Binimetinib versus dacarbazine in patients with advanced *NRAS*-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial

Reinhard Dummer, Dirk Schadendorf, Paolo A Ascierto, Ana Arance, Caroline Dutriaux, Anna Maria Di Giacomo, Piotr Rutkowski, Michele Del Vecchio, Ralf Gutzmer, Mario Mandala, Luc Thomas, Lev Demidov, Claus Garbe, David Hogg, Gabriella Liszkay, Paola Queirolo, Ernesto Wasserman, James Ford, Marine Weill, L Andres Sirulnik, Valentine Jehl, Viviana Bozón, Georgina V Long, Keith Flaherty

Summary

Background There are no established therapies specific for *NRAS*-mutant melanoma despite the emergence of immunotherapy. We aimed to assess the efficacy and safety of the MEK inhibitor binimetinib versus that of dacarbazine in patients with advanced *NRAS*-mutant melanoma.

Methods NEMO is an ongoing, randomised, open-label phase 3 study done at 118 hospitals in 26 countries. Patients with advanced, unresectable, American Joint Committee on Cancer stage IIIC or stage IV *NRAS*-mutant melanoma who were previously untreated or had progressed on or after previous immunotherapy were randomised (2:1) to receive either binimetinib 45 mg orally twice daily or dacarbazine 1000 mg/m² intravenously every 3 weeks. Randomisation was stratified by stage, performance status, and previous immunotherapy. The primary endpoint was progression-free survival assessed by blinded central review in the intention-to-treat population. Safety analyses were done in the safety population, consisting of all patients who received at least one study drug dose and one post-baseline safety assessment. This study is registered with ClinicalTrials.gov, number NCT01763164 and with EudraCT, number 2012-003593-51.

Findings Between Aug 19, 2013, and April 28, 2015, 402 patients were enrolled and randomly assigned, 269 to binimetinib and 133 to dacarbazine. Median follow-up was 1·7 months (IQR 1·4–4·1). Median progression-free survival was 2·8 months (95% CI 2·8–3·6) in the binimetinib group and 1·5 months (1·5–1·7) in the dacarbazine group (hazard ratio 0·62 [95% CI 0·47–0·80]; one-sided p<0·001). Grade 3–4 adverse events seen in at least 5% of patients the safety population in either group were increased creatine phosphokinase (52 [19%] of 269 patients in the binimetinib group *vs* none of 114 in the dacarbazine group), hypertension (20 [7%] *vs* two [2%]), anaemia (five [2%] *vs* six [5%]), and neutropenia (two [1%] *vs* ten [9%]). Serious adverse events (all grades) occurred in 91 (34%) patients in the binimetinib group and 25 (22%) patients in the dacarbazine group.

Interpretation Binimetinib improved progression-free survival compared with dacarbazine and was tolerable. Binimetinib might represent a new treatment option for patients with *NRAS*-mutant melanoma after failure of immunotherapy.

Funding Array BioPharma and Novartis Pharmaceuticals Corporation.

Lancet Oncol 2017; 18: 435–45

Published Online
March 8, 2017
http://dx.doi.org/10.1016/S1470-2045(17)30180-8

See Comment page 414

Department of Dermatology, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland (Prof R Dummer MD); **Department of Dermatology, University Hospital Essen, Essen, Germany** (Prof D Schadendorf MD); **German Cancer Consortium, Heidelberg, Germany** (Prof D Schadendorf); **Melanoma Unit, Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori Fondazione Pascale, Via Mariano Semmola, Naples, Italy** (P A Ascierto MD); **Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain** (A Arance MD); **Department of Oncologic Dermatology, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France** (C Dutriaux MD); **Medical Oncology and Immunotherapy, University Hospital of Siena, Viale Bracci, Siena, Italy** (A M Di Giacomo MD); **Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland** (Prof P Rutkowski MD); **Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian, Milan, Italy** (M Del Vecchio MD); **Department of Dermatology and Allergy, Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany** (Prof R Gutzmer MD); **Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital,**

Introduction

Melanomas are a heterogeneous group of neural crest-derived malignancies characterised by distinct clinical and molecular features.[1,2] Most melanomas have genetic alterations activating the MAPK pathway, such as *BRAF*, *NRAS*, or *NF1* mutations.[3] Activating *NRAS* and *BRAF* mutations are present in about 20% and 35–50% of metastatic melanomas, respectively.[4,5] Direct targeting of the RAS GTPase is technically challenging.[6] Preclinical in-vitro investigations have suggested that *BRAF*-mutant and *NRAS*-mutant melanomas are sensitive to MEK inhibition.[7]

Several kinase inhibitors, including BRAF[8,9] and MEK inhibitors[10] alone or in combination[11,12] have been approved for the treatment of *BRAF*-mutant metastatic melanoma. In a phase 2 clinical trial,[13] the MEK1/2 inhibitor binimetinib (MEK162) showed clinical activity with a response in 15% of patients with *NRAS*-mutant metastatic melanoma.

Despite the documented benefit of immunotherapy[14–16] in most melanoma subtypes, there is a substantial unmet medical need for new therapeutic opportunities in metastatic *NRAS*-mutant disease. In the metastatic setting, patients with *NRAS*-mutant melanoma appear to have a more aggressive disease course than patients whose tumours harbour *BRAF* mutations or are wild-type for *BRAF* and *NRAS*, although these findings have not yet been confirmed.[4,17] Therefore, we developed the *NRAS* melanoma and MEK inhibitor (NEMO) trial to compare the efficacy of binimetinib with dacarbazine in patients (either treatment-naive or have received previous immunotherapy) with advanced unresectable or metastatic melanoma harbouring an *NRAS* mutation.

Bergamo, Italy (M Mandala, MD); **Department of Dermatology, Centre Hospitalier Lyon Sud, Lyons Cancer Research Center, Lyon 1 University, Pierre Bénite, France** (Prof L Thomas MD); **N N Blokhin Russian Cancer Research Center, Ministry of Health, Moscow, Russian Federation** (Prof L Demidov MD); **Department of Dermatology, University Hospital Tuebingen, Tuebingen, Germany** (Prof C Garbe MD); **Department of Medicine, University Health Network/Princess Margaret Hospital, Toronto, ON, Canada** (D Hogg MD); **Department of Dermatology, National Institute of Oncology, Budapest, Hungary** (Prof G Liszkay MD); **Department of Medical Oncology, Institute for Cancer Research, IRCCS San Martino, Largo Rosanna Benzi, Genova, Italy** (P Queirolo, MD); **Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ, USA** (E Wasserman MD, J Ford MS, L A Sirulnik MD); **Novartis Pharma AG, Basel, Switzerland** (M Weill MSc, V Jehl MSc); **Array BioPharma, Boulder, CO, USA** (V Bozón MD); **Melanoma Institute Australia, The University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia** (Prof G V Long MBBS); **and Department of Medical Oncology, Massachusetts General Hospital, Boston, MA, USA** (K Flaherty MD)

Correspondence to:
Prof Reinhard Dummer, Department of Dermatology, University Hospital Zürich Skin Cancer Center, 8091, Zürich, Switzerland
reinhard.dummer@usz.ch

See Online for appendix

Research in context

Evidence before this study

Evidence was identified during the development of this manuscript via PubMed and Embase searches for articles and abstracts published between Jan 1, 2014, and Dec 20, 2016. Search terms were comprehensive (melanoma + treatment + phase [all fields]; NRAS + melanoma [all fields]). Selected abstracts were not limited to the English language, and focused on phase 3 clinical trial data. Our findings indicated that emerging immunotherapies and MEK pathway inhibitors have efficacy in melanoma. However, substantial unmet need exists, particularly for patients with *NRAS*-mutant melanoma. Preclinical and early clinical data suggest that the MEK inhibitor binimetinib could be a promising treatment for patients with *NRAS*-mutant melanoma.

