in phase 3 trials of advanced melanoma.[7,8] In a phase 2 trial of previously untreated patients with *BRAF* wild-type melanoma (CheckMate 069),[9] the combination of nivolumab and ipilimumab was associated with a significantly greater proportion of patients achieving objective responses and significantly longer progression-free survival than with ipilimumab alone. More recently, the results of a phase 3 trial (CheckMate 067)[7] also showed that nivolumab in combination with ipilimumab leads to longer progression-free survival and a greater proportion of patients achieving objective responses than does ipilimumab alone in previously untreated patients with advanced melanoma. In a phase 1 dose-finding study of nivolumab in combination with ipilimumab, follow-up over 33 months has shown 3-year overall survival of 68% in both previously treated and untreated patients with advanced melanoma.[10] In the present study, we analysed 2-year overall survival data from the CheckMate 069 trial of nivolumab and ipilimumab in advanced melanoma.

Methods

Study design and participants

In this multicentre, randomised, controlled, double-blind, phase 2 study, we recruited patients from 19 specialist cancer centres in two countries (France and the USA; appendix p 15). Eligible patients were aged 18 years or older and had histologically confirmed, unresectable stage III or stage IV metastatic melanoma with an Eastern Cooperative Oncology Group performance status of 0 or 1, and known $BRAF^{V600}$ mutation status. Patients were also required to have measurable disease by CT or MRI, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and to have sufficient tumour tissue available for biomarker analyses (assessment of PD-L1). Patients who were pregnant or breastfeeding were not allowed to enrol. We excluded patients with active brain metastases or leptomeningeal metastases and those with ocular melanoma. However, patients with mucosal melanoma were allowed to enrol. Patients who had received previous systemic anticancer therapy for unresectable or metastatic melanoma were

See Online for appendix

excluded, but previous adjuvant or neoadjuvant treatment for melanoma was allowed if it had been completed at least 6 weeks before the date of first dose, and all related adverse events either returned to baseline or stabilised. Any prior radiotherapy must have been completed at least 2 weeks before study drug administration. *BRAF*^{V600} mutation testing was done during the screening period using a US Food and Drug Administration-approved test (cobas 4800 BRAF V600 Mutation Test, Roche Molecular Diagnostics, Pleasanton, CA, USA). Patients provided written, informed consent to participate in this study, including follow-up for survival outcomes. The protocol, amendments, and patient consent forms were approved by the institutional review board or independent ethics committee at each study site before the start of the trial.

Randomisation and masking

Patients were randomly assigned 2:1 to receive either nivolumab plus ipilimumab or ipilimumab alone by use of an interactive voice response system. Once enrolled in the interactive voice response system, patients who met all eligibility criteria were randomly assigned to a treatment group if information was available for patient number, date of birth, and *BRAF*^{V600} mutation status. We stratified randomisation by *BRAF* mutation status (V600 mutation positive *vs* V600 wild-type). The randomisation was done with the use of permuted blocks (block size of six) within each stratum. The study funder, patients, investigators, and study site staff were masked to the study drug given. Each study site assigned an unmasked pharmacist or designee who phoned the interactive voice response system to obtain the treatment assignment for each patient. Patients who had investigator-assessed disease progression could be treated beyond progression (with blinding maintained) or have blinded study therapy discontinued (after which time the treatment assignment could be disclosed to the investigator and patient). After unblinding, patients in the ipilimumab monotherapy group had the option of receiving nivolumab at a dose of 3 mg/kg every 2 weeks until further disease progression.

Procedures

In the combination treatment group, nivolumab was administered intravenously at a dose of 1 mg/kg over a period of 60 min, once every 3 weeks for four doses. 30 min after the completion of each nivolumab infusion, patients received intravenous ipilimumab at 3 mg/kg over a period of 90 min. After the fourth dose of both agents (the induction phase), ipilimumab was discontinued and nivolumab was then administered as a single agent at 3 mg/kg over a period of 60 min, once every 2 weeks (maintenance phase). In the ipilimumab alone group, the same dosing schedule was used, except that nivolumab was replaced with matched placebo during both the induction and maintenance phases of the trial. Treatment was continued as long as clinical benefit (as defined by the investigator) was observed, until unacceptable side-effects occurred, the patient requested to stop study treatment or withdrew consent, pregnancy, or termination of the study by the sponsor. Dosing interruptions were allowed to manage drug-related adverse events (grade 2 or worse non-skin drug-related adverse events except for fatigue or laboratory abnormalities, or grade 3 or worse skin adverse events or laboratory abnormalities); dosing could be resumed when these adverse events resolved to a maximum grade 1 severity or to baseline values, but dose reductions were not permitted. Criteria for permanently discontinuing treatment included patient request to stop study treatment; any clinical adverse event, laboratory abnormality or intercurrent illness that, in the opinion of the investigator, showed that continued participation in the study would not be in the best interest of the patient; pregnancy; imprisonment or involuntary incarceration; and additional protocol-specified reasons, which were introduced based on our earlier trial experience (details available in the appendix). Patients who had disease progression and were tolerating study therapy could be treated beyond progression (with blinding maintained) or discontinue blinded study therapy. After unblinding, patients in the ipilimumab alone group could crossover to receive nivolumab at 3 mg/kg every 2 weeks until further disease progression; patients in the combination group were required to discontinue treatment.

