Biomarker results from a phase II study of MEK1/2 inhibitor binimetinib (MEK162) in patients with advanced NRAS- or BRAF-mutated melanoma


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ABSTRACT

BRAF and RAS are the most frequently mutated mitogen-activated protein kinase (MAPK) genes in melanoma. Binimetinib is a highly selective MAPK kinase (MEK) 1/2 inhibitor with clinical antitumor activity in NRAS- and BRAFV600-mutant melanoma. We performed a nonrandomized, open-label phase II study, where 183 metastatic melanoma patients received binimetinib 45 mg / 60 mg twice-daily (BRAF arms), or binimetinib 45 mg twice-daily (NRAS arm). Biomarker analyses were prespecified as secondary and exploratory objectives. Here we report the extent of MAPK pathway inhibition by binimetinib, genetic pathway alterations of interest, and potential predictive markers for binimetinib efficacy. Twenty-five fresh pre- and post-dose tumor sample pairs were collected for biomarker analyses, which included assessment of binimetinib on MEK/MAPK signaling by pharmacodynamic analysis of pERK and DUSP6 expression in pre- vs post-dose tumor biopsies; identification of pERK and DUSP6 expression/efficacy correlations; assessment of baseline tumor
molecular status; and exploration of potential predictive biomarkers of efficacy of binimetinib. The postbaseline pERK and DUSP6 expression decreased across all arms; no association between reduced pERK or DUSP6 levels with clinical efficacy was observed. Genetic aberrations were similar to previously reported data on clinical melanoma samples. Genetic pathway alterations occurred predominantly within CDKN2A/B, PTEN, and TRRAP (BRAF-mutation) and CDKN2A/B, TP53, and NOTCH2 (NRAS-mutation). Several patients with BRAF mutations had amplification of genes on chromosome 7q; these patients tended to have shorter progression-free survival than other patients with BRAF-mutant melanoma. Further analysis of genetic alterations, including amplifications of growth factor genes, will determine utility as biomarkers for efficacy.

INTRODUCTION

The MAPK signaling pathway (i.e., RAS-RAF-MEK-ERK pathway) regulates cellular proliferation, survival, and differentiation and contributes to the pathogenesis of melanoma [1]. Multiple genetic changes can lead to hyperactivation of this pathway, and are involved in the pathogenesis of various solid tumor types, including melanoma and thyroid, colorectal, and ovarian cancer [2–5]. Constitutive MAPK pathway activation in cancer can occur through several mechanisms, most frequently via mutations in BRAF or RAS. Activating NRAS and BRAF mutations are present in approximately 20% [6, 7] and 50% [6, 8] of primary cutaneous melanomas, respectively.

A number of therapies that directly target the MAPK pathway have been approved for BRAF-mutated melanoma, including the BRAFV600- specific inhibitors vemurafenib (single agent), and dabrafenib (single agent or in combination with trametinib), and mitogen-activated protein kinase (MEK) inhibitors trametinib (single agent or in combination with dabrafenib) and cobimetinib (in combination with vemurafenib) [9–15]. The combination of BRAF and MEK inhibitor therapies has shown significantly improved benefit over BRAF inhibitor monotherapy in phase III clinical trials [16–18]. In addition to the nonspecific immunotherapies, three immune checkpoint modulators, ipilimumab (anti-cytotoxic T-lymphocyte associated antigen 4 [CTLA-4]), nivolumab (anti–programmed cell death protein 1 [PD-1]), and pembrolizumab (anti–PD-1), have been approved for the treatment of melanoma [19].

Therapies targeting either mutated BRAF or NRAS alone can encounter a number of challenges, including resistance to BRAF inhibitors, which occurs frequently, mostly through reactivation of the MAPK pathway; common paths to resistance include BRAF amplification or alternative splicing and mutations in RAS, MAP2K1, and CDKN2A [20, 21], among other mechanisms.

