Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial

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Summary

Background Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, can result in durable responses in patients with melanoma who have progressed after ipilimumab and BRAF inhibitors. We assessed the efficacy and safety of nivolumab compared with investigator's choice of chemotherapy (ICC) as a second-line or later-line treatment in patients with advanced melanoma.

Methods In this randomised, controlled, open-label, phase 3 trial, we recruited patients at 90 sites in 14 countries. Eligible patients were 18 years or older, had unresectable or metastatic melanoma, and progressed after ipilimumab, or ipilimumab and a BRAF inhibitor if they were *BRAF*^{V600} mutation-positive. Participating investigators randomly assigned (with an interactive voice response system) patients 2:1 to receive an intravenous infusion of nivolumab 3 mg/kg every 2 weeks or ICC (dacarbazine 1000 mg/m² every 3 weeks or paclitaxel 175 mg/m² combined with carboplatin area under the curve 6 every 3 weeks) until progression or unacceptable toxic effects. We stratified randomisation by *BRAF* mutation status, tumour expression of PD-L1, and previous best overall response to ipilimumab. We used permuted blocks (block size of six) within each stratum. Primary endpoints were the proportion of patients who had an objective response and overall survival. Treatment was given open-label, but those doing tumour assessments were masked to treatment assignment. We assessed objective responses per-protocol after 120 patients had been treated with nivolumab and had a minimum follow-up of 24 weeks, and safety in all patients who had had at least one dose of treatment. The trial is closed and this is the first interim analysis, reporting the objective response primary endpoint. This study is registered with ClinicalTrials.gov, number NCT01721746.

Findings Between Dec 21, 2012, and Jan 10, 2014, we screened 631 patients, randomly allocating 272 patients to nivolumab and 133 to ICC. Confirmed objective responses were reported in 38 (31·7%, 95% CI 23·5–40·8) of the first 120 patients in the nivolumab group versus five (10·6%, 3·5–23·1) of 47 patients in the ICC group. Grade 3–4 adverse events related to nivolumab included increased lipase (three [1%] of 268 patients), increased alanine aminotransferase, anaemia, and fatigue (two [1%] each); for ICC, these included neutropenia (14 [14%] of 102), thrombocytopenia (six [6%]), and anaemia (five [5%]). We noted grade 3–4 drug-related serious adverse events in 12 (5%) nivolumab-treated patients and nine (9%) patients in the ICC group. No treatment-related deaths occurred.

Interpretation Nivolumab led to a greater proportion of patients achieving an objective response and fewer toxic effects than with alternative available chemotherapy regimens for patients with advanced melanoma that has progressed after ipilimumab or ipilimumab and a BRAF inhibitor. Nivolumab represents a new treatment option with clinically meaningful durable objective responses in a population of high unmet need.

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See Online for interview with Jeffery Weber

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Introduction

The checkpoint inhibitor protein PD-1 is located on T cells and pro-B cells, and interacts with its ligands PD-L1 and PD-L2 to inhibit T cell activation and proliferation, thereby promoting immunological self-tolerance.[1–5] PD-1 is highly expressed on T cells from patients with tumours, and causes tumour-related immune suppression.[6] Checkpoint protein inhibition directed against the interaction of PD-1 with PD-L1 on tumour cells has emerged as an effective therapeutic option for various cancers, including melanoma, renal cell cancer, and non-small-cell lung cancer.[7] High proportions of patients achieving a response with excellent duration have occurred in patients with metastatic melanoma given antibodies that block PD-1.[7–14] Patients with head and neck squamous cancer, ovarian cancer, bladder cancer, and Hodgkin's lymphoma are also responsive to antibody treatment directed against PD-1 and PD-L1.[15–18]

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Research in context

Evidence before this study

To identify other studies of inhibitors of PD-1 or PD-L1 in advanced cancers, including melanoma, we did a detailed search of PubMed and congress abstracts from the annual meetings of the American Society of Clinical Oncology, European Society of Medical Oncology/European Cancer Congress, and Society for Melanoma Research, between Jan 1, 2010 and Jan 13, 2015. We used the search terms "PD-1", "PD-L1", "nivolumab", "MK-3475", "pembrolizumab", "lambrolizumab", "MPDL3280A", and "MEDI4736". Our search identified several non-randomised, non-controlled phase 1/2 studies with promising levels of antitumour response for PD-1 and PD-L1 inhibitors in patients with advanced solid tumours, including melanoma. Although these data suggest activity for PD-1 inhibition in patients with melanoma that have progressed after ipilimumab and BRAF inhibitors, the sample sizes were too small to allow firm conclusions to be drawn on the efficacy and safety of PD-1 inhibition. Our review identified only one randomised, controlled, phase 3 study comparing an anti-PD-1 drug (nivolumab) with dacarbazine, but this study was done in treatment-naive patients who had *BRAF* wild-type tumours.

Added value of this study

For the patient population investigated in this study, treatment options are very restricted, and no prospective, randomised, controlled trial comparing an anti-PD-1 drug with any approved treatment has been done. Our data show that nivolumab led to clinically meaningful improvements in the proportion of patients achieving an objective response and provided a manageable safety profile when compared with chemotherapy.

Implications of all the available evidence

Nivolumab can now be deemed a new treatment option for patients that have progressed after ipilimumab, or a BRAF inhibitor and ipilimumab if their melanoma is $BRAF^{V600}$-mutated. These data resulted in the accelerated approval of nivolumab by the US Food and Drug Administration for this indication in December, 2014.

Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor with broad anticancer activity in early studies.[7,8] In a phase 1 study,[8] nivolumab given at doses of 0·1–10 mg/kg produced a response in 31% of 107 previously treated, ipilimumab-naive patients with metastatic melanoma. The median duration of response at all doses was 22 months, with a median overall survival of 17·3 months.[8] In another phase 1/2 trial,[11] nivolumab given alone or with a peptide vaccine produced a response in 26% of patients and a median survival of 18 months in 90 patients with metastatic melanoma with disease progression after receiving ipilimumab. In a phase 3 study of treatment-naive patients with metastatic melanoma,[14] nivolumab resulted in 40% of patients achieving an objective response compared with 14% of those treated with dacarbazine. We did a randomised phase 3 trial to compare nivolumab with investigator's choice of chemotherapy (ICC) in patients whose disease had progressed after previous ipilimumab treatment, or both ipilimumab and a BRAF inhibitor if tumours harboured a $BRAF^{V600}$ mutation. Here we present the results of the initial planned analysis of objective responses.

