Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial

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Summary

Background Previously reported results from the phase 3 CheckMate 067 trial showed a significant improvement in objective responses, progression-free survival, and overall survival with nivolumab plus ipilimumab or nivolumab alone compared with ipilimumab alone in patients with advanced melanoma. The aim of this report is to provide 4-year updated efficacy and safety data from this study.

Methods In this phase 3 trial, eligible patients were aged 18 years or older with previously untreated, unresectable, stage III or stage IV melanoma, known *BRAF*^{V600} mutation status, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned 1:1:1 to receive intravenous nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses, followed by nivolumab 3 mg/kg every 2 weeks, or nivolumab 3 mg/kg every 2 weeks plus placebo, or ipilimumab 3 mg/kg every 3 weeks for four doses plus placebo. Randomisation was done via an interactive voice response system with a permuted block schedule (block size of six) and stratification by PD-L1 status, *BRAF* mutation status, and metastasis stage. The patients, investigators, study site staff, and study funder were masked to the study drug administered. The co-primary endpoints were progression-free survival and overall survival. Efficacy analyses were done on the intention-to-treat population, whereas safety was assessed in all patients who received at least one dose of study drug. The results presented in this report reflect the 4-year update of the ongoing study with a database lock date of May 10, 2018. This study is registered with ClinicalTrials.gov, number NCT01844505.

Findings Between July 3, 2013, and March 31, 2014, 945 patients were enrolled and randomly assigned to nivolumab plus ipilimumab (n=314), nivolumab (n=316), or ipilimumab (n=315). Median follow-up was 46·9 months (IQR 10·9–51·8) in the nivolumab plus ipilimumab group, 36·0 months (10·5–51·4) in the nivolumab group, and 18·6 months (7·6–49·5) in the ipilimumab group. At a minimum follow-up of 48 months from the date that the final patient was enrolled and randomised, median overall survival was not reached (95% CI 38·2–not reached) in the nivolumab plus ipilimumab group, 36·9 months (28·3–not reached) in the nivolumab group, and 19·9 months (16·9–24·6) in the ipilimumab group. The hazard ratio for death for the combination versus ipilimumab was 0·54 (95% CI 0·44–0·67; p<0·0001) and for nivolumab versus ipilimumab was 0·65 (0·53–0·79; p<0·0001). Median progression-free survival was 11·5 months (95% CI 8·7–19·3) in the nivolumab plus ipilimumab group, 6·9 months (5·1–10·2) in the nivolumab group, and 2·9 months (2·8–3·2) in the ipilimumab group. The hazard ratio for progression-free survival for the combination versus ipilimumab was 0·42 (95% CI 0·35–0·51; p<0·0001) and for nivolumab versus ipilimumab was 0·53 (0·44–0·64; p<0·0001). Treatment-related grade 3–4 adverse events were reported in 185 (59%) of 313 patients who received nivolumab plus ipilimumab, 70 (22%) of 313 who received nivolumab, and 86 (28%) of 311 who received ipilimumab. The most common treatment-related grade 3 adverse events were diarrhoea in the nivolumab plus ipilimumab group (29 [9%] of 313) and in the nivolumab group (nine [3%] of 313) and colitis in the ipilimumab group (23 [7%] of 311); the most common grade 4 adverse event in all three groups was increased lipase (15 [5%] of 313 in the combination group, ten [3%] of 313 in the nivolumab group, and four [1%] of 311 in the ipilimumab group). Serious adverse events were not analysed for the 4-year follow-up. In total for the study, there were four treatment-related deaths: two in the nivolumab plus ipilimumab group (one cardiomyopathy and one liver necrosis), one in the nivolumab group (neutropenia), and one in the ipilimumab group (colon perforation). No additional treatment-related deaths have occurred since the previous (3-year) analysis.

Interpretation The results of this analysis at 4 years of follow-up show that a durable, sustained survival benefit can be achieved with first-line nivolumab plus ipilimumab or nivolumab alone in patients with advanced melanoma.

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Research in context

Evidence before this study

We searched PubMed and congress abstracts, including 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 from January, 2011, up to June 30, 2018. Our search focused on studies that evaluated combinations of immune checkpoint inhibitors or other combination therapies approved for the treatment of advanced melanoma. We selected studies in which overall survival was a study endpoint, and ultimately selected those with survival follow-up times of at least 3 years. We included the search terms "PD-1", "PD-L1", "CTLA-4", "BRAF", "nivolumab", "pembrolizumab", "ipilimumab", "dabrafenib", "trametinib", "encorafenib", "binimetinib", "vemurafenib", "cobimetinib", AND "melanoma"; each search term AND "melanoma" AND "overall survival"; and each search term AND "melanoma" AND "landmark analysis". Before the current report, the longest survival follow-up for patients who received an immune checkpoint inhibitor in a randomised, controlled study was from the phase 3 KEYNOTE-006 trial, which evaluated pembrolizumab monotherapy versus ipilimumab monotherapy in advanced melanoma. Updated results from this study were reported at the 2018 American Society for Clinical Oncology Annual Meeting (Chicago, IL, USA), showing a 4-year overall survival of 44% in treatment-naive patients given pembrolizumab monotherapy at a median follow-up of 45·9 months. For combination studies involving BRAF and MEK inhibitors, a phase 2 study of dabrafenib plus trametinib in patients with *BRAF*-mutant metastatic melanoma showed 4-year and 5-year overall survivals of 30% and 28%, respectively. The current study is a 4-year follow-up of the 3-year overall survival results of CheckMate 067 that were published in 2017.

Added value of this study

To the best of our knowledge, the current analysis from the CheckMate 067 trial represents the longest follow-up so far for patients who received a combination of immune checkpoint inhibitors in a randomised, controlled trial. The overall survival data are consistent with the previous report and progression-free survival data have matured. Additionally, the survival data seem to have stabilised with extended follow-up, with the emergence of an apparent plateau in the survival curves in both nivolumab-containing groups. The current report also presents new exploratory analyses of interest, which represent the longest follow-up analysis of patients who remain treatment free (off study treatment and free of subsequent therapy) and survival outcomes in patients who discontinued nivolumab plus ipilimumab early because of treatment-related adverse events.

Implications of all the available evidence

Our results show that long-term survival outcomes can be achieved with the combination of nivolumab and ipilimumab in patients with previously untreated advanced melanoma, including in patients who discontinued treatment early because of treatment-related adverse events. Although the CheckMate 067 study was not designed to compare the two nivolumab-containing groups, descriptive analyses suggest that improved 4-year survival might be achieved with nivolumab plus ipilimumab than with nivolumab alone. Importantly, patients who received nivolumab plus ipilimumab had longer treatment-free intervals and a higher proportion of patients were free of subsequent therapies at 4 years than was observed for patients who received nivolumab alone or ipilimumab alone. Median duration of response has now been reached with the combination of nivolumab and ipilimumab, and exceeded 50 months in the current analysis. Overall, our results show durable clinical benefit with nivolumab plus ipilimumab in patients with advanced melanoma, and that first-line combination therapy might reduce the need for subsequent therapy or prolong the time to subsequent therapy when needed.

