Selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment for BRAF-mutant metastatic melanoma: a phase 2 double-blind randomised study

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Summary

Background Patients with metastatic melanoma, 50% of whose tumours harbour a BRAF mutation, have a poor prognosis. Selumetinib, a MEK1/2 inhibitor, has shown antitumour activity in patients with BRAF-mutant melanoma and in preclinical models when combined with chemotherapy. This study was designed to look for a signal of improved efficacy by comparing the combination of selumetinib and dacarbazine with dacarbazine alone.

Methods This double-blind, randomised, placebo-controlled phase 2 study investigated selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment in patients older than 18 years with histologically or cytologically confirmed advanced BRAF-mutant cutaneous or unknown primary melanoma. Patients were randomly assigned by central interactive voice response system (1:1 ratio, block size four) to take either oral selumetinib (75 mg twice daily in a 21-day cycle) or placebo; all patients received intravenous dacarbazine (1000 mg/m² on day 1 of a 21-day cycle). Patients, investigators, and the study team were masked to the treatment assigned. The primary endpoint was overall survival analysed by intention to treat. This study is registered at ClinicalTrials.gov, NCT00936221.

Findings Between July 20, 2009, and April 8, 2010, 91 patients were randomly assigned to receive dacarbazine in combination with selumetinib (n=45) or placebo (n=46). Overall survival did not differ significantly between groups (median 13.9 months, 80% CI 10.2–15.6, in the selumetinib plus dacarbazine group and 10.5 months, 9.6–14.7, in the placebo plus dacarbazine group; hazard ratio [HR] 0.93, 80% CI 0.67–1.28, one-sided p=0.39). However, progression-free survival was significantly improved in the selumetinib plus dacarbazine group versus the placebo plus dacarbazine group (HR 0.63, 80% CI 0.47–0.84, one-sided p=0.021), with a median of 5.6 months (80% CI 4.9–5.9) versus 3.0 months (2.8–4.6), respectively. The most frequent adverse events included nausea (28 [64%] of 44 patients on selumetinib vs 25 [56%] of 45 on placebo), acneiform dermatitis (23 [52%] vs one [2%]), diarrhoea (21 [48%] vs 13 [29%]), vomiting (21 [48%] vs 15 [33%]), and peripheral oedema (19 [43%] vs three [7%]). The most common grade 3–4 adverse event was neutropenia (six [14%] patients in the selumetinib plus dacarbazine group vs four [9%] in the placebo plus dacarbazine group).

Interpretation Selumetinib plus dacarbazine showed clinical activity in patients with BRAF-mutant cutaneous or unknown primary melanoma, reflected by a significant benefit in progression-free survival compared with placebo plus dacarbazine group, although no significant change in overall survival was noted. The tolerability of this combination was generally consistent with monotherapy safety profiles.

Funding AstraZeneca.

Introduction Melanoma is an aggressive and highly metastatic form of skin cancer with a median overall survival of around 8 months from diagnosis of stage IV disease.1 About 46,000 deaths from the disease were reported worldwide in 2008.2 Traditionally, dacarbazine has been the approved first-line treatment for metastatic melanoma in routine clinical practice. During the course of the study, two targeted therapies, the BRAF inhibitor vemurafenib3 and the cytotoxic T-lymphocyte antigen 4 (CTLA4)-blocking monoclonal antibody ipilimumab,4 were licensed for this indication.

BRAF Val600 mutations are detected in the tumours of about 50% of patients with metastatic melanoma, with Val600Glu being the most common.5 This high frequency suggests that the RAS-RAF-MEK-ERK pathway, which is often deregulated in cancer, is a potential therapeutic target for inhibition. The overall survival benefit recorded with the BRAF kinase inhibitor vemurafenib has since confirmed this hypothesis.6 Preclinical and clinical data have shown that cell lines and tumours harbouring BRAF Val600 mutations are also sensitive to MEK inhibition.7,8 Selumetinib (AZD6244, ARRY-142886) is an orally available, potent, selective, non-ATP-competitive inhibitor of MEK1/2.9 Early phase monotherapy clinical studies have shown target inhibition10 and tumour responses in patients with BRAF-mutant advanced melanoma,11 although clinical efficacy was not significant.12 However, selumetinib in combination with docetaxel has shown
tumour regression in melanoma xenograft models, highlighting the potential for MEK inhibitor plus chemotherapy combinations.\textsuperscript{16} Furthermore, selumetinib plus docetaxel has shown promising efficacy in previously treated patients with KRAS-mutant advanced non-small-cell lung cancer.\textsuperscript{15} Studies in human tumour xenograft models using selumetinib and temozolomide, which has the same active metabolite as dacarbazine, have shown highly significant tumour regression as well as an increased cellular DNA damage rate compared with either treatment as monotherapy.\textsuperscript{12}

On the basis of these promising preclinical data, the aim of this study was to assess the efficacy and safety of selumetinib combined with dacarbazine as first-line treatment in patients with BRAF-mutant advanced cutaneous or unknown primary melanoma.