Methods

Study design and patients

In this randomised, controlled, open-label, phase 3 study, we recruited patients at 90 sites in 14 countries. Eligible patients were aged 18 years or older and had histologically confirmed, unresectable stage IIIC or IV metastatic melanoma, with an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with *BRAF* wild-type tumours must have had progression after anti-CTLA-4 treatment, such as ipilimumab, and patients with a $BRAF^{V600}$ mutation-positive tumour mutation must have had progression on anti-CTLA-4 treatment and a BRAF inhibitor. We excluded patients with active brain metastases; individuals who had had previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies; those who had grade 4 toxic effects or used infliximab to manage adverse events from previous ipilimumab treatment; or patients with a primary ocular melanoma.

Laboratory test results must have met the following criteria before randomisation: white blood cell count of 2000×10^9 cells per L or more; neutrophil count of 1500×10^9 cells per L or more; platelet count of 100×10^9 cells per L or more; haemoglobin concentration of 90 g/L or more; serum creatinine 1·5 times the upper limit of the normal range or less (ULN); creatinine clearance of 40 mL/min or more (with the Cockcroft-Gault formula); aspartate aminotransferase and alanine aminotransferase three times the ULN or less; and bilirubin concentration of 1·5 times the ULN or less (except for patients with Gilbert's syndrome, who could have less than 51·31 µmol/L). We excluded patients if they had any grade 4 laboratory test abnormality, except for aspartate aminotransferase, alanine aminotransferase, and bilirubin abnormalities.

Patients with the following disorders were not allowed to enrol: active, known, or suspected autoimmune disease (except for some non-serious disorders, such as vitiligo and type 1 diabetes mellitus, as specified in the study protocol); active brain or leptomeningeal metastasis; grade 2 or worse eye pain or reduction of visual activity related to previous anti-CTLA-4 treatment; and previous malignancies (with some exceptions as specified in the study protocol). A full set of inclusion and exclusion criteria are provided in the appendix.

The study protocol was approved by the institutional review boards of the participating centres, and the study

See Online for appendix

was done in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written consent to participate in the study. We established a data monitoring committee to provide oversight of safety and efficacy considerations.

Randomisation and masking

Participating investigators randomly allocated patients 2:1 to either nivolumab or ICC using an interactive voice response system. We stratified randomisation by tumour PD-L1 status by immunohistochemistry using an automated Bristol-Myers Squibb (New Jersey, USA)/Dako (California, USA) assay[19] (positive in at least 5% of tumour cells *vs* negative or indeterminate), *BRAF* status (*BRAF* wild-type *vs* $BRAF^{V600}$ mutant), and clinical benefit from previous ipilimumab (anti-CTLA-4) treatment (best overall response as complete response, partial response, or stable disease [had clinical benefit] *vs* best overall response as progressive disease [had no clinical benefit]). We used permuted blocks (block size of six) within each stratum for randomisation. Treatment was given open-label because of the choices available to the investigators in the ICC group. Tumour assessments were done centrally by radiologists on an independent review committee who were masked to patients' treatment assignments.

Procedures

Patients received either nivolumab (Bristol-Myers Squibb, New Jersey, USA) at 3 mg/kg every 2 weeks or ICC (either dacarbazine 1000 mg/m² every 3 weeks, or carboplatin area under the curve 6 plus paclitaxel 175 mg/m² every 3 weeks) by intravenous infusion (appendix). We chose the dosing schedule for nivolumab on the basis of findings from a phase 1 dose-escalation trial across different tumour types.[7,8] We did not allow dose reductions with nivolumab treatment (dose reductions for chemotherapy were per institutional standards of care); however, we allowed dose delays (for non-dose-limiting toxicities that we judged likely to resolve with dose delay). We continued treatment until investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1-defined[20] disease progression or unacceptable toxic effects. We allowed treatment with nivolumab beyond progression for patients experiencing clinical benefit and tolerating the drug as established by the investigator.

Central radiologists did tumour assessments according to RECIST version 1.1[20] at baseline, week 9, every 6 weeks for the first year, and then every 12 weeks until disease progression, death, or withdrawal from the study. Patients who were eligible for continued treatment beyond progression underwent tumour assessments according to the protocol (eligibility criteria for this assessment are provided in the appendix). We confirmed all responses with either CT or MRI, obtaining scanning at least 4 weeks after the first RECIST response. We assessed safety in all patients who received at least one dose of the study treatment. The site investigator graded adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 throughout the study until 100 days after discontinuation of study treatment. We monitored study drug-related toxicities until they resolved, returned to baseline, or were deemed irreversible.

Tumour cell-surface expression of PD-L1 was assessed in a central laboratory (laboratory staff and pathologists were masked to treatment group and clinical site staff were masked to PD-L1 status) with an automated Bristol-Myers Squibb/Dako immunohistochemistry assay described previously.[19] We defined PD-L1 positivity as at least 5% of tumour cells exhibiting cell-surface PD-L1 staining of any intensity in a section containing at least 100 evaluable cells. We attributed indeterminate status to samples for which tumour cell surface expression could not be discerned because of melanin content or high cytoplasmic staining.

