MEK162 for patients with advanced melanoma harbouring *NRAS* or Val600 *BRAF* mutations: a non-randomised, open-label phase 2 study

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Summary

Background Patients with melanoma harbouring Val600 *BRAF* mutations benefit from treatment with BRAF inhibitors. However, no targeted treatments exist for patients with *BRAF* wild-type tumours, including those with *NRAS* mutations. We aimed to assess the use of MEK162, a small-molecule MEK1/2 inhibitor, in patients with *NRAS*-mutated or Val600 *BRAF*-mutated advanced melanoma.

Methods In our open-label, non-randomised, phase 2 study, we assigned patients with *NRAS*-mutated or *BRAF*-mutated advanced melanoma to one of three treatment arms on the basis of mutation status. Patients were enrolled at university hospitals or private cancer centres in Europe and the USA. The three arms were: twice-daily MEK162 45 mg for *NRAS*-mutated melanoma, twice-daily MEK162 45 mg for *BRAF*-mutated melanoma, and twice-daily MEK162 60 mg for *BRAF*-mutated melanoma. Previous treatment with BRAF inhibitors was permitted, but previous MEK inhibitor therapy was not allowed. The primary endpoint was the proportion of patients who had an objective response (ie, a complete response or confirmed partial response). We report data for the 45 mg groups. We assessed clinical activity in all patients who received at least one dose of MEK162 and in patients assessable for response (with two available CT scans). This study is registered with ClinicalTrials.gov, number NCT01320085, and is currently recruiting additional patients with *NRAS* mutations (based on a protocol amendment).

Findings Between March 31, 2011, and Jan 17, 2012, we enrolled 71 patients who received at least one dose of MEK162 45 mg. By Feb 29, 2012 (data cutoff), median follow-up was 3·3 months (range 0·6–8·7; IQR 2·2–5·0). No patients had a complete response. Six (20%) of 30 patients with *NRAS*-mutated melanoma had a partial response (three confirmed) as did eight (20%) of 41 patients with *BRAF*-mutated melanoma (two confirmed). The most frequent adverse events were acneiform dermatitis (18 [60%] patients with *NRAS*-mutated melanoma and 15 [37%] patients with the *BRAF*-mutated melanoma), rash (six [20%] and 16 [39%]), peripheral oedema (ten [33%] and 14 [34%]), facial oedema (nine [30%] and seven [17%]), diarrhoea (eight [27%] and 15 [37%]), and creatine phosphokinase increases (11 [37%] and nine [22%]). Increased creatine phosphokinase was the most common grade 3–4 adverse event (seven [23%] and seven [17%]). Four patients had serious adverse events (two per arm), which included diarrhoea, dehydration, acneiform dermatitis, general physical deterioration, irregular heart rate, malaise, and small intestinal perforation. No deaths occurred from treatment-related causes.

Interpretation To our knowledge, MEK162 is the first targeted therapy to show activity in patients with *NRAS*-mutated melanoma and might offer a new option for a cancer with few effective treatments.

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Introduction

Treatment of metastatic melanoma has evolved substantially in recent years. Traditionally, treatment was restricted to chemotherapy (eg, with dacarbazine or temozolomide) and non-specific immunotherapy (eg, with interleukin 2), which controlled disease in 20% or less of patients and was associated with median overall survival of about 8–10 months.[1–4] An improved understanding of the genetic mutations in melanoma and the role of the immune system in combating of malignant disease has resulted in advancements in the treatment of melanoma, including selective BRAF inhibitors and the antibody ipilimumab, which blocks the cytotoxic T-lymphocyte antigen 4.[5]

The discovery of mutations in large subsets of melanomas has also led to the development of rational targeted therapies.[6] Several mutations have been identified in melanoma that might affect downstream signalling to decrease apoptosis and increase cell proliferation. The MAPK pathway (also termed the RAS–RAF–MEK–ERK pathway) is a key signalling cascade driving cell proliferation, differentiation, and survival, and has a key role in pathogenesis of melanoma.[7] Constitutive MAPK pathway activation can occur through several mechanisms, including mutations in *RAS* and *BRAF*.[8] Mutations in *BRAF* are noted in 40–60% of melanomas and mutations in *NRAS* are noted in 15–25% of these cancers.[9–12] Several inhibitors of BRAF and

downstream mediators of RAF activation (especially MEK and ERK) are under investigation in clinical trials.