In contrast to BRAF-mutated melanoma, no approved targeted therapies exist for NRAS-mutated melanoma, but positive phase III data on PFS have been reported for a study comparing the efficacy of binimetinib (MEK162) versus dacarbazine in unresectable or metastatic NRAS-mutated melanoma (NEMO study) [22]. Binimetinib is an oral, selective, ATP-competitive inhibitor of MEK 1 and MEK 2 [23].

Binimetinib has shown promising results in BRAF-mutated melanoma, both alone [24] and in combination [25]. In addition, preclinical MEK inhibitor activity has been shown in BRAF-mutated melanoma [26]. The safety profile of binimetinib and preliminary signs of antitumor activity were shown in a phase I trial in patients with advanced solid tumors [27, 28]. This open-label phase II study assessed the use of binimetinib in patients with BRAFV600- or NRAS-mutated advanced melanoma. The efficacy and safety results from an earlier data cut-off of February 29, 2012 (smaller subgroups of patients with NRAS- or BRAF-mutated melanoma) have been previously reported [24]. No patients had a complete response, and 6 of 30 patients (20%) with NRAS-mutated melanoma (3 confirmed) and 8 of 41 patients (20%) with BRAF-mutated melanoma (2 confirmed) had a partial response. Binimetinib was the first targeted therapy to show activity in patients with NRAS-mutated melanoma.

In this study (NCT01320085), biomarker data from binimetinib-treated patients with NRAS- and BRAF-mutated melanoma were analysed as prespecified secondary and exploratory objectives to investigate the extent of MAPK pathway inhibition and further genetic pathway alterations, in order to find potential predictive markers of response to binimetinib. Among others, dual-specificity phosphatase 6 (DUSP6) and phosphorylated extracellular signal-regulated kinase (pERK) are known/predicted biomarkers of MAPK inhibition and could potentially predict the extent of response to treatment with binimetinib [20, 29].

RESULTS

Patient disposition and characteristics

At the trial data cut-off date (7 January 2014), a total of 183 patients were enrolled. Sixty-six patients with
BRAF mutations were treated: 41 received binimetinib 45 mg twice daily (BID), and 25 received binimetinib 60 mg BID (subsequently reduced to 45 mg BID). A total of 117 patients with NRAS mutations received binimetinib 45 mg BID (Table 1). Patient demographics and disease characteristics are shown in Supplementary Table 1.

Efficacy and safety analysis

Efficacy and safety results for this study have been previously reported for the BRAF- and NRAS-mutated arms for two data cut-off points, 29 February 2012 [24] and 7 January 2014 [31]. Biomarker results presented herein are derived from the later cut-off date.

Biomarker analysis

Biomarkers were analyzed to evaluate MAPK pathway inhibition and analysis was undertaken to evaluate on-treatment biomarker expression and frequency of tumor genetic alterations at baseline. Results were compared against melanoma cases in The Cancer Genome Atlas (TCGA) database and in the context of clinical outcomes, where appropriate. Twenty-five fresh, paired (baseline and on Cycle 1, Day 15) tumor samples were collected for pharmacodynamic biomarker analysis. Fifteen pairs were evaluable for pERK analysis (three pairs in the BRAF-mutated 45 mg subgroup; four and eight pairs, respectively, in the BRAF-mutated 60 mg and NRAS-mutated arms). Fourteen pairs were evaluable for DUSP6 analysis (three pairs each in the BRAF-mutated 45 mg and 60 mg arms and eight pairs in the NRAS-mutated arm).