Outcomes

Primary endpoints were an estimation of the proportion of patients who achieved an objective response, which was planned after 120 patients had received nivolumab and

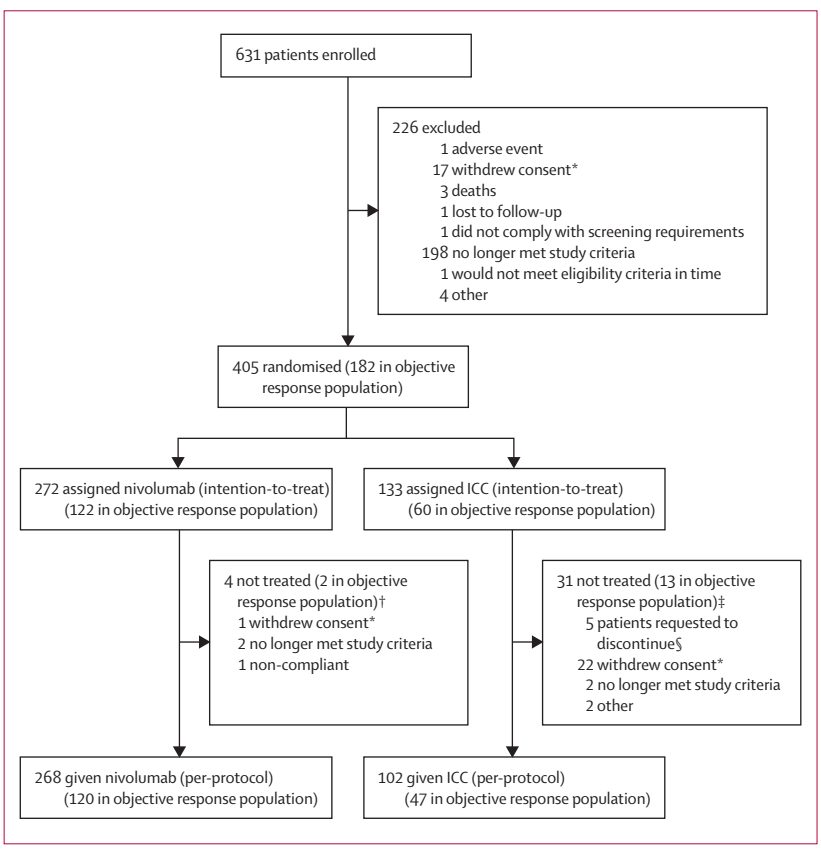

Figure 1: **Trial profile**
ICC=investigator's choice of chemotherapy. *Patient withdrawing consent from the full protocol, including study treatment, study procedures, and survival follow-up. †One non-compliant and one withdrew consent. ‡Three requested to discontinue, nine withdrew consent, and one no longer met study criteria. §Patient does not want to receive study drug but is willing to continue in the survival follow-up period.

were followed up for at least 24 weeks, and a comparison of overall survival between the two groups. Secondary endpoints were a descriptive comparison of progression-free survival between groups and an assessment of PD-L1 expression as a predictive biomarker for objective response, overall survival, and health-related quality of life as assessed by European Organisation for Research and Treatment of Care quality of life questionnaire (QLQ-C30).

Statistical analysis

We planned a sample size of about 390 patients randomised 2:1 to treatment groups. We included a non-comparative estimation of the proportion of patients with an objective response in the nivolumab group, with the ICC group being the reference group, and descriptively assessed progression-free survival in both treatment groups. We analysed the proportion of patients who achieved an objective response when the first 120 patients given nivolumab had a minimum follow-up of 24 weeks. We also planned to analyse objective responses in the patients enrolled in the ICC group, with 24 weeks follow-up, at the same time-point. Thus, the predefined population for the primary analysis of objective response would include about 180 patients, with 120 in the nivolumab arm and 60 in the ICC arm on the basis of the 2:1 randomisation ratio. This analysis of objective response was done in a per-protocol population.

We also analysed the proportion of patients with an objective response in the intention-to-treat population at the same timepoint as for the first analysis. A descriptive interim progression-free survival analysis was done (at the same timepoint) on an intention-to-treat basis. Safety analyses were to be done for all treated patients who received at least one dose of study treatment at both the interim and final analysis.

We present the estimate of the proportion of patients with an objective response and difference between the two treatment groups for completeness in the context of a randomised study, with a descriptive 95% CI and no statistical test on the proportion done. We arbitrarily spent an administrative alpha of 0·1% in acknowledgment of this single-arm estimation but did not define a significance level, therefore a 99·9% CI would not be consistent with the intended objective. We allocated the remaining 4·9% to the formal comparative analyses of overall survival. The maximum width of the exact two-sided 95% CI was 17·1% when the proportion of patients with an objective response was expected to be in the 5–30% range. For analysis of overall survival, we needed at least 260 deaths to provide a roughly 90% power to detect a hazard ratio of 0·65, corresponding to a median overall survival of 8 months for the ICC group versus 12·3 months for the nivolumab group, with an overall two-sided type I error of 4·9%. We will assess overall survival when the minimum number of events is achieved for all randomly allocated patients, along with the final progression-free survival analysis. We did all statistical analyses using SAS version 9.2. This study is registered with ClinicalTrials.gov, number NCT01721746.

Role of the funding source

The study was designed jointly by the funder of the study and the senior investigators (JSW and JL). Data collected

	Nivolumab (n=272)	ICC (n=133)
Age (years)	59 (23–88)	62 (29–85)
Sex		
Male	176 (65%)	85 (64%)
Female	96 (35%)	48 (36%)
ECOG performance status		
0	162 (60%)	84 (63%)
1	110 (40%)	48 (36%)
Stage M1c at study entry	203 (75%)	102 (77%)
AJCC stage IV at study entry	261 (96%)	131 (98%)
History of brain metastasis	53 (19%)	18 (14%)
Lactate dehydrogenase >ULN	139 (51%)	46 (35%)
Tumour size at baseline (mm)	96 (10–422)	87 (13–400)
Number of previous systemic treatments*		
1	77 (28%)	34 (26%)
2	139 (51%)	68 (51%)
>2	56 (21%)	31 (23%)
Type of previous treatment*		
Ipilimumab	271 (>99%)	133 (100%)
Vemurafenib	49 (18%)	23 (17%)
Chemotherapy	145 (53%)	72 (54%)
Other immunotherapy†	37 (14%)	35 (26%)
Pretreatment PD-L1-positive‡	134 (49%)	67 (50%)
BRAF mutant	60 (22%)	29 (22%)
No previous ipilimumab benefit§	173 (64%)	86 (65%)

Data are median (range) or n (%). ICC=Investigator's choice of chemotherapy. ECOG=Eastern Cooperative Oncology Group. AJCC=American Joint Committee on Cancer. ULN=upper limit of normal. *In metastatic disease setting. †Excluding previous ipilimumab treatment. We documented previous interferon α2a and b, interleukin 2 and 21, and T-cell infusion immunotherapies. ‡Defined as a tumour specimen with 5% or higher tumour cell membrane staining measured by Bristol-Myers Squibb (New Jersey, USA)/Dako (California, USA) immunohistochemistry assay.[19] §Best overall response of progressive disease.