Added value of this study

In this study, which represents the largest controlled study to date in patients with *NRAS*-mutant melanoma to our knowledge, treatment with the MEK inhibitor binimetinib improved progression-free survival and overall response compared with dacarbazine, with acceptable tolerability. The progression-free survival benefit with binimetinib was also observed in patients who failed previous immunotherapy, which is currently the guideline-recommended first-line treatment.

Implications of all the available evidence

Future treatment algorithms for metastatic melanoma might incorporate binimetinib therapy in patients with advanced *NRAS*-mutant melanoma, including after the failure of immunotherapy.

Methods

Study design and participants

The NEMO trial is an ongoing, randomised, open-label, multicentre, phase 3 trial. Screening occurred at 169 hospitals in 27 countries; patients were randomised at 118 centres in 26 countries (appendix pp 2–5).

Patients aged at least 18 years with histologically confirmed locally advanced unresectable or metastatic cutaneous melanoma or metastatic melanoma with unknown primary site of origin (American Joint Committee on Cancer [AJCC] stage IIIC or IV) harbouring an *NRAS* Gln61Arg, Gln61Lys, or Gln61Leu mutation who were previously untreated or whose disease had progressed on or after immunotherapy were eligible for enrolment. Protocol amendment 3, issued after the randomisation of 47 patients (appendix p 8), modified the eligibility criteria to allow enrolment of patients who had received any number of previous immunotherapy treatments (ie, patients who had received more than one line of immunotherapy for metastatic melanoma were no longer excluded). All patients had to have at least one measurable lesion as documented by radiological or photographic methods according to criteria based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1;[18] an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; left ventricular ejection fraction of at least 50%; and adequate bone marrow, organ function, and laboratory parameters (absolute neutrophil count ≥1·5×10⁹ cells per L; haemoglobin ≥9 g/dL; ≥100×10⁹ platelets per L without transfusions; aspartate aminotransferase or alanine aminotransferase ≤2·5×upper limit of normal [ULN] or ≤5×ULN for patients with liver metastases; total bilirubin ≤2×ULN; and creatinine ≤1·5 mg/dL). Key exclusion criteria were uncontrolled arterial hypertension; impairment of gastrointestinal function (eg, active ulcerative disease, uncontrolled nausea, vomiting, diarrhoea, or malabsorption syndrome); previous therapy with a MEK inhibitor, a final dose of immunotherapy less than 6 weeks before randomisation, or any previous systemic chemotherapy for unresectable locally advanced or metastatic melanoma; and a history of neuromuscular disorders that are associated with increased creatine phosphokinase or any planned strenuous exercise regimen that might result in significant increases in plasma creatine phosphokinase. Additional exclusion criteria are noted in the appendix (p 6). Patients taking concomitant medications were permitted to continue on the same dose and schedule during the study (as feasible), with special precautions for medications known to interfere with the metabolism of binimetinib or dacarbazine, or which could potentially induce torsades de pointes.

Independent ethics committees or independent review boards at each study site approved the study protocol and all amendments. The study was conducted in accordance with Good Clinical Practice guidelines and according to the ethical requirements outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients before screening procedures were initiated.

Randomisation and masking

Patients were enrolled by clinical sites and randomised (2:1) by interactive response technology (PAREXEL Informatics, Waltham, MA, USA) to receive either binimetinib or dacarbazine. A block randomisation schedule was used to generate the random allocation sequence. Allocation was done with stratifying factors and a block size of six. To conceal the sequence, records were pre-allocated to each stratum. Patients and clinicians were not masked with respect to treatment group, but aggregate data summaries and analyses remained blinded until database lock for the primary analysis. Randomisation was stratified by AJCC stage (IIIC, IVM1a, IVM1b *vs* IVM1c), ECOG performance status (0 *vs* 1), and previous immunotherapy for unresectable or metastatic disease (yes *vs* no).

Procedures

NRAS mutations were assessed centrally in fixed tumour samples by a real-time PCR assay developed internally at Novartis and done at Genoptix Laboratories (Carlsbad, CA, USA). Patients received binimetinib (45 mg orally twice daily; manufactured by Almac Pharma Services [Craigavon, UK] and supplied by Novartis Drug Supply Management) or dacarbazine (1000 mg/m² intravenously once every 3 weeks; supplied locally if possible or centrally to countries where it could not be obtained locally). Study visits occurred at 3-week intervals.

Patients continued on study treatment until documented disease progression, intolerable toxicity, withdrawal of consent, death, physician decision, or early termination. One dose reduction of binimetinib to 30 mg orally twice daily was permitted; patients not able to tolerate binimetinib at this lower dose were permanently discontinued (appendix p 11). No re-escalation was allowed if the dose reduction was because of left ventricular ejection fraction dysfunction or prolonged heart rate-corrected QT interval, Fridericia's formula, of longer than 500 ms; otherwise, dose re-escalation of binimetinib to 45 mg orally twice daily was permitted if the adverse event improved to the baseline toxicity level and remained stable for at least 21 days. The study protocol provided specific guidelines for dose interruption for binimetinib-related adverse events. In general, doses were not held for grade 1 toxicities. For other grade toxicities, treatment was interrupted until resolution to grade 1 or better, unless guidelines specified permanent discontinuation from treatment. Patients unable to tolerate the dacarbazine dosing schedule were permitted a maximum of two dose reductions, first to 750 mg/m² and then to 500 mg/m². Any patient requiring further dose reduction of dacarbazine was removed from study treatment. Re-escalation of dacarbazine dose was not permitted. Dacarbazine could be held for up to 6 weeks; patients who had continued toxicity were discontinued from the study.

Baseline tumour imaging assessments occurred within 21 days before randomisation; follow-up tumour assessments were done every 6 weeks thereafter until week 25, and then every 9 weeks. Additional tumour assessments were permitted in the case of suspected disease progression. Baseline imaging included chest, abdomen, and pelvis MRI or CT; brain MRI or CT to assess CNS disease; colour photography for all skin lesions; and, if bone metastases were suspected, a whole-body bone scan. Additional imaging by CT, MRI, or radiography could be done to identify skeletal lesions or assess other areas of disease. The same imaging modality used at baseline for each patient was used at all further assessments during the study. All imaging data underwent blinded independent central review, and disease progression was confirmed by blinded independent central review according to RECIST version 1.1. Progression was also assessed by local investigator. A response status was deemed unknown if progression had not been documented and one or more lesions were not assessed or had been assessed using a different method than at baseline. If no baseline scans were available, subsequent overall lesion responses were deemed unknown. Reasons for an unknown response included receipt of subsequent therapy before the first assessment, assessments of stable disease or progressive disease not within the allowable window, and cases where, for example, image quality was judged insufficient by the central assessor.

Safety and tolerability were assessed by the incidence and severity of adverse events (monitored continuously through to 30 days after the end of treatment); assessments of haematology and chemistry values, vital signs, electrocardiograms, and physical examinations (done at every study visit); multigated acquisition scans or echocardiograms (done at weeks 4 and 7 and then every 9 weeks through to the end of treatment); and ocular examinations, including optical coherence tomography. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Ophthalmic examinations were required at each study visit for all patients with baseline retinal abnormalities and as indicated for patients receiving dacarbazine. After adoption of protocol amendment 4 (initiated when 200 patients had been randomly assigned; Oct 9, 2014; appendix pp 8–9), optical coherence tomography was done at screening for all patients, at each study visit for patients receiving binimetinib, and as indicated for patients receiving dacarbazine.

Outcomes

The primary endpoint was progression-free survival (defined as time from randomisation until progression according to blinded independent central review or death). Overall survival (defined as time from randomisation until death from any cause) was the only secondary endpoint that was type I error controlled. Other secondary endpoints included overall response (according to RECIST version 1.1, with all complete and partial responses confirmed by a second determination at least 4 weeks later) before progression; disease control (the percentage of patients with a best overall response of complete response, partial response, stable disease, or non-complete response or non-progressive disease); time to objective response (defined as time from randomisation to confirmed complete or partial response); and duration of objective response (defined as time from first confirmed response to disease progression or death due to underlying cancer).