Targeting of the MAPK pathway has shown clinical benefit in trials that compared the selective BRAF inhibitors vemurafenib or dabrafenib with dacarbazine in patients with previously untreated Val600 *BRAF*-mutated melanoma.[9,13] In the frontline BRIM-3 trial,[9,14] vemurafenib improved response rates compared with dacarbazine (57% for vemurafenib *vs* 9% for dacarbazine), median progression-free survival (PFS; 5·3 months *vs* 1·9 months), and median overall survival (13·6 months *vs* 9·7 months). In the frontline BREAK-3 trial,[13] dabrafenib also improved response rates compared with dacarbazine (50% with dabrafenib *vs* 6% with dacarbazine) and median PFS (5·1 months *vs* 2·7 months). In the phase 3 METRIC trial,[15] patients were treated with trametinib, a MEK inhibitor, or dacarbazine after failure of at least one previous regimen of chemotherapy. In the study, which excluded patients who had previously received a BRAF inhibitor, oral trametinib significantly improved median PFS compared with intravenous chemotherapy (4·8 months for trametinib *vs* 1·5 months for chemotherapy; p<0·001), response rates (22% *vs* 8%), and 6 month overall survival (81% *vs* 67%; hazard ratio 0·54, p=0·01) in patients with advanced melanoma carrying Val600 *BRAF* mutations.[15] Furthermore, two recent trials showed significant clinical benefits for combined BRAF inhibitors and MEK inhibitor therapy with dabrafenib plus trametinib and vemurafenib plus GDC-0973.[16,17]

Resistance to BRAF-targeted therapy is not fully understood, but one potential mechanism involves reactivation of the MAPK pathway, including upregulation of BRAF protein, BRAF splice variants, activation of other kinases, and MEK mutation.[18–20] Several clinical studies support inhibition of other targets within the MAPK pathway as treatment for patients with *BRAF*-mutated melanoma, either alone or in combination with *BRAF*-targeted therapy.[15–17,21–23]

NRAS mutations are mutually exclusive to *BRAF* mutations.[10,24] The most common *NRAS* mutations are noted in the Gln61 codon (about 80–90%).[25] Patients with *NRAS*-mutated tumours are older at diagnosis than are patients with *BRAF* mutations (median age 55·7 years for *NRAS* *vs* 49·8 years for *BRAF*) and more frequently have melanoma due to chronic sun damage.[24,26,27] *NRAS* mutations are also associated with thicker primary tumours and increased rates of mitosis compared with *NRAS* wild-type and Val600Glu *BRAF*-mutated melanomas.[28] *NRAS* mutations are an independent predictor of poor overall survival and are associated with an increased incidence of CNS metastases.[11] Some *NRAS*-mutated cell lines are sensitive to MEK inhibition in vitro.[29]

Unlike for patients with *BRAF* mutations, no approved targeted therapies exist for patients with *NRAS*-mutated melanoma.[11] Such patients are treated with chemotherapy (eg, dacarbazine) or ipilimumab, and none of these treatments has been specifically investigated in *NRAS*-mutated melanoma.[11,12]

MEK162, manufactured by Almac Pharma Services (Craigavon, UK) for Novartis, is a potent, selective, non-ATP-competitive allosteric inhibitor of MEK1 and MEK2. MEK162 inhibited growth of *NRAS*-mutated and Val600Glu *BRAF*-mutated melanoma in preclinical studies that used in-vitro and in-vivo models.[30] The safety profile of MEK162 and preliminary signs of antitumour activity were previously reported in a phase 1 trial in patients with advanced solid tumours.[31,32] On the basis of these preclinical and clinical data, we aimed to assess the use of MEK162 in an open-label phase 2 study of patients with *NRAS*-mutated or Val600 *BRAF*-mutated advanced melanoma.

Methods

Study design and patients

In this non-randomised, open-label, phase 2 study, we assessed patients with unresectable, locally advanced, or metastatic stage IIIB–IV cutaneous melanoma. We enrolled adults (aged ≥18 years) who had tumours harbouring *NRAS* or Val600 *BRAF* mutations, WHO performance status 0–2, and adequate organ function. Previous treatment, including ipilimumab, was permitted if it had ended at least 4 weeks (or more than one cycle) before initiation of MEK162. Previous treatment with a BRAF inhibitor was also allowed, but previous treatment with a MEK inhibitor was not permitted.

Progression on previous systemic therapies was defined by the participating investigator according to local procedures. However, we collated information about best response to previous therapies in a clinical database. Exclusion criteria were present or historical evidence of central serous retinopathy or retinal vein occlusion; impaired cardiac function; HIV, hepatitis B, or hepatitis C infection; and pregnancy. Patients with CNS metastases were ineligible unless their lesions were previously treated with surgery, whole-brain radiation, or stereotactic radiosurgery, and had remained stable for at least 2 months without steroid use or they had been receiving a stable dose of steroids for at least 1 month before the first dose of MEK162.

This study was designed, undertaken, and reported in accordance with the Declaration of Helsinki and the ICH Harmonised Tripartite Guidelines for Good Clinical Practice. The protocol was approved by an institutional review board, independent ethics committee, or research ethics board at each institution. All patients provided written informed consent before screening and additional consent if participating in an exploratory biomarker analysis.

Procedures

Patients were enrolled at ten university hospitals or private cancer centres in Europe and the USA into one of three open-label treatment arms according to baseline *NRAS* or *BRAF* status, identified from mutation documentation from local laboratories or from samples sent to a central laboratory (Molecular MD, Portland, OR, USA) for analysis with a bidirectional Sanger sequencing

assay. The three arms were: twice-daily MEK162 45 mg for *BRAF*-mutated tumours, twice-daily MEK162 45 mg for *NRAS*-mutated tumours, and twice-daily MEK162 60 mg for *BRAF*-mutated tumours. Patients received the study drug until disease progression, unacceptable toxicity, investigator discretion, or withdrawal of consent by the patient. Each treatment cycle lasted 28 days. This analysis reports data from patients in the 45 mg arms because at the time of data cutoff, too few patients would have been eligible for analysis in the 60 mg arm. Future analyses and publications will report these data.