**Methods**

**Study design and patients**

This phase 2, double-blind, randomised, placebo-controlled study was undertaken at 44 hospitals across 12 countries (France, Germany, Netherlands, Norway, Spain, Sweden, Switzerland, UK, Czech Republic, Hungary, Brazil, USA). Patients aged 18 years or older with histologically or cytologically confirmed advanced (inoperable American Joint Committee on Cancer stage III and IV), BRAF-mutant, cutaneous or unknown primary melanoma were included. BRAF mutation status was confirmed before randomisation by an AstraZeneca-appointed central laboratory (Cranford, NJ, USA) using Amplification Refractory Mutation System (ARMS) analysis\textsuperscript{17} or Sanger sequencing, or by an AstraZeneca-agreed local laboratory using agreed methods (DNA sequencing, allele-specific PCR, pyrosequencing, or TaqMan). ARMS analysis uses sequence-specific PCR primers that allow amplification of test DNA only when the target allele is contained within the sample.\textsuperscript{2} Additional inclusion criteria included WHO performance status 0–1 and adequate bone marrow, renal, and liver function. Patients were ineligible if they had a lactate dehydrogenase concentration two or more times the upper limit of normal or had received any previous cytotoxic chemotherapy, biochemotherapy, CTLA4-blocking monoclonal antibodies for advanced melanoma, adjuvant biochemotherapy containing temozolomide or dacarbazine, or any previous treatment with a MEK, RAF, or RAS inhibitor. Previous isolated limb perfusion (unless done with dacarbazine), previous monotherapy with cytokines (interleukin 2, interferon, or GM-CSF), adjuvant anti-CTLA4, vaccines or adjuvant biochemotherapy (unless containing dacarbazine or temozolomide) were allowed. Patients with brain metastases or spinal cord compression were eligible if they were asymptomatic, treated, and stable off treatment for at least 3 months.

All patients provided written informed consent and the study was undertaken in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board at each study site and complied with local country regulations.

**Randomisation and masking**

Eligible patients were randomly assigned, in a 1:1 ratio (block size of four), to receive dacarbazine in combination with either selumetinib or placebo. Treatment groups were assigned by means of an interactive voice response system at central locations (Nottingham, UK, and East Windsor, NJ, USA). The voice response system allocated randomisation numbers and drug pack codes. Patients, investigators, and the study team were masked to the treatment assigned.

**Procedures**

Patients received intravenous dacarbazine 1000 mg/m\textsuperscript{2} on day 1 of every 21-day cycle and were expected to receive up to eight cycles. More than eight cycles could be given when such treatment did not contravene local practice. Patients also received either selumetinib hydrogen sulphate capsules 75 mg twice a day or matched placebo until disease progression or intolerable adverse effects occurred. The selumetinib dose could be reduced up to...
three times to manage toxicity. Once reduced, the dose was not allowed to return to a previous level.

Treatment was withheld if an adverse event of grade 3 or higher (except neutropenia continuing for ≥7 days) or an intolerable adverse event, irrespective of grade, deemed at least partly related to treatment was recorded, despite optimum supportive care. After disease progression, patients could receive any subsequent therapy at the discretion of the treating physician. No crossover was allowed. Investigators were required to provide drug data, including subsequent anticancer therapies, after discontinuation of selumetinib or placebo until the end of the 30-day follow-up, after which there was no obligation for the investigators to provide this information.

The primary endpoint was overall survival, defined as the time from randomisation until the date of death from any cause. Secondary endpoints included progression-free survival, proportion of patients alive and progression-free at 6 months, proportion of patients who had an objective response, duration of response, and safety.

Tumour response was based on investigator assessment of target and non-target lesions using CT or MRI at baseline, week 12, and then every 12 weeks, relative to date of randomisation. Modified Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) assessments were used to evaluate progression-free survival, proportion of patients alive and progression-free at 6 months, proportion of patients who had an objective response, and duration of response. Response was confirmed at the next scheduled RECIST assessment no less than 4 weeks after the date on which the criteria for response were first met, but this confirmation was not required for inclusion in analysis of objective response. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3).