Analyses of other secondary outcomes, including quality of life, comparison of ECOG performance status, pharmacokinetic analysis, and concordance of *NRAS* mutational status by different assays, will be reported elsewhere.

Statistical analysis

For sample size calculations, assumptions on progression-free survival medians were based on data from the BRIM-3 trial,[19] the METRIC trial,[20] and a previous phase 2 study of binimetinib.[21] The final progression-free survival analysis was planned after documentation of 260 progression-free survival events, which would provide 89% power to detect a hazard ratio (HR) of 0·5 using a log-rank test at a one-sided 2·5% level of significance, after accounting for the single interim futility analysis at 50% information fraction. The futility analysis was formally non-binding (eg, for boundary critical value determination), but power calculations were developed assuming a binding futility analysis. Additionally, a conservative approach was considered and the type I error rate was reduced from the nominal one-sided 2·5% level at the final analysis to account for the intermediate assessment even though stopping for efficacy was not foreseen. With an assumed 20% dropout rate, we estimated that 393 patients would be required to observe 260 events (262 patients in the binimetinib group and 131 in the dacarbazine group). If the primary endpoint was positive, the key secondary endpoint of overall survival was to be tested using a group-sequential Lan-DeMets spending function with O'Brien-Fleming-like boundaries, with the interim overall survival analysis done at the time of the final progression-free survival analysis and a final overall survival analysis (presented in this study) planned after 224 patient deaths. In the BRIM-3 trial,[22] median overall survival for previously untreated patients with *BRAF*-mutant melanoma receiving dacarbazine was 9·6 months.

Primary and secondary efficacy endpoints were analysed in the intention-to-treat population, which comprised all randomly assigned patients. Patients were analysed by treatment group and strata as assigned during randomisation. Safety was analysed in the safety population, which comprised all patients who received at least one dose of study drug and had at least one post-baseline safety assessment; patients were analysed according to treatment actually received.

Comparisons of progression-free survival and overall survival between treatment groups were done with a stratified log-rank test at a one-sided 2·5% cumulative level of significance. Progression-free survival events were derived considering the actual date of assessment rather than the scheduled visit date, as recommended by the US Food and Drug Administration.[23] Because bias might be introduced if the frequency of follow-up visits is dissimilar between the treatment groups or if dropouts are not random, a scatterplot of the timing of assessments by treatment group and an estimate of the censoring distribution by treatment group were produced (appendix p 20). No apparent bias between treatment groups was observed, supporting the use of the proposed analysis.

Progression-free survival was analysed by blinded investigator review and local review. Distributions of progression-free survival and overall survival were estimated using the Kaplan-Meier method. Stratified Cox regressions were used to estimate the HRs for progression-free survival and overall survival, along with 95% CIs. Overall response and disease control comparisons between treatment groups were done using the Cochran-Mantel-Haenszel χ^2 test. Time to objective response and duration of objective response were estimated in the two treatment groups using the Kaplan-Meier method. Best overall response was summarised by treatment group. Statistical tests on secondary efficacy endpoints were done at a one-sided significance level of 2·5%, unless otherwise noted. Efficacy was also analysed in prespecified subgroups by the methods noted above. A post-hoc analysis was done to assess overall response in patients who received previous ipilimumab or previous anti-PD-1 therapy. For selected adverse events, the time to first occurrence of any grade event above a specific grade threshold was summarised using Kaplan-Meier methods. Median time to onset and 95% CI were summarised. A post-hoc analysis of time to treatment discontinuation due to an adverse event was done with the Kaplan-Meier method. The data cutoff date for analyses of overall survival and post-treatment

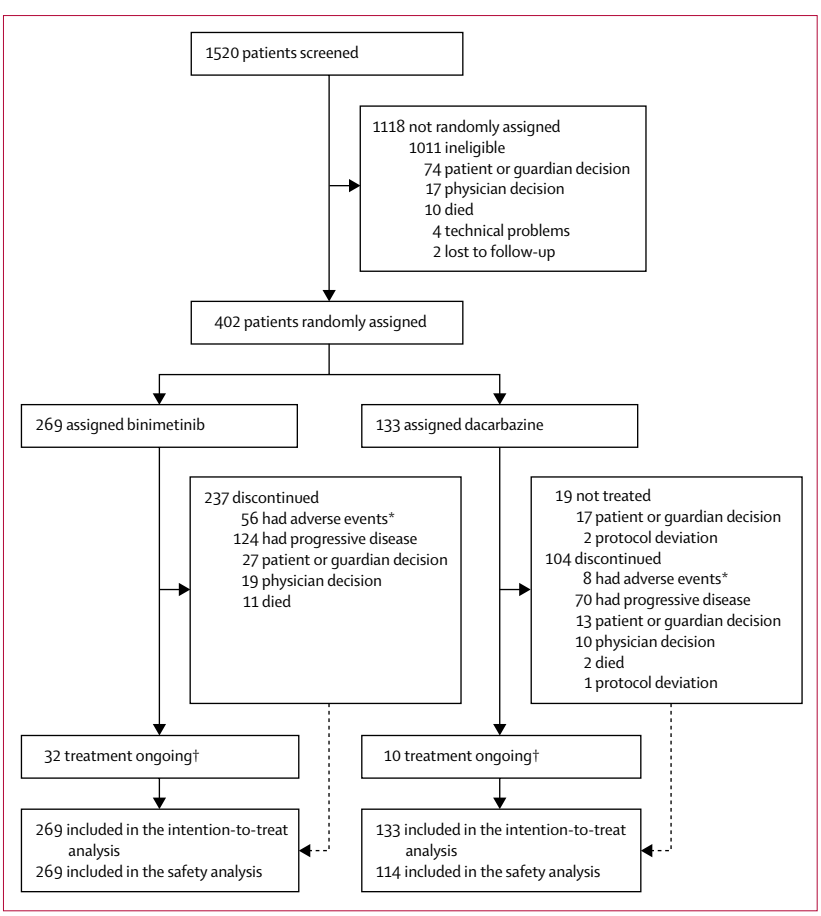

Figure 1: **Trial profile**
*Primary reason for treatment discontinuation. †As of data cutoff (Aug 24, 2015).

therapy was March 18, 2016. The data cutoff date for all other analyses was Aug 24, 2015. SAS version 9.4 was used for all analyses. This study is registered with ClinicalTrials.gov, number NCT01763164 and with EudraCT, number 2012-003593-51.

Role of the funding source

Novartis Pharmaceuticals Corporation designed the study with input from the study steering committee. The steering committee also contributed to the creation of adverse event management guidelines and supervised patient recruitment. Data were collected by both sponsors, analysed by the sponsors' statistical team, and interpreted by the sponsors in collaboration with the study authors. KF and RD wrote the manuscript with editorial support funded by the study sponsors, had full access to all study data, and held final responsibility for the decision to submit for publication.

Results

Between July 12, 2013, and March 20, 2015, 1520 patients were screened; of these, 1118 (74%) patients were not randomly assigned (figure 1). The most common reason for not meeting eligibility criteria was not having the required NRAS Gln61 mutation per the central laboratory analysis (789 [71%] of 1118 patients). 402 patients were randomly assigned between Aug 19, 2013, and April 28, 2015; 269 were assigned to receive binimetinib and 133 to receive dacarbazine. Baseline patient characteristics were well balanced across the two treatment groups (table 1). One patient in the dacarbazine group did not have an *NRAS* mutation. 19 (14%) of 133 patients randomly assigned to the dacarbazine group did not receive study drug, 17 because of patient or guardian decision, and two because of protocol deviation. All patients assigned to binimetinib received at least one dose of the drug. The median duration of exposure to binimetinib was 12·6 weeks (IQR 7·4–19·9) and to dacarbazine was 9·0 weeks (6·0–18·0).