Table 1: **Baseline characteristics of the intention-to-treat population**

	Nivolumab (n=120)	ICC (n=47)
Objective response	38 (31·7% [23·5–40·8])	5 (10·6% [3·5–23·1])
Best overall response		
Complete response	4 (3·3%)	0
Partial response	34 (28·3%)	5 (10·6%)
Stable disease	28 (23·3%)	16 (34·0%)
Progressive disease	42 (35·0%)	15 (31·9%)
Unable to establish†	12 (10·0%)	11 (23·4%)

Data are n (% [95% CI]) or n (%). *Confirmed response by independent radiology review committee per Response Evaluation Criteria in Solid Tumors version 1.1. †Patients who did not have a protocol-specified scan at 9 months, most commonly because of clinical progression, consent withdrawal, or receiving of subsequent treatment. ICC=investigator's choice of chemotherapy.

Table 2: **Response* to treatment in the per-protocol objective response population**

by the funder were analysed in collaboration with all authors. The funder of the study funded writing and editorial support. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Dec 21, 2012, to Jan 10, 2014, we screened 631 patients at 90 sites in 14 countries, randomly allocating 272 patients nivolumab and 133 ICC (appendix, figure 1). The most common reasons for screening failure were because patients no longer met study criteria (198 [31%] patients) or withdrew consent (17 [3%]). In the nivolumab group, four (1%) patients did not receive study treatment compared with 31 (23%) patients in the ICC arm; the most common reason for not being treated was no longer meeting study criteria (two [1%]) in the nivolumab group and consent withdrawal (22 [17%]) in the ICC group. In the population assessed for the primary analysis of objective response, 13 (22%) of the 60 patients assigned to ICC did not receive study treatment compared with two (2%) of 122 patients assigned to nivolumab. Thus, the per-protocol population analysed for the first assessment of objective responses consisted of 120 patients who received nivolumab and 47 patients who received ICC. The intention-to-treat population analysed for first assessment

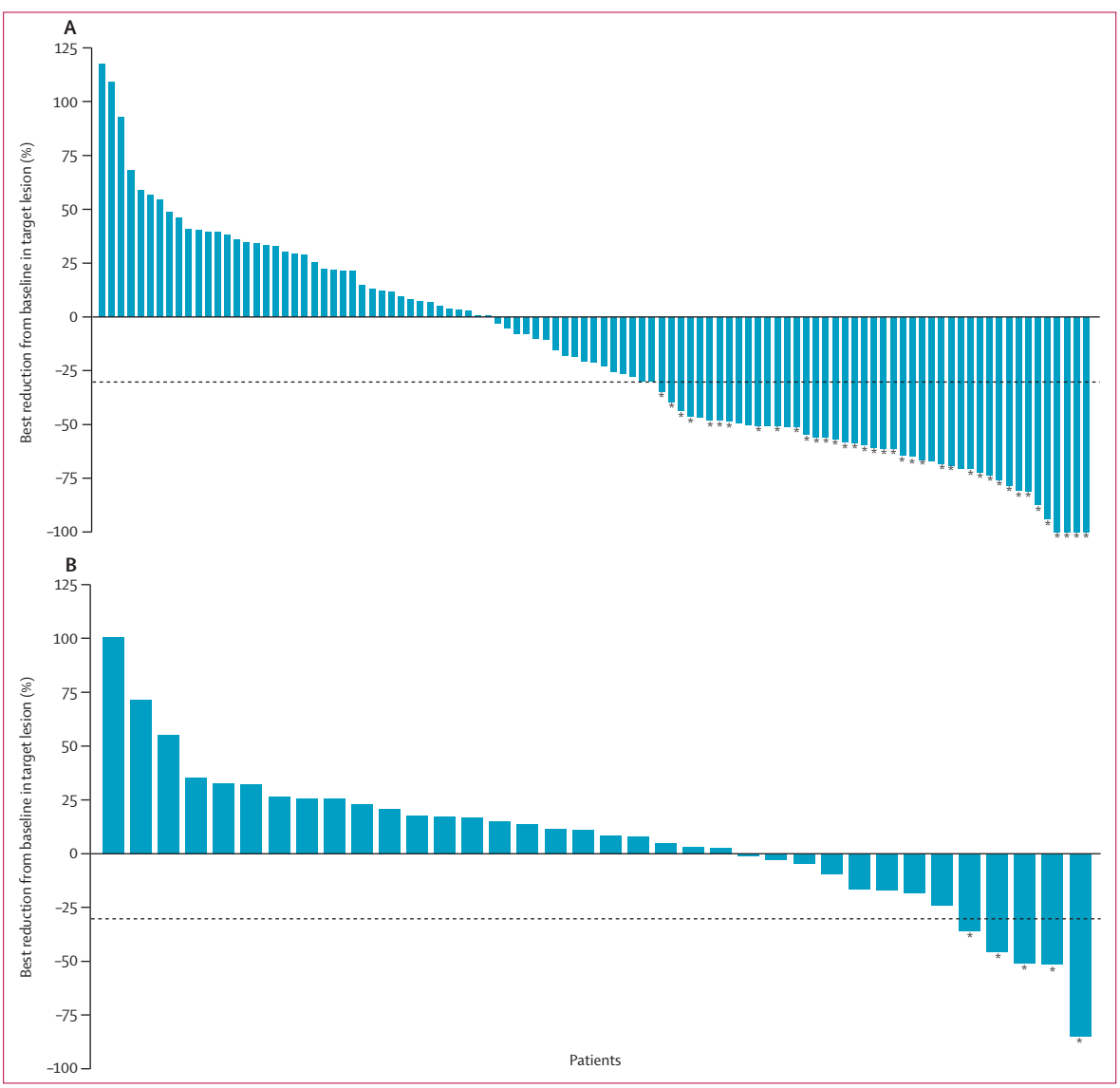

Figure 2: **Best tumour burden change from baseline in target lesions in patients who received nivolumab (A) and patients who received investigator's choice of chemotherapy (B)**

Waterfall plots show tumour response, which measure the change from baseline in the sum of the longest diameters of target lesions, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Asterisks denote confirmed responders, defined as those who had a repeat scan at least 4 weeks after the first scan that confirmed a response.

of objective responses consisted of 122 patients randomly allocated to nivolumab and 60 patients to ICC.