Tumour response was assessed by the investigators on CT or MRI in accordance with RECIST version 1.1 at the following timepoints: within 28 days before the first dose (baseline), 12 weeks after the first treatment, every 6 weeks thereafter for the first year, then every 12 weeks until disease progression or discontinuation of treatment. Responses had to be confirmed via a subsequent scan at least 4 weeks later. Patients were assessed for safety if they received any study drug. Baseline local laboratory assessments were done 14 days before the first dose, and safety assessments were done continuously throughout the treatment phase. These assessments, which included standard laboratory evaluations (eg, complete blood count with differential, liver function tests, and creatinine), were done within 72 h before the subsequent dose, up to cycle 7 of therapy. Safety was then assessed every alternate dose thereafter. Patients were followed up to 100 days after study treatment. Additional testing or assessments were done as clinically necessary or where required by institutional or local regulations. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. An adverse event was deemed to be on study if it occurred within 30 days after the last dose of study treatment. On-study laboratory assessments (including chemistry and haematology tests) were done within 72 h before each dose during the induction phase; during the nivolumab maintenance phase, laboratory assessments were done within 72 h

before the first dose and every alternate dose thereafter. Tumour expression of PD-L1 was assessed in pre-treatment samples at a central laboratory by use of a validated, automated immunohistochemical assay (PD-L1 IHC 28-8 pharmDx, Dako, Carpinteria, CA, USA), as described previously.[11] In each tumour tissue sample, PD-L1 positivity was defined as at least 5% of tumour cells showing cell-surface PD-L1 staining of any intensity in a section containing at least 100 evaluable tumour cells.

Outcomes

The primary endpoint of this trial was the proportion of patients with *BRAF*^{V600} wild-type tumours achieving a confirmed objective response (as assessed by the investigators), which has been reported previously.[9] Secondary endpoints were investigator-assessed progression-free survival in patients with *BRAF* wild-type tumours, the proportion of patients achieving an objective response among patients with *BRAF*^{V600} mutation-positive tumours (reported previously[9]) and progression-free survival for patients with *BRAF*^{V600} mutant tumours, and health-related quality of life (reported previously[12]). Overall survival was a key exploratory endpoint that is the focus of this paper; other exploratory endpoints included safety and tolerability and biomarker analyses.

Statistical analysis

We planned to recruit a sample size of 100 patients with *BRAF* wild-type tumours who would be randomly assigned 2:1 to the two treatment groups. Given a two-sided α of 0·05, this number of patients would provide 87% power to detect a significant difference between the groups in the proportion of patients achieving an objective response, assuming that 40% of patients would achieve an objective response with the combination therapy versus 10% with ipilimumab alone.[9] Assuming that 66% of the patients had *BRAF* wild-type tumours, we planned to randomly assign 150 patients to treatment, including 50 with *BRAF* mutation-positive tumours. Analyses in the population with *BRAF* mutation-positive tumours were intended to be descriptive only and thus were not part of the sample size calculations.[9] We applied a hierarchical testing approach to key secondary endpoints after analysis of the primary endpoint: the proportion of all randomly assigned patients who achieved objective responses was tested first, followed by progression-free survival in randomly assigned patients with *BRAF* wild-type tumours, and then progression-free survival in all randomly assigned patients.

For the primary endpoint, we compared the proportions of patients achieving investigator-assessed objective responses between treatment groups using Fisher's exact test. The associated odds ratio and corresponding two-sided 95% CI were calculated. We estimated time-to-event distributions (ie, progression-free survival, overall survival, time to response, and duration of response) and values at fixed timepoints using Kaplan-Meier methods. Hazard ratios (HRs) and corresponding two-sided 95% CIs were estimated with a stratified Cox proportional hazards model. We calculated p values for comparisons between groups using a two-sided log-rank test with stratification by *BRAF* mutation status. In accordance with the statistical analysis plan, each efficacy analysis was adjusted for the baseline stratification factor (*BRAF* mutation status). Analyses of efficacy endpoints were done on the intention-to-treat population, and safety was assessed in all patients who received at least one dose of study drug. Analyses were done on prespecified subgroups based on age (<65 years and ≥65 years), sex, baseline ECOG performance status, *BRAF* mutation status, PD-L1 tumour expression status (using a 5% cutoff), M stage at study entry, and baseline lactate dehydrogenase levels. For overall survival analyses, we did sensitivity analysis in which patients were censored on the date that they received subsequent therapy (including ipilimumab-treated patients who crossed over to receive nivolumab monotherapy per protocol). We did all statistical analyses with SAS version 9.2.