Ophthalmic assessments (visual fields, visual acuity, colour vision, intraocular pressure, and slit-lamp examination) were done at baseline, week 6, and on the occurrence of visual symptoms. Visual assessments were generally not available at the time of the adverse event and optical tomography was not done as part of the study.

Statistical analysis
We planned to do the primary overall survival analysis after at least 58 deaths (80% power to detect a hazard ratio [HR] of 0·57 for death from any cause, with a one-sided α level of 0·10). On the basis of this calculation, 91 patients were randomly assigned to treatment groups (1:1). This trial was sized with a one-sided significance level of 10% because it was a phase 2 study looking for a signal of improved efficacy. If a one-sided p value of less than 0·1 was observed, the results were regarded as promising (but not definitive) because there was a less than one in ten probability that such a result could have been detected if there was truly no treatment effect.

Efficacy data were analysed with SAS (version 9.1). The primary overall survival analysis was by intention to treat and used a Cox proportional hazards model, allowing for the effect of treatment and including terms for WHO performance status (0 vs 1), lactate dehydrogenase (≤ vs > upper limit of normal based on local reference ranges), histopathological type (superficial spreading melanoma vs other), and metastatic status (M1c vs other).

Progression-free survival was analysed with a grouped survival method for interval censored data (0–18, 18–30, 30–42, and greater than 42 weeks). Kaplan-Meier estimates of proportion of patients alive and progression-free at 6 months were calculated and compared between treatment groups. The log HR was calculated with the difference in log (–log) of the Kaplan-Meier estimates of this proportion. Results were back-transformed and presented as HR together with 80% CIs. The proportion of patients who had an objective response was compared between groups using a logistic regression model. The same covariates used in the overall survival analysis were used in the progression-free survival and objective response analyses. Duration of response was analysed by calculation of the ratio of expected durations of response.
with the Weibull probability distribution for duration of response in responding patients. All patients who received at least one dose of selumetinib or placebo were included in the safety population; we undertook no formal analysis of safety data.

This study is registered at ClinicalTrials.gov, number NCT00936221.

Role of the funding source

The trial was funded by the study sponsor and designed by the coprincipal investigators (CR and MRM) and the sponsor. The sponsor was responsible for data collection, analysis, and interpretation. The authors vouch for the completeness and accuracy of the data and the data analyses. This report was written by the lead author, with editorial assistance funded by the sponsor, and was reviewed and approved for publication by all coauthors and the sponsor. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 20, 2009, and April 8, 2010, 385 patients were screened, 91 of whom were randomly assigned to receive selumetinib plus dacarbazine (n=45) or placebo plus dacarbazine (n=46; figure 1). Most patients failed screening because their tumour was not \( \text{BRAF} \) mutant; for some patients who failed screening for other reasons, the \( \text{BRAF} \) status of their tumour is unknown. Two patients (one from each group) did not receive allocated treatment and were excluded from the safety and per-protocol analyses. The study population was representative of first-line patients with \( \text{BRAF} \)-mutant advanced cutaneous or unknown melanoma (table 1). The two groups were generally well balanced, with the exception of histopathological type (superficial spreading melanoma), sex, and previous systemic anticancer treatments. A statistical model, adjusting for all the potentially imbalanced baseline characteristics, did not affect the interpretation of the primary endpoint (data not shown).