Pharmacodynamic analysis of postbaseline pERK and DUSP6 expression in patients with BRAF and NRAS mutations showed MAPK pathway inhibition (Figure 1). Decreased postbaseline cytoplasmic and nuclear pERK expression was observed in 11 of 15 and in 9 of 15 paired samples, respectively, and decreased total DUSP6

![Figure 1](image-url): Change from baseline in pERK and DUSP6 expression in patients with (A) BRAF or (B) NRAS mutation and correlation with best overall response. Single dots represent unpaired biopsies. BOR, best overall response; Cq, quantification cycle; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.
Table 1: Patient disposition

<table>
<thead>
<tr>
<th></th>
<th>BRAF-mutant</th>
<th>NRAS-mutant</th>
<th>All patients</th>
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<tr>
<td></td>
<td>Binimetinib</td>
<td>Binimetinib</td>
<td>Binimetinib</td>
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<tr>
<td></td>
<td>45 mg</td>
<td>60 mg</td>
<td>45 mg</td>
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<tr>
<td></td>
<td>(n = 41)</td>
<td>(n = 25)</td>
<td>(n = 117)</td>
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<tr>
<td>Patients treated, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment discontinued</td>
<td>41 (100)</td>
<td>23 (92.0)</td>
<td>104 (88.9)</td>
</tr>
<tr>
<td>Treatment ongoing**</td>
<td>0</td>
<td>2 (8.0)</td>
<td>13 (11.1)</td>
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<tr>
<td>Primary reason for end of treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adverse event(s)**</td>
<td>12 (29.3)</td>
<td>5 (20.0)</td>
<td>14 (12.0)</td>
</tr>
<tr>
<td>Patient withdrew consent</td>
<td>2 (4.9)</td>
<td>1 (4.0)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>26 (63.4)</td>
<td>16 (64.0)</td>
<td>86 (73.5)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>1 (2.4)</td>
<td>1 (4.0)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of exposure, median (range), weeks</td>
<td>9.6 (1.1–26.6)</td>
<td>8.0 (2.0–102)</td>
<td>15.9 (0.3–87.9)</td>
</tr>
</tbody>
</table>

BRAF mutation status, n (%)c

|                      |             |             |             |         |
| None (no wild-type mutation detected) | 0           | 0           | 3 (2.6)     |         |
| V600E                | 34 (82.9)   | 19 (76.0)   | 0           |         |
| V600K                | 5 (12.2)    | 1 (4.0)     | 0           | –        |
| Unknown mutation     | 1 (2.4)†    | 2 (8.0)†    | 0           |         |
| Other (mutations other than V600E/K)‡ | 1 (2.4)‡    | 0           | 0           |         |
| Missing (no V600 BRAF mutation data)§ | 0           | 3 (12.0)‡   | 114 (97.4)  |         |

NRAS mutation status, n (%)c

|                      |             |             |             |         |
| None (no mutation detected) | 0           | 5 (20.0)    | 4 (3.4)§    |         |
| Q61                   | 0           | 0           | 100 (85.5)  |         |
| G12/13                | 0           | 0           | 2 (1.7)     | –        |
| Unknown mutation†     | 1 (2.4)     | 0           | 1 (0.9)§    |         |
| Missing (no NRAS mutation data)‡ | 40 (97.6) | 20 (80.0)  | 10 (8.5)‡   |         |

Clinical activityª [24] (n = 35) NR (n = 28)

DCR, n (%) | 21 (60) | NR | 19 (68) |

ªTreatment ongoing at the time of the cut-off (Jan 7, 2014)

-appendix notes:
- **Treatment ongoing at the time of the cut-off (Jan 7, 2014)
- **Includes fatal case with liver failure in the BRAF-mutated 60-mg treatment group;
- †Any other mutation not known; known mutation includes all Q61, A59T, A11T, G12V, G13R;
- ‡Any other known mutation (L597, D594, G606, K60);
- §Analysis results are missing;
- †V600E according to local laboratory;
- ‡V600R according to local laboratory;
- †Three Q61R (1 result received after database lock) and one G12 (result received after database lock);
- †Q61R according to local laboratory;
- †Three Q61R, two Q61L, two Q61K, two Q61, and one G12 mutation according to local laboratory.
- †Data for clinical activity available for 63 patients for response-rate analysis set (Ascierto, 2013).
- DCR, disease control rate; NR, not reported.
expression postbaseline was observed in 10 of 14 paired samples. Median reduction in pERK H-score was 47% and 70% in the cytoplasmic and nuclear compartments, respectively, and median DUSP6 reduction, in Δ Ct, was 36%. MAPK pathway inhibition was shown in both responders and nonresponders, with no apparent association between reduced expression of either pERK or DUSP6 with overall response rates.