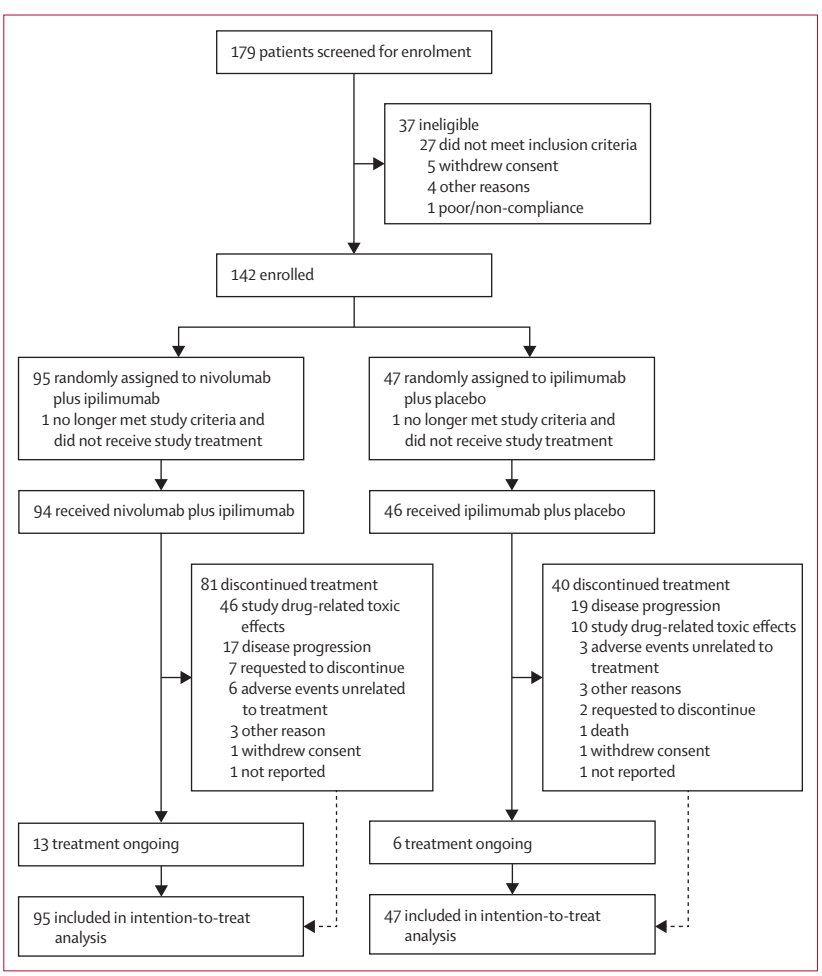

Figure 1: **Trial profile**

This study is registered with ClinicalTrials.gov, number NCT01927419.

Role of the funding source

Data collected by the funder were analysed in collaboration with all authors. The study funder paid for writing and editorial support. All authors had full access to all the data in the current analyses and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Sept 16, 2013, and Feb 6, 2014, we enrolled 179 patients and randomly assigned 142 eligible patients (including 109 with *BRAF* wild-type tumours and 33 with *BRAF*^{V600} mutation-positive tumours) to receive either nivolumab and ipilimumab combination therapy (95 patients) or ipilimumab and placebo (ipilimumab monotherapy; 47 patients [figure 1]). Of these patients who were assigned to treatment, 72 in the nivolumab plus ipilimumab group and 37 in the ipilimumab plus placebo group had *BRAF* wild-type tumours. One patient in each treatment group no longer met the study criteria after randomisation and therefore did not receive their assigned study drug: one had an adverse event (pleural effusion) unrelated to study medication and the second decided to pursue surgery instead of continued participation in a clinical trial. Baseline characteristics were well balanced between the study groups (appendix p 4).

At a median follow-up of 24·5 months (IQR 9·1–25·7), with database lock on Feb 29, 2016, 13 (14%) of 94 patients who began treatment in the nivolumab and ipilimumab group were continuing treatment compared with six (13%) of 46 in the ipilimumab monotherapy group. 59 (63%) patients in the nivolumab plus ipilimumab group and 22 (48%) patients in the ipilimumab group were continuing with follow-up in the study at the time of database lock. The most common reasons for treatment discontinuation were disease progression (17 [18%] of 94 patients in the combination group *vs* 19 [41%] of 46 in the ipilimumab group) and study drug toxicity (46 [49%] patients in the combination group *vs* ten [22%] in the ipilimumab group). Patients in the combination group received a median of four doses of nivolumab (IQR 2–15) and ipilimumab (2–4), with 38 (40%) of 94 having received at least one dose of nivolumab maintenance therapy. Patients in the ipilimumab alone group received a median of four doses (IQR 3–4) of ipilimumab. A greater proportion of patients randomly assigned to ipilimumab therapy received subsequent treatment following disease progression (33 [70%] of 47 patients) than did patients assigned to combination therapy (33 [35%] of 95 patients; appendix p 5). The most common subsequent treatment was anti-PD-1 therapy, which was received by 29 (62%) of 47 patients assigned to the ipilimumab alone group (26 received crossover nivolumab as per protocol and three received off-study nivolumab or pembrolizumab) and 17 (18%) of 95 patients assigned to the combination therapy group (16 received pembrolizumab and one received nivolumab off protocol; (appendix p 5). Median time to subsequent therapy was not reached for combination therapy and was 6·1 months (95% CI 4·2–7·4) for ipilimumab.

As previously reported,[9] of all patients who were assigned to treatment, a significantly larger proportion in the nivolumab plus ipilimumab group had objective responses

	All randomised patients		Patients with *BRAF* wild-type tumours		Patients with *BRAF* mutation-positive tumours	
	Nivolumab and ipilimumab (n=95)	Ipilimumab (n=47)	Nivolumab and ipilimumab (n=72)	Ipilimumab (n=37)	Nivolumab and ipilimumab (n=23)	Ipilimumab (n=10)
Objective response*	56 (59% [48–69])	5 (11% [3–23])	44 (61% [49–72])	4 (11% [3–25])	12 (52% [31–73])	1 (10% [0·3–45])
Odds ratio for comparison	12·2 (4·4–33·7)	..	13·0 (3·9–54·5)	..	9·8 (1·0–465·4)	..
p value for comparison	<0·0001	..	<0·0001	..	Not calculated	..
Best overall response*						
Complete response	21 (22%)	0	16 (22%)	0	5 (22%)	0
Partial response	35 (37%)	5 (11%)	28 (39%)	4 (11%)	7 (30%)	1 (10%)
Stable disease	12 (13%)	14 (30%)	9 (13%)	13 (35%)	3 (13%)	1 (10%)
Progressive disease	15 (16%)	22 (47%)	10 (14%)	15 (41%)	5 (22%)	7 (70%)
Unable to determine	12 (13%)	6 (13%)	9 (13%)	5 (14%)	3 (13%)	1 (10%)
Duration of response†						
Ongoing responders	45/56 (80%)	4/5 (80%)	35/44 (80%)	3/4 (75%)	10/12 (83%)	1/1 (100%)
Median (95% CI, months)	NR	NR (6·9–NR)	NR (NR–NR)	NR (6·9–NR)	NR (6·1–NR)	NR

Data are n (% [95% CI]), n (%), or n/N (%) unless otherwise specified. Percentages may not add to 100% due to rounding. A p value was not calculated to compare objective response in people with *BRAF* mutation-positive tumours because this analysis was not predetermined in the statistical analysis plan and because of the small number of patients in the comparitor arm. NR=not reached. *Based on original database lock on Jan 30, 2015. †Based on database lock on Feb 29, 2016.