Progression-free survival according to blinded independent central review was analysed after 267 events (179 events in the binimetinib group and 88 events in the dacarbazine group), and after a median follow-up of 1·7 months (IQR 1·4–4·1). The median progression-free survival was 2·8 months (95% CI 2·8–3·6) in the binimetinib group and 1·5 months (1·5–1·7) in the dacarbazine group (HR 0·62 [95% CI 0·47–0·80]; one-sided p<0·001; figure 2A).

Local review of progression-free survival was analysed after 279 events (192 events in the binimetinib group and 87 events in the dacarbazine group). Median progression-free survival based on local review was 3·0 months (95% CI 2·8–4·1) in the binimetinib group and 1·8 months (1·5–2·8) in the dacarbazine group (HR 0·63 [95% CI 0·48–0·82]; one-sided p<0·001).

Median overall survival was analysed after 228 deaths (161 in the binimetinib group and 67 in the dacarbazine group). Median follow-up for overall survival was 9·2 months (IQR 4·8–13·9). At the time of overall survival analysis, 136 patients with current follow-up were censored and at risk for a future overall survival event. Median overall survival was 11·0 months (95% CI 8·9–13·6) in the binimetinib group and 10·1 months (7·0–16·5) in the dacarbazine group (HR 1·00 [95% CI 0·75–1·33]; one-sided p=0·50; figure 2B).

Binimetinib treatment was associated with a higher proportion of patients with a confirmed overall response compared with dacarbazine treatment (41 [15%; 95% CI 11–20] *vs* 9 [7%; 3–13]; two-sided p=0·015; table 2). Additionally, binimetinib was associated with a higher proportion of patients with disease control than was dacarbazine (table 2). 40 (15%) of 269 patients in the

	Binimetinib (n=269)	Dacarbazine (n=133)
Age (years)	65 (18–90)	62 (27–89)
Sex		
Male	166 (62%)	85 (64%)
Female	103 (38%)	48 (36%)
NRAS mutation		
Gln61Lys	100 (37%)	51 (38%)
Gln61Leu	32 (12%)	17 (13%)
Gln61Arg	137 (51%)	64 (48%)
Wild-type	0	1 (1%)
ECOG performance status*		
0	193 (72%)	96 (72%)
1	76 (28%)	36 (27%)
Tumour stage at study entry†		
IIIC	10 (4%)	9 (7%)
IVM1a	27 (10%)	16 (12%)
IVM1b	45 (17%)	23 (17%)
IVM1c with normal LDH concentration	109 (41%)	50 (38%)
IVM1c with increased LDH concentration	78 (29%)	35 (26%)
LDH concentration‡		
Normal	184 (68%)	95 (71%)
High§	71 (26%)	32 (24%)
Missing	14 (5%)	6 (5%)
Previous immunotherapy	57 (21%)	28 (21%)
Previous ipilimumab¶	36 (13%)	17 (13%)
Previous anti-PD-1 or PD-L1¶	17 (6%)	7 (5%)
Patients who received previous lines of immunotherapy (used in therapeutic or metastatic setting)	49 (18%)	24 (18%)
1 line	43 (88%)	23 (96%)
≥2 lines	6 (12%)	1 (4%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. LDH=lactate dehydrogenase. *One patient in the dacarbazine group had a performance status of 2. †Extent of melanoma according to American Joint Committee on Cancer stage. ‡Low and high categories of LDH defined by normal concentrations; no patients in either group were in the the low LDH category. §Discrepant LDH values due to missing or erroneously reported values at screening. ¶Metastatic setting.

***Table 1*: Baseline characteristics**

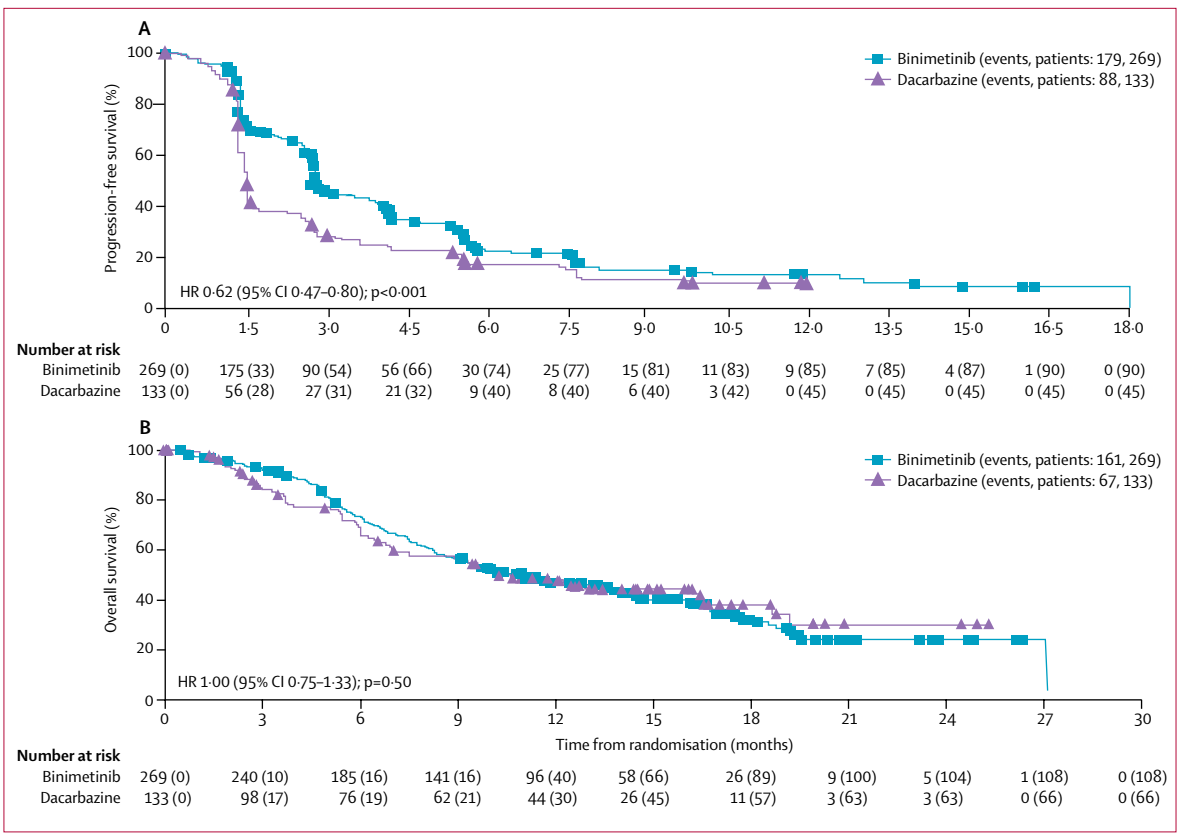

Figure 2: **Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)**
Stratified log-rank test and stratified Cox model using strata defined by American Joint Committee on Cancer stage, previous line immunotherapy, and Eastern Cooperative Oncology Group performance status, with one-sided p values. HR=hazard ratio.

binimetinib group and 41 (31%) of 133 patients in the dacarbazine group had an unknown best overall response; of these, 17 (6%) of 269 patients in the binimetinib group and 30 (23%) of 133 patients in the dacarbazine group had no valid post-baseline assessments. Median duration of objective response for confirmed complete or partial responses was 6·9 months (95% CI 4·2–11·1) for binimetinib and not estimable (4·1–not estimable) for dacarbazine. Percentage tumour size change from baseline is shown in the appendix (p 21).