Dose adjustments from 45 mg twice-daily to 30 mg twice-daily were permitted for patients who did not tolerate the protocol-defined dosing schedule. In patients treated with the 60 mg twice-daily dose, two dose reductions were permitted: one from 60 mg to 45 mg twice-daily and a subsequent reduction to 30 mg twice-daily if needed.

The primary endpoint was the proportion of patients who achieved an objective response (ie, complete or partial response). Secondary endpoints included PFS, time to response, duration of response, safety, tolerability, pharmacokinetics, and change in pharmacodynamics parameters from baseline. We classified tumour response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 criteria. We assessed responses at the end of every second cycle of treatment. Patients who had not progressed at the time of discontinuation of MEK162 were followed up every 8 weeks until progression, start of subsequent cancer treatment, or death. We assessed outcomes in a full analysis set, defined as patients who received at least one dose of MEK162, and in an analysis set for objective responses, which included patients who had at least two CT scans (ie, a confirmed response).

We monitored adverse events until 30 days after the last dose of study drug or until resolution. If an adverse event was ongoing after 30 days, it was followed up until resolution or until it was deemed to be permanent. We classified adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4. We summarised tolerability from the number of dose interruptions and reductions in each study group and calculated relative dose intensity of MEK162 by study group. We assessed safety in all patients receiving at least one dose of MEK162 with at least one valid safety assessment after baseline. All patients were monitored by an experienced ophthalmologist supported by optical coherence tomography.

Blood samples for pharmacokinetic analysis were obtained before and after dosing. Serial blood samples were obtained from at least 12 patients receiving MEK162 45 mg twice-daily; sparse blood samples were collected from the remaining patients. Plasma concentrations of MEK162 and its active metabolite AR00426032 were analysed at QPS (Newark, DE, USA) with high-performance liquid chromatography tandem mass spectrometry.

	NRAS 45 mg (n=30)	*BRAF* 45 mg (n=41)
Age (years)		
Median	59·5 (45–68)	57 (45–65)
Sex		
Male	20 (67%)	22 (54%)
Female	10 (33%)	19 (46%)
WHO performance status		
0	18 (60%)	33 (80%)
1	9 (30%)	8 (20%)
2	3 (10%)	0
AJCC disease stage		
Stage III	0	2 (5%)
Stage IIIb	0	1 (2%)
Stage IIIc	0	1 (2%)
Stage IV	30 (100%)	39 (95%)
Stage IV	19 (63%)	20 (49%)
Stage IVa	0	3 (7%)
Stage IVb	0	1 (2%)
Stage IVc	11 (37%)	15 (37%)
Mutation subtypes (by central read)		
NRAS exon 2 assessed	27 (90%)*	NA
NRAS exon 2 mutation	25 (83%)	NA
Gln61Leu *NRAS*	1 (3%)	NA
Gln61Lys *NRAS*	9 (30%)	NA
Gln61Arg *NRAS*	15 (50%)	NA
No mutation detected†	2 (7%)	NA
BRAF exon 15 evaluated	NA	41 (100%)
BRAF exon 15 mutation	NA	40 (98%)
Val600Glu *BRAF*	NA	33 (80%)
Val600Glu/Lys601Glu *BRAF*	NA	1 (2%)
Val600Lys *BRAF*	NA	5 (12%)
Val600Arg/Gly606Glu *BRAF*	NA	1 (2%)
Unknown‡	NA	1 (2%)
Patients with previous anticancer therapy§	23 (77%)	27 (66%)
BRAF inhibitor	0	7 (17%)
Chemotherapy	16 (53%)	14 (34%)
Immunotherapy (including ipilimumab)	14 (47%)	18 (44%)
Ipilimumab	9 (30%)	6 (15%)
Interferon	2 (7%)	11 (27%)
Interleukin 2	1 (3%)	3 (7%)
Other therapy	1 (3%)	2 (5%)
Radiotherapy	9 (30%)	10 (24%)
Number of previous systemic anticancer therapies (range)	1 (0–6)	1 (0–4)
0	7 (23%)	14 (34%)
1–2	18 (60%)	21 (51%)
≥3	5 (17%)	6 (15%)

Data are median (IQR) or n (%), unless otherwise stated. AJCC=American Joint Committee on Cancer. NA=not applicable. *One patient had Gln61Leu mutation and two patients had exon 3 codon 61Arg mutations documented by a local laboratory. †One patient had a Gln61Lys *NRAS* mutation and one patient had an *NRAS* exon 3 codon 61Arg mutation documented by a local laboratory. ‡One Val600Glu *BRAF* mutation was documented by a local laboratory. §Patients with more than one previous line of therapy are counted more than once.