Table 1: **Response to treatment**

than did those in the ipilimumab group (table 1). Complete responses were reported for 21 (22%) of 95 patients in the combination group and no patients in the ipilimumab group. In patients with *BRAF* mutation-positive tumours, responses were achieved by substantially more patients in the combination group than in the ipilimumab group (table 1).[9] In the present study, at a median 2 years' follow-up, median duration of response had not been reached in either group for all patients who were assigned to treatment (table 1). Responses were durable, with 45 (80%) of 56 responses ongoing in the combination group and four (80%) of five ongoing in the ipilimumab group (table 1, figure 2). Median change in tumour volume was a 70% reduction (IQR –94·0 to –40·5) in the combination group and a 5% increase (–24·9 to 32·2) in the ipilimumab alone group.

For our 2-year follow-up of progression-free survival in all patients who were assigned to treatment, median progression-free survival had not been reached for the combination therapy group and was 3·0 months (95% CI 2·7–5·1) in the ipilimumab group (HR 0·36, 95% CI 0·22–0·56; p<0·0001; figure 3). 43 (45%) of 95 patients had disease progression or died in the combination group versus 35 (74%) of 47 patients in the ipilimumab group. Progression-free survival at 1 year was 52·5% (95% CI 41·6–62·3) in the combination group and 16·0% (6·6–28·9) for ipilimumab alone and seemed to plateau after 12 months; at 2 years, it was 51·3% (40·4–61·2) in the combination group and 12·0% (3·8–25·2) for ipilimumab alone.

At a median follow-up of 2 years, median overall survival in all patients assigned to treatment (with and without a $BRAF^{V600}$ mutation) had not been reached in either group (HR 0·74, 95% CI 0·43–1·26; p=0·26; figure 4). Overall survival was 73·4% (95% CI 63·2–81·2) at 1 year and 63·8% (53·3–72·6) at 2 years in the combination group and 64·8% (49·1–76·8) at 1 year and 53·6% (38·1–66·8) at 2 years in the ipilimumab alone group. A sensitivity analysis for overall survival in patients who received ipilimumab alone, with censoring at the time of crossover to their first dose of nivolumab, yielded similar results (appendix p 10).

We also did a prespecified subgroup analysis for overall survival with the combination of nivolumab and ipilimumab versus ipilimumab alone across subgroups (appendix p 11). This subgroup analysis included analysis by *BRAF* mutation status (appendix pp 11, 13) and showed no difference in overall survival at 2 years between *BRAF*-mutant and *BRAF* wild-type patients. Similarly, we also did a prespecified subgroup analysis for progression-free survival with the combination versus ipilimumab alone in prespecified subgroups (appendix p 12). In patients with *BRAF* mutation-positive tumours, median progression-free survival was 8·5 months (95% CI 2·8–not reached [NR]) for the combination group and 2·7 months (1·0–5·4) for ipilimumab alone (HR 0·38, 95% CI 0·15–1·00, p=0·041; appendix p 14). 2-year progression-free survival in these *BRAF* mutation-positive patients was 44·1% (95% CI 22·9–63·4) in the combination group and 12·5% (95% CI 0·7–42·3) for ipilimumab alone.

In a prespecified exploratory biomarker analysis, we investigated efficacy outcomes as reported at original database lock by tumour PD-L1 status in the combination group, in which 80 (85%) of 94 patients had quantifiable

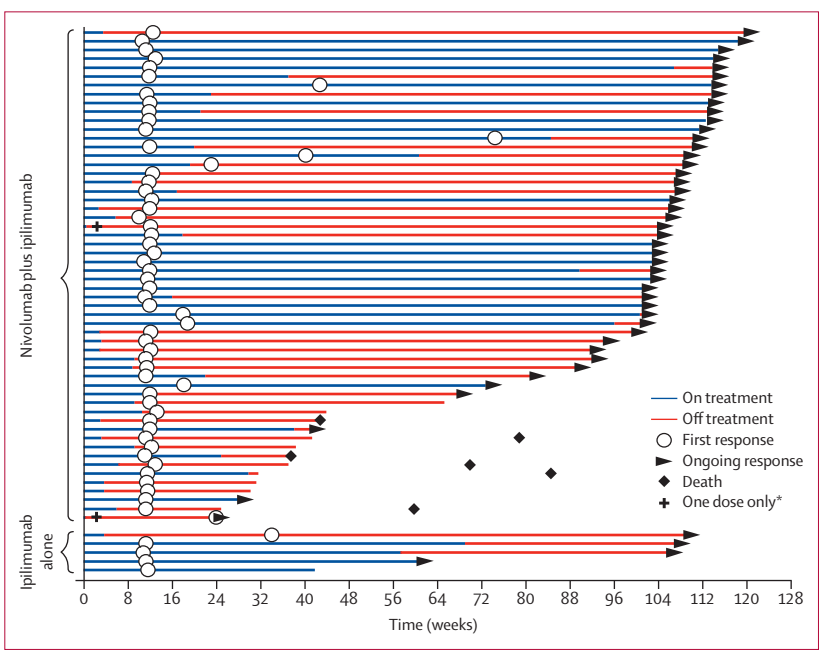

***Figure 2*: Time to and duration of response**
Swimmer plots show time to first response and duration of response (in accordance with Response Evaluation Criteria in Solid Tumors version 1.1), for responders who received nivolumab plus ipilimumab or ipilimumab plus placebo. *These patients received only one dose of combination therapy before discontinuing treatment.