Use of immunotherapy (ipilimumab, nivolumab, or pembrolizumab) after study drug discontinuation was similar in the treatment groups (125 [46%] of 269 patients in the binimetinib group and 59 [44%] of 133 patients in the dacarbazine group). The numbers of patients in the binimetinib versus dacarbazine groups who received ipilimumab, nivolumab, or pembrolizumab after study drug discontinuation were 90 (33%) versus 48 (36%), 34 (13%) versus 12 (9%), and 31 (12%) versus 9 (7%), respectively.

Progression-free survival in most prespecified patient subgroups was consistent with the overall population (figure 3). Among the stratification factor subgroups, median progression-free survival for patients with AJCC stage IIIC IVM1a,b disease was 3·8 months (95% CI 2·8–4·6) in the binimetinib group and 2·8 months (1·5–5·5) in the dacarbazine group. For patients with AJCC stage IVM1c disease, median progression-free survival was 2·8 months (2·4–2·9) in the binimetinib group and 1·5 months (CI 1·4–1·6) in the dacarbazine group. Median progression-free survival for patients with ECOG PS 0 was 3·0 months (2·8–4·2) in the binimetinib group and 1·5 months (1·5–2·3) in the dacarbazine group; for patients with ECOG PS 1 disease, median progression-free survival was 2·8 months (1·5–2·9) in the binimetinib group and 1·5 months (1·4–2·6) in the dacarbazine group. In the stratum of patients who received previous immunotherapy, median progression-free survival was longer for those who received binimetinib than for those who received dacarbazine (5·5 months [2·8–7·6] *vs* 1·6 months [1·5–2·8]; appendix p 22). Furthermore, the confirmed overall response per central review in patients who received previous immunotherapy was nine (16%) of 57 in the binimetinib group versus one (4%) of 28 in the dacarbazine group, and the median duration of objective response was 11·1 months (95% CI 2·8–not evaluable) in the binimetinib group versus 4·1 months (95% not evaluable) in the dacarbazine group. In a post-hoc analysis, an overall response was achieved in six (17%) of 36 patients treated with binimetinib who

received previous ipilimumab and three (18%) of 17 patients who received previous anti-PD-1 therapy. One patient in the dacarbazine group who had received previous ipilimumab had a partial response.

Adverse events were assessed in all patients who had at least one dose of study treatment and at least one post-baseline safety assessment (n=383). The most frequent adverse events reported in either study group regardless of attribution are shown in table 3; the full list is shown in the appendix (pp 12–16). The grade 3–4 adverse events reported in at least 5% of patients in either group were increased blood creatine phosphokinase (52 [19%] of 269 patients in the binimetinib group *vs* none of 114 in the dacarbazine group), hypertension (20 [7%] *vs* two [2%]), anaemia (five [2%] *vs* six [5%]), and neutropenia (two [1%] *vs* ten [9%]). Creatine phosphokinase elevation was generally asymptomatic and benign. A time-to-event Kaplan-Meier analysis of grade 3–4 adverse events, excluding adverse events of isolated grade 3–4 increased creatine phosphokinase, showed that the frequency of a grade 3–4 event was similar between the treatment groups in the first 3 months of treatment, after which time few patients remained in the dacarbazine group (appendix pp 10, 23). At the time of the data cutoff, 32 (12%) of 269 patients in the binimetinib group and 10 (8%) of 133 patients in the dacarbazine group were continuing treatment.

Serious adverse events of any grade were reported in 91 (34%) of 269 patients in the binimetinib group and 25 (22%) of 114 patients in the dacarbazine group. In the binimetinib group, adverse events resulted in a dose reduction in 163 (61%) patients and dose interruption in 157 (58%). In the dacarbazine group, adverse events that resulted in a dose reduction occurred in 18 (16%) patients; those resulting in dose interruption occurred in 33 (29%). Adverse events leading to discontinuation, as either the primary reason for discontinuation (figure 1) or as contributing to discontinuation, occurred in 66 (25%) patients in the binimetinib group and in nine (8%) patients in the dacarbazine group. A post-hoc analysis of time to discontinuation because of an adverse event is shown in the appendix (p 10). The most frequent adverse events leading to study discontinuation with binimetinib were decreased ejection fraction (ten [4%] of 269), increased creatine phosphokinase (five [2%]), retinal vein occlusion (five [2%]), and retinal detachment (four [1%]). Adverse events leading to study discontinuation with dacarbazine (one [1%] instance each) included abdominal pain, cholestasis, hepatobiliary disease, decreased neutrophil count, fatigue, febrile neutropenia, increased aspartate aminotransferase, increased blood alkaline phosphatase, increased blood bilirubin, increased γ-glutamyltransferase, neoplasm, metastases to the central nervous system, pancytopenia, syncope, and tachyarrhythmia. Discontinuation as a result of adverse events suspected to be related to study drug treatment was reported in 55 (20%) patients in the binimetinib group and six (5%) patients in the dacarbazine group.

	Binimetinib (n=269)	Dacarbazine (n=133)
Best overall response		
Complete response*	4 (1%)	0
Partial response	37 (14%)	9 (7%)
Stable disease	109 (41%)	23 (17%)
Progressive disease	72 (27%)	59 (44%)
Non-complete response or non-progressive disease	7 (3%)	1 (1%)
Unknown†	40 (15%)	41 (31%)
Overall response‡	41 (15%; 11·2–20·1)§	9 (7%; 3·1–12·5)
Disease control¶	157 (58%; 52·2–64·3)**	33 (25%; 17·7–33·0)

Data are n (%) or n (%; 95% CI). *Complete response durations were 209 days, more than 126 days (ongoing as of data cutoff), more than 273 days (ongoing as of data cutoff), and more than 443 days (ongoing as of data cutoff). †Most patients with a best overall response of unknown had no valid post-baseline assessments (43 [53%] of 81), 15 in the binimetinib group and 28 patients in the dacarbazine group, of whom 19 in the dacarbazine group were never treated. Other reasons for an unknown response included receipt of subsequent therapy before the first assessment, assessments of stable disease or progressive disease not within the allowable window, and cases where all assessments had outcomes of unknown (eg, if image quality was judged insufficient by the central assessor). ‡Overall response was defined as complete response plus partial response. §Two-sided p=0·015 versus the dacarbazine group. ¶Two-sided p<0·001 versus the dacarbazine group. **Complete response plus partial response plus stable disease plus non-complete response or non-progressive disease.

***Table 2*: Confirmed disease response per central review in the intention-to-treat population**

Rash events were reported under the combined term of rash (appendix pp 17–18). Grade 3–4 rash (combined term) was reported in 21 (8%) of 269 patients treated with binimetinib and the median time to onset of first grade 2 or worse rash event was 0·4 months (95% CI 0·3–0·5). No patients in the dacarbazine group had a grade 3–4 rash (combined term) adverse event. Dose modifications recommended in conjunction with rash treatment for grade 2 or worse events were sometimes required, but discontinuation of study treatment because of rash was infrequent, occurring in six (2%) patients in the binimetinib group. The most common grade 3–4 individual event in the combined grouping of rash was rash, reported in 11 (4%) of 269 patients in the binimetinib group, followed by dermatitis acneiform in seven (3%) of 269 patients treated with binimetinib (appendix p 16). Skin infections (appendix p 17), which were often secondary to other dermatological reactions, occurred in 69 (26%) of 269 patients in the binimetinib group and 15 (6%) of these events were grade 3. Skin infections resulted in hospital admission in three (1%) of 269 of patients receiving binimetinib.