Table 1: **Baseline characteristics**

Statistical analysis

Analyses were descriptive and exploratory in nature and no formal hypotheses were tested. Statistical inference was done only to estimate clinical activity. We calculated exact 95% CIs with the Clopper-Pearson method for partial responses (confirmed and unconfirmed), confirmed responses, the proportion of patients who achieved disease control (defined as a best response of at least stable disease), and disease stabilisation (defined as a best overall response of stable disease excluding unconfirmed partial responses). All complete responses and partial responses had to be confirmed by a second assessment no less than 4 weeks after diagnosis to be regarded as a confirmed response. We regarded best response as stable disease if at least one assessment showed stable disease more than 6 weeks after start of treatment and the response did not qualify as a complete or partial response. To be deemed to have stable disease, a patient also needed to have stable disease of target lesion, non-progressive disease or unknown effects on non-target lesions, and no new lesions.

See Online for appendix

We defined follow-up as time from date of first treatment to the date of final study follow-up visit for patients who finished the study before the cutoff date, or as time from date of first treatment to the cutoff date for patients who were ongoing at the time of data cutoff.

We calculated PFS with the Kaplan-Meier method as per RECIST, with all patients included in the calculation. We calculated 95% CIs for median PFS with the Brookmeyer and Crowley method.[33] We censored patients without a PFS event at the time of last tumour assessment before the cutoff date. We summarised time to response and duration of response as median and range, and we summarised other endpoints as mean (SD), median (range) for continuous data and n (%) for categorical data. No statistical testing was done to compare groups. Analyses were done with SAS version 9.2 and R version 2-13.2.

We chose the sample size to ensure a low probability (<5%) of observing a particular response rate (25% for *NRAS* and 30% for *BRAF*) under a truly ineffective scenario, while ensuring a high probability (about 90%) of observing this particular response rate under a truly effective scenario (see appendix for details).

We estimated pharmacokinetic parameters with WinNonlin (Pharsight, Mountain View, CA, USA) using non-compartmental methods, if feasible. We calculated median drug exposure including median relative dose intensity by study arm.

This study is registered with ClinicalTrials.gov, number NCT01320085.

Role of the funding source

This study was designed by Novartis with input from the investigators. Data were collected by the sponsor using a web-based remote data capture system and analysed by the sponsor's statistical team. The data was interpreted with the study management committee and in collaboration with the senior academic authors (RD, PAA, and DS). RD, PAA, and DS wrote the report with editorial support funded by the study sponsor. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. RD, PAA, SW, AZ, and FN had full access to the raw data.

Results

By data cutoff on Feb 29, 2012, 71 patients had been enrolled into the 45 mg groups of the trial (30 patients with *NRAS*-mutated melanoma and 41 patients with *BRAF*-mutated melanoma; table 1). The first patient was treated on March 31, 2011, and the last patient received their first treatment on Jan 17, 2012. Median follow-up was 3·3 months (range 0·6–8·7; IQR 2·2–5·0). By data cutoff, only ten patients had been enrolled in the MEK162 60 mg BRAF mutant melanoma group; thus, these data were restricted and preliminary. We report data from the 45 mg group unless otherwise stated.

	NRAS 45 mg (n=30)		*BRAF* 45 mg (n=41)	
	All grades	Grade 3–4	All grades	Grade 3–4
Skin-related				
Rash	6 (20%)	1 (3%)	16 (39%)	0
Acneiform dermatitis	18 (60%)	1 (3%)	15 (37%)	3 (7%)
Pruritus	7 (23%)	0	2 (5%)	0
Oedema				
Peripheral	10 (33%)	1 (3%)	14 (34%)	1 (2%)
Facial	9 (30%)	1 (3%)	7 (17%)	0
Gastrointestinal-related				
Diarrhoea	8 (27%)	2 (7%)	15 (37%)	1 (2%)
Nausea	7 (23%)	0	7 (17%)	0
Vomiting	6 (20%)	0	3 (7%)	0
Increase in blood creatine phosphokinase	11 (37%)	7 (23%)	9 (22%)	7 (17%)
Fatigue	4 (13%)	0	10 (24%)	2 (5%)
Dysgeusia	0	0	8 (20%)	0
Retinal events*	8 (27%)	0	5 (12%)	0

Data are n (%). *Includes retinal detachment, retinal pigment epitheliopathy, retinoschisis, retinal oedema, chorioretinopathy, retinopathy, and retinal exudates.

Table 2: **Treatment-related adverse events occurring in ≥10% of patients**

	NRAS 45 mg (n=30)		*BRAF* 45 mg (n=41)	
	All grades	Grade 3–4	All grades	Grade 3–4
Total serious adverse events*	2 (7%)	2 (7%)	2 (5%)	2 (5%)
Diarrhoea	2 (7%)	2 (7%)	1 (2%)	1 (2%)
Dehydration	1 (3%)	1 (3%)	1 (2%)	1 (2%)
Acneiform dermatitis	0	0	1 (2%)	0
General physical health deterioration	0	0	1 (2%)	1 (2%)
Irregular heart rate	1 (3%)	0	0	0
Malaise	0	0	1 (2%)	1 (2%)
Small intestinal perforation	1 (3%)	1 (3%)	0	0

Data are n (%). *Patients could have more than one serious adverse event.

