Phase Ib/II Trial of Ribociclib in Combination with Binimetinib in Patients with *NRAS*-mutant Melanoma

Martin Schuler[1,2], Lisa Zimmer[3], Kevin B. Kim[4], Jeffrey A. Sosman[5], Paolo A. Ascierto[6], Michael A. Postow[7,8], Filip Y.F.L. De Vos[9], Carla M.L. van Herpen[10], Matteo S. Carlino[11,12], Douglas B. Johnson[13], Carola Berking[14], Micaela B. Reddy[15], Allison S. Harney[15], Jordan D. Berlin[13], and Rodabe N. Amaria[16]

ABSTRACT

Purpose: Enhanced MAPK pathway signaling and cell-cycle checkpoint dysregulation are frequent in *NRAS*-mutant melanoma and, as such, the regimen of the MEK inhibitor binimetinib and the selective CDK4/6 inhibitor ribociclib is a rational combination.

Patients and Methods: This is a phase Ib/II, open-label study of ribociclib + binimetinib in patients with *NRAS*-mutant melanoma (NCT01781572). Primary objectives were to estimate the MTD/recommended phase II dose (RP2D) of the combination (phase Ib) and to characterize combination antitumor activity at the RP2D (phase II). Tumor genomic characterization and pharmacokinetics/pharmacodynamics were also evaluated.

Results: Ten patients (16.4%) experienced dose-limiting toxicities in cycle 1 of phase Ib. Overall response rate in the phase II cohort ($n = 41$) for the selected RP2D (binimetinib 45 mg twice daily + ribociclib 200 mg once daily, 21 days on/7 days off) was 19.5% [8/41; 95% confidence interval (CI), 8.8–34.9]. The response rate was 32.5% (13/40; 95% CI, 20.1–48.0) in patients with *NRAS* mutation with concurrent alterations of *CDKN2A*, *CDK4*, or *CCND1*. Median progression-free survival was 3.7 months (95% CI, 3.5–5.6) and median overall survival was 11.3 months (95% CI, 9.3–14.2) for all patients. Common treatment-related toxicities included creatine phosphokinase elevation, rash, edema, anemia, nausea, diarrhea, and fatigue. Pharmacokinetics and safety were consistent with single-agent data, supporting a lack of drug–drug interaction.

Conclusions: Ribociclib + binimetinib can be safely administered and is clinically active in patients with *NRAS*-mutant melanoma. Co-mutations of cell-cycle genes may define a population with greater likelihood of treatment benefit.

See related commentary by Moschos, p. 2977

Introduction

Melanoma is associated with a high frequency of activating alterations in the RAS/RAF/MEK/ERK pathway (MAPK pathway; refs. 1–4). While $BRAF^{V600}$ mutations are the most prevalent in cutaneous melanoma, *NRAS* is mutated in 15% to 25% of melanomas and can include cutaneous, mucosal, and acral melanoma subtypes. Similar to *BRAF* mutations, *NRAS* mutations result in activation of the MAPK signaling pathway and activation of downstream RAF, MEK, and ERK. Direct selective inhibition of activated NRAS has been technically challenging in part due to the GTPase activity being a poor target for small-molecule antagonists. Thus, approaches have focused on inhibiting downstream pathways activated by NRAS in addition to the components of the MAPK pathway. Dysregulation of cell-cycle checkpoints is also common in melanoma (5). Frequent aberrations include loss of p16 (INK4A) by mutation, deletion, or transcription silencing (6), as well as activating mutations and amplifications of cyclin-dependent kinase 4 (*CDK4*) and cyclin D (7). Furthermore, in preclinical *in vivo* murine models of *NRAS*-mutant melanoma (murine and human), effective treatment requires more than MEK inhibition (8), consistent with clinical experience. Considering the limited clinical activity of MEK inhibition in patients with *NRAS*-mutant melanoma, cell-cycle inhibition with CDK4/6 inhibition appears to mimic the antitumor effect of direct NRAS inhibition in these animal models, and preclinical evidence has suggested synergy of MEK and CDK4/6 inhibition (8). Targeting these pathways may provide