Introduction

The recent evolution in the treatment landscape for advanced melanoma has been accompanied by continuously improving survival outcomes for these patients in the past 10 years. Historically, patients with advanced melanoma had a median overall survival of around 8 months and a 5-year overall survival of approximately 10%.[1] Survival outcomes began to improve in 2011 with the regulatory approval of ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 antibody, in the USA; survival follow-up of 1861 patients with advanced melanoma who had received ipilimumab in clinical and observational studies showed that approximately 20% of patients survived to 5 years or more.[2] Additionally, targeted monotherapy treatments have had a survival impact on patients with *BRAF*-mutated melanoma, with a 4-year overall survival of 17% reported with vemurafenib and a 5-year overall survival of 24% reported with dabrafenib.[3,4]

Newer agents that target the programmed death 1 receptor (PD-1) within the tumour microenvironment, thus blocking interaction with its ligands PD-L1 and PD-L2 on tumour cells,[5] have shown that overall survival times can be extended beyond those achieved with ipilimumab alone. In the phase 3 CheckMate 067[6] and KEYNOTE-006[7] trials, the anti-PD-1 agents nivolumab and pembrolizumab, respectively, have demonstrated significantly improved overall survival compared with ipilimumab monotherapy in patients with advanced melanoma. At a minimum follow-up of 36 months, 3-year overall survival was 52% with nivolumab and 34% with ipilimumab in the CheckMate 067 study.[6] In the KEYNOTE-006 study, at a median follow-up of 45·9 months (range 0·3–50·0), the proportions of previously untreated patients alive at 3 years and 4 years when treated with pembrolizumab were 51% and 44%, respectively, compared with

41% and 36%, respectively, of those treated with ipilimumab.[8]

Several combination therapies have been evaluated for advanced melanoma in recent years, and patient follow-up time is now sufficient in some of these studies to suggest that these combination therapies might provide a greater long-term overall survival benefit than approved monotherapies. In the phase 3 COMBI-d trial,[9] the BRAF inhibitor dabrafenib combined with the MEK inhibitor trametinib led to a 3-year overall survival of 44% (95% CI 36–51), compared with 32% (25–38) with dabrafenib alone, in patients with *BRAF*-mutant metastatic melanoma.[9] More recently, the results of the phase 3 COLUMBUS trial[10] in patients with *BRAF*-mutant metastatic melanoma showed a 3-year overall survival of 47% with the BRAF inhibitor encorafenib plus the MEK inhibitor binimetinib versus 32% with vemurafenib alone. In the CheckMate 067 trial,[6] involving previously untreated patients with *BRAF* wild-type or *BRAF*-mutant advanced melanoma, we previously reported a 3-year overall survival of 58% with the combination of nivolumab and ipilimumab, 52% with nivolumab alone, and 34% with ipilimumab alone. Along with a numerically higher 3-year overall survival, patients in the combination group had a longer time to subsequent therapy and a higher percentage were free of subsequent therapy at 3 years compared with patients in either of the two monotherapy groups. Moreover, in a pooled analysis of data from the phase 2 CheckMate 069 trial[11] and the CheckMate 067 trial, efficacy outcomes in patients who discontinued nivolumab plus ipilimumab early because of treatment-related adverse events were similar to those in patients who did not discontinue treatment for treatment-related adverse events.[12]

In the present Article, we provide a 4-year update of efficacy and safety data from the CheckMate 067 trial, including analyses of time without subsequent therapy, patients free of subsequent therapy, and efficacy outcomes for those who discontinued nivolumab plus ipilimumab early because of treatment-related adverse events.

Methods

Study design and participants

In this multicentre, randomised, controlled, double-blind, phase 3 trial, we recruited patients from 137 cancer centres in 21 countries (appendix pp 22–24). The study protocol is available in the appendix, and the methods have been published previously.[6] 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 (ECOG) performance status of 0 or 1, and known $BRAF^{V600}$ mutation status. Patients were also required to have measurable disease by CT or MRI scan, 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 expression). Patients who had received previous systemic anticancer therapy for unresectable or metastatic melanoma were excluded, but previous adjuvant or neoadjuvant treatment for melanoma was allowed if it was completed at least 6 weeks before randomisation, and all treatment-related adverse events had either returned to baseline or had stabilised. Exclusions included women who were pregnant or breastfeeding; patients with active brain metastases or leptomeningeal metastases; patients with ocular melanoma (mucosal melanoma was allowed); patients with active autoimmune disease or a condition requiring corticosteroids or immunosuppressive medication within 14 days of study drug administration.

All patients provided written informed consent to participate in this study. The trial was done in accordance with the provisions of the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. The study 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 1:1:1 to receive nivolumab plus ipilimumab, nivolumab alone, or ipilimumab alone by use of an interactive voice response system with a permuted block schedule (block size of six). We stratified randomisation by tumour PD-L1 status (PD-L1 positive [≥5% PD-L1 expression] *vs* PD-L1 negative [<5% PD-L1 expression] or indeterminate), *BRAF* mutation status (*BRAF* mutant *vs* *BRAF* wild-type), and metastasis stage (M10, M1a, or M1b *vs* M1c). The patients, investigators, study site staff, and study funder were masked to the study drug administered. To achieve masking, infusion volumes of the treatments were matched and placebos were provided and prepared using the same guidance as for the active treatment. Each study site assigned an unmasked pharmacist or designee, and an unmasked site monitor was assigned by the study funder to provide oversight of drug supply and study documentation. Upon progression of disease and treatment discontinuation, the investigator and patient could be unmasked to the treatment assignment through the interactive voice response system. After the 3-year analysis, the protocol was unmasked and patients who had received ipilimumab alone were discontinued from the nivolumab-matched placebo.[6]

See Online for appendix

Procedures

In the combination treatment group, patients received intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses (induction phase), then nivolumab 3 mg/kg every 2 weeks. In the monotherapy groups, patients received either intravenous nivolumab 3 mg/kg every 2 weeks plus ipilimumab-matched placebo or intravenous ipilimumab 3 mg/kg every 3 weeks for four doses plus

nivolumab-matched placebo. The treatment was continued until maximum clinical benefit (defined by the investigator) was recorded; unacceptable adverse events occurred; the patient requested to stop study treatment or withdrew consent; pregnancy; or termination of the study by the sponsor. Dose escalation or reduction was not allowed. Dose interruptions were permitted to manage treatment-related adverse events (grade 2 or worse non-skin adverse events except for grade 2 fatigue or laboratory abnormalities, or grade 3 skin adverse events or laboratory abnormalities), as well as investigator judgment for any type of adverse event.

Tumour response was assessed by the investigators according to RECIST version 1.1 using CT or MRI scans, at 12 weeks after randomisation, then every 6 weeks for the first 12 months, and then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. Progression-free survival was not centrally reviewed because the study was blinded. Patients were assessed for safety if they received any study treatment. Baseline local laboratory assessments were done 14 days before randomisation, and safety assessments were done throughout the treatment phase. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Tumour expression of PD-L1 was assessed in pretreatment samples at a central laboratory (Mosaic Laboratories, Lake Forest, CA, USA) by use of a validated, automated immunohistochemical assay (PD-L1 IHC 28-8 PharmDx; Dako, Carpinteria, CA, USA), as described.[13]

Outcomes

The co-primary endpoints of the study were progression-free survival (defined as time from randomisation to progression or death from any cause, whichever occurred first) and overall survival (defined as time from randomisation to death from any cause); these endpoints were compared between combination treatment or nivolumab monotherapy versus ipilimumab alone in all enrolled and randomly assigned patients.[6] Secondary endpoints were to compare the proportion of objective responses achieved with combination treatment or nivolumab monotherapy versus ipilimumab monotherapy treatment (defined as complete or partial responses according to RECIST 1.1); to evaluate differences in overall survival, progression-free survival, and objective responses between nivolumab plus ipilimumab versus nivolumab monotherapy (a descriptive analysis); to evaluate PD-L1 as a predictive biomarker for progression-free survival and overall survival; and to assess health-related quality of life.[6] Exploratory endpoints included duration of response (defined as time from first response to tumour progression or death, with patients censored at their last assessment if they neither progressed nor died) and the overall safety and tolerability of the three treatments.