Table 3: **Serious adverse effects suspected to be related to treatment**

Most patients had received at least one previous anticancer therapy (range 0–6; table 1). Seven (17%) of 41 patients in the *BRAF*-mutated group had previously received a BRAF inhibitor. Nearly half of patients had received previous chemotherapy, and about half had received immunotherapy (including ipilimumab; table 1). However, a greater proportion of patients with *NRAS*-mutated melanoma had previously received ipilimumab than had those with *BRAF*-mutated melanoma (table 1). Eight (20%) patients with *BRAF*-mutated melanoma had had either stable disease or a partial response in response to last previous therapy compared with three (10%) of 30 patients with *NRAS*-mutated melanoma.

The most common treatment-related adverse events were peripheral oedema and increased creatine phosphokinase concentrations or affected the skin and gastrointestinal tract (table 2). Increases in creatine phosphokinase concentration were the most common grade 3–4 adverse event related to treatment, although they were mostly asymptomatic. The most frequent symptoms of increased creatine phosphokinase concentrations were muscle weakness in four patients and myalgia in two patients. 13 (18%) of 71 patients had central serous retinopathy-like events, none of which was grade 3–4 in severity (table 2). Most retinal events were transient in nature and resolved without treatment discontinuation, after dose reduction, or after interruption of treatment. Ophthalmoscopical presentations, including large yellowish spots and detachment and thickening of the pigment and photoreceptor complex, resembled central serous retinopathy.[34] However, most patients had no symptoms and the alterations were self-limiting despite treatment continuation. Three patients had asymptomatic decreases in left ventricular ejection fraction (two grade 2 and one grade 3 in a patient with a history of hypertension). At data cutoff, the adverse event profile was much the same for the ten patients enrolled in the 60 mg *BRAF*-mutated group (appendix).

15 patients (four [13%] in the *NRAS*-mutated group and 11 [27%] in the *BRAF*-mutated group) discontinued treatment because of adverse events, most commonly because of peripheral oedema (one patient with *NRAS* mutations and one patient with *BRAF* mutations) and skin-related toxicity (one patient and two patients). 17 patients (57%) in the *NRAS* group and 16 (39%) patients in the *BRAF* group had at least one dose reduction. The most common cause of dose reduction was an increase in blood creatine phosphokinase concentration (seven patients and five patients). Two patients in each group had serious adverse events related to treatment (table 3). All these patients had two to three serious adverse events that included cardiac arrhythmia, dehydration, diarrhoea, malaise, reduced performance status, small intestinal perforation, and rash. We noted no deaths related to treatment. In the *NRAS* group, both patients had to permanently discontinue study drug due to serious adverse events. In the *BRAF* group, one patient

	Full analysis set		Analysis set for response rate*	
	NRAS 45 mg (n=30)	*BRAF* 45 mg (n=41)	*NRAS* 45 mg (n=28)	*BRAF* 45 mg (n=35)
CR	0	0	0	0
Total PR	6 (20%)	8 (20%)	6 (21%)	8 (23%)
Confirmed PR	3 (10%)	2 (5%)	3 (11%)	2 (6%)
Unconfirmed PR	3 (10%)†	6 (15%)‡	3 (11%)†	6 (17%)‡
Overall response rate (CR or confirmed PR)	3 (10%)	2 (5%)	3 (11%)	2 (6%)
Stable disease	13 (43%)	13 (32%)	13 (46%)	13 (37%)
Progressive disease	9 (30%)	12 (29%)	9 (32%)	12 (34%)
Unknown§	2 (7%)	8 (20%)	0 (0%)	2 (6%)
Disease control rate (CR, PR, or SD)	19 (63%)	21 (51%)	19 (68%)	21 (60%)

Data are n (%). CR=complete response. PR=partial response. SD=stable disease. *Includes only patients who had two CT scans available for assessment of response; we excluded two patients in the *NRAS* group who were not enrolled for enough time to assess efficacy and were in follow-up at time of data cutoff (at the next available CT scan after data cutoff, one of these patients had SD and one had PD); six patients in the *BRAF* group were excluded because of death (two patients), discontinuation due to an adverse event (three), and withdrawn consent (one). †One patient had progressive disease, one had an adverse event, and one was too early to confirm (PR was confirmed at the next available CT scan after data cutoff). ‡Three patients had PD and three had an adverse event. §Unknown response in non-target lesion or because target lesions were not measured.