Baseline characteristics were similar in the nivolumab and ICC study groups, with the exception of history of brain metastases and high lactate dehydrogenase, which were higher in the nivolumab than the ICC group (table 1). Additionally, patients were heavily treated, with half of all randomly allocated patients receiving at least two previous systemic therapies. The proportion of patients receiving previous immunotherapies other than ipilimumab was also higher in the ICC than the nivolumab group. The type and extent of previous treatments were generally consistent between treatment groups.

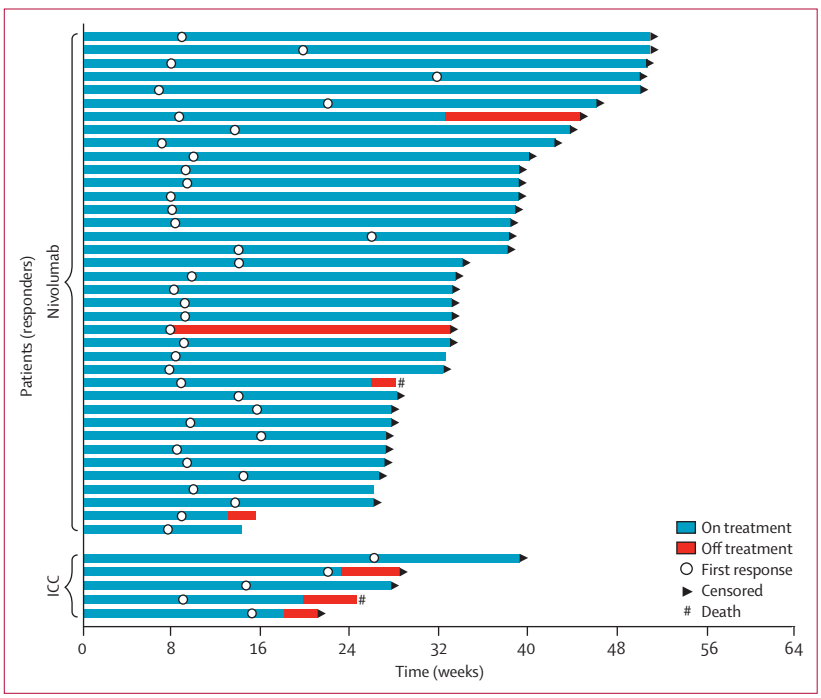

Figure 3: **Time to and duration of response**
Swimmer plots show time to first response and duration of response, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, for responders who received nivolumab (top) or ICC (bottom). ICC=investigator's choice of chemotherapy.

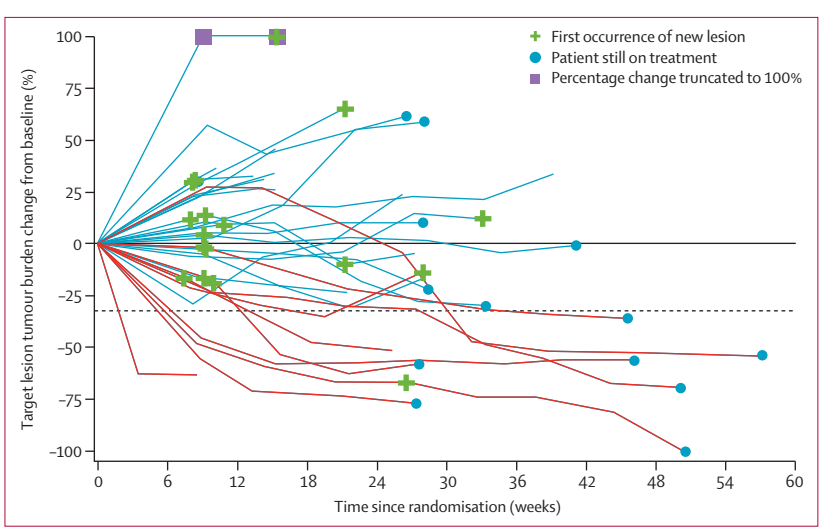

Figure 4: **Immune-related response pattern in patients treated beyond RECIST-defined progression**
We noted immune-related response pattern (red lines) in ten of the 37 patients given nivolumab beyond RECIST version 1.1-defined progression—a greater than 30% reduction in the target lesion subsequent to initial progression. Blue lines are patients who did not have an unconventional response and had either stable disease or progressed during continuing treatment with nivolumab; lines in red denote patients who had an unconventional response. RECIST= Response Evaluation Criteria in Solid Tumors.

Patients received nivolumab for a median of 5·3 months (95% CI 3·3–6·5) compared with 2·0 months (1·6–2·9) for chemotherapy, and 84 (82%) patients undergoing chemotherapy discontinued treatment compared with 139 (52%) patients given nivolumab, most because of disease progression. We did not allow dose reduction in the nivolumab group, and for patients given dacarbazine, five (11%) needed a dose reduction compared with 29 (51%) for carboplatin and 22 (39%) for paclitaxel, most frequently because of haematological toxic effects. In all nivolumab-treated patients, ten (4%) needed an infusion interruption and eight (3%) needed a reduction in infusion rate; a slightly higher percentage of patients in the ICC than nivolumab group who received dacarbazine, carboplatin, or paclitaxel needed an infusion interruption (three [7%] of 45 patients given dacarbazine, two [4%] of 57 patients given carboplatin, and four [7%] of 57 patients given paclitaxel) or a reduction in infusion rate (eight [18%] on dacarbazine, four [7%] on carboplatin, and seven [12%] on paclitaxel).

At the time of the primary analysis of the proportion of patients who had achieved an objective response, after 182 patients had been randomly allocated to treatment, median follow-up was 8·4 months (IQR 7·0–9·8). Confirmed objective responses, as per independent radiology review committee in the per-protocol population, were noted in 38 (31·7%, 95% CI 23·5–40·8) of the 120 patients in the nivolumab group and in five (10·6%, 3·5–23·1) of the 47 patients in the ICC group (table 2, figure 2). For this first assessment of objective responses in the intention-to-treat population, the independent radiology review committee noted confirmed objective responses in 38 (31·1% [95% CI 23·1–40·2) of the 122 patients in the nivolumab group and five (8·3% [2·8–18·4]) of the 60 patients in the ICC group. Within the ICC group, although no comparison was intended, more responses were noted with paclitaxel or carboplatin treatment than with dacarbazine treatment (appendix). Median duration of response had not yet been reached (range 1·4+ to 10·0+) in the nivolumab group and was 3·5 months (range 1·3+ to 3·5) in the ICC group. Median time to response was 2·1 months (range 1·6–7·4) in the nivolumab group and 3·5 months (2·1–6·1) in the ICC group.