Statistical analysis

Efficacy endpoints were analysed in the intention-to-treat population and safety was assessed in all patients who received at least one dose of study drug. Approximately 915 patients were to be randomly assigned to account for the co-primary endpoints of progression-free survival and overall survival with an α allocation of 0·01 and 0·04, respectively, applied at separate, prespecified timepoints.[6,13] The primary analysis of progression-free survival was done after all patients had at least 9 months of follow-up.[13] The primary analysis of overall survival was done at 28 months of follow-up, with 3-year follow-up also presented.[6] The current report presents a follow-up 4-year survival analysis at a database lock of May 10, 2018; a final follow-up survival analysis is planned for the 5-year follow-up. Hochberg's procedure was applied to control the overall type I error rate at 0·04 for overall survival and a Bonferroni adjustment was used to control the overall type I error rate at 0·01 for progression-free survival. We estimated time-to-event distributions (ie, progression-free survival and overall survival) and values at fixed timepoints using Kaplan-Meier methods. Hazard ratios and corresponding two-sided 95% CIs were estimated with a stratified Cox proportional hazards model, with descriptive p values also provided. The proportion of patients achieving an objective response was calculated using a two-sided Cochran-Mantel-Haenszel test for comparison between the groups. The trial design was not powered for a comparison between the two nivolumab-containing groups, but descriptive analyses without formal hypothesis testing were performed between the two nivolumab-containing groups at any timepoint. Overall survival and progression-free survival analyses were done on clinically relevant subgroups (prespecified: PD-L1 expression, *BRAF* status, metastasis stage, age, ECOG performance status, lactate dehydrogenase, and American Joint Committee on Cancer stage; post hoc: tumour lesion and tumour burden). Receiver operating characteristic (ROC) analyses were done on overall survival results based on PD-L1 expression to generate ROC curves post hoc, in an attempt to distinguish a discrimination threshold of PD-L1 expression for this endpoint.[14,15]

For this 4-year update, we also estimated the median treatment-free interval at the 4-year data cutoff (May 10, 2018). Median treatment-free interval was evaluated for all patients in each group who were alive or who had received subsequent systemic therapy and died by the time of the data cutoff. The beginning of the treatment-free interval was defined as the time of discontinuation of study therapy for all patients analysed. Patients who discontinued study follow-up or died before receipt of subsequent systemic therapy were excluded. The treatment-free interval was defined as the time from the end of study therapy (last study dose) until subsequent cancer therapy or the last known date alive (for those who never received subsequent cancer therapy). Additionally,

an exploratory analysis was done on patients who were still alive and still being followed on study at the 4-year data cutoff to ascertain the proportions of patients in each treatment group who were still on study therapy, those who were treatment free (off study therapy and free from subsequent systemic therapy), and those who had received subsequent systemic therapy. In another exploratory post-hoc analysis, survival outcomes were also evaluated for patients in the combination group who discontinued treatment early (during the induction phase) because of treatment-related adverse events compared with those who did not discontinue because of treatment-related adverse events.

We used SAS version 9.4 for all statistical analyses.

This trial is registered with ClinicalTrials.gov, number NCT01844505.

Role of the funding source

This study was designed by the sponsor, in collaboration with the lead and senior authors. Data were collected by the sponsor and were analysed and interpreted in collaboration with all authors. The study sponsor 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.

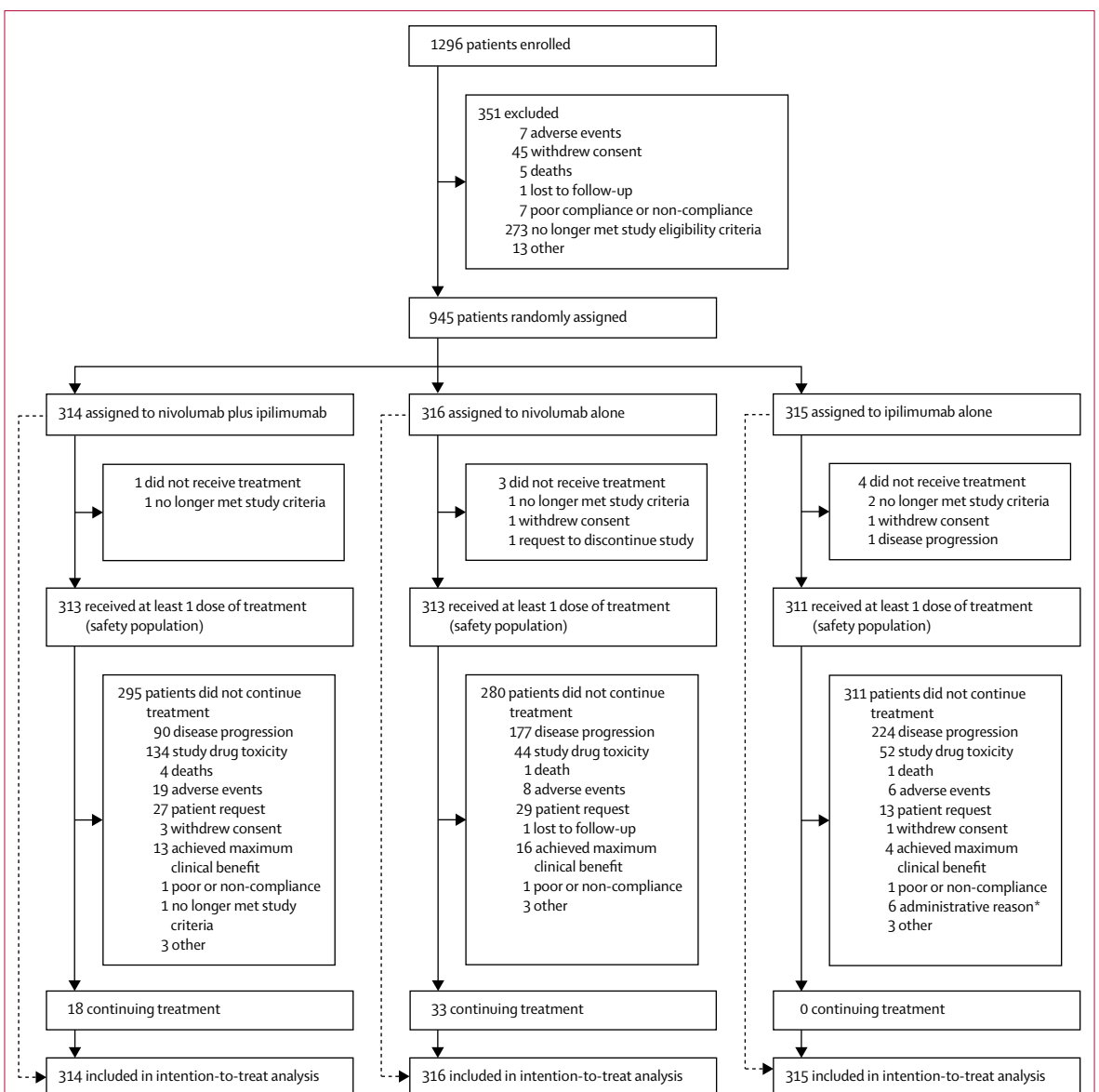

Figure 1: **Trial profile**

*Since the 3-year analysis, patients were unmasked and seven patients were discontinued from maintenance nivolumab placebo (six for an administrative reason and one a reason reported as other; this patient is represented within the three patients in this group with a reason for treatment discontinuation as "other").

Results

Between July 3, 2013, and March 31, 2014, we enrolled 1296 patients at 137 sites in 21 countries and randomly assigned 945 patients to study treatment: 314 to combination nivolumab plus ipilimumab, 316 to nivolumab alone, and 315 to ipilimumab alone (efficacy population for the primary and secondary endpoints; figure 1). The safety population consisted of 313 patients in the combination group and in the nivolumab group and 311 patients in the ipilimumab group (figure 1). Patient demographics and characteristics were generally well balanced across the treatment groups, as previously reported (appendix p 2). At the database lock on May 10, 2018, with a minimum follow-up of 4 years from the randomisation date of the final enrolled patient, the median follow-up was 46·9 months (IQR 10·9–51·8) in the combination group, 36·0 months (10·5–51·4) in the nivolumab group, and 18·6 months (7·6–49·5) in the ipilimumab group. At database lock, 51 patients were continuing treatment (18 in the combination group and 33 in the nivolumab group; figure 1). The most common reason for study discontinuation for nivolumab or ipilimumab was disease progression and the most common reason for discontinuation in the combination group was treatment-related toxicity (figure 1). In the combination group, patients received a median of four doses of nivolumab (IQR 2–32) and four doses of ipilimumab (2–4); in the monotherapy groups, patients received a median of 15 doses of nivolumab (IQR 6–54) or a median of four doses of ipilimumab (3–4).