At the time of the planned data cutoff, Nov 20, 2011, 66 deaths had occurred (73% maturity) and median follow-up was 12·3 months (IQR 7·4–20·2). The median number of dacarbazine cycles was eight (range 2–22) in the selumetinib group and five (1–16) in the placebo group. Overall survival did not differ significantly between groups: median overall survival in the selumetinib plus dacarbazine group was 13·9 months (95% CI 10·2–15·6) versus 10·5 months (9·6–14·7) in the placebo plus dacarbazine group (HR 0·93, 95% CI 0·67–1·28, one-sided \( p=0·39 \); figure 2). Progression-free survival was significantly improved in the selumetinib plus dacarbazine group (HR 0·63, 95% CI 0·47–0·84, one-sided \( p=0·021 \)): median progression-free survival in the selumetinib plus dacarbazine group was 5·6 months (95% CI 4·9–5·9) versus 3·0 months (2·8–4·6) in the placebo plus dacarbazine group (figure 2). Table 2 summarises key efficacy findings. The proportion of patients alive and progression-free at 6 months in the selumetinib plus dacarbazine group was larger than in the placebo plus dacarbazine group (40% vs 22%; HR 0·60, 95% CI 0·42–0·85, one-sided \( p=0·03 \)). The proportion of patients with an objective response, including confirmed and unconfirmed responses (complete or partial), was 40% (18 of 45) in the selumetinib plus dacarbazine group versus 26% (12 of 46) in the placebo plus dacarbazine group (odds ratio 1·95, 95% CI 1·06–3·66, one-sided \( p=0·081 \)). 29% (13 of 45) in the selumetinib plus dacarbazine group and 13% (six of 46) in the placebo plus dacarbazine group had a confirmed response (table 2). The median duration of response was longer in the selumetinib plus dacarbazine group (3·5 months, 95% CI 5·0–5·6) versus the placebo plus dacarbazine group (4·1 months, 2·6–5·7). The ratio of the expected duration of response between treatment groups was 1·88 (95% CI 1·08–3·26, one-sided \( p=0·071 \)).
22 patients were reported to have received anticancer drugs that have shown an overall survival benefit, after discontinuation of study treatment; 16 received ipilimumab (seven in the selumetinib plus dacarbazine group vs nine in the placebo plus dacarbazine group) and six received vemurafenib (two selumetinib plus dacarbazine group vs four placebo plus dacarbazine group). Two additional patients received anticancer drugs after discontinuation of study treatment that were being investigated in clinical trials; one patient in the placebo plus dacarbazine group received an experimental MEK inhibitor followed by ipilimumab, and one patient in the selumetinib plus dacarbazine group received an experimental BRAF inhibitor.

The addition of selumetinib does not seem to have compromised the relative dose intensity of dacarbazine treatment received, with patients in the selumetinib plus dacarbazine group receiving 89% of their planned dacarbazine dose (up until the earliest of progression or eight cycles) compared with 90% for those in the placebo plus dacarbazine group.

The most frequent adverse events by preferred term were nausea, acneiform dermatitis, diarrhoea, vomiting, and peripheral oedema (table 3). On the basis of pharmacological class effects and previous selumetinib studies, the grouped adverse events regarded to be of pharmacological effects and previous selumetinib population were reported. The most common dermatological disorders, particularly rash, were the most common adverse events of interest in the selumetinib group. Visual disturbances and hypertension also occurred more frequently with selumetinib, but all were grade 1 or 2. The incidence of blurred vision and reduced visual acuity (data not shown) was similar in both groups. The following discrete visual disturbance adverse events were reported in the selumetinib plus dacarbazine group but not in the placebo plus dacarbazine group: phosphenes (n=2), photophobia (n=2), oscillopsia (n=1), paraneoplastic retinopathy (n=1), photopsia (n=1), retinal vein thrombosis (n=1), and vitreous floaters (n=1). One patient with retinal vein occlusion needed a selumetinib dose interruption; other visual disturbance adverse events did not affect selumetinib dosing. No hyperkeratotic lesions or cutaneous carcinomas were reported.

A higher incidence of infection was reported in the selumetinib plus dacarbazine group than in the placebo plus dacarbazine group (64% [28 of 44] vs 40% [18 of 45]). The most common infections (all grades) were those relating to epithelial disruption (nail infections, pustular rash, folliculitis, and erysipelas) and urinary tract infections. A higher proportion of patients in the selumetinib plus dacarbazine group had a reduction from baseline in platelet count compared with the placebo plus dacarbazine group (48% [21 of 44] vs 36% [16 of 45]); the difference between groups was mainly due to a higher incidence of one-grade reduction from baseline in the selumetinib plus dacarbazine group. Asymptomatic reductions in left ventricular ejection fraction (LVEF) of 10 or more percentage points and to lower than 55% were recorded in seven patients in the selumetinib plus dacarbazine group versus one patient in the placebo plus dacarbazine group. In the selumetinib plus dacarbazine group, LVEF returned to within normal
In this phase 2 study, the addition of selumetinib to dacarbazine showed improved clinical activity in patients with BRAF-mutant advanced cutaneous or unknown primary melanoma (panel). Overall survival did not differ significantly between treatment groups and the largest separation between the curves was at the median, thus the median difference was not representative of the treatment difference over time. However, a significant benefit in progression-free survival was recorded. The median progression-free survival achieved with selumetinib plus dacarbazine was 5.6 months. By comparison, median progression-free survival recorded with the MEK1/2 inhibitors trametinib and MEK162 as single treatments were 4.0 months and 3.6 months, respectively. As monotherapy, the BRAF inhibitors vemurafenib and dabrafenib showed median progression-free survival of 5.3 months and 5.1 months, respectively. However, significant improvements in overall survival have been reported in phase 3 monotherapy trials with trametinib and vemurafenib. Of note, median overall survival with selumetinib plus dacarbazine in this study was similar to that recorded in the trametinib monotherapy phase 2 study (13.9 vs 14.2 months).