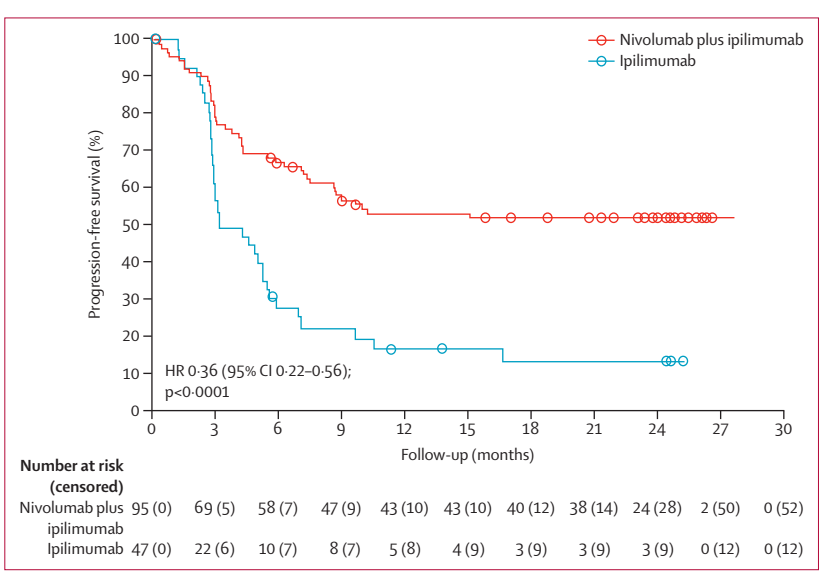

***Figure 3*: Progression-free survival**
Kaplan-Meier curves of investigator-assessed disease progression (in accordance with Response Evaluation Criteria in Solid Tumors version 1.1) at a median follow-up of 2 years in all patients assigned to treatment.

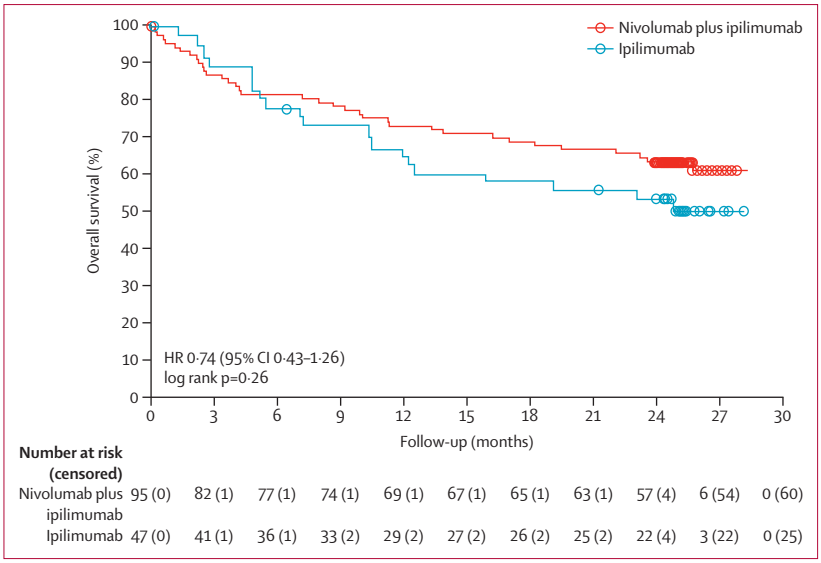

Figure 4: **Overall survival**
Kaplan-Meier curves of overall survival at a median follow-up of 2 years for all patients assigned to treatment.

PD-L1 expression. The proportion of patients achieving objective responses in this treatment group did not differ substantially between patients with tumour PD-L1 expression of 5% or more (14 of 24 patients; 58% [95% CI 37–78]) and those with tumour PD-L1 expression less than 5% (31 of 56 patients; 55% [42–69]; appendix p 6). Results were similar for progression-free and overall survival (appendix p 7). In patients who were assigned to combination therapy, 2-year overall survival was 67% (95% CI 44–82) for the 24 patients with PD-L1 expression of 5% or more and 60% (46–72) for the 56 patients with PD-L1 expression below 5%. At a 1% cutoff for tumour PD-L1 expression, there were no significant differences in the proportion of patients in the combination therapy group achieving objective responses, progression-free survival, or overall survival by PD-L1 expression of 1% or more versus PD-L1 expression below 1%, as indicated by overlapping confidence intervals (appendix pp 6, 7).

At the time of the most recent database lock (Feb 29, 2016), 86 (92%) of 94 patients who received the combination therapy and 43 (94%) of 46 patients who received ipilimumab alone had treatment-related adverse events of any grade. Diarrhoea (42 [45%] of 94 patients in the combination group *vs* 16 [35%] of 46 in the ipilimumab group), rash (40 [43%] *vs* 14 [30%]), fatigue (34 [36%] *vs* 22 [48%]) and pruritus (38 [40%] *vs* 15 [33%]) were the most common treatment-related adverse events (table 2). Treatment-related grade 3–4 adverse events were more common in the combination group than in the ipilimumab group (51 [54%] patients *vs* nine [20%] patients) and led to treatment discontinuation in 28 (30%) of 94 patients in the combination group and four (9%) of 46 patients in the ipilimumab group. Serious treatment-related grade 3–4 adverse events (ie, those considered to be life threatening or that resulted in death or required inpatient hospital admission) were reported for 34 (36%) patients in the nivolumab plus ipilimumab group (the most common of which were colitis in ten [11%] patients and diarrhoea in five [5%]) and four (9%) patients in the ipilimumab alone group (the most common were diarrhoea in two [4%] patients, colitis in one [2%], and hypophysitis in one [2%]). No new types of treatment-related adverse events were recorded in the updated analyses.