Any subsequent therapy was received by 135 (43%) of 314 patients in the combination group, 182 (58%) of 316 in the nivolumab group, and 236 (75%) of 315 patients in the ipilimumab group, and subsequent systemic therapy was received by 104 (33%) of 314, 150 (48%) of 316, and 206 (65%) of 315 patients, respectively (appendix p 3). Excluding patients who died and did not receive subsequent therapy (ie, n=256 in the combination group, n=271 in the nivolumab group, and n=267 in the ipilimumab group), median time from randomisation to subsequent systemic therapy was not reached in the combination group, 25·2 months (95% CI 16·0–43·2) in the nivolumab group, and 8·1 months (6·5–8·7) in the ipilimumab group.

For this 4-year analysis (at a minimum follow-up of 48 months since the final patient was enrolled and randomly assigned), in the combination group, 182 (58%) of 314 patients had a progression-free survival event, along with 201 (64%) of 316 patients in the nivolumab group, and 258 (82%) of 315 in the ipilimumab group. Median progression-free survival was 11·5 months (95% CI 8·7–19·3) in the combination group, 6·9 months (5·1–10·2) in the nivolumab group, and 2·9 months (2·8–3·2) in the ipilimumab group, with 4-year progression-free survival of 37% (95% CI 31–42) in the combination group, 31% (25–36) in the nivolumab group, and 9% (6–13) in the ipilimumab group (figure 2A). The hazard ratio for progression-free survival for the combination versus ipilimumab was 0·42 (95% CI 0·35–0·51; p<0·0001) and for nivolumab versus ipilimumab was 0·53 (0·44–0·64; p<0·0001). In a descriptive analysis, the hazard ratio for progression-free survival with nivolumab plus ipilimumab versus nivolumab was 0·79 (95% CI 0·65–0·97).

In the intention-to-treat population, at data cutoff, the numbers of patients who had died were 147 (47%) of 314 patients in the combination group, 168 (53%) of 316 in the nivolumab group, and 218 (69%) of 315 in the ipilimumab group. Median overall survival was not reached (95% CI 38·2–not reached) in the combination group, 36·9 months (28·3–not reached) in the nivolumab group, and 19·9 months (16·9–24·6) in the ipilimumab group (figure 2B). 4-year overall survival was 53% (95% CI 47–58) in the combination group, 46% (41–52) in the nivolumab group, and 30% (25–35) in the ipilimumab group. The hazard ratio for overall survival for the combination versus ipilimumab was 0·54 (95% CI 0·44–0·67; p<0·0001) and for nivolumab versus ipilimumab was 0·65 (0·53–0·79; p<0·0001); the descriptive hazard ratio for the combination versus nivolumab was 0·84 (0·67–1·05). Subgroup analyses (most of which were prespecified) of progression-free survival and overall survival are shown in the appendix (pp 13–16). Overall, both progression-free and overall survival outcomes were significantly better in the nivolumab-containing groups than in the ipilimumab monotherapy group for most subgroups assessed, with some exceptions (appendix pp 14–15). In an analysis of overall survival by *BRAF* mutation status, 4-year overall survival for patients with *BRAF*-mutated tumours was 62% (95% CI 52–71) in the combination group, 50% (39–59) in the nivolumab group, and 33% (24–42) in the ipilimumab group, whereas these results for patients with wild-type *BRAF* were 49% (42–55), 45% (38–52), and 28% (22–35), respectively (appendix pp 17–18). In a descriptive comparison between treatments in patients with a *BRAF* mutation, the combination treatment seemed to provide more benefit than nivolumab monotherapy, with a progression-free survival hazard ratio of 0·62 (95% CI 0·44–0·88) and an overall survival hazard ratio of 0·70 (95% CI 0·46–1·07; appendix p 16).

In another analysis, using a 5% cutoff for tumour PD-L1 expression (the percentage used as a study stratification factor), in patients with less than 5% PD-L1 expression, 4-year overall survival was 52% (95% CI 45–58) in the combination group, 45% (38–52) in the nivolumab group, and 28% (22–35) in the ipilimumab group, whereas in patients with 5% or more PD-L1 expression these values were 61% (48–71), 54% (42–64), and 36% (25–47), respectively (appendix pp 13–16, 19–20). For all PD-L1 expression levels evaluated, both progression-free survival and overall survival in the combination group were significantly improved versus ipilimumab monotherapy (appendix p 15). In a comparison of nivolumab versus ipilimumab monotherapy,

progression-free survival was significantly better with nivolumab versus ipilimumab at all PD-L1 expression levels, and overall survival was significantly better with nivolumab at some—but not all—PD-L1 expression levels (appendix p 14). Additionally, compared with the 3-year analysis of overall survival with the combination versus nivolumab in patients with at least 5% PD-L1 expression, greater separation was observed between the overall survival curves for the combination group and the nivolumab group (hazard ratio for overall survival of 0·99 at the 3-year analysis and 0·86 [95% CI 0·53–1·41] in the current analysis).[6] Time-dependent ROC curves generated for PD-L1 expression for the 4-year overall survival outcome showed that PD-L1 alone is an insufficient predictive biomarker of overall survival, since area under the curve (AUC) values were 0·54 (95% CI 0·47–0·61) for the combination group and 0·55 (0·49–0·62) for the nivolumab group (appendix p 21).[14,15] Similar results to the overall survival results were observed in progression-free survival by PD-L1 status (appendix pp 4, 13–16), and objective responses were higher in the combination therapy group than with nivolumab alone or with ipilimumab alone for all PD-L1 levels assessed (appendix p 4).