Because of the known class effect of ocular toxicity reported with MEK inhibitors, extensive ophthalmic monitoring, including the use of optical coherence

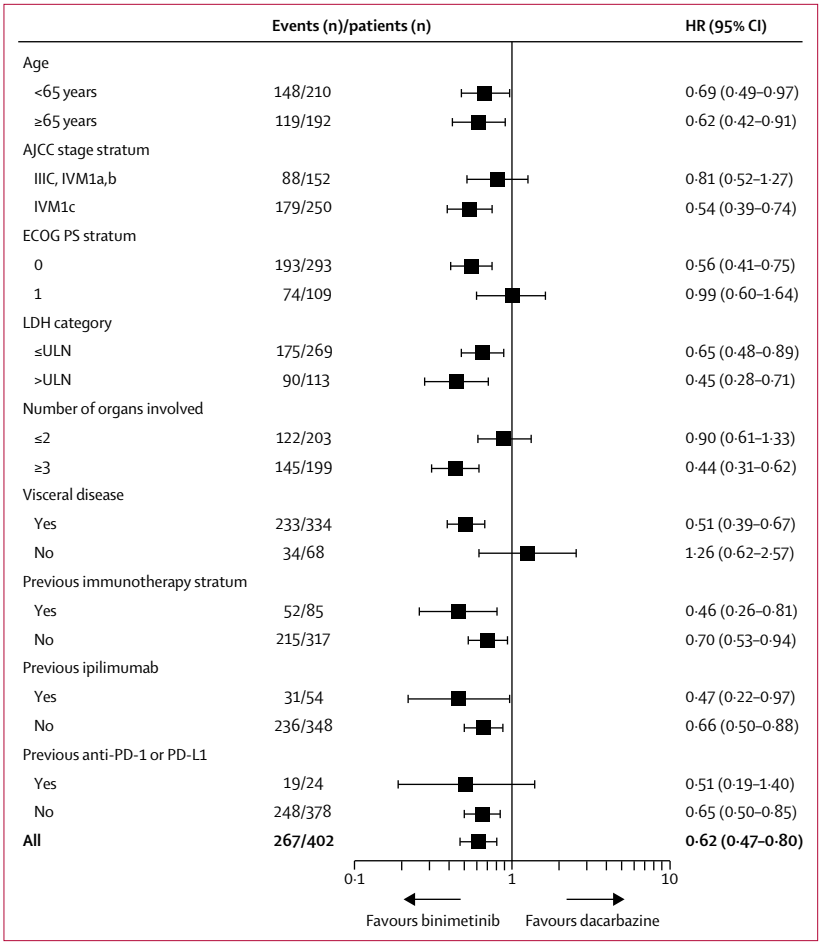

Figure 3: **Progression-free survival in prespecified subgroups of patients according to baseline characteristics**
HRs for subgroups from an unstratified proportional hazard model. Patient numbers in the figure might differ from those in table 1 because values entered into the randomisation system might have differed from those ultimately reported in case report forms after data cleaning. AJCC=American Joint Committee on Cancer. ECOG PS=Eastern Cooperative Oncology Group performance status. HR=hazard ratio. LDH=lactate dehydrogenase. ULN=upper limit of normal.

tomography, was done to assess binimetinib effects in the eye. Retinal events were commonly reported using several different descriptive terms, and many of these events showed a similar spectrum of findings. This probably represents the same underlying pathophysiology of retinal pigment epithelial detachment. These terms were grouped under the combined term of retinal pigment epithelial detachment and are defined in the appendix (p 17). Most retinal pigment epithelial detachment events were grade 1 (49 [18%] of 269 patients), defined as asymptomatic, or grade 2 (37 [14%]); grade 3 retinal pigment epithelial detachment was reported in only three (1%) of patients in the binimetinib group. One (1%) grade 1 event of retinopathy was reported in the dacarbazine group. The median time to onset of retinal pigment epithelial detachment (all grades) was 22 days (95% CI 22–24). Retinal pigment epithelial detachment was generally self-limiting, reversible in most cases, and easily managed, with 28 (10%) patients requiring dose modifications. Retinal vein occlusion was reported in six (2%) of patients treated with binimetinib; four of these events were reported as grade 3–4. For patients who developed retinal vein occlusion, the median time to onset was 3·1 months (95% CI 1·4–6·3). All patients were permanently discontinued from therapy per protocol, and no patient had permanent blindness. Even though ocular events were reported frequently based on extensive monitoring, events of visual impairment (group term; appendix p 17) occurred in only 39 (14%) of 269 patients, with one (<1%) patient reporting the event as grade 3–4.

Hypertension events were grouped into a combined term of hypertension (appendix p 17). Grade 3–4 hypertension (combined term) occurred in 23 (9%) patients who received binimetinib and two (2%) patients who received dacarbazine. Dose modifications were required in 14 (5%) patients and one (<1%) patient required study discontinuation; no dose modifications or discontinuations occurred in the dacarbazine group. Cardiac events, mostly events related to asymptomatic ejection fraction decrease, were reported in 35 (13%) patients in the binimetinib group and two (2%) of patients in the dacarbazine group. Grade 3 decreased ejection fraction was reported in ten (4%) patients treated with binimetinib and one (1%) patient treated with dacarbazine. For patients who developed a left ventricular ejection fraction below 50%, the median time to onset was 1·4 months (95% CI 0·7–1·5). Left ventricular dysfunction, used as a combined term to group related adverse events (appendix p 17), led to discontinuation in 12 (4%) patients in the binimetinib group and no patients in the dacarbazine group. Venous thromboembolism (combined term), including pulmonary embolism and deep vein thrombosis (appendix p 17), was reported as grade 2 in eight (3%) patients, grade 3 in five (2%) patients, and grade 4 in one (<1%) patients in the binimetnib group and grade 2 in two (2%) of 114 patients in the dacarbazine group. Grade 3 pulmonary embolism was reported in three (1%) of patients who received binimetinib. Pneumonitis occurred in three (1%) patients treated with binimetinib; one (<1%) of these patient had a grade 3–4 event. No patients in the dacarbazine group had pulmonary embolism or pneumonitis.

Deaths (including those that occurred more than 30 days after the end of treatment) were reported for 120 patients in the binimetinib and 50 patients in the dacarbazine group, as of the data cutoff (Aug 24, 2015). Deaths during study drug treatment or within 30 days of the last study drug dose were reported for 23 patients in the binimetinib group and three patients in the dacarbazine group. Most deaths resulted from patients' underlying melanoma (110 [92%] of 120 in the binimetinib group and 48 [96%] of 50 patients in the dacarbazine group). Other causes of death in the binimetinib group were unknown cause (four), sepsis (two), and myocardial infarction (one), multi-organ failure (one), cerebrovascular accident (one), and

embolism (one). In the dacarbazine group, one patient died as a result of tumour haemorrhage, and one patient died as a result of multi-organ failure. One death (multi-organ failure in the binimetinib group) was considered by the investigator as suspected to be related to the study treatment.

Discussion

In this randomised, phase 3 study, progression-free survival was significantly longer in the binimetinib group than in the dacarbazine group. The proportion of patients with a confirmed response was twice as high with binimetinib compared with dacarbazine. Outcomes observed with dacarbazine are concordant with published reports assessing progression-free survival.[8,9,24] Effective treatment options in *NRAS*-mutant advanced melanoma are urgently needed, especially after failure of immunotherapy with anti-CTLA4 or anti-PD-1 antibodies. *NRAS*-mutant melanoma has been reported to present an aggressive natural history compared with *BRAF*-mutant melanoma or melanoma lacking either a *BRAF* or *NRAS* mutation, although these data need confirmation.[4,17]

With the emergence of several effective therapies for advanced melanoma, we postulated that previous or subsequent therapy could affect our ability to assess long-term outcomes, such as overall survival, associated with the treatments received in this study. We attempted to control for this by stratifying patients at study entry based on previous receipt of immunotherapy. Additionally, follow-up included documentation of post-protocol therapy. In this descriptive analysis, the use of known, effective immunotherapies post-study was evenly distributed between the binimetinib and dacarbazine groups.