At the time of the database lock, 35 (37%) of 94 patients who received treatment in the combination group and 22 (48%) of 46 who received treatment in the ipilimumab group had died, with 25 (71%) of 35 deaths in the combination group and 20 (91%) of 22 deaths in the ipilimumab group due to disease progression. As originally reported, three deaths in the combination group were attributed by the investigators to treatment-related adverse events (one from ventricular arrhythmia, one from panhypopituitarism with severe cortisol deficiency and adrenal crisis, and one from pneumonitis), whereas no patients in the ipilimumab group died from treatment-related adverse events.[9] In the updated analyses, no additional treatment-related deaths have been reported.

Some treatment-related adverse events of potentially immune-mediated cause occurred more frequently in the nivolumab and ipilimumab group (83 [88%] of 94 patients) than in the ipilimumab alone group (37 [80%] of 46 patients; appendix p 8). The most common potentially immune-mediated grade 3–4 treatment-related adverse events in the combination group were colitis (12 [13%] of 94 patients), increased alanine aminotransferase (ten [11%]), and diarrhoea (nine [10%] of 94 patients). Diarrhoea was the most commonly reported treatment-related potentially immune-mediated grade 3–4 adverse event in the ipilimumab group (five [11%] of 46 patients), followed by hypophysitis (two [4%] of 46 patients). With the use of immune-modulating agents such as corticosteroids, most grade 3–4 potentially immune-mediated adverse events resolved in both groups (appendix p 9) following established treatment algorithms.[9] Time to resolution across all organ categories was typically between 4 and 8 weeks. However, because of the requirement for long-term hormone replacement therapy for endocrine adverse events, most endocrine events were not deemed by the investigators to have been resolved, even if they were well controlled. Of 35 patients who discontinued nivolumab plus ipilimumab treatment at any time due to study drug toxicity, 23 (66%) developed a response, of which 17 (74%) responses have been maintained.[13]

Discussion

To the best of our knowledge, this analysis represents the longest follow-up so far of patients with advanced melanoma who received the combination of nivolumab and ipilimumab in a randomised, controlled trial. At a median follow-up of 2 years, the improved objective

	Nivolumab and ipilimumab (n=94)			Ipilimumab (n=46)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Overall						
Any treatment-related adverse event	34 (36%)	41 (44%)	10 (11%)	34 (74%)	8 (17%)	1 (2%)
Adverse events						
Rash	36 (38%)	4 (4%)	0	14 (30%)	0	0
Pruritus	37 (39%)	1 (1%)	0	15 (33%)	0	0
Maculopapular rash	12 (13%)	3 (3%)	0	6 (13%)	0	0
Diarrhoea	33 (35%)	8 (9%)	1 (1%)	11 (24%)	4 (9%)	1 (2%)
Nausea	19 (20%)	1 (1%)	0	8 (17%)	1 (2%)	0
Colitis	5 (5%)	11 (12%)	1 (1%)	2 (4%)	1 (2%)	0
Abdominal pain	12 (13%)	0	0	4 (9%)	1 (2%)	0
Vomiting	11 (12%)	1 (1%)	0	3 (7%)	0	0
Fatigue	29 (31%)	4 (4%)	1 (1%)	22 (48%)	0	0
Pyrexia	14 (15%)	2 (2%)	1 (1%)	6 (13%)	0	0
Chills	11 (12%)	0	0	5 (11%)	0	0
Increased aspartate aminotransferase	19 (20%)	7 (7%)	0	4 (9%)	0	0
Increased alanine aminotransferase	14 (15%)	8 (9%)	2 (2%)	4 (9%)	0	0
Increased lipase	8 (9%)	5 (5%)	4 (4%)	2 (4%)	0	0
Increased amylase	9 (10%)	1 (1%)	1 (1%)	0	0	0
Headache	11 (12%)	2 (2%)	0	4 (9%)	0	0
Hypothyroidism	16 (17%)	0	0	6 (13%)	0	0
Hypophysitis	10 (11%)	2 (2%)	0	1 (2%)	2 (4%)	0
Cough	10 (11%)	0	0	4 (9%)	0	0
Decreased appetite	11 (12%)	0	0	4 (9%)	0	0
Myalgia	9 (10%)	0	0	5 (11%)	0	0
Dyspnoea	7 (7%)	2 (2%)	0	0	0	0
Pneumonitis	7 (7%)	2 (2%)	0	0	0	0
Dizziness	7 (7%)	0	1 (1%)	0	0	0
Constipation	7 (7%)	1 (1%)	0	0	0	0
Hyponatraemia	5 (5%)	1 (1%)	0	0	0	0
Dehydration	4 (4%)	2 (2%)	0	1 (2%)	0	0
Adrenal insufficiency	4 (4%)	1 (1%)	0	1 (2%)	0	0
Pain	2 (2%)	0	0	1 (2%)	0	0
Paraesthesia	3 (3%)	1 (1%)	0	0	0	0
Autoimmune colitis	0	3 (3%)	0	2 (4%)	0	0
Hyperglycaemia	1 (1%)	1 (1%)	1 (1%)	0	0	0
Hypokalaemia	3 (3%)	0	0	1 (2%)	0	0
Hypotension	1 (1%)	2 (2%)	0	0	0	0
Autoimmune thyroiditis	1 (1%)	1 (1%)	0	0	0	0
Increased blood creatinine	1 (1%)	0	1 (1%)	0	0	0
Pancreatitis	0	1 (1%)	1 (1%)	0	0	0
Eye pain	1 (1%)	1 (1%)	0	0	0	0
Hepatitis	0	2 (2%)	0	0	0	0
Ventricular arrhythmia	1 (1%)	0	0	0	0	0
Diabetic ketoacidosis	0	0	1 (1%)	0	0	0
Neutropenia	0	0	1 (1%)	0	0	0
Respiratory failure	0	0	1 (1%)	0	0	0

(Table 2 continues on next page)