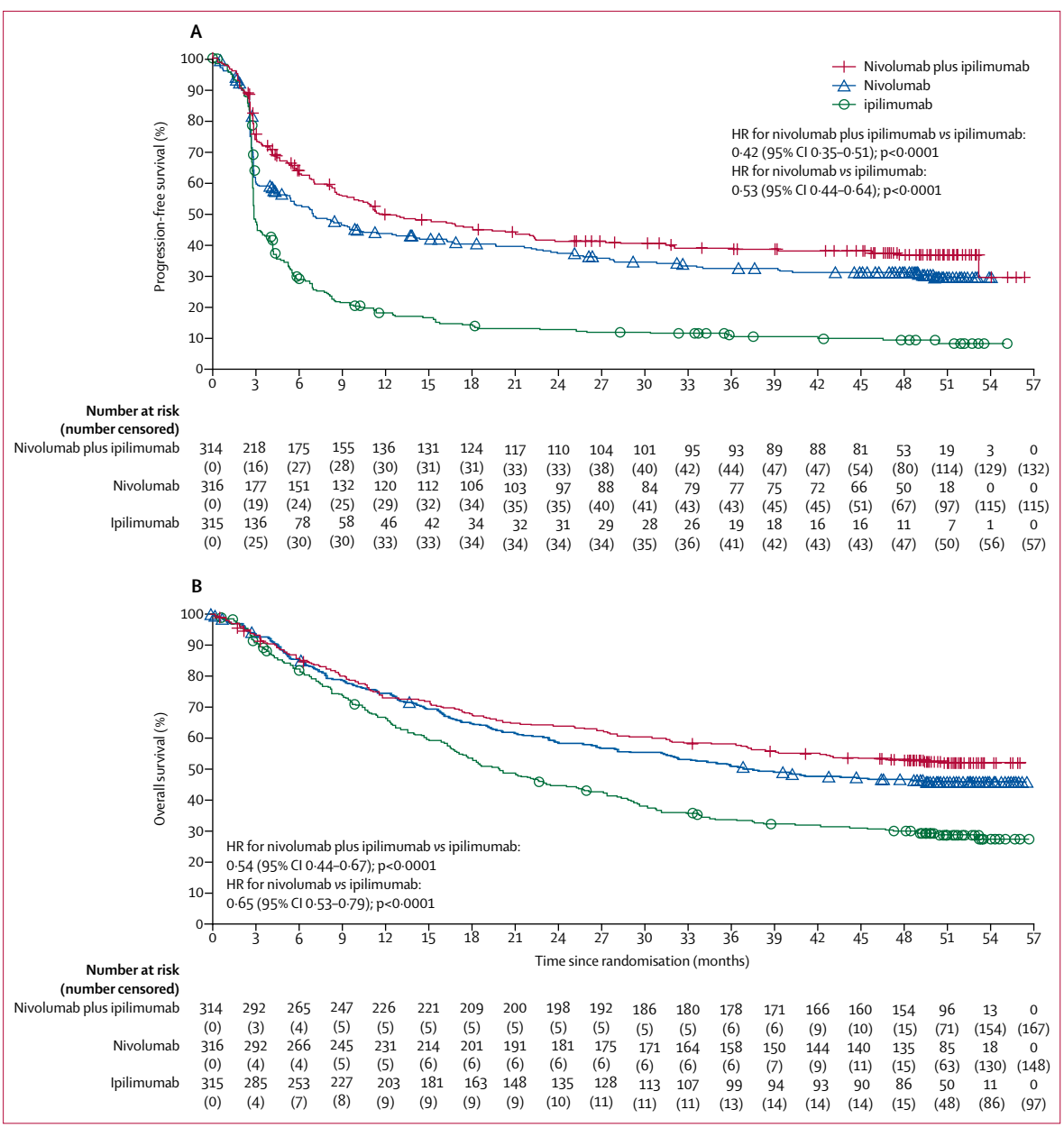

Figure 2: **Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival**
HR=hazard ratio.

	Nivolumab plus ipilimumab group (n=314)	Nivolumab group (n=316)	Ipilimumab group (n=315)
Best overall response, n (%)			
Complete response	67 (21%)	56 (18%)	16 (5%)
Partial response	116 (37%)	85 (27%)	44 (14%)
Stable disease	38 (12%)	30 (10%)	68 (22%)
Progressive disease	74 (24%)	121 (38%)	159 (51%)
Unable to determine	19 (6%)	24 (8%)	28 (9%)
Objective responses*			
Number of patients (% [95% CI])	183 (58% [52·6–63·8])	141 (45% [39·1–50·3])	60 (19% [14·9–23·8])
Odds ratio for comparison (95% CI), p value†	6·35 (4·38–9·22), p<0·0001	3·54 (2·46–5·10), p<0·0001	..
Duration of response			
Ongoing responders/patients with objective response (%)	71/183 (39%)	53/141 (38%)	34/60 (57%)
Median duration of response, months (95% CI)	50·1 (44·0–NR)	NR (45·7–NR)	14·4 (8·3–NR)

Data are n (%), n (% [95% CI]), or n/N (%), unless otherwise indicated. NR=not reached. *Data include patients with a complete response or partial response; 95% CI based on Clopper and Pearson method. †Compared with ipilimumab.

Table 1: **Responses to treatment**

Objective responses remained consistent with those recorded at the 3-year analysis[6] and were achieved by 183 (58%) of 314 patients in the combination group, 141 (45%) of 316 patients in the nivolumab group, and 60 (19%) of 315 patients in the ipilimumab group. However, the best overall responses increased slightly in this updated analysis, with complete responses achieved by 67 (21%) of 314 patients in the combination group, 56 (18%) of 316 patients in the nivolumab group, and 16 (5%) of 315 patients in the ipilimumab group (table 1), whereas at 3 years the numbers of patients with a complete response were 61 (19%) of 314 in the combination group, 52 (16%) of 316 in the nivolumab group, and 16 (5%) of 315 in the ipilimumab group. The median duration of objective response was 50·1 months (95% CI 44·0–not reached) in the combination group, not reached (45·7–not reached) in the nivolumab group, and 14·4 months (8·3–not reached) in the ipilimumab group.

In a post-hoc analysis at this 4-year update, we investigated patients off study treatment. Median treatment-free interval was longer in the combination group than in the nivolumab group or ipilimumab group (figure 3A). Additionally, a higher proportion of patients who were alive at the time of the 4-year analysis were treatment free (off study treatment and free of systemic subsequent therapy) in the combination group than in either of the monotherapy groups (figure 3B).

In a separate post-hoc analysis in the combination group, both progression-free survival and overall survival outcomes were similar at 4 years regardless of whether patients discontinued treatment early because of treatment-related adverse events (figure 4). In the combination group, median progression-free survival was 11·1 months (95% CI 6·9–26·7; 43 events in 74 patients) and median overall survival was not reached (95% CI 30·5–not reached; 35 events in 74 patients) in patients who discontinued because of treatment-related adverse events during the induction phase, and 8·6 months (95% CI 5·3–13·2; 120 events in 187 patients) and 37·1 months (25·1–not reached; 98 events in 187 patients), respectively, in patients who did not discontinue treatment because of a treatment-related adverse event. 4-year progression-free survival was 35% (95% CI 23–47) in patients who discontinued nivolumab plus ipilimumab early because of treatment-related adverse events during the induction phase, and 30% (23–37) in those who did not discontinue treatment because of a treatment-related adverse event, and 4-year overall survival was 54% (95% CI 42–64) versus 46% (39–54), respectively.

At this 4-year update, treatment-related adverse events were consistent with those previously reported and occurred in 300 (96%) of 313 patients in the combination group, 270 (86%) of 313 patients in the nivolumab group, and 268 (86%) of 311 patients in the ipilimumab group; treatment-related grade 3–4 adverse events occurred in 185 (59%) of 313, 70 (22%) of 313, and 86 (28%) of 311 patients, respectively (table 2, appendix pp 5–8).[6] The most common treatment-related grade 3 adverse events were diarrhoea in the nivolumab plus ipilimumab group (29 [9%] of 313) and in the nivolumab group (nine [3%] of 313) and colitis in the ipilimumab group (23 [7%] of 311); the most common grade 4 adverse event in all three groups was increased lipase (15 [5%] of 313 in the combination group, ten [3%] of 313 in the nivolumab group, and four [1%] of 311 in the ipilimumab group). Serious adverse events were not analysed for the 4-year follow-up. Treatment-related adverse events of any grade that led to discontinuation of treatment were reported in 126 (40%) of 313 patients in the combination group, 39 (13%) of 313 patients in the nivolumab group, and 47 (15%) of 311 patients in the ipilimumab group, including treatment-related grade 3–4 adverse events that led to discontinuation in 95 (30%) of 313, 25 (8%) of 313, and 42 (14%) of 311 patients, respectively. The most common reasons for discontinuation due to treatment-related adverse events were diarrhoea in the nivolumab group (in seven [2%] of 313 patients), and colitis in the combination group and ipilimumab group (in 30 [10%] of 313 and 21 [7%] of 311 patients, respectively). Potentially immune-related adverse events were reported with a similar frequency as in the original report, and those of any grade that occurred in at least 2% of patients are listed in appendix pp 9–10.[6] As reported previously, most treatment-related potentially immune-related adverse events had a quicker time to onset in both the combination therapy and ipilimumab groups compared with the nivolumab group, and most treatment-related grade 3 or worse adverse events requiring immune-modulating medication resolved within 6 weeks, except

endocrine adverse events that might require long-term hormone therapy (appendix pp 11–12).[6]

As of the 4-year analysis, deaths were reported for 146 (47%) of 313 patients in the combination group (123 disease progression, two study drug toxicity, and 21 unknown or other), 167 (53%) of 313 patients in the nivolumab group (145 progression, one study drug toxicity, and 21 unknown or other), and 216 (70%) of 311 patients in the ipilimumab group (197 progression, one study drug toxicity, and 18 unknown or other). In total, and as previously reported, two treatment-related deaths occurred within 100 days after the last dose of study drug (neutropenia [n=1] in the nivolumab group and colon perforation [n=1] in the ipilimumab group), and two treatment-related deaths occurred more than 100 days after the last treatment (cardiomyopathy [n=1] and liver necrosis [n=1], both in the combination group).[6] No new treatment-related deaths have occurred since the 3-year analysis.