[1]West German Cancer Center Essen, Department of Medical Oncology, University Hospital Essen, Essen, Germany. [2]German Cancer Consortium (DKTK), partner site University Hospital Essen, Essen, Germany. [3]West German Cancer Center Essen, Department of Dermatology, University Hospital Essen, Essen, Germany. [4]California Pacific Medical Center Research Institute, San Francisco, California. [5]Robert H. Lurie Cancer Center, Northwestern Medical Group, Chicago, Illinois. [6]Melanoma Unit, Cancer Immunotherapy and Development Therapeutics, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy. [7]Memorial Sloan Kettering Cancer Center, New York, New York. [8]Weill Cornell Medical College, New York, New York. [9]Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands. [10]Radboud University Medical Center, Nijmegen, the Netherlands. [11]Westmead Hospital, Crown Princess, Mary Cancer Centre, Corner of Hawkesbury and Darcy Roads, Westmead, New South Wales, Australia. [12]Australia Melanoma Institute Australia, The University of Sydney, Sydney, New South Wales, Australia. [13]Vanderbilt Ingram Cancer Center, Vanderbilt University Medical Center, The Vanderbilt Clinic, Nashville, Tennessee. [14]Department of Dermatology, Universitätsklinikum Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany. [15]Pfizer Inc., New York, New York. [16]Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas.

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Corresponding Author: Rodabe N. Amaria, Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030. Phone: 713-745-5530; E-mail: RNAmaria@mdanderson.org

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Translational Relevance

Neuroblastoma RAS viral oncogene homolog *(NRAS)*-mutant melanoma makes up 15%–25% of all melanomas, has a poor prognosis, and has no approved targeted therapies. Enhanced MAPK pathway signaling and cell-cycle checkpoint dysregulation are characteristic of most *NRAS*-mutant melanomas. Simultaneous inhibition of MAPK kinase (MEK) and cyclin-dependent kinase 4/6 (CDK4/6) has shown synergistic antitumor activity in several preclinical models of *NRAS*-mutant melanoma. The regimen of MEK inhibitor binimetinib and the selective CDK4/6 inhibitor ribociclib is a rational combination to assess in an *NRAS*-mutant melanoma population for toxicity and efficacy. In this phase Ib/II study, the combination of ribociclib + binimetinib achieved target inhibition and tolerability consistent with the known profile of the two agents. Antitumor activity was observed particularly in *NRAS*-mutant melanomas with concurrent genetic alterations in cell-cycle regulators.

therapeutic benefit in those melanomas characterized by *NRAS*-activating mutations; most notably hotspot mutations in the Q61 codon and at the G12 and G13 codons (9).

On the basis of the phase III COLUMBUS study, binimetinib in combination with encorafenib is approved in several countries for the treatment of advanced *BRAF*-mutant melanoma (10). It has shown modest activity as a single agent in *NRAS*-mutant melanoma (11). In a phase I study, binimetinib demonstrated a manageable safety profile, target inhibition, and dose-proportional exposure, with 45 mg twice daily identified as the recommended phase II dose (RP2D; ref. 12). In the randomized, open-label phase III NEMO study in 402 patients with advanced, previously untreated, unresectable, stage IIIC or IV *NRAS*-mutant melanoma, binimetinib 45 mg orally twice daily improved progression-free survival (PFS) compared with dacarbazine 1,000 mg/m^2 intravenously every 3 weeks (11). In this study, median PFS was 2.8 months [95% confidence interval (CI), 2.8–3.6] in the binimetinib group and 1.5 months (1.5–1.7) in the dacarbazine group [HR, 0.62 (95% CI, 0.47–0.80); one-sided $P < 0.001$]. For patients who received prior immunotherapy, median PFS was longer for those who received binimetinib than for those who received dacarbazine [5.5 months (2.8–7.6) vs. 1.6 months (1.5–2.8), respectively (11)]. However, overall survival (OS) did not differ between the two cohorts, with Kaplan–Meier curves completely overlapping with an HR of 1.00 (95% CI, 0.75–1.33; one-sided $P = 0.50$; ref. 11).