Progression-free survival was longer for patients who received binimetinib than for those who received dacarbazine; this was consistent in almost all subgroups analysed, including in patients who received previous immunotherapy and in patients with characteristics associated with an unfavourable prognosis, such as stage M1c disease or elevated lactate dehydrogenase serum concentrations. We also observed that patients in the binimetinib group who received previous immunotherapy had a similar overall response (16%) and longer median duration of response (11 months) when compared with all intention-to-treat patients in the binimetinib group (overall response 15%; median duration of response 6·9 months). The effect of binimetinib compared with dacarbazine on progression-free survival was modest in patients who did not receive previous immunotherapy. Although the reasons for this are unclear, we speculate that pathways outside of the MAPK pathway contribute to widespread de novo and acquired resistance in the context of *NRAS* mutations.

Despite the difference in progression-free survival between the groups, no difference was observed for overall survival. Immunotherapies with a long-term effect on overall survival became more widely available during the conduct of this trial, and the percentage of patients who received immune checkpoint antibodies in this study was higher than in previously reported phase 3 trials of BRAF or MEK inhibitors in melanoma.[9–11,19,25,26] The use of these drugs might have confounded our ability to observe a difference in overall survival. Outside of the context of *NRAS*-mutant melanoma, MEK inhibitor monotherapy was associated with progression-free survival and overall survival benefits in *BRAF*-mutant melanoma,[27] but increased progression-free survival in the absence of overall survival improvement

	Binimetinib (n=269)			Dacarbazine (n=114)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	104 (39%)	4 (1%)	0	12 (11%)	1 (1%)	0
Peripheral oedema	96 (36%)	1 (<1%)	0	3 (3%)	0	0
Dermatitis acneiform	88 (33%)	7 (3%)	0	1 (1%)	0	0
Rash	87 (32%)	11 (4%)	0	1 (1%)	0	0
Nausea	75 (28%)	4 (1%)	0	36 (32%)	1 (1%)	0
Blood creatine phosphokinase increased	61 (23%)	33 (12%)	19 (7%)	3 (3%)	0	0
Fatigue	54 (20%)	6 (2%)	0	33 (29%)	3 (3%)	0
Vomiting	51 (19%)	6 (2%)	0	14 (12%)	0	0
Asthenia	40 (15%)	8 (3%)	0	14 (12%)	5 (4%)	0
Retinal detachment	39 (14%)	0	0	0	0	0
Constipation	35 (13%)	2 (1%)	0	21 (18%)	0	0
Pruritus	30 (11%)	2 (1%)	0	2 (2%)	0	0
Aspartate aminotransferase increased	29 (11%)	6 (2%)	0	4 (4%)	0	0
Decreased appetite	29 (11%)	2 (1%)	0	17 (15%)	1 (1%)	0
Pyrexia	28 (10%)	0	0	17 (15%)	0	0
Skin fissures	28 (10%)	0	0	0	0	0
Dyspnoea	26 (10%)	3 (1%)	0	4 (4%)	2 (2%)	0
Ejection fraction decreased	20 (7%)	10 (4%)	0	1 (1%)	1 (1%)	0
Hypertension	17 (6%)	20 (7%)	0	2 (2%)	2 (2%)	0
Alanine aminotransferase increased	15 (6%)	7 (3%)	0	5 (4%)	2 (2%)	0
Anaemia	14 (5%)	4 (1%)	1 (<1%)	5 (4%)	6 (5%)	0
General physical health deterioration	7 (3%)	9 (3%)	2 (1%)	2 (2%)	0	0
γ-glutamyltransferase increased	5 (2%)	3 (1%)	0	3 (3%)	3 (3%)	0
Lymphopenia	3 (1%)	3 (1%)	1 (<1%)	3 (3%)	3 (3%)	0
Thrombocytopenia	2 (1%)	0	1 (<1%)	13 (11%)	2 (2%)	2 (2%)
Neutropenia	1 (<1%)	2 (1%)	0	11 (10%)	5 (4%)	5 (4%)
Neutrophil count decreased	1 (<1%)	0	0	5 (4%)	2 (2%)	1 (1%)
Leukopenia	0	0	0	4 (4%)	4 (4%)	0

Preferred terms are presented by descending order of frequency of grade 1–2 adverse events in the binimetinib group. A patient with multiple occurrences of an adverse event under a preferred term is counted only once for that preferred term. A patient with multiple adverse events is counted only once in the total row. As per the study protocol, deaths were not graded and therefore were not included in this table; please see main text for causes of all deaths.

***Table 3*: Adverse events irrespective of causality in at least 10% (grade 1 or 2) or at least 2% (grade 3 or 4) of patients in either treatment group**

was observed with combination treatment with a MEK inhibitor and chemotherapy in *KRAS*-mutant non-small-cell lung cancer.[28]

Reported adverse events were consistent with MEK inhibitor treatment: maculopapular rash; transient, mostly asymptomatic retinopathy; diarrhoea; peripheral oedema; and mostly asymptomatic increased creatine phosphokinase.[16,21,26,29–31] These adverse events were manageable with dose interruption and reduction, when needed. Retinal events are recognised as a class toxicity of MEK inhibitors, and more recent clinical programmes (including this trial) incorporate intensive monitoring, including optical coherence tomography, to detect these events. Whether earlier studies, which lacked frequent monitoring, underestimated the incidence of retinal events is not known.[10] In light of the low rate of severe ocular toxicity observed in this study, whether regularly scheduled ophthalmological examinations are necessary in asymptomatic patients is not clear. Furthermore, we did not identify any baseline cardiac risk factors that predicted risk of cardiac toxicity in either treatment group that would enable modified monitoring for this toxicity.

Since the initiation of the trial, anti-PD-1 antibody therapy, with or without ipilimumab, has become available in most countries worldwide, and treatment guidelines[30,32] recommend these drugs for the first-line therapy of patients with advanced melanoma. In this study, the median progression-free survival difference favouring binimetinib was greater in the subpopulation that had received previous immunotherapy than in those that had not received immunotherapy, a finding that might have clinical relevance given that binimetinib is most likely to find use in this post-immunotherapy setting; however, this observation needs further confirmation.

From a mechanistic standpoint, these clinical data confirm the validity of the approach of selectively inhibiting the MAPK pathway in this melanoma subpopulation in the context of melanoma as a "RASopathy".[3] Preclinical investigations in *NRAS*-mutant melanoma showed that MEK inhibition induces apoptosis; the addition of a cyclin dependent kinase 4/6 (CDK4/6) inhibitor to a MEK inhibitor results in improved cell cycle arrest.[31] MDM2 antagonists also appear promising in combination with MEK inhibition in preclinical models of *NRAS*-mutant melanoma.[33] As a consequence, clinical trials with combinations of binimetinib with the CDK4/6 inhibitor ribociclib and investigational MDM2 antagonists are in progress or in preparation.[34] Pan-RAF inhibitors that do not cause paradoxical activation of MEK and ERK, and ERK inhibitors are additional future options to be investigated preferentially in combination with MEK inhibition.

A primary strength of this study is its size; to our knowledge, NEMO is the largest controlled study done to date in patients with *NRAS*-mutant melanoma, with 1520 patients screened in 27 countries worldwide, which represented a substantial logistical challenge. An important limitation of the study is that treatment was not masked to patients or investigators, with the exception of the blinded independent central review to confirm disease progression and assess response. The open-label design might account for the fact that 19 patients who were randomised to dacarbazine did not receive the drug. Additionally, NEMO was done during the time of a changing treatment landscape, which probably affected statistical assumptions for the power calculation of overall survival differences between the treatment groups.

In conclusion, a progression-free survival benefit was observed in treatment-naive and immunotherapy pre-treated patients who received binimetinib compared with dacarbazine. Binimetinib is another promising treatment option for advanced melanoma and the first molecularly targeted therapy with demonstrated benefit in the *NRAS*-mutant population. Improved clinical efficacy of binimetinib in immunotherapy-pretreated patients needs further confirmation and more detailed mechanistic assessment.