Two effective drugs, the BRAF inhibitor vemurafenib and the CTLA4-blocking monoclonal antibody ipilimumab, were licensed for treatment of metastatic melanoma while the study was ongoing. The study participants might have been treated with these drugs after disease progression, potentially having an effect on the assessment of overall survival. Although there was no clear imbalance between the two groups in the use of subsequent therapies that have shown a survival benefit, it is probable that not all post-progression therapies were reported and their effect on overall survival cannot be assessed.

The proportion of patients with a confirmed response in this combination study (29%) was lower than that reported for the BRAF inhibitors vemurafenib and dabrafenib (48–53%) as monotherapy, but similar to the MEK inhibitors trametinib (22–28%) and MEK162 (20%), and greater than selumetinib monotherapy (6%). The reason for the difference in responses recorded between BRAF and MEK inhibitors is unknown, but might be due to differences in mode of action, degree of pathway inhibition, or acquired drug-resistance mechanisms. The encouraging number of responses with trametinib might be due to the compound’s unique exposure profile.

The combination of selumetinib plus dacarbazine was less well tolerated than placebo plus dacarbazine and broadly consistent with the monotherapy safety profiles of both selumetinib and dacarbazine. The most frequent adverse events were consistent with the MEK inhibitors’ toxicities. The table below shows adverse events leading to discontinuation, dose reduction, and dose interruption.

Table 4: Summary of grouped adverse events of interest (safety population)

<table>
<thead>
<tr>
<th>Event</th>
<th>Selumetinib plus dacarbazine (n=44)</th>
<th>Placebo plus dacarbazine (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>44 (100%)</td>
<td>44 (98%)</td>
</tr>
<tr>
<td>Judged to be related to selumetinib</td>
<td>44 (100%)</td>
<td>44 (98%)</td>
</tr>
<tr>
<td>Any CTCAE grade ≥3</td>
<td>30 (68%)</td>
<td>18 (41%)</td>
</tr>
<tr>
<td>Judged to be related to dacarbazine</td>
<td>28 (64%)</td>
<td>33 (73%)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>22 (50%)</td>
<td>18 (40%)</td>
</tr>
<tr>
<td>With outcome of death</td>
<td>2 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Any adverse event leading to discontinuation</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Selumetinib or placebo</td>
<td>3 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>6 (14%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Any adverse event leading to a dose reduction</td>
<td>7 (16%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Selumetinib or placebo</td>
<td>6 (14%)</td>
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</tr>
<tr>
<td>Dacarbazine</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Any adverse event leading to a dose interruption</td>
<td>18 (41%)</td>
<td>4 (9%)</td>
</tr>
</tbody>
</table>

Data are n (%). CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. *Cause of death was intracranial tumour haemorrhage attributed to disease progression and disseminated intravascular coagulation. †Cause of death was deep vein thrombosis attributed to disease progression (n=1), suicide (n=1).

Table 5: Summary of adverse events in either treatment group (safety population)

<table>
<thead>
<tr>
<th>Event</th>
<th>Selumetinib plus dacarbazine (n=44)</th>
<th>Placebo plus dacarbazine (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>33 (73%)</td>
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<tr>
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<tr>
<td>With outcome of death</td>
<td>2 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
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<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Selumetinib or placebo</td>
<td>3 (7%)</td>
<td>0</td>
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<td>Dacarbazine</td>
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</table>

Data are n (%). CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. *Cause of death was intracranial tumour haemorrhage attributed to disease progression and disseminated intravascular coagulation. †Lymphoedema was not included under the fluid retention term.

See Online for appendix.
Selumetinib in combination with docetaxel has shown monotherapy has not shown statistically significant when combined with the antimitotic drug docetaxel.14 that selumetinib monotherapy is cytostatic, but cytotoxic patients with a short life expectancy. discontinuations is a consideration in this population of frequency of severe or serious adverse events and events were clinically manageable, the increased affection the clinical efficacy of the selumetinib plus dacarbazine group. These dose changes could have affected the clinical efficacy of the selumetinib plus dacarbazine combination. Although most adverse events were clinically manageable, the increased frequency of severe or serious adverse events and discontinuations is a consideration in this population of patients with a short life expectancy.