Comparison of patients in the BRAF- and NRAS-mutated arms with TCGA melanoma cases showed overall concordance of the tumor genetic landscape with regard to the percentage of patients experiencing alterations in the most frequently mutated genes (Supplementary Figure 1A and 1B). Within the BRAF-mutated group, concordance was observed in PTEN, TRRAP, and TP53. Slightly more CDKN2A alterations and fewer CDKN2B alterations were observed in study patients compared with the cases in the TCGA database, possibly due to higher sequencing depth and more systematic annotation of variants in this study, respectively. Within the NRAS-mutated group, concordance was observed in CDKN2A/B, TP53, and NOTCH2. There were no trends showing any association between efficacy and the subtype of NRAS Q61 mutations (Supplementary Figure 2). Supplementary Table 2 provides additional context for the BRAF and NRAS mutations, including mutation type and presence or absence in the Catalogue of Somatic Mutations in Cancer (Supplementary Table 2).

A weak association between specific mutations or total number of mutations with either measure of efficacy was shown among patients with either BRAF- or NRAS-mutated melanoma (Figure 2A and 2B, respectively). Notable differences between BRAF- and NRAS-mutated melanomas at baseline included PTEN (21% vs 2.5% of patients, respectively) and P53 (13% vs 22%, respectively). Five BRAF-mutated tumors had broad amplifications on chromosome 7 and five others on chromosome 1, while three NRAS-mutated tumors exhibited amplifications on chromosome 11. Amplifications tended to be associated with shorter progression-free survival (PFS); for example, amplifications in CCND1 or CCND3 occurred only in five NRAS-mutated patients with a PFS shorter than the median (≤ 3.6 months).

Among the NRAS-mutated group, 45 of 78 patients (58%) had alterations in the cell cycle genes; 27 of 65 patients (42%) had both alterations within the cell cycle genes and a short PFS (≤ 110 days).

**DISCUSSION**

The biomarker analyses of this study aimed to describe the biological impact of MEK-targeted inhibition of the MAPK pathway with binimetinib, establish the BRAF- and NRAS-mutated tumor genetic landscape, and explore the link between genetic pathway alterations and the response tobinimetinib. Understanding the biological impact of MEK inhibition, and the predictive value of tumor genetic markers and pathway alterations on response, could be invaluable for optimizing the efficacy of targeted therapy. Pharmacodynamic analyses showed MAPK pathway inhibition by binimetinib on Day 15 through decreased pERK levels and DUSP6 gene expression. These decreases were observed in both BRAF- and NRAS-mutated arms, and were moderate and consistent with observations in other cancer studies with MEK inhibitors, such as the observed suppression of pERK by cobimetinib (GDC-0973) both in vitro and in vivo [32]. However, no association between reduced pERK or DUSP6 levels with clinical efficacy was observed, likely due to limited data or sampling time points. Another consideration is that in certain genomic contexts, including some tumors with RAS mutations (ie, preclinical data of BRAF/RAS-WT tumor cells) [33], the MEK-ERK pathway may not be fundamental for tumor cell proliferation; thus, inhibition of the MEK-ERK pathway may not reduce the survival of certain tumor cells.

Overall, the tumor genetic landscape for patients with BRAF- and NRAS-mutated melanoma was concordant with that reported in TCGA melanoma cases. This observation demonstrated a consistency of genetic alterations in this patient subset with historical samples. This equivalence also contributes to the validation of these biomarker results, leading toward a better understanding of changes that occur within patients with BRAF- and NRAS-mutated melanoma and their predictive value.