Contributors

KF and RD did the literature search and wrote the manuscript with editorial support provided by Complete Publication Solutions (North Wales, PA, USA) and funded by Array BioPharma. The study was designed by Novartis Pharmaceuticals Corporation with input from the study steering committee (RD [co-chairman], KF [co-chairman], DS, PAA, and GVL). MW and VJ provided statistical support. All authors were involved in the interpretation of data and reviewed and approved the manuscript.

Declaration of interests

RD has received personal fees and non-financial support as a consultant and advisory board participant for Roche, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Amgen, and Takeda; and grants from Roche, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, and Novartis. DS has received personal fees from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Roche, and Merck Sharp & Dohme. PAA has received personal fees for advisory board participation from Bristol-Myers Squibb, Roche/Genentech, Array BioPharma, Merck Sharp & Dohme, Novartis, Amgen, and Merck Serono; and research funding and grants from Bristol-Myers Squibb, Roche/Genentech, and Array BioPharma. AA has been a member of a speaker's bureau for Novartis, Roche, Merck Sharp & Dohme, and Bristol-Myers Squibb. AMDG has served in an advisory role for Pierre Fabre; and participated in compensated educational activities for Bristol-Myers Squibb, Roche, and Merck Sharp & Dohme. PR has received honoraria for lectures from Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Amgen, Pfizer, and Roche; personal fees for advisory board participation from Novartis, Roche, Amgen, Merck Sharp & Dohme, and Bristol-Myers Squibb; and research funding from Novartis for the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology. MDV has received honoraria for lectures and personal fees for advisory board participation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, and Novartis. RG has received study documentation fees from Novartis and Array BioPharma for conduct of this study; honoraria for lectures and personal fees for advisory board participation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Novartis, Almirall, LEO, Amgen, Merck Serono, Boehringer Ingelheim, Galderma, Janssen, and Pierre Fabre; and research grants from Pfizer and Johnson & Johnson. MM has received honoraria from Novartis, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche; personal fees for speaker's bureau participation from Novartis, GlaxoSmithKline, Roche, and Bristol-Myers Squibb; personal fees for advisory board participation from Novartis,

Amgen, Merck Sharp & Dohme, and Bristol-Myers Squibb; and research funding from Roche. CG has received personal fees for advisory board participation and presentations from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Philogen, and LEO; and grants from Bristol-Myers Squibb, Novartis, and Roche. DH has served as an advisory board member for Merck, EMD Serono, Roche, Bristol-Myers Squibb, and Novartis. PQ has received personal fees for consulting and advisory roles from Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Roche/Genentech. EW, JF, MW, and VJ are employed by Novartis AG. LAS was employed by Novartis AG during conduct of the study. VB is employed by Array BioPharma. GVL has received personal fees from Amgen, Array BioPharma, Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, and Novartis. KF has received personal fees for consulting from Novartis, Array BioPharma, and Roche; and has received grant and research support from Novartis. All other authors declare no competing interests.

Acknowledgments

We thank the patients and their families who participated in this study. The authors of the study also gratefully acknowledge the efforts of the NEMO study drug monitoring committee, Antoni Ribas (chairperson), Caroline Robert, Daniel J Sargent, and Tara McCannel. This study was sponsored by Array BioPharma, with funding support from Novartis Pharmaceuticals Corporation. Editorial support was provided by Mariana Ovnic of Complete Publication Solutions, LLC (North Wales, PA, USA) and was funded by Array BioPharma.

References

1 Boiko AD, Razorenova OV, van de Rijn M, et al. Human melanoma-initiating cells express neural crest nerve growth factor receptor CD271. *Nature* 2010; **466:** 133–37.

2 Shain AH, Yeh I, Kovalyshyn I, et al. The genetic evolution of melanoma from precursor lesions. *N Engl J Med* 2015; **373:** 1926–36.

3 Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. *Nat Genet* 2015; **47:** 996–1002.

4 Jakob JA, Bassett RL Jr, Ng CS, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. *Cancer* 2012; **118:** 4014–23.

5 Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. *Cell* 2015; **161:** 1681–96.

6 Singh H, Longo DL, Chabner BA. Improving prospects for targeting RAS. *J Clin Oncol* 2015; **33:** 3650–59.

7 Solit DB, Garraway LA, Pratilas CA, et al. BRAF mutation predicts sensitivity to MEK inhibition. *Nature* 2006; **439:** 358–62.

8 Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; **364:** 2507–16.

9 Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012; **380:** 358–65.

10 Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med* 2012; **367:** 107–14.

11 Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015; **372:** 30–39.

12 Menzies AM, Long GV. Systemic treatment for BRAF-mutant melanoma: where do we go next? *Lancet Oncol* 2014; **15:** e371–81.

13 Van Herpen C, Agarwala SS, Hauschild A, et al. Overall survival and biomarker results from a phase 2 study of MEK1/2 inhibitor or binimetinib (MEK162) in patients with advanced NRAS-mutant melanoma. *Ann Oncol* 2015; **25:** LBA35.

14 Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; **364:** 2517–26.

15 Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; **372:** 320–30.

16 Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol* 2015; **16:** 908–18.

17 Mangana J, Cheng PF, Schindler K, et al. Analysis of BRAF and NRAS mutation status in advanced melanoma patients treated with anti-CTLA-4 antibodies: association with overall survival? *PLoS One* 2015; **10:** e0139438.

18 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228–47.

19 McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol* 2014; **15:** 323–32.

20 Robert C, Flaherty KT, Hersey P, et al. METRIC phase III study: efficacy of trametinib (T), a potent and selective MEK inhibitor (MEKi), in progression-free survival (PFS) and overall survival (OS), compared with chemotherapy (C) in patient (pts) with BRAFV600E/K mutant advanced or metastatic melanoma (MM). *Proc Am Soc Clin Oncol* 2012; **30** (suppl)**:** abstr LBA8509.

21 Ascierto PA, Schadendorf D, Berking C, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. *Lancet Oncol* 2013; **14:** 249–56.

22 Chapman PB, Hauschild A, Robert C, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patient with BRAFV600E mutated melanoma. *J Clin Oncol* 2012; **30** (suppl)**:** abstr 8502.

23 US Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. *Biotechnol Law Rep* 2007; **26:** 375–86.

24 McDermott DF, Sosman JA, Gonzalez R, et al. Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group. *J Clin Oncol* 2008; **26:** 2178–85.

25 Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med* 2014; **371:** 1877–88.

26 Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014; **371:** 1867–76.

27 Gupta A, Love S, Schuh A, et al. DOC-MEK: a double-blind randomized phase II trial of docetaxel with or without selumetinib in wild-type BRAF advanced melanoma. *Ann Oncol* 2014; **25:** 968–74.

28 Janne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol* 2013; **14:** 38–47.

29 Kirkwood JM, Bastholt L, Robert C, et al. Phase II, open-label, randomized trial of the MEK1/2 inhibitor selumetinib as monotherapy versus temozolomide in patients with advanced melanoma. *Clin Cancer Res* 2012; **18:** 555–67.

30 Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26:** v126–32.

31 Kwong LN, Costello JC, Liu H, et al. Oncogenic NRAS signaling differentially regulates survival and proliferation in melanoma. *Nat Med* 2012; **18:** 1503–10.

32 National Comprehensive Cancer Network. Clinical practice guidelines in oncology, melanoma version 2. Fort Washington, PA: National Comprehensive Cancer Network, 2016.

33 Gembarska A, Luciani F, Fedele C, et al. MDM4 is a key therapeutic target in cutaneous melanoma. *Nat Med* 2012; **18:** 1239–47.

34 Van Herpen C, Postow MA, Carlino MS, et al. A phase 1b/2 study of ribociclib (LEE011; CDK4/6 inhibitor) in combination with binimetinib (MEK162; MEK inhibitor) in patients with NRAS-mutant melanoma. *Eur J Cancer* 2015; **51:** S66.