Ribociclib is approved in combination with an aromatase inhibitor for the treatment of hormone receptor–positive, HER2-negative advanced or metastatic breast cancer and in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor–positive, HER2-negative advanced or metastatic breast cancer (13). In a phase I study, the MTD for ribociclib was established as 900 mg/day and the recommended dose for expansion was 600 mg/day, both at a schedule of 3 weeks on/1 week off (14).

Despite the benefit of immunotherapy for many patients with melanoma, minimal options exist for those patients who do not have *BRAF*^{V600} mutations or who are not candidates for, are refractory to, or have progressed after initial response to immune checkpoint inhibitors. On the basis of the compelling preclinical evidence, inhibition of the MAPK pathway and cell-cycle checkpoint regulators was hypothesized to be a rational approach for optimal treatment of *NRAS*-mutant melanoma (14). In this phase Ib/II study, we investigated the combination of ribociclib, an orally available, small-molecule inhibitor of CDK4/6, and binimetinib, an orally available, ATP noncompetitive, highly selective inhibitor of MEK1/2.

The primary purpose of the initial phase Ib part was to define the MTD and RP2D of the ribociclib + binimetinib combination in patients with advanced *NRAS*-mutant melanoma. Consecutively, at the RP2D in a phase II expansion cohort (phase II), the trial evaluated overall response rate (ORR) and PFS, while further assessing the overall safety of the combination of these agents. Pharmacodynamic parameters of target inhibition, and baseline genomic alterations for further definition of the most responsive patient population were also explored.

Patients and Methods

Study design and participants

This was a multicenter, open-label, phase Ib/II study of ribociclib in combination with binimetinib in adult patients with locally advanced or metastatic *NRAS*-mutant melanoma.

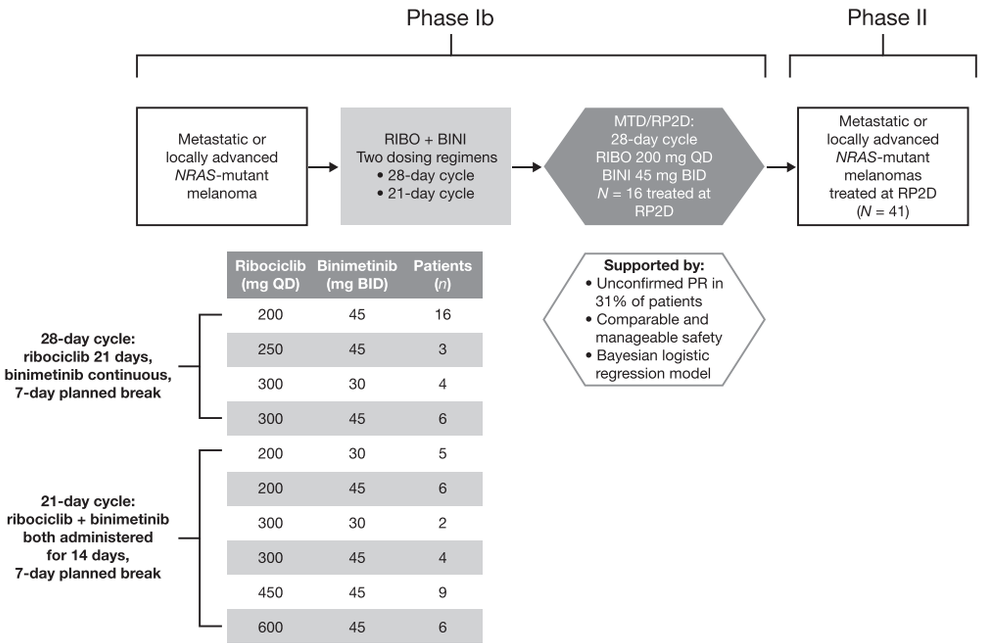
Eligible patients were ≥18 years old with a locally advanced or metastatic melanoma with documented *NRAS* alteration by local assessment; Eastern Cooperative Oncology Group (ECOG) performance status ≤1; evidence of evaluable disease (phase Ib dose escalation) or measurable disease (phase II dose expansion) by RECIST version 1.1 (15); and with adequate hematologic, renal, and hepatic function. There were no restrictions on the number of prior regimens, although in the dose–expansion phase, prior exposure to CDK4/6 or MEK inhibitors was prohibited. Patients with symptomatic brain metastases, impaired gastrointestinal function, uncontrolled hypertension, impaired cardiac function, or treatment with agents that can cause QT prolongation or torsades de pointes were excluded.