At the time of analysis, 33 (87%) of 38 nivolumab responses were continuing on treatment without progression (figure 3). 37 (31%) of 120 patients given nivolumab continued nivolumab treatment beyond progression, and ten (8%) subsequently had a greater than 30% reduction in the sum of the longest diameters of target lesions, consistent with an unconventional,

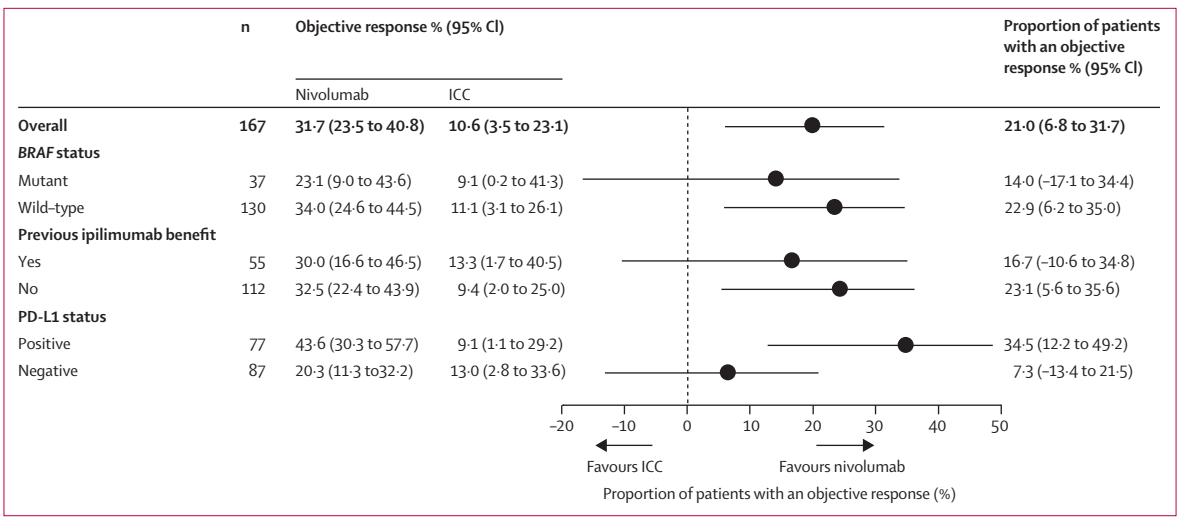

Figure 5: **Exploratory analysis of objective responses in predefined patient subgroups**
ICC=investigator's choice of chemotherapy.

immune-related response (regression occurred or was maintained after progression; figure 4).[21–23]

In the intention-to-treat objective response analysis population (ie, all 182 patients who had been randomised at the point of the first planned assessment of objective responses), median progression-free survival was 4·7 months (95% CI 2·3–6·5) for the nivolumab group and 4·2 months (2·1–6·3) for the ICC group (hazard ratio 0·82; 99·99% CI 0·32–2·05, a descriptive comparison; appendix). 6-month progression-free survival was 48% (95% CI 38–56) in the nivolumab group and 34% (18–51) in the ICC group.

In exploratory analyses across predefined patient subgroups, we noted complete or partial responses more frequently in the nivolumab group than in the ICC group, irrespective of *BRAF* status or previous anti-CTLA-4 benefit (figure 5). Objective responses were noted in six (23·1%) of 26 $BRAF^{V600}$ mutation-positive patients and 32 (34·0%) of 94 *BRAF* wild-type patients treated with nivolumab; objective responses were noted in one (9·1%) of 11 $BRAF^{V600}$ mutation-positive patients and four (11·1%) of 36 *BRAF* wild-type patients treated with chemotherapy. In patients with previous anti-CTLA-4 benefit, objective responses were noted in 12 (30·0%) of 40 patients treated with nivolumab and two (13·3%) of 15 treated with chemotherapy, whereas in patients without previous anti-CTLA-4 benefit, objective responses were noted in 26 (32·5%) of 80 patients treated with nivolumab and three (9·4%) of 32 treated with chemotherapy. In patients with PD-L1-positive tumours, objective responses were noted in 24 (43·6%) of 55 patients treated with nivolumab versus two (9·1%) of 22 treated with chemotherapy; in those with PD-L1-negative tumours, objective responses were noted in 13 (20·3%) of 64 patients treated with nivolumab and three (13·0%) of 23 treated with chemotherapy. These exploratory subgroup analyses were descriptive in nature and it is important to note that sample sizes within a stratum are small.

	Nivolumab (n=268)				ICC (n=102)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Overall								
Any event	157 (59%)	22 (8%)	2 (1%)	0	49 (48%)	25 (25%)	7 (7%)	0
Adverse events reported in 10% or more of patients								
Fatigue	65 (24%)	2 (1%)	0	0	31 (30%)	4 (4%)	0	0
Pruritus	43 (16%)	0	0	0	2 (2%)	0	0	0
Diarrhoea	29 (11%)	1 (<1%)	0	0	13 (13%)	2 (2%)	0	0
Nausea	25 (9%)	0	0	0	36 (35%)	2 (2%)	0	0
Anaemia	10 (4%)	2 (1%)	0	0	18 (18%)	5 (5%)	0	0
Decreased appetite	14 (5%)	0	0	0	16 (16%)	0	0	0
Arthralgia	14 (5%)	0	0	0	11 (11%)	1 (1%)	0	0
Vomiting	8 (3%)	1 (<1%)	0	0	18 (18%)	2 (2%)	0	0
Constipation	6 (2%)	0	0	0	13 (13%)	1 (1%)	0	0
Alopecia	1 (<1%)	0	0	0	28 (27%)	0	0	0
Neutropenia	0	0	0	0	5 (5%)	8 (8%)	6 (6%)	0