	Nivolumab and ipilimumab (n=94)			Ipilimumab (n=46)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Ventricular tachycardia	0	0	1 (1%)	0	0	0
Aphthous stomatitis	0	1 (1%)	0	0	0	0
Ascites	0	1 (1%)	0	0	0	0
Atrial fibrillation	0	1 (1%)	0	0	0	0
Enterocolitis	0	1 (1%)	0	0	0	0
Febrile neutropenia	0	1 (1%)	0	0	0	0
Guillain-Barré syndrome	0	1 (1%)	0	0	0	0
Hypoalbuminaemia	0	1 (1%)	0	0	0	0
Hypothermia	0	1 (1%)	0	0	0	0
Increased transaminases	0	1 (1%)	0	0	0	0
Leucocytosis	0	1 (1%)	0	0	0	0
Malabsorption	0	1 (1%)	0	0	0	0
Myocardial infarction	0	1 (1%)	0	0	0	0
Pneumonia	0	1 (1%)	0	0	0	0
Rash (generalised%)	0	1 (1%)	0	0	0	0
Syncope	0	1 (1%)	0	0	0	0
Adverse events leading to treatment discontinuation						
Any event	6 (6%)	23 (24%)	5 (5%)	0	3 (7%)	1 (2%)

Data are n (%). One grade 5 event noted in the nivolumab and ipilimumab group during the safety reporting period per protocol (ie, up to 30 days after the last dose of study drug). The death was due to ventricular arrhythmia. Two other deaths occurred in the nivolumab and ipilimumab group outside of the safety window reporting period: one in a patient who was clinically improving from pneumonitis and had an iatrogenic pneumothorax (69 days after the last treatment) and one in a patient with panhypopituitarism with cortisol deficiency and adrenal crisis (87 days after the last treatment).

Table 2: **Treatment-related adverse events**

response outcomes and progression-free survival results in the combination therapy group compared with the ipilimumab alone group were maintained, but overall survival did not differ significantly between combination therapy and ipilimumab alone in all patients assigned to treatment. The results in the overall patient population were generally consistent across subgroups of patients, including those with elevated lactate dehydrogenase levels and M1c disease, although the small numbers of patients within the subgroups warrant caution in the interpretation of these results.

Notably, in the current study, fewer patients than in other trials of nivolumab for advanced melanoma[7] had raised lactate dehydrogenase concentrations and stage M1c disease, which might have favourably affected survival outcomes. The interpretation of overall survival differences within the subgroup of patients with *BRAF*^{V600} mutation-positive melanoma was limited by small numbers of patients and the probable effect of crossover of patients in the ipilimumab monotherapy group to anti-PD-1 monotherapy, as well as BRAF or MEK inhibitor treatment after progression.

At 53·6%, 2-year overall survival was higher than expected in the ipilimumab monotherapy group compared with the values of 25·3%[3] and 28·9%[14] reported previously in phase 3 trials of ipilimumab. This difference was probably due to the fact that 57% of ipilimumab-treated patients crossed over to receive nivolumab monotherapy while on study, and patients could receive additional subsequent off-study therapies that were not commercially available during previous ipilimumab trials. We did not formally characterise the response to subsequent anti-PD-1 therapy after progression on ipilimumab in this trial, because this has been addressed in other studies in advanced melanoma.[15,16] Median progression-free survival was significantly longer in the combination group than in the ipilimumab alone group for all patients assigned to treatment and for those with *BRAF* mutation-positive tumours. Progression-free survival was noticeably higher in the combination group than in the ipilimumab group, which, unlike overall survival, would not be affected by ipilimumab-treated patients crossing over to receive nivolumab or other subsequent therapies.

Although the prognosis for patients with advanced melanoma has historically been very poor, several agents approved since 2011 have shown promise for improving survival outcomes. 2-year overall survival with nivolumab monotherapy was 58% in a phase 3 study[6] of previously untreated patients with *BRAF* wild-type tumours. In a phase 1 study[17] of heavily pretreated patients who received

nivolumab monotherapy at 3 mg/kg, 2-year overall survival was 47% and 5-year survival was 35%. Subsequently, the results of a pooled analysis of data from a phase 1b study of pembrolizumab monotherapy showed 2-year overall survival to be 49% in previously treated and treatment-naive patients (survival was 60% in treatment-naive patients alone).[18] How overall survival with nivolumab and ipilimumab combination therapy compares with that of initial anti-PD-1 monotherapy remains unclear, and further follow-up of patients in the phase 3 CheckMate 067 trial might provide important information on this topic.

In our trial[9] and the phase 3 CheckMate 067 trial,[7] the proportion of patients achieving confirmed objective responses was higher with nivolumab plus ipilimumab than with ipilimumab alone,[7] and the combination resulted in more complete responses. Our current updated analysis showed that the median reduction in tumour burden with combination therapy and the small increase in tumour with ipilimumab alone persisted with continued follow-up. Responses remained durable, as shown by most responders remaining in response and median duration of response not having been reached.

As previously reported for objective responses,[9] and extended here to include survival data, the improved objective response and progression-free survival results reported with the combination of nivolumab and ipilimumab compared with ipilimumab alone were recorded irrespective of tumour PD-L1 expression if a 5% cutoff was used. Results from previous studies of anti-PD-1 monotherapy have suggested that the efficacy of nivolumab is better in patients with tumour PD-L1 expression of 5% or more than in patients with PD-L1 expression lower than 5%.[8,15] The absence of such differences in patients given combination therapy in our study might be due to ipilimumab causing T-cell infiltration into the tumour, which then provides a more favourable tumour microenvironment in which anti-PD-1 agents can act.[9,16] In the CheckMate 067 trial in which PD-L1 status was a stratification factor, the combination of ipilimumab and nivolumab led to longer progression-free survival and a larger proportion of patients achieving a reponse in those with tumour PD-L1 expression of 5% or more than in those with expression less than 5%.[7]