Several patients with BRAF-mutated tumors had amplification of genes on the long arm of chromosome 7 (7q); seven patients exhibited MET and/or HGF amplifications, with coamplification occurring in three of them. Five of these seven patients (including the three patients with coamplification) had a PFS that was shorter than the median PFS of 3.5 months for the population with BRAF mutations. Particular genes of high interest on 7q include HGF, MET, EZH2, and SMO. The latter two have been associated with driving the progression of melanoma [34, 35]; HGF and MET form a functional pair since they are cognate ligand and receptor, respectively. Among patients in the NRAS-mutated group, CCND1 or CCND3 amplifications were exclusively seen in five patients with
shorter PFS, indicating that constitutive CDK4/6 pathway signaling may lead to resistance. In this regard, a phase Ib/II study (NCT01781572) with binimetinib in combination with the CDK4/6 inhibitor ribociclib (LEE011) in patients with NRAS-mutant melanoma has recently completed, with preliminary data from the initial Phase 1b study suggesting a manageable safety profile and favourable efficacy [36]. Furthermore, positive phase III data have been reported for the NEMO study comparing the efficacy of binimetinib single agent versus dacarbazine in

![Genetic landscape of tumor samples and efficacy in patients with (A) BRAF mutation and (B) NRAS mutation.](image)

Figure 2: Genetic landscape of tumor samples and efficacy in patients with (A) BRAF mutation and (B) NRAS mutation. *The genetic landscape shows gene alterations that occurred in ≥ 3 patients in the BRAF-mutant population; *Blue indicates patients with PFS ≥ 3.5 months (median PFS in the 45 mg BRAF\textsuperscript{V600} arm); *Blue indicates patients with reduction in sum of the longest diameter from baseline ≥ 30%; *Red indicates patients with PFS ≥ 3.6 months (median PFS in the NRAS-mutated arm); *Red indicates patients with reduction in sum of the longest diameter from baseline ≥ 30%; *Patients in the BRAF-mutant group receiving binimetinib 60 mg BID who were dose reduced to 45 mg BID; *Patients in the BRAF-mutant group receiving binimetinib 60 mg BID who were not dose reduced. MET and HGF amplifications in the BRAF panel CCND3 and CCND1 amplifications in the NRAS panel are indicated with a black box. BID, twice daily; fs, frameshift; ns, nonsense; PFS, progression-free survival.
unresectable or metastatic NRAS-mutant melanoma [22]. We cannot rule out other genetic alterations that were observed in patients with progressive disease that may have had an effect on PFS.

Binimetinib showed activity in patients with BRAF- or NRAS-mutated melanoma through MAPK pathway inhibition, and genomic profiling highlighted genetic alterations of interest that could be used as potential predictive biomarkers of response to binimetinib. Although all comparisons with patient outcomes for these data are currently observational in nature, they are indicative of the potential predictive use of genetic data in future larger cohorts. Combined with interpretation of biomarker data from other ongoing studies of binimetinib, these data could provide context toward understanding the biological impact of and prediction of response to binimetinib. Of relevance, assessment of potential additional biomarkers of efficacy or safety was incorporated in the aforementioned NEMO trial, in the phase III COLUMBUS trial (NCT01909453) comparing binimetinib plus encorafenib with encorafenib or vemurafenib in patients with BRAF-mutated melanoma, and in the phase II LOGIC-2 trial (NCT02159066) investigating sequential encorafenib/binimetinib combination therapy followed by a combination with targeted agents after disease progression in patients with BRAF<sup>V600E</sup>-mutated melanoma.

**MATERIALS AND METHODS**

**Patients**

Details of the study have been published previously [24]. Briefly, baseline BRAF or NRAS status was assessed using archival or fresh tumor biopsies either at a local or central laboratory (MolecularMD) and analyzed by a semiquantitative polymerase chain reaction (BRAF) or bidirectional Sanger sequencing assay (NRAS). After patient enrollment, all tumor biopsies assessed at local laboratories were sent to the central laboratory for mutational status confirmation.