All patients provided written informed consent and the studies were conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki. An Institutional Review Board or independent ethics committee and the responsible regulatory authorities approved the protocol at all study sites.

The phase Ib study component (dose-escalation phase) evaluated the combination for toxicity, dose-limiting toxicity (DLT), MTD, and RP2D and schedule of ribociclib and binimetinib for the phase II component (dose-expansion cohort). The objective of the phase II part was to describe the antitumor activity of the combination at the RP2D and schedule.

Patients were assigned to one of two schedules: a 28-day schedule with ribociclib given once daily for 21 consecutive days followed by a 7-day planned break, plus binimetinib twice daily on a continuous dosing schedule, or a 21-day schedule of ribociclib once daily plus binimetinib twice daily with both administered for 14 consecutive days followed by a 7-day planned break (**Fig. 1**). The initial dose levels were as outlined in **Table 1**.

With the possibility of deescalating binimetinib and different ribociclib and binimetinib dosing schedules investigated, several combinations could have corresponded to the MTD definition and more than one MTD could have been identified with different doses/schedules of the study drugs. In that case, a discussion between all institutional principal investigators and the sponsor would have been convened to collectively select a phase II schedule based on data gathered. Once the RP2D and schedule were determined, the dose-expansion phase started at the RP2D on the chosen



Ribociclib (mg QD)	Binimetinib (mg BID)	Patients (*n*)
200	45	16
250	45	3
300	30	4
300	45	6
200	30	5
200	45	6
300	30	2
300	45	4
450	45	9
600	45	6

Figure 1.
Study design. BID, twice daily; BINI, binimetinib; PR, partial response; QD, once daily; RIBO, ribociclib.

schedule to assess antitumor activity of the ribociclib + binimetinib combination. Data from enrolled patients were also used to better characterize safety, tolerability, and the pharmacokinetic profiles of the two study drugs.

Assessments

Safety assessments included physical examination, vital signs, height and weight, ECOG performance status evaluation, electrocardiogram, ocular assessments, laboratory evaluations, and documentation of DLTs, adverse events (AE), and serious AEs (SAE). AEs were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Tumor response was evaluated locally by the investigator according to RECIST version 1.1 (15). CT scans were performed every 6–8 weeks preferably on day 22 of the second cycle in the 28-day schedule or day 14 of the third cycle in the 21-day schedule. After the first 6 months, evaluations were performed every 16 weeks per standard of care, or upon clinical evidence of disease progression.

For the pharmacokinetic analysis, the single-dose and multiple-dose pharmacokinetic profiles of ribociclib and binimetinib were calculated. Plasma concentrations of ribociclib and binimetinib were determined using validated LC/MS assays. For biomarkers, tumor samples were collected at baseline and on study (cycle 1, day 15) in the dose-escalation and dose-expansion phases to investigate the effects of the ribociclib + binimetinib combination on changes in key pharmacodynamic markers [e.g., phosphorylated (p) ERK (pERK)]. IHC data are reported as histologic scores (H-scores). The pathologist determined whether the staining was absent (0+), slight (1+), moderate (2+), or strong (3+). The H-score used to assess pERK and pMEK for each cellular compartment was then calculated as the sum of the percentages of stained cells multiplied by their intensity, or (%1+) + (2 * %2+) + (3 * %3+) and ranged between 0 and 300. IHC results for paired samples at baseline and on study were obtained for 15 patients. In the dose-expansion phase II, tumor samples were tested (Foundation Medicine, Inc., Cambridge, MA) by hybridization capture of exonic regions of 296 cancer-related genes from formalin-fixed, paraffin-embedded clinical tumor specimens. Sequencing to profile genomic alterations in the cancer-related genes allowed identification of genes altered in the D-cyclin-CDK4/6-INK4a-Rb and RAS/RAF/MEK/ERK pathways. Informative sequencing results were obtained for formalin-fixed paraffin-embedded pretreatment tumor samples from 80 patients. These analyses were descriptive and exploratory in nature, and no inferential analysis was performed.