Data are n (%). Nivolumab-related grade 3–4 adverse events that we noted in 2–10% of patients were increased aspartate aminotransferase (one [<1%]), increased alanine aminotransferase (two [1%]), increased blood alkaline phosphatase (one [<1%]), increased lipase (three [1%]), decreased lymphocytes (one [<1%]), lymphopenia (one [<1%]), herpes zoster (one [<1%]), and an infusion-related reaction (one [<1%]). ICC-related grade 3–4 adverse events that we noted in 2–10% of patients were pyrexia (one [1%]), influenza-like illness (one [1%]), increased lipase (one [1%]), decreased lymphocyte count (one [1%]), decreased white blood cell count (one [1%]), decreased platelet count (one [1%]), decreased neutrophil count (three [3%]), peripheral neutropathy (one [1%]), peripheral sensory neuropathy (one [1%]), lymphopenia (one [1%]), leucopenia (two [2%]), and thrombocytopenia (six [6%]). ICC=investigator's choice of chemotherapy.

Table 3: **Treatment-related adverse events within 30 days of last dose of study treatment for the per-protocol population**

We did safety analyses on the 370 patients who received at least one dose of treatment (table 3). Most patients developed adverse events related to treatment: 181 (68%) of 268 patients in the nivolumab group and 81 (79%) of 102 patients in the ICC group. The most frequent adverse events in the nivolumab group were fatigue, pruritus,

and diarrhoea. The most frequent adverse events in the ICC group were nausea, fatigue, and alopecia. Grade 3–4 treatment-related adverse events occurred in 24 (9%) of the 268 patients in the nivolumab group versus 32 (31%) of the 102 patients in the ICC group. In the nivolumab group, the most common treatment-related grade 3–4 adverse events were increased lipase (three [1%] patients), increased alanine aminotransferase (two [1%]), fatigue (two [1%]), and anaemia (two [1%]). In the ICC group, the most common treatment-related grade 3–4 adverse events were neutropenia (14 [14%]), thrombocytopenia (six [6%]), and anaemia (five [5%]). We noted no differences in adverse events between patients given dacarbazine, paclitaxel, or carboplatin within the ICC group. We noted grade 3–4 drug-related serious adverse events in 12 (5%) nivolumab-treated patients and nine (9%) patients in the ICC group.

We noted few grade 3–4 select adverse events, defined as adverse events with a potential immunological cause that need frequent monitoring and potential intervention with immune suppression or endocrine treatment in the nivolumab group (table 3, appendix). We reviewed the case histories of all patients who developed nivolumab-related, select adverse events and did not find any association between ipilimumab-related and nivolumab-related toxic effects. Only one of the seven patients who developed a nivolumab-related select adverse event had a history of ipilimumab-related toxic effects (hypophysitis). This patient developed liver function test abnormalities (grade 2–3), which resolved after dose delay and adverse event management by steroids. We noted no grade 3–4 immune-mediated pulmonary events. All nivolumab treatment-related grade 3–4 select adverse events resolved with use of immunosuppressive drugs and established management guidelines (appendix).

The most common reason for discontinuation of treatment was disease progression: 116 (43%) of 268 patients in the nivolumab group compared with 62 (61%) of 102 in the ICC group. Study drug toxic effects led to seven (3%) of 268 patients given nivolumab and seven (7%) of 102 given ICC discontinuing treatment. We noted no treatment-related deaths for either group.

Discussion

Anti-PD-1 and anti-PD-L1 antibodies have shown broad-ranging antitumour activity in early-phase trials.[24–27] In this study, the proportion of patients with an objective response was higher for nivolumab than for ICC; there was no clinically or statistically significant difference in progression-free survival in the intention-to-treat objective response population. We noted complete responses more frequently in the nivolumab group than the ICC group. The absence of significant difference in progression-free survival could be attributed in part to the imbalance in distribution of adverse prognostic factors in favour of the ICC group, immaturity of the data, and the false-positive disease progression in the nivolumab group due to the use of RECIST version 1.1 as opposed to immune-related response criteria for tumour assessment.

We used ICC as an active treatment for the control group because it is common practice in North America, the European Union, and Australia, but no evidence from prospective clinical trials suggests that chemotherapy after ipilimumab improves progression-free survival or overall survival. The benefit seen with nivolumab in this study was similar to that seen in previous phase 1/2 trials in patients previously treated with melanoma (panel).[8,11] The data are also consistent with results from a phase 3 trial in previously untreated patients with melanoma,[14] in which the proportion of patients achieving a response defined by RECIST version 1.1, duration of response, progression-free survival, and overall survival were all significantly improved in patients that received nivolumab compared with those that received dacarbazine. Pembrolizumab, another anti-PD-1 drug, has also shown similar effects on progression-free survival and objective responses (21–25%) at 6 months compared with chemotherapy (4%; p<0·0001) in a patient population similar to that of this study.[28]

Notably, the proportion of patients with an objective response was the chosen primary endpoint for both nivolumab and pembrolizumab development programmes for treatment of patients with melanoma who have progressed after ipilimumab, and a BRAF inhibitor if the tumour was *BRAF* mutation-positive. The US Food and Drug Administration (FDA) has approved both drugs for this group of patients on the basis of these data with responses of long duration. Ultimately, the overall survival primary endpoint will shed light on the potential survival benefit of nivolumab compared with ICC, as has been shown in treatment-naive patients.[14] According to projections, the necessary number of deaths for the final overall survival analysis will be reached by the end of 2015. The fact that 8·3% of patients given nivolumab ultimately showed substantial tumour regression beyond RECIST 1.1-defined progression suggests that these response criteria might not fully take account of the potential benefit of nivolumab, and this result might account for the absence of a large difference observed in progression-free survival in this descriptive interim analysis.[20,21–23] In the groups for which the trial was stratified to achieve balance between arms, objective responses were more common in the nivolumab group than in the ICC group. Overall, our data suggest that nivolumab would be a reasonable choice compared with ipilimumab reinduction for progressing patients that had responded to ipilimumab previously.[29]

Similar to previous trials,[8] positive tumour PD-L1 expression as assessed by the immunohistochemical assay seemed to be associated with a higher response rate for nivolumab than that for patients with PD-L1 negative tumours; however, nivolumab treatment provided benefit for patients with PD-L1-negative tumours. We chose a cutoff of 5% tumour cell-surface expression of PD-L1

because in the phase 1 study,[7,8] about half (17 [45%] of 38) of melanoma patients tested were classified PD-L1-positive with this threshold. Thus, use of the 5% cutoff for stratification was hypothesised to create an even distribution of PD-L1-positive and PD-L1-negative patients in each treatment group, allowing an exploratory assessment of tumour PD-L1 expression as a potential prognostic variable for efficacy measures.