Discussion

This 4-year analysis of the CheckMate 067 trial showed similar overall survival benefit with the combination of nivolumab and ipilimumab to the 3-year update with matured progression-free survival results and no new safety concerns. Median overall survival was not reached in the nivolumab plus ipilimumab group and 36·9 months in the nivolumab group versus 19·9 months in the ipilimumab group. Median progression-free survival was 11·5 months in the nivolumab plus ipilimumab group, 6·9 months in the nivolumab group, and 2·9 months in the ipilimumab group. To the best of our knowledge, the current analysis represents the longest follow-up so far for patients who received nivolumab and ipilimumab combination therapy in a randomised, controlled trial and showed that more than half of the patients treated with nivolumab plus ipilimumab (53%) survived to 4 years. Also to the best of our knowledge, this improved overall survival has not been described with any available treatment at this follow-up time in a randomised setting, demonstrating long-term benefit of this treatment combination in this setting.

Although this study was not designed for a formal comparison between the nivolumab-containing groups, the continued separation of the survival curves could suggest sustained improvement of survival for the combination over nivolumab monotherapy. With more mature data and further follow-up since the initial overall survival analysis, descriptive analyses continued to show improved overall survival with nivolumab plus ipilimumab compared with nivolumab alone (3-year analysis, 58% and 52%, respectively; 4-year analysis, 53% and 46%, respectively).[6] The observed separation of the survival curves between the groups is not surprising, in view of the long-term survival associated with ipilimumab monotherapy,[2] and was also apparent across patient subgroups, including *BRAF* mutation status.

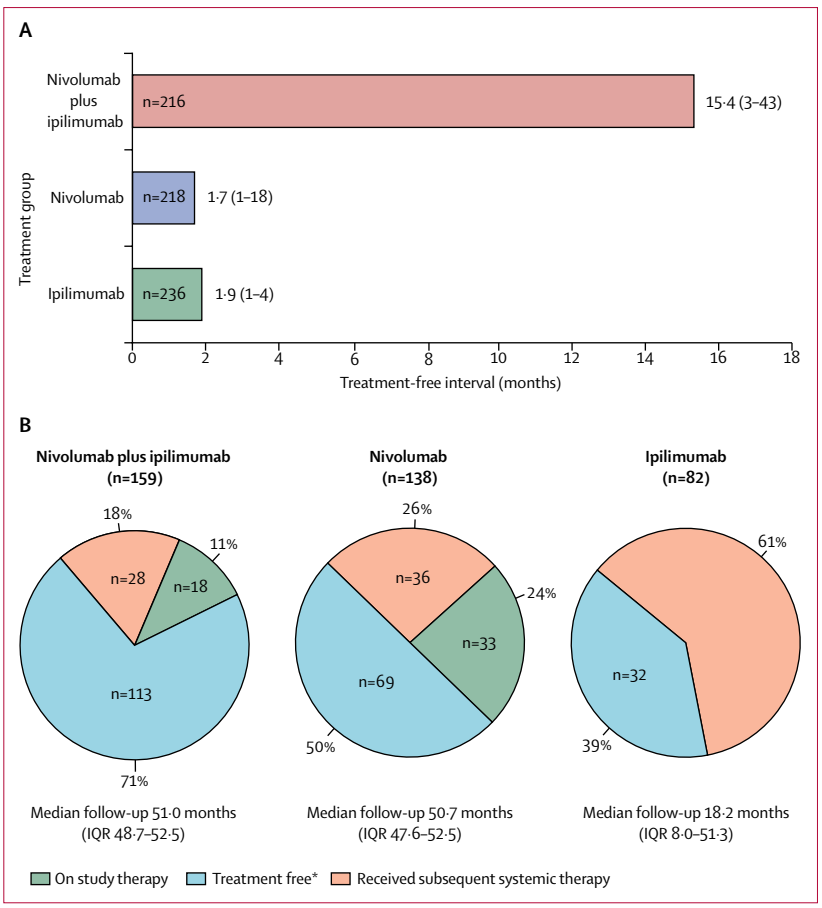

Figure 3: **Post-hoc analyses of treatment-free interval and post-treatment outcomes in each group**
(A) Median (IQR) treatment-free interval. In the combination group, 216 patients from the treated population were included in the treatment-free interval analysis and 97 were excluded (ie, were still on study treatment, died and never received subsequent systemic therapy, or were lost to follow-up); in the nivolumab group, 218 patients were included and 95 were excluded; and in the ipilimumab group, 236 patients were included and 75 were excluded. (B) Proportion of patients alive at the 4-year data cutoff who were still on therapy, treatment free, or received subsequent systemic therapy. *Off study therapy for any reason and never received subsequent systemic therapy.

Consistent with the initial analysis, regardless of PD-L1 expression, both combination therapy and nivolumab monotherapy showed improved objective responses, progression-free survival, and overall survival over ipilimumab.[6,13] Additionally, combination therapy showed improved objective responses, progression-free survival, and overall survival over nivolumab monotherapy. The current analysis showed that with longer follow-up, further separation in overall survival curves has emerged between the nivolumab-containing groups for tumour PD-L1 expression ≥5% (hazard ratio of 0·99 at the 3-year analysis *vs* 0·86 in the current analysis), suggesting an improved overall benefit with the combination for this population that is becoming more apparent with longer follow-up.[6] Variations in overall survival results across PD-L1 cutoffs analysed combined with time-dependent ROC curves generated for PD-L1 expression for the 4-year overall survival outcome suggest that PD-L1 alone is a poor predictive biomarker of overall survival.