Statistical methods

The full analysis set included all patients who received at least one dose of ribociclib or binimetinib and was used for the analysis of all endpoints unless noted otherwise. The safety set included all patients who received at least one dose of ribociclib or binimetinib and had at least one valid postbaseline safety assessment. The biomarker analysis set consisted of all patients who provided a biomarker sample for DNA sequencing and had at least one reported result, even if the result was that no gene alteration was found.

The primary objective of the phase Ib part (dose escalation) was to estimate the MTD/RP2D of the combination using a Bayesian logistic regression model with overdose control. The primary endpoint in the dose-escalation phase was the incidence of DLTs in cycle 1. The safety endpoints included DLTs and the incidence of AEs. Assessment of safety was based on the type and frequency of AEs and SAEs, and laboratory values outside the predetermined ranges of CTCAE version 4.03.

In the dose-expansion phase II, the primary endpoint was ORR, defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) by RECIST version 1.1. Summary tables for ORR at the RP2D, along with two-

Table 1. Baseline patient characteristics.

	Dose-escalation phase Ib		Dose-expansion phase II
	28-day schedule ***N* = 29**	**21-day schedule** ***N* = 32**	**28-day schedule[a]** ***N* = 41**
Age, years, *n* (%)			
Mean (SD)	58.5 (14.84)	60.6 (10.59)	64.0 (12.35)
Median (min, max)	60.0 (21, 79)	62.0 (31, 76)	65.0 (21, 86)
<65	17 (58.6)	18 (56.3)	19 (46.3)
≥65	12 (41.4)	14 (43.8)	22 (53.7)
Sex, *n* (%)			
Female	12 (41.4)	14 (43.8)	15 (36.6)
Male	17 (58.6)	18 (56.3)	26 (63.4)
Body mass index (kg/m^2)[b]			
Mean (SD)	28.39 (6.083)	26.95 (5.641)	26.69 (5.014)
ECOG performance status, *n* (%)			
0	15 (51.7)	22 (68.8)	28 (68.3)
1	12 (41.4)	10 (31.3)	13 (31.7)
2	2 (6.9)	0	0
Median prior regimens (range)	2 (1–6)	2 (1–7)	2 (1–6)
Prior immunotherapy, *n* (%)[c]	16 (55.2)	18 (56.3)	35 (85.4)
Prior MEK inhibitor, *n* (%)[d]	0	2 (6.3)	1 (2.4)
Baseline LDH, *n* (%)			
<ULN	0	1 (3.1)	0
1–1.5 × ULN	14 (48.3)	14 (43.8)	25 (61.0)
>1.5 × ULN	15 (51.7)	17 (53.1)	16 (39.0)
Stage at study entry, *n* (%)[e]			
III (unknown)	1 (3.4)	0	0
IIIB	0	1 (3.1)	0
IIIC	2 (6.9)	1 (3.1)	3 (7.3)
IV (unknown)	4 (13.8)	2 (6.3)	22 (53.7)
IVA	3 (10.3)	3 (9.4)	2 (4.9)
IVB	1 (3.4)	5 (15.6)	3 (7.3)
IVC	18 (62.1)	20 (62.5)	10 (24.4)
Missing	0	0	1 (2.4)

Abbreviations: LDH, lactate dehydrogenase; max, maximum; min, minimum; *N*, number of patients in each treatment group; *n*, number of patients with the event; ULN, upper limit of normal.