A limitation of interpretation of the efficacy data is that 22 (17%) of patients randomly allocated ICC withdrew consent compared with only one (<1%) in the nivolumab group; this result might have been unavoidable in an open-label, non-crossover study design, but could have biased the results in favour of the ICC group because patients who withdrew consent might have done so because they were more informed and able to travel than those who did not, possibly allowing these patients in the ICC group to seek alternative treatment elsewhere. Longer follow-up is clearly needed to discern possible late changes in overall progression-free survival.

We used standard RECIST version 1.1 in this study. Although use of immune-related response criteria, which is often felt to take account of the true benefit of immune treatment, might have altered assessment of progression-free survival and objective responses in this trial,[21] it has not been a validated endpoint acceptable to regulatory agencies. Patients who received nivolumab could continue treatment beyond RECIST-defined progression because of well documented antitumour responses seen after progression of disease with immunotherapy, but not with chemotherapy. This difference might have contributed to the longer time on treatment in the nivolumab cohort than in the chemotherapy cohort.

The overall safety profile of nivolumab was tolerable, with manageable toxic effects that appeared less frequently than with chemotherapy. Fatigue, pruritus, and diarrhoea were the most common side-effects seen with nivolumab treatment. We noted nausea, fatigue, alopecia, and anaemia most commonly in the ICC group. The safety profiles of both nivolumab and chemotherapy in this study were similar to those seen in a phase 3 trial of nivolumab versus dacarbazine in previously untreated patients,[14] suggesting that previous ipilimumab treatment does not seem to affect the safety profile of nivolumab or chemotherapy. In this study, we gave nivolumab 6 weeks or more after previous ipilimumab treatment, suggesting that nivolumab can safely be given after this waiting period. No grade 3–4 adverse events of probable immunological causation that were noted with previous ipilimumab were reproduced with nivolumab. Only one patient who developed grade 3–4 adverse events with probable immunological relation when treated with nivolumab had a history of ipilimumab-related toxic effects; no studies support the hypothesis that the previous ipilimumab-related toxic effect (hypophysitis) in this patient could be linked to the nivolumab-related adverse events (infusion reaction and liver function test abnormalities). Further results from a study of sequential ipilimumab and nivolumab (CheckMate 064; NCT01783938) will shed more light on this issue.

We managed the grade 3–4 immunologically related adverse events in this trial with algorithms generated by investigators and the funder during the ipilimumab development programme (appendix).[30] Symptoms in most patients resolved to baseline with use of steroids. Only two patients receiving nivolumab needed infliximab for select adverse event management.

Findings from our study show that nivolumab leads to clinically meaningful improvements in the proportion of patients achieving an objective response and provide a manageable safety profile when compared with chemotherapy. Nivolumab can now be considered as a new treatment option for patients that have progressed after ipilimumab, or a BRAF inhibitor and ipilimumab if their melanoma is *BRAF*^{V600}-mutated. These findings, with additional support from the results of the phase 1 study,[7,8] resulted in accelerated approval of nivolumab by the FDA for this indication in December, 2014. In the first-line setting for *BRAF* wild-type patients, nivolumab has shown significantly better survival and higher numbers of objective responses than with dacarbazine, one of the chemotherapy choices in this study.[14] A continuing trial (CheckMate 067; NCT01844505) will define the role of nivolumab monotherapy and nivolumab in combination with ipilimumab compared with ipilimumab monotherapy in previously untreated patients with metastatic melanoma.

Contributors

JSW, ASY, and JL conceived the study. JSW and JL wrote the first draft of the manuscript. All authors contributed to subsequent revisions and approved the final draft for submission. JSW, ASY, AL, CHor, DM, and JL designed the study. JSW, SPD'A, FSH, RG, BN, CHoe, NIK, WHM, CDL, GPL, LT, PL, KFG, JCH, MM, MS, PAA, PM, BC, AB, IMS, J-JG, AMK, DM, and JL treated patients and acquired data. JSW, SPD'A, DM, RG, BN, CHoe, NIK, WHM, CDL, GPL, LT, PL, KFG, JCH, MM, MS, PAA, PM, BC, AB, IMS, J-JG, AMK, FSH, ASY, CHor, and JL interpreted data. AL analysed data.

Declaration of interests

JSW has received honoraria from Bristol-Myers Squibb, Merck, Genentech, AstraZeneca, and AbbVie; clinical research funding from Bristol-Myers Squibb, Merck, GlaxoSmithKline, and Macrogenics; and payment for participation in scientific advisory boards from Ichor Therapeutics, Lion Biotechnologies, and Pierisl; and holds stocks in Celldex Therapeutics, Altor BioScience, and cCAM Biotherapeutics. DM reports personal fees from Bristol-Myers Squibb and GlaxoSmithKline. FSH reports grants from Bristol-Myers Squibb and a pending patent for Immune Target. RG has served as a consultant and received speaker's honoraria and meeting and project support from Roche, GlaxoSmithKline, Novartis, Bristol-Myers Squibb, Merck Sharp and Dohme, Merck Serono, Almirall-Hermal, LEO Pharma, Amgen, Galderma, Janssen, and Boehringer Ingelheim. BN has received honoraria from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp and Dohme, Merck-Serono, and Pfizer, and clinical research funding from Pfizer, Merck-Serono, and GlaxoSmithKline. CHoe reports personal fees from Bristol-Myers Squibb, Merck Sharp and Dohme, Roche, Amgen, GlaxoSmithKline, and Novartis. NIK reports personal fees from Bristol-Myers Squibb, Genentech, Amgen, Provectus, and Prometheus; grants from the National Comprehensive Cancer Network, Merck, Pfizer, Celgene, Genentech, Threshold, Eisai, and Bristol-Myers Squibb; and grant funding from general research support through Roche, Pfizer, and Allos. WHM has received personal fees and

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