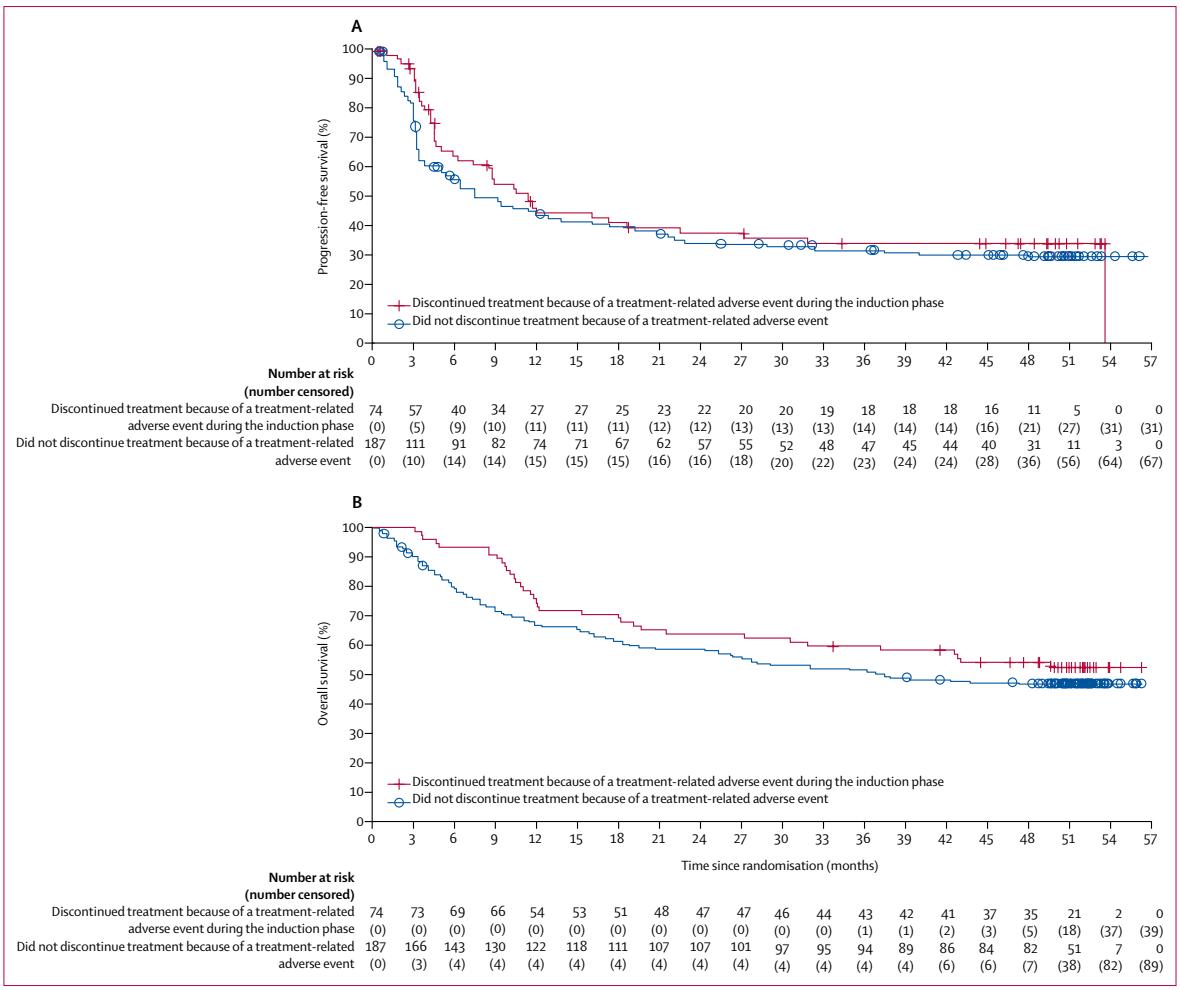

Figure 4: **Post-hoc Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival in patients treated with combination therapy who discontinued treatment because of a treatment-related adverse event during the induction phase and those who did not discontinue treatment because of a treatment-related adverse event**

Across the three treatment groups, fewer patients initially treated with nivolumab plus ipilimumab than in either of the monotherapy groups had received subsequent therapy at the time of the current analysis. In a descriptive analysis, the median time from randomisation to subsequent systemic therapy was also longer in the combination group than in either of the two monotherapy groups. Thus, our results suggest that combination therapy might reduce the need for subsequent therapies or prolong the time to initiation of subsequent therapies when they are needed. Indeed, among patients who were still alive at 4 years, 50% of patients treated with nivolumab and 71% of patients treated with the combination were treatment free (ie, off study treatment and had not received subsequent therapy). The effect was more pronounced in patients receiving combination therapy, shown by the longer median treatment-free interval in the combination group than in the nivolumab monotherapy group or the ipilimumab monotherapy group.

Although objective responses in each treatment group have remained consistent with the previous analyses,[6,13] the proportions of patients with complete responses have continued to increase, especially in the nivolumab plus ipilimumab combination group. These results are consistent with the possibility that best overall responses can improve over time with immune checkpoint inhibitors, even without further treatment.

Patients with *BRAF*-mutant metastatic melanoma have several options for initial therapy. 3-year overall survival was 44% (95% CI 36–51) in the phase 3 COMBI-d trial[9] of dabrafenib plus trametinib and was 47% in the phase 3 COLUMBUS trial[10] of encorafenib plus binimetinib. Long-term follow-up of a phase 2 trial of patients treated with dabrafenib plus trametinib showed a 5-year overall survival of 28% (95% CI 17–41) or 33%, depending on trametinib dose (2 mg/day *vs* 1 mg/day).[16] Although direct comparisons cannot be made between studies, in CheckMate 067 the 3-year and 4-year survival results for nivolumab plus ipilimumab in patients with

	Nivolumab plus ipilimumab group (n=313)			Nivolumab group (n=313)			Ipilimumab group (n=311)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse event	115 (37%)	151 (48%)	34 (11%)	200 (64%)	54 (17%)	16 (5%)	181 (58%)	74 (24%)	12 (4%)
Diarrhoea	112 (36%)	29 (9%)	1 (<1%)	60 (19%)	9 (3%)	0	87 (28%)	18 (6%)	0
Fatigue	107 (34%)	13 (4%)	0	111 (36%)	3 (1%)	0	86 (28%)	3 (1%)	0
Pruritus	106 (34%)	6 (2%)	0	68 (22%)	1 (<1%)	0	112 (36%)	1 (<1%)	0
Rash	83 (27%)	10 (3%)	0	73 (23%)	1 (<1%)	0	64 (21%)	5 (2%)	0
Nausea	81 (26%)	7 (2%)	0	41 (13%)	0	0	49 (16%)	2 (1%)	0
Pyrexia	58 (19%)	1 (<1%)	1 (<1%)	21 (7%)	0	0	20 (6%)	1 (<1%)	0
Decreased appetite	56 (18%)	4 (1%)	0	35 (11%)	0	0	40 (13%)	1 (<1%)	0
Hypothyroidism	53 (17%)	1 (<1%)	0	32 (10%)	0	0	14 (5%)	0	0
Vomiting	41 (13%)	7 (2%)	0	21 (7%)	1 (<1%)	0	23 (7%)	1 (<1%)	0
Arthralgia	41 (13%)	2 (1%)	0	31 (10%)	1 (<1%)	0	22 (7%)	0	0
Headache	33 (11%)	2 (1%)	0	24 (8%)	0	0	25 (8%)	1 (<1%)	0
Increased aspartate aminotransferase	33 (11%)	18 (6%)	1 (<1%)	11 (4%)	3 (1%)	0	10 (3%)	2 (1%)	0
Increased alanine aminotransferase	33 (11%)	25 (8%)	2 (1%)	9 (3%)	3 (1%)	1 (<1%)	7 (2%)	4 (1%)	1 (<1%)
Dyspnoea	33 (11%)	3 (1%)	0	18 (6%)	1 (<1%)	0	12 (4%)	0	0
Maculopapular rash	32 (10%)	6 (2%)	0	14 (5%)	2 (1%)	0	37 (12%)	1 (<1%)	0
Hyperthyroidism	32 (10%)	3 (1%)	0	14 (5%)	0 (0%)	0	3 (1%)	0	0
Vitiligo	28 (9%)	0	0	30 (10%)	1 (<1%)	0	16 (5%)	0	0
Hypophysitis	19 (6%)	5 (2%)	0	1 (<1%)	1 (<1%)	0	7 (2%)	5 (2%)	0
Increased amylase	17 (5%)	9 (3%)	0	14 (5%)	7 (2%)	0	11 (4%)	3 (1%)	1 (<1%)
Colitis	14 (5%)	25 (8%)	1 (<1%)	5 (2%)	3 (1%)	0	11 (4%)	23 (7%)	1 (<1%)
Increased lipase	11 (4%)	19 (6%)	15 (5%)	13 (4%)	6 (2%)	10 (3%)	6 (2%)	8 (3%)	4 (1%)
Dehydration	9 (3%)	5 (2%)	0	1 (<1%)	0	0	3 (1%)	2 (1%)	0
Adrenal insufficiency	5 (2%)	5 (2%)	1 (<1%)	2 (1%)	2 (1%)	0	3 (1%)	1 (<1%)	0
Increased transaminases	2 (1%)	9 (3%)	1 (<1%)	1 (<1%)	1 (<1%)	0	3 (1%)	0	0
Hepatotoxicity	2 (1%)	8 (3%)	0	0	1 (<1%)	0	1 (<1%)	0	0
Hepatitis	2 (1%)	5 (2%)	0	0	0	0	0	0	0

Data are n (%). The table shows grade 1–2 adverse events occurring in at least 10% of patients in any treatment group and all grade 3 and 4 adverse events occurring in at least 2% of patients in any treatment group. A complete table of adverse events showing grade 1–2 events occurring in at least 5% of patients in any group and all grade 3 and 4 events is in the appendix (pp 5–8).