[a]Binimetinib twice daily on a continuous dosing schedule plus ribociclib once daily for 21 consecutive days followed by a 7-day planned break.

[b]Body mass index (kg/m^2) is defined as: weight (kg)/[height (m)^2].

[c]Immunotherapy = ipilimumab, nivolumab, pembrolizumab.

[d]One patient received prior trametinib in the 28-day dose-escalation group and 1 patient in the 28-day dose-expansion group received prior binimetinib.

[e]American Joint Committee on Cancer 7th edition.

sided exact binomial 95% CIs were produced. Secondary efficacy endpoints included PFS, OS, disease control rate (DCR), duration of response (DOR), time to progression, and time to overall response. ORR and DOR were provided with their corresponding 95% exact binomial CIs. An estimate for the survival function for time-to-event endpoints was assessed using Kaplan–Meier estimates with 95% CIs. In the dose-expansion phase II, it was estimated that approximately 40 patients were to be enrolled for the model to have less than 10% posterior risk of the true ORR being less than 25% (i.e., unacceptable efficacy) given an observed ORR equal to 35%.

Pharmacokinetic parameters for plasma ribociclib and binimetinib were determined for all pharmacokinetic-evaluable patients using noncompartmental method(s) with Phoenix® WinNonlin® version 6.4 (Certara, Princeton, NJ).

For the IHC biomarker data analysis, pMEK and pERK, the mean, SD, coefficient of variation (CV), median, minimum, and maximum were reported for baseline H-score and percentage of change from baseline H-score.

Data availability

The data generated in this study are available within the article and its Supplementary Data files.

Results

Between June 27, 2013 and November 10, 2016 (data cutoff May 21, 2018), 102 patients were enrolled: 61 in the dose-escalation phase and 41 in the dose-expansion phase. For the 61 patients in the dose-escalation phase, 29 were treated in the 28-day treatment cycle and 32 in the 21-day treatment cycle. In both treatment schedules, the most common primary reason for treatment discontinuation was progressive disease [PD; 17 patients (58.6%) in the 28-day schedule and 27 patients (84.4%) in the 21-day schedule] followed by AEs [9 patients (31.0%) in the 28-day schedule and 3 patients (9.4%) in the 21-day schedule]. In the dose-expansion phase, 41 patients were treated with binimetinib 45 mg twice daily + ribociclib 200 mg once daily on the 28-day schedule based on dose-escalation meetings between the Sponsor and the Investigators. The reasons for discontinuation of treatment

were PD [23 patients (56.1%)], AEs [11 patients (26.8%)], physician decision [4 patients (9.8%)], patient decision [2 patients (4.9%)], and death [1 patient (2.4%)].

Baseline clinical and demographic characteristics for the dose-escalation and dose-expansion phases are summarized in **Table 1**. Patient characteristics were balanced between the 28- and 21-day schedules as well as between the dose-escalation and dose-expansion phases. All 29 patients in the 28-day schedule were Caucasian, and there were more males enrolled [17 (58.6%)] than females [12 (41.4%)]. The median age was 60.0 (range, 21–79) years. Patients in the 28-day schedule had a baseline ECOG performance status of 0 [15 patients (51.7%)], 1 [12 patients (41.4%)], or 2 [2 patients (6.9%)]. The majority of patients in the 21-day schedule [31 (96.9%)] were Caucasian, with more males [18 (56.3%)] than females [14 (43.8%)] enrolled. Median age was 62.0 (range, 31–76) years and patients had a baseline ECOG performance status of 0 [22 patients (68.8%)] or 1 [10 patients (31.3%)]; no patients had baseline ECOG performance status >1 in the 21-day schedule.