Table 4: **Clinical activity**

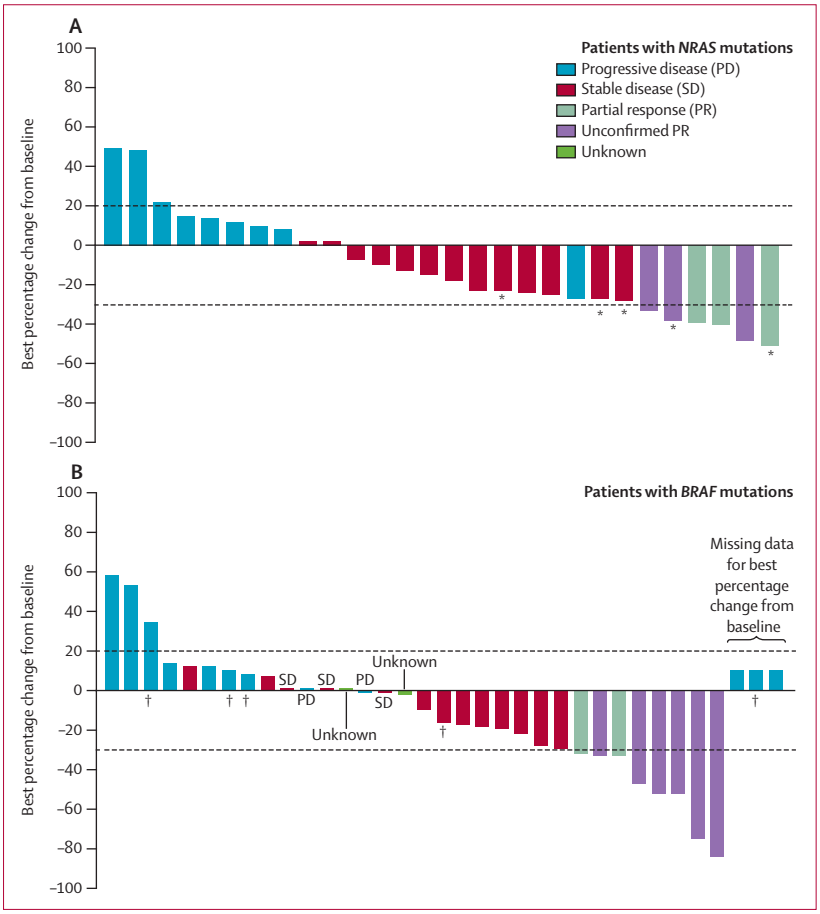

Figure 1: **Waterfall plot of best percentage change from baseline in the analysis set for response**
(A) 28 patients with *NRAS* mutations. (B) 35 patients with Val600 *BRAF* mutations. *Patients in follow-up. †Previous treatment with a BRAF inhibitor. Unknown shows patients not qualifying for confirmed complete response or PR but without SD after more than 6 weeks, or early progression within the first 12 weeks.

had to permanently discontinue study drug due to serious adverse events.

Pharmacokinetic profiling of 22 patients showed that MEK162 was absorbed rapidly, with a median time to maximum plasma concentration (T_{max}) of 1·48 h on day 15 and with moderate variability between patients (appendix). The median relative dose intensity was 1 (range 0·5–1·0) in the *BRAF* group and 0·81 (range 0·4–1·0) in the *NRAS* group.

Data for clinical activity were available for 71 patients in the full analysis set (table 4). Six (20%, 95% CI 8–39) of 30 patients with *NRAS*-mutated melanoma had a partial response, as did eight (20%, 9–35) of 41 patients with *BRAF*-mutated melanoma. We confirmed partial responses for three patients (10%, 2–27) with *NRAS*-mutated melanoma and two patients (5%, 1–17) with *BRAF*-mutated melanoma. We noted no partial responses in the seven patients with *BRAF* mutations who were previously treated with a BRAF inhibitor. We also assessed clinical efficacy in 63 patients (28 patients with *NRAS*-mutated melanoma and 35 with *BRAF*-mutated melanoma) who had at least two CT scans available at data cutoff (table 4).

Three patients had target brain lesions (two *NRAS*-mutated and one *BRAF*-mutated). Two of these patients (both with *NRAS* mutations) had shrinkage of the target brain metastases (decreasing from 2·3 cm to 1·6 cm in one patient and from 3·4 cm to 3·0 cm in the other patient). Two patients had non-target brain lesions; the brain lesion remained stable for three CT assessments (six cycles) for one patient and one CT evaluation (two cycles) for the other patient. One patient with an irradiated brain lesion, classified by investigator as the target lesion, was recorded as a protocol deviation. Five of ten patients enrolled in the 60 mg arm were assessable; two of these patients had unconfirmed partial responses by data cutoff and one patient had stable disease (appendix).

Median time to response (confirmed or unconfirmed) was 7·9 weeks (range 7·0–14·7) for patients with *NRAS*-mutated melanoma and 8·5 weeks (7·6–13·6) for patients with *BRAF*-mutated melanoma. Median duration of response was 7·6 weeks (0·1–17·3) for patients with *NRAS*-mutated melanoma and 9·2 weeks (0·1–16·1) for patients with *BRAF*-mutated melanoma.

Most patients achieved disease control in both groups (19 patients [63%, 95% CI 44–80] in the *NRAS*-mutated group and 21 [51%, 35–67] in the *BRAF*-mutated group; table 4) and most patients had some degree of tumour shrinkage (figure 1). Several patients with disease stabilisation (13 patients [43%, 25–63] in the *NRAS* group and 13 [32%, 18–48] in the *BRAF* group) showed durable disease control (range 6·4–26·1 weeks for those in the *NRAS* group and 7·9–33·0 weeks for those in the *BRAF* group), with several patients with ongoing disease control at the time of analysis.