Generally, the incidence of treatment-related adverse events is higher with nivolumab plus ipilimumab than with ipilimumab alone.[7,9] In our current analysis, treatment-related adverse events of any grade were reported by 92% of patients in the combination group (including 54% who reported grade 3–4 adverse events) and 94% of patients in the ipilimumab alone group (20% reported grade 3–4 adverse events), as compared with 91% and 93%, respectively (54% and 24% reported grade 3–4 adverse events, respectively), at the time of the original database lock.[9] The types and frequencies of treatment-related adverse events and proportion of events leading to discontinuation were consistent with previous results and no new types of adverse events occurred. One exception is the incidence of colitis in patients who received ipilimumab alone, which was lower in the current analysis than has previously been reported in larger, phase 3 studies.[7,8] Possible explanations include the generally better health of patients in our study compared with other studies, and the possible reassignment of grade 3 or 4 colitis to other causes at follow-up.

Three study drug-related deaths were originally reported in CheckMate 069,[9] but no new deaths related to treatment occurred during 2-year follow-up. These results suggest an acceptable risk–benefit profile for either treatment, with most potentially immune-mediated adverse events having been resolved in both groups by use of established safety guidelines involving immune-modulating medications as needed. Further investigation of the combination of anti-PD-1 agents and ipilimumab to improve the benefit–risk profile remains an area of particular interest. Data from the KEYNOTE-029 phase 1 study[19] of advanced melanoma, in which patients received pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg, followed by pembrolizumab 2 mg/kg as maintenance therapy, showed investigator-assessed responses in 57% of patients, with grade 3–4 treatment-related adverse events reported by 38% of patients.

The results of our current analysis suggest that the combination of first-line nivolumab plus ipilimumab might lead to improved outcomes compared with first-line ipilimumab alone in patients with advanced melanoma. Patients continue to be followed up for overall survival. Further information about survival outcomes with the nivolumab and ipilimumab combination in patients with previously untreated advanced melanoma will be provided by this continued follow-up, and upon maturity of overall survival data from the larger CheckMate 067 trial.

Contributors

FSH contributed to the conception and design of the study, data collection, data interpretation, and writing of the report. JC, ACP, KFG, DFM, GPL, NM, JKG, SSA, MS, MSE, DRM, AKS, MHT, and PAO contributed to the data collection and data interpretation. CR contributed to the conception and design of the study, data collection, and data interpretation. CH was the biomarker lead for the study. PG was the medical monitor for the study and JJ was the lead statistician for the current analyses. JDW and MAP contributed to the conception and design of the study, data collection, data interpretation, and writing of the report.

Declaration of interests

FSH reports a consulting or advisory role with and research funding from Bristol-Myers Squibb and a pending patent from ImmuneTarget. JC has served on advisory boards for and received research funding from Bristol-Myers Squibb. ACP has had a paid consulting or advisory role with Amgen and Bristol-Myers Squibb, and has been paid to participate in a speakers' bureau for Bristol-Myers Squibb. CR has received honoraria from and had a paid consulting or advisory role with Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novartis, and Roche. DFM has had a paid consulting or advisory role with Bristol-Myers Squibb, Genentech, Merck, and Pfizer, and has received clinical research funding from Prometheus Labs. NM has received honoraria from and had a paid consulting or advisory role with Amgen, Bristol-Myers Squibb, GlaxoSmithKline, and Roche; provided expert testimony for Amgen, Bristol-Myers Squibb, and Roche; and has had travel or

other expenses paid or reimbursed by Roche. MSE owns stock in Abbott, Bristol-Myers Squibb, and Johnson & Johnson; has had a paid consulting or advisory role with Bristol-Myers Squibb and Merck; has received research funding from Alkermes, Argus, Bristol-Myers Squibb, ImmuNext, Johnson & Johnson, Merck, and Polynoma; and has had travel or other expenses paid or reimbursed by Bristol-Myers Squibb and Merck. DRM owns stock in Bristol-Myers Squibb; has had a paid consulting or advisory role with Atreca and Bristol-Myers Squibb; and has been paid to participate in a speakers' bureau for Bristol-Myers Squibb, GlaxoSmithKline, and Merck. AKS has received research funding from Bristol-Myers Squibb, Genentech, GlaxoSmithKline, and Merck. MHT has had a paid consulting or advisory role with Eisai, Onyx Pharmaceuticals, and PDX Pharma, and has received research funding from AstraZeneca, Bristol-Myers Squibb, Celldex, Eisai, Merck KGaA, and Novartis. PAO has had a paid consulting or advisory role with Amgen and Bristol-Myers Squibb and has received research funding from Armo Biosciences, Bristol-Myers Squibb, MedImmune, and Merck. CH is employed by and owns stock in Bristol-Myers Squibb. PG is employed by Bristol-Myers Squibb and owns stock in Abbott, Bristol-Myers Squibb, Johnson & Johnson, and Merck. JJ is employed by Bristol-Myers Squibb. JDW has received honoraria from EMD Serono and Janssen Oncology; has had a paid consulting or advisory role with Bristol-Myers Squibb, GlaxoSmithKline, Jounce Therapeutics, MedImmune, Merck, Polaris Pharma, Polynoma, Sellas Life Sciences, and Ziopharm; has received research funding from Bristol-Myers Squibb, GlaxoSmithKline, MedImmune, and Merck; is a co-investigator on an issued patent for the use of xenogeneic DNA immunisation as a means to overcome tolerance to self antigens, specifically for cancer in companion animals (pets); and has had travel or other expenses paid or reimbursed by Bristol-Myers Squibb. MAP reports advisory board participation for and research grant support from Bristol-Myers Squibb. KFG, GPL, JKG, SSA, and MS declare no competing interests.

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