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

BRAF-mutant metastatic melanoma were 68% and 62%, respectively; notably, however, this subgroup of patients might have been generally healthier (ie, with a lower incidence of poor prognostic factors) than the patients enrolled in COMBI-d or COLUMBUS. Moreover, the median duration of response for dabrafenib plus trametinib was 12·0 months (95% CI 9·3–17·1) in the COMBI-d trial (which enrolled patients with *BRAF* mutations), whereas the median duration of response for nivolumab plus ipilimumab in CheckMate 067 (which enrolled patients with wild-type and mutant *BRAF*) was 50·1 months (95% CI 44·0–not reached) in the overall population of both studies.[9]

The updated safety analysis was similar to the prior analysis, with no new safety signals recorded. Importantly, no new deaths related to study drug have occurred since the previous safety analysis. Although 30% of patients experienced grade 3–4 adverse events with combination therapy that led to early discontinuation of treatment, the rates of discontinuation because of drug-related adverse events were consistent with the previous analysis.[6] Moreover, long-term immunological memory for the nivolumab plus ipilimumab combination treatment is suggested by the fact that the 4-year overall survival and progression-free survival results were similar in patients who discontinued treatment early because of an adverse event and those who did not. A recent study of combined anti-CTLA-4 and PD-1 therapy (nivolumab plus ipilimumab or pembrolizumab plus ipilimumab) in metastatic melanoma has shown that anti-PD-1 treatment of patients who had received combination checkpoint therapy can induce responses (56 [70%] of 80 patients achieved a complete response or partial response); however, almost 40% of patients experienced recurrent or clinically significant distinct toxicities.[17]

This study has some notable limitations caused by the non-hypothesis-based analyses in the study. Although informative, inherent limitations always exist with a

post-hoc analysis, such as the treatment-free analyses in this study. Another limitation is the absence of potential statistical comparison between nivolumab plus ipilimumab combination treatment and nivolumab monotherapy because of the study design. Additionally, the unblinding of the study following the 3-year analysis might have affected the results of the follow-up analyses. However, at the time of unblinding, most patients were no longer on study therapy, and this change allowed for those patients randomly assigned to the ipilimumab group to discontinue nivolumab-matched placebo. Finally, the absence of quality-of-life data could be viewed as a limitation of the study. Although quality-of-life data might offer insight to the benefit-to-risk ratio of the combination treatment, evaluation at this long-term follow-up would be confounded by the fact that most patients are no longer on study therapy and might have received one or more subsequent therapies. Therefore, the data would provide little additional insight relating to the study treatments.

In conclusion, our updated results show that a durable, sustained clinical benefit can be achieved with first-line nivolumab plus ipilimumab or nivolumab alone in patients with advanced melanoma, regardless of *BRAF* mutation status, and with the possibility of improved survival outcomes with the combination treatment than with nivolumab monotherapy. The results also indicate that PD-L1 status is insufficient to predict a benefit from combination therapy. Patients continue to be followed up in this study, and future analyses will focus on long-term survival outcomes for the combination and nivolumab monotherapy groups.

Contributors

FSH, JL, and JDW contributed to the conception and design of the study, patients' treatment, data acquisition, data interpretation, and writing of the report. VC-S, RG, J-JG, PR, CLC, CDL, DS, JW, RD, PFF, MS, AH, DH, and IM-R contributed to patients' treatment, data acquisition, data interpretation, and writing of the report. JJ is the lead statistician and JR is the medical monitor. All authors approved the final version of the manuscript.

Declaration of interests

FSH has received research grant support from and had a paid consulting or advisory role with Bristol-Myers Squibb; has had a paid consulting or advisory role with Aduro, Partners Therapeutics, Sanofi, Pfizer, 7 Hills Pharma, Verastem, Pionyr, Merck, EMD Serono, Novartis, Celldex, Genentech/Roche, Incyte, Apricity, Bayer, and Amgen; is a co-investigator on an issued patent on the use of tumour antigens; has four pending patents and one issued patent on therapeutic peptides; and has three pending patents on the methods for treating MHC class I chain-related molecules A (MICA)-related disorders, angiopoietin-2 biomarkers predictive of anti-immune checkpoint response, and compositions and methods for identifying and treating PD-L1 isoforms. VC-S has had a paid consulting or advisory role with Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, Novartis, and Merck Serono. RG has received research funding support from Amgen, Incyte, Novartis, Checkmate Pharmaceuticals, Boston Biomedical, Takeda/Millennium, Syndax, Reata, Array BioPharma, Dynavax, Prometheus, Eisai, and Celldex; reports advisory board participation for and research funding support from Incyte and Novartis; and has had a paid consulting or advisory role and had travel or other expenses paid or reimbursed by New Link Genetics. J-JG has had a paid consulting or advisory role with Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Merck, Amgen, and Pierre Fabre. PR has had a paid consulting or advisory role with and has received honoraria from Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Amgen, Pfizer, and Blueprint Medicines. CLC reports advisory board participation for and research grant support from Bristol-Myers Squibb. CDL has received research funding from Bristol-Myers Squibb. DS has had a paid consulting or advisory role with and received research grant support from Bristol-Myers Squibb; and has received honoraria from Bristol-Myers Squibb, Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Merck Sharp & Dohme, Incyte, Regeneron, 4SC, AstraZeneca, Immunocore, Pierre Fabre, Merck-EMD, Pfizer, Philogen, and Array BioPharma. JW has had a paid consulting or advisory role with and has received research grant support from Pfizer, Bristol-Myers Squibb, Roche, Merck, Astellas, Johnson & Johnson, AstraZeneca, and Bayer. RD has had a paid consulting or advisory role with Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Amgen, Takeda, and Pierre Fabre. PFF has had a paid consulting or advisory role with and has had travel or other expenses paid or reimbursed by Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, and Novartis. MS has received honoraria from Bristol-Myers Squibb, Merck, Novartis, and Roche. AH has received honoraria from Bristol-Myers Squibb and Merck; and has had travel or other expenses paid or reimbursed by Merck. DH has had a paid consultancy or advisory role with Bristol-Myers Squibb, EMD Serono, Merck, Novartis, and Roche. IM-R has had a paid consulting or advisory role with Bristol-Myers Squibb, Merck, Novartis, Roche, Amgen, and Pierre Fabre; and has had travel or other expenses paid or reimbursed by Bristol-Myers Squibb and Merck. JR and JJ are employed by Bristol-Myers Squibb. JL has had a paid consulting or advisory role with Eisai, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Kymab, Pfizer, Novartis, Roche/Genentech, Secarna, Pierre Fabre, and EUSA Pharma; and has received research grant support from Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, and Novartis. JDW has had a paid consulting or advisory role with Advaxis, Bristol-Myers Squibb, Ono, Celgene, Merck, Genentech, and MedImmune; and has received research funding from Bristol-Myers Squibb, Merck, Genentech, and MedImmune. In addition, for non-related work, JDW has been a paid consultant and has stock ownership with BeiGene and Apricity Therapeutics; is co-founder, has been a paid consultant, and has stock ownership with Potenza Therapeutics, Tizona Therapeutics, and Imvaq Therapeutics; has stock ownership with Adaptive Biotech; and has been a paid consultant with Surface Oncology, Polaris Pharma, Polynoma, Array BioPharma, Ascentage Pharma, Puretech, Chugai, FStar, Amgen, Sellas Life Sciences, Serametrix, Neon Therapeutics, Eli Lilly, Kleo Pharma, PsiOxus Therapeutics, Syndax, and Recepta Biopharma.

Data sharing

Bristol-Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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