Results from preclinical models in melanoma suggest that selumetinib monotherapy is cytostatic, but cytotoxic when combined with the antimiotic drug docetaxel.14 Selumetinib in combination with docetaxel has shown positive results in KRAS-mutant non-small-cell lung cancer,15 and is currently being investigated in BRAF wild-type melanoma.25 These findings suggest that selumetinib might work synergistically with docetaxel, and future clinical investigations are warranted. The proportion of patients with a confirmed response in this study was higher than that recorded with selumetinib monotherapy in BRAF-mutant melanoma,11 supporting the rationale for exploration of selumetinib plus chemotherapy combinations. The potential reduced tolerability and the extent to which chemotherapy adds value to efficacy must be considered. Sequencing of these drugs could affect efficacy by enhancing apoptotic signalling,11 and this effect might be another factor to consider in future clinical studies.

Several mechanisms of resistance to inhibitors of components of the RAS-RAF-MEK-ERK pathway have been described.27-28 MEK inhibitors could potentially counteract this reactivation and have shown promising results when combined with a BRAF inhibitor, significantly improving progression-free survival and objective responses.29 However, MEK inhibitor monotherapy has not shown statistically significant clinical activity as sequential treatment in patients who have progressed on BRAF-inhibitor therapy,9 but MEK inhibitors in combination with a chemotherapy distinct from dacarbazine or in combination with a BRAF inhibitor might be beneficial. Additionally, preclinical data have shown that acquired resistance to vemurafenib and selumetinib in melanoma cell lines might be reversed by AKT or mTOR inhibitors.30 Thus, combination of selumetinib with an AKT or mTOR inhibitor could also be explored.

In conclusion, selumetinib in combination with dacarbazine showed a significant improvement in progression-free survival in patients with BRAF-mutant cutaneous or unknown primary melanoma compared with dacarbazine alone, with no significant overall survival benefit in this population. Safety and tolerability of this combination was consistent with the safety profiles of either component and generally reversible and manageable. Future studies, driven by preclinical rationale, investigating selumetinib with other chemotherapeutic drugs or BRAF, AKT, and mTOR inhibitors, or both, are warranted.

**Contributors**

CR, MC, and MM made substantial contributions to the conception and design of the study. CR, RD, RG, PL, KBK, MN, AA, GI, DS, and MRM collected data and recruited patients for this study. SS was the study statistician and CR, RD, RG, PL, KBK, AA, DS, MC, SS, and MRM contributed to analysis and interpretation of data. All authors revised the Article critically for important intellectual content and approved the final version to be published.

**Confl icts of interest**

CR and DS have received funding for consultancy, board membership (DS only), and lectures including service on speakers’ bureaux (DS only) from Bristol-Myers Squibb, GlaxoSmithKline, MSD, Roche, and Amgen (DS only). CR and DS have also received funding for consultancy and
board membership (DS only) from Novartis. Universitätsklinikum Essen (DS) has received a grant from Merck. RG has received funding for an advisory role and honoraria from GlaxoSmithKline, Bristol-Myers Squibb, Roche, MSD, Almirall, and Novartis. RG has also received funding for honoraria from Angen, Merck Serono, and Janssen. Additionally, RG has received research funding from Novartis and Roche, and remuneration from GlaxoSmithKline, Bristol-Myers Squibb, and Roche. Christie NHS Foundation Trust (Pl) has received funding for a clinical fellow meeting from AstraZeneca. MRM has received funding for travel expenses from AstraZeneca for the study. Rikshospitalet-Radiumhospitalet HF (MN) has received travel expenses for the study start-up meeting from AstraZeneca, and funding for board membership at the Nordic advisory board and travel expenses for the American Society of Clinical Oncology meeting from Bristol-Myers Squibb. Rikshospitalet-Radiumhospitalet HF (MN) has also received funding for lectures including service on speakers’ bureaus from Bristol-Myers Squibb and Roche. Országos Onkológiai Intézet (GI) has received funding for employment for a study of RO5184526 in metastatic melanoma from Roche M025515. MC and SS are employees and shareholders of AstraZeneca. MRM has received honoraria for advice on the development of selumetinib and travel expenses reimbursed for the investigator meeting from AstraZeneca. Oxford University Hospitals NHS Trust (MRM) has received grants for aspects of investigator-initiated studies and research funding towards preclinical research projects, on which MRM is the collaborator, from AstraZeneca. RD and AA declare that they have no conflicts of interest.

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References