MTD and RP2D determination

Sixty-one patients in the dose-escalation phase were given ribociclib + binimetinib. The median relative dose intensity was 72% and 74% for binimetinib and 95% and 91% for ribociclib for the 28- and 21-day schedule, respectively. The highest dose evaluated (binimetinib 45 mg twice daily + ribociclib 300 mg once daily) for the 28-day schedule exceeded the MTD with blood creatine phosphokinase (CPK) elevations being the most commonly observed DLT. However, the posterior probability of DLT occurrence in the target interval was similar for the remaining doses. For the 21-day schedule, the MTD was not reached. There was no clear dose–response relationship in the dose ranges studied for either schedule in terms of ORR, PFS, and DOR that would justify taking forward any treatment other than the lowest ribociclib dose tested in either schedule.

For the 28-day schedule, 6 patients (20.7%) experienced a total of seven DLTs during cycle 1 [acute kidney injury, face edema, and rash (binimetinib 45 mg twice daily + ribociclib 200 mg once daily); intracranial hemorrhage due to underlying brain metastasis (binimetinib 30 mg twice daily + ribociclib 300 mg once daily); anemia, increased CPK levels, and peripheral edema (binimetinib 45 mg twice daily + ribociclib 300 mg once daily)]; each DLT was reported in a single patient. For the 21-day schedule, four patients (12.5%) had DLTs in cycle 1, including increased blood CPK levels (binimetinib 45 mg twice daily + ribociclib 200 mg once daily and binimetinib 45 mg twice daily + ribociclib 450 mg once daily), skin rash (binimetinib 45 mg twice daily + ribociclib 300 mg once daily), and macular edema (binimetinib 45 mg twice daily + ribociclib 450 mg once daily); each DLT was reported in a single patient.

Patients on the 28-day schedule appeared to have numerically better ORR, PFS, and DOR than patients on the 21-day schedule. Tolerability was comparable in the two schedules. On the basis of the available data, the RP2D and schedule to be evaluated in the dose-expansion phase of the study was binimetinib 45 mg twice daily continuously + ribociclib 200 mg once daily 21 days on/7 days off (the 28-day schedule).

Safety

In the dose-escalation phase, the median exposure to the combination during the 28-day and 21-day schedules was 141 (range, 8–406) days and 122 (range, 10–862) days, respectively. The median binime-

Table 2. Adverse events.

	Dose-escalation phase Ib				Dose-expansion phase II	
	28-day schedule *N* = 29		21-day schedule *N* = 32		28-day schedule[a] *N* = 41	
	Any grade *n* (%)	Grade 3–4 *n* (%)	Any grade *n* (%)	Grade 3–4 *n* (%)	Any grade *n* (%)	Grade 3–4 *n* (%)
Any AE	29 (100)	26 (89.7)	32 (100)	24 (75.0)	41 (100)	38 (92.7)
Serious AEs	16 (55.2)	14 (48.3)	14 (43.8)	11 (34.4)	22 (53.7)	18 (43.9)
AEs leading to discontinuation[b]	10 (34.5)	7 (24.1)	3 (9.4)	3 (9.4)	13 (31.7)	11 (26.8)
AEs requiring dose interruption and/or changes	21 (72.4)	21 (72.4)	23 (71.9)	16 (50.0)	31 (75.6)	25 (61.0)
AEs in >20% of patients in either group						
Blood CPK increase	20 (69.0)	5 (17.2)	13 (40.6)	5 (15.6)	24 (58.5)	10 (24.4)
Diarrhea	14 (48.3)	0	19 (59.4)	1 (3.1)	21 (51.2)	3 (7.3)
Nausea	15 (51.7)	2 (6.9)	12 (37.5)	2 (6.3)	22 (53.7)	1 (2.4)
Fatigue	10 (34.5)	0	16 (50.0)	1 (3.1)	15 (36.6)	2 (4.9)
Vomiting	14 (48.3)	3 (10.3)	11 (34.4)	0	14 (34.1)	2 (4.9)
Peripheral edema	14 (48.3)	1 (3.4)	7 (21.9)	0	18 (43.9)	2 (4.9)
Anemia	13 (44.8)	2 (6.9)	8 (25.0)	1 (3.1)	10 (24.4)	0
AST increase	12 (41.4)	4 (13.8)	9 (28.1)	2 (6.3)	20 (48.8)	9 (22.0)
Rash	9 (31.0)	3 (10.3)	11 (34.4)	1 (3.1)	6 (14.6)	0
Acneiform dermatitis	9 (31.0)	1 (3.4)	8 (25.0)	0	18 (43.9)	3 (7.3)
ALT increase	9 (31.0)	4 (13.8)	7 (21.9)	2 (6.3)	18 (43.9)	10 (24.4)
Neutropenia	7 (24.1)	2 (6.9)	8 (25.0)	6 (18.8)	5 (12.2)	0
Hypoalbuminemia	11 (37.9)	2 (6.9)	3 (9.4)	0	6 (14.6)	1 (2.4)
Constipation	9 (31.0)	1 (3.4)	5 (15.6)	1 (3.1)	8 (19.5)	1 (2.4)
Pyrexia	5 (17.2)	0	9 (28.1)	3 (9.4)	11 (26.8)	1 (2.4)
Hypomagnesemia	9 (31.0)	0	4 (12.5)	0	3 (7.3)	0
Hypokalemia	4 (13.8)	2 (6.9)	0	0	9 (22.0)	2 (4.9)