Median PFS was 3·7 months (95% CI 2·5–5·4) for patients with *NRAS*-mutated melanoma and 3·6 months (2·0–3·8) for patients with *BRAF*-mutated melanoma (figure 2). Median PFS for the seven patients pretreated with a BRAF inhibitor was 1·7 months (1·6–2·0). In the *NRAS* group, median PFS for the nine patients who received previous treatment with ipilimumab was 3·7 months (3·6–7·6) and 3·3 months (1·9–5·4) for the 21 patients who did not receive such treatment. In the *BRAF* group, median PFS for the six patients who received previous treatment with ipilimumab was 5·5 months (2·0–5·6) and 3·2 months (2·0–3·7) for the 35 patients who did not receive such treatment. Five of the seven patients who had previously been treated with a BRAF inhibitor had not received ipilimumab. PFS for the ten patients in the 60 mg group is shown in the appendix.

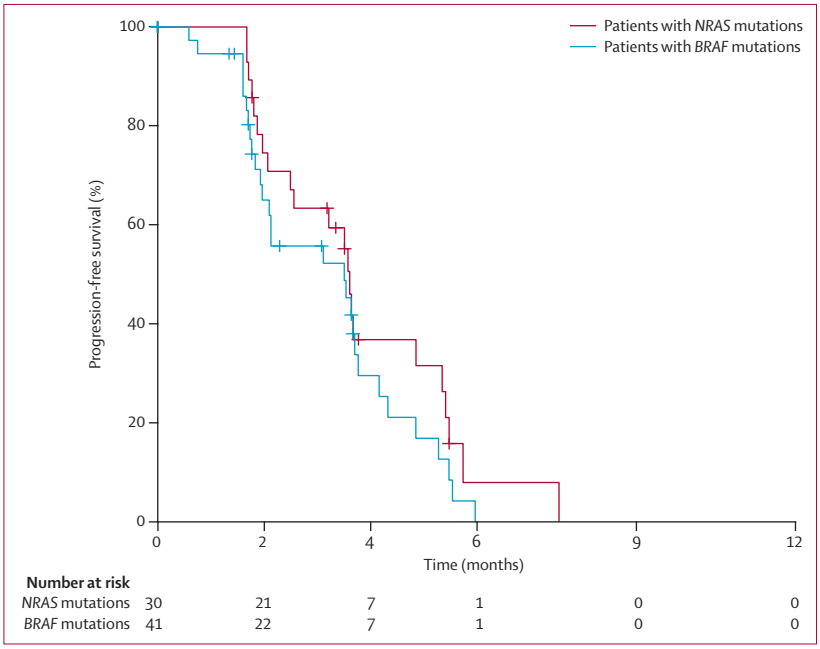

Figure 2: **Kaplan-Meier estimates of progression-free survival**
22 patients had documented events in the *NRAS*-mutation group; 26 patients had documented events in the *BRAF*-mutation group. 20 patients were censored (12 patients in the *BRAF* group and eight patients in the *NRAS* group) because either consent was withdrawn (two patients in the *BRAF* group), the patient started new treatment (nine patients in the *BRAF* group and one in the *NRAS* group), analysis was ongoing at the time of data cutoff (six patients in the *NRAS* group), or no follow-up data were available (one patient in the *BRAF* group and one patient in the *NRAS* group).

Discussion

Recent advances in the understanding of melanoma biology have strikingly changed the treatment landscape (panel). Characterisation of the MAPK pathway in melanoma, including BRAF and MEK1/2, has led to the development of new drugs with encouraging phase 3 data.[9,13,15,16,21,23] Although these studies represented a substantial advance in therapy, improvements were restricted to patients with *BRAF* mutations[24] and few treatment options exist for patients with *NRAS*-mutated melanoma. 15–25% of patients with melanoma have *NRAS*-mutated tumours and generally have poor overall prognosis compared with those without such mutations.[11,24] In this phase 2 study, monotherapy with the MEK1/2

inhibitor MEK162 showed early signs of activity in patients with *NRAS*-mutated metastatic melanoma.

Other MEK inhibitors (selumetinib and trametinib) have been assessed retrospectively in patients with *NRAS*-mutated melanoma. In a phase 2 study[35] of selumetinib in 104 patients with metastatic melanoma, none of ten patients with *NRAS*-mutated tumours responded to treatment. Similarly, in a subanalysis of 97 patients enrolled in a phase 1 trial testing trametinib in melanoma, none of seven patients with *NRAS*-mutated tumours responded to treatment, and only two (2%) patients had stable disease.[36] Pimasertib, another MEK inhibitor in clinical development, reportedly showed activity in 17 patients with *NRAS*-mutated melanoma including two partial responses and one complete response (response rate 18%).[37] In a retrospective study[38] aimed to identify possible molecular characteristics that predict response to high-dose interleukin 2 in a subset of 103 patients with an *NRAS*-mutated melanoma prevalence of 15%, patients with *NRAS* mutation had improved outcomes compared with patients with *NRAS* wild-type melanoma, with a relative risk of 47% (p=0·05) and a non-statistically significant increase in PFS (214 days for *NRAS*-mutated melanoma *vs* 70 days for wild-type melanoma; p=0·13) and overall survival (5·3 years *vs* 2·4 years; p=0·30).[38]