The study was designed, undertaken, and reported in accordance with the Declaration of Helsinki and the ICH Harmonised Tripartite Guideline 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 the exploratory biomarker analysis.

**Study design and treatments**

This study was a nonrandomized, open-label phase II study in which patients were divided into one of three treatment arms according to tumor NRAS or BRAF status: binimetinib 45 mg BID or 60 mg BID for BRAF-mutant tumors, or binimetinib 45 mg BID for NRAS-mutant tumors. The 60 mg BID dose of binimetinib for patients with BRAF-mutated tumors was subsequently reduced to 45 mg BID per a protocol amendment following two serious adverse events (grade 4 acute liver failure in 1 patient; grade 3 cardiomyopathy, decreased ejection fraction and tachycardia in a second patient). Treatment was administered in 28-day cycles. Binimetinib was administered orally (film-coated tablet) BID from Day 1 of Cycle 1 and continuously throughout the study.

The primary endpoint was the proportion of patients who achieved an objective response (complete response + partial response). Secondary endpoints included PFS, time to response, safety, tolerability, pharmacokinetics, and pharmacodynamics. Biomarker analyses, the focus of this manuscript, were prespecified secondary and exploratory objectives, and included: assessment of pharmacodynamic effects of binimetinib on MEK/MAPK signaling by analysis of pERK and DUSP6 gene expression in pre- versus post-dose tumor biopsies; examination of correlations between pERK, DUSP6 expression and efficacy; assessment of the baseline molecular status of the tumors and exploration of potential predictive biomarkers of response to binimetinib.

**Study procedures**

Safety and pharmacokinetic assessments and overall efficacy data from an earlier cut-off were reported previously [24]. Biomarker-related efficacy data are presented here. A whole blood sample (~6.0 mL) was taken from all patients (at Cycle 1 Day 1) to provide a non-tumorous tissue sample to perform genetic analysis (if compliant with local IRB requirements) This sample was analyzed to compare tumor-specific gene alterations in DNA from tumor samples with DNA from normal-non-tumor cells. Baseline and on-study (Cycle 1, Day 15) fresh tumor biopsy samples were collected from patients in all three treatment arms and analyzed for the pharmacodynamic markers pERK and DUSP6. Immunohistochemistry (IHC) data reported from the lab included quantitative data (eg, percent tumor and percent positive cells) or a semi quantitative measure of protein expression reported as 3 individual components, 1+ 2+ and 3+. The pathologist determined whether the staining in a cellular compartment was absent (0+), slight (1+), moderate (2+), or strong (3+). The H-Score used to assess pERK for each cellular compartment was then calculated as the sum of (the percentages of stained cells * their intensity), or (%1+) + (%2+) + (%3+) and ranged between 0 and 300. Δ Ct (cycle threshold), a relative measure of the concentration of target in the PCR reaction, was used to measure DUSP-6. Δ Ct is the normalization of Raw Ct that is calculated by subtracting the baseline (reference sample): (Δ Ct = Ct Gene of interest – Ct Internal control). Deep sequencing of formalin-fixed, paraffin-embedded tumor samples from enrolled patients...
was used to profile genomic alterations in 296 cancer-related genes in order to identify potential predictive markers of binimetinib sensitivity, as previously described [30]. Briefly, DNA was sequenced at high depth (median 744X) on an Illumina HiSeq 2500 sequencer following probe-based targeted exome capture.

Analyses were descriptive and exploratory in nature, and no inferential analysis was performed. Data were summarized with respect to demographic and baseline characteristics and all relevant pharmacodynamics and genetic alteration measurements.

Author contributions

All authors contributed to the collection and assembly of data, manuscript writing, and final approval of the manuscript. CvH, RRP, AD, VA, HN, AZ, and RD contributed to the study concept and design and analyses and interpreted the data.

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CONFLICTS OF INTEREST

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