Consistent with the previous reports for trametinib,[15] we also noted activity of MEK162 in patients with *BRAF*-mutated melanoma.[19] However, the rate of confirmed responses (22%) and median PFS (4·8 months) was greater in the trametinib study than in our study with MEK162. However, several key differences exist between the populations assessed. Previous chemotherapy, ipilimumab, and BRAF inhibitors were allowed in this study, but previous treatment with BRAF inhibitors and ipilimumab were exclusion criteria from the trametinib study.[15] In our study, no responses were reported in patients previously treated with a BRAF inhibitor, which is consistent with the trametinib data reported in a phase 1 study[35] of advanced melanoma. Clinical activity of the combination treatment of MEK and BRAF inhibitors shown in patients with Val600 *BRAF*-mutated melanoma who received previous BRAF inhibitor treatment suggests that dual MAPK blockade might abrogate some mechanisms of acquired BRAF inhibitor resistance.[16,17,39–41] BRAF and MEK inhibition after BRAF inhibitor failure is not well understood.

Overall, MEK162 was well tolerated and adverse events were manageable with standard treatments and dose modifications, as needed. The most common toxicities were skin-related[42] or gastrointestinal-related and fluid retention. Grade 3–4 adverse events were not common and the incidence of such adverse events was not substantially different from rates reported for other MEK inhibitors in melanoma. The most common grade 3–4 adverse event was an asymptomatic rise in creatine phosphokinase. The safety profile of MEK162 was much the same as the phase 3 study of trametinib and suggests a class effect of MEK inhibition in patients with metastatic melanoma.

Our findings support clinical activity of MEK162 in patients with *NRAS*-mutated and *BRAF*-mutated metastatic melanoma. To our knowledge, these findings are the first prospective data of a targeted drug to show clinical activity in patients with *NRAS*-mutated melanoma. The protocol of this trial was amended in September, 2012, to enrol an additional 70 patients with *NRAS*-mutated melanoma to gain more robust efficacy and safety data in this population of patients; as of December, 2012, ten further patients had been enrolled. Further clinical assessment of MEK162 in a randomised trial in patients with *NRAS* mutations is planned.

Panel: Research in context

Systematic review

We searched PubMed and recent melanoma congresses to identify recent clinical trials of MEK inhibitors in melanoma. The search parameter was not limited by time or language; however, most research in this area has been published in the previous 5 years. Several clinical trials have reported benefit of MEK inhibitors for treatment of melanoma in patients with *BRAF* mutations. Data from in-vitro studies suggest that the growth of some *NRAS*-mutated melanoma cells can be reduced by MEK inhibition but little information exist about the efficacy of MEK inhibitors in patients with *NRAS*-mutated melanoma.

Interpretation

Our data provide an early signal of activity for MEK inhibition in patients with *NRAS*-mutated melanoma and this finding justifies a phase 3 randomised trial for MEK162 as first-line therapy in patients with stage IV *NRAS*-mutated melanoma and additional studies in subpopulations such as patients with brain metastases. The data in our study correspond well with findings from in-vitro studies and our findings support the role of *NRAS* mutation status testing, particularly in patients with *BRAF* wild-type tumours, because there is now an option to refer patients with *NRAS*-mutated tumours to clinical trial centres that offer therapies based on MEK inhibitors.

Contributors

PAA, CB, CUB, RD, AH, DS, and AZ did the literature search. AH, RD, and SW developed the figures. PAA, JTB, FN, MP, AS-P, CMLvH, SW, and AZ designed the study. PAA, SSA, CB, CUB, JTB, RD, AH, FN, PQ, and CMLvH collected data. PAA, CB, CUB, JTB, RD, AH, FN, MP, PQ, DS, AS-P, CMLvH, SW, and AZ analysed and interpreted data. All authors drafted and approved the report.

Conflicts of interest

SSA, JTB, PQ, and CMLvH declare that they have no conflicts of interest. PAA has consulted for Bristol-Myers Squibb, MSD, Roche-Genentech, GlaxoSmithKline, Amgen, Celgene, and Novartis and received honoraria from Bristol-Myers Squibb, MSD, and Roche-Genentech. CB has consulted and received travel grants from Roche and Bristol-Myers Squibb and received honoraria from Roche, Bristol-Myers Squibb, GlaxoSmithKline, MSD, and Novartis. CUB has consulted and received honoraria from Novartis. AH has consulted, received honoraria, and been on speakers' bureaux for Amgen, AstraZeneca, Biovex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eisai, GlaxoSmithKline, IGEA, Eli Lilly, Medac, MelaSciences, MSD/Merck, Novartis, Roche, SOBI, Vical, and Janssen. RD has consulted for Novartis, Bristol-Myers Squibb, Roche, and GlaxoSmithKline. DS has consulted and received honoraria from Novartis, Amgen, GlaxoSmithKline, Bristol-Myers Squibb, and Roche. FN, MP, AS-P, SW, and AZ are employed by Novartis. MP owns stock in Novartis.

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