Abbreviations: *N*, total number of patients in treatment group; *n*, number of patients with the event.
[a]Binimetinib twice daily on a continuous dosing schedule plus ribociclib once daily for 21 consecutive days followed by a 7-day planned break.
[b]AEs associated with discontinuation although may not be primary reason for discontinuation.

tinib and ribociclib relative dose intensities for all patients were 73.0% and 91.0%, respectively, and were similar for both treatment schedules.

All the treated patients in both phases reported at least one AE (**Table 2**). In the dose-escalation phase, the most frequently reported AEs in the 28-day schedule were increased blood CPK levels [20 patients (69.0%)]; nausea [15 patients (51.7%)]; and diarrhea, vomiting, and peripheral edema [14 patients (48.3%) each], whereas the most frequently reported AEs in the 21-day schedule were diarrhea [19 patients (59.4%)], fatigue [16 patients (50.0%)], and increased blood CPK levels [13 patients (40.6%)]. In the dose-expansion phase, the most frequently reported AEs were increased blood CPK levels [24 patients (58.5%)] followed by nausea [22 patients (53.7%)] and diarrhea [21 patients (51.2%)]. Increased blood CPK levels, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) elevations were the most common grade 3/4 AEs (**Table 2**).

Six patients in the dose-escalation [28-day schedule: 4 patients (13.8%); 21-day schedule: 2 patients (6.3%)] and 3 patients (7.3%) in the dose-expansion phases died during the study while on study treatment or within 30 days of the last dose of study treatment. None of the deaths were considered related to study treatment by the investigator, with the exception of an event of intracranial hemorrhage in 1 patient (28-day schedule: binimetinib 30 mg twice daily + ribociclib 300 mg once daily).

Differences of >10% in the incidence of AEs between the 28-day and 21-day schedules in the escalation phase included increased blood CPK levels, nausea, peripheral edema, anemia, increased AST levels, vomiting, hypoalbuminemia, constipation, and hypomagnesemia, which were more commonly reported in the 28-day schedule than in the 21-day schedule. Diarrhea, fatigue, and pyrexia were more commonly reported in the 21-day schedule than in the 28-day schedule in the dose-escalation phase.

Efficacy

The BOR results for the phase Ib portion of the study are summarized in **Table 3**. In the dose-escalation phase 28-day schedule cohort, 6 patients (20.7%) had a PR, 14 patients (48.3%) had stable disease (SD) as best response, and 4 patients (13.8%) had PD. The confirmed ORR was 20.7% (95% CI, 8.0–39.7) and the confirmed DCR was 69.0% (95% CI, 49.2–84.7), based on the investigator's assessment. In the 21-day schedule cohort, 6 patients (18.8%) had a PR by the end of the study, 12 patients (37.5%) had SD as best response, and 9 patients (28.1%) had PD, with a confirmed ORR and DCR of 18.8% (95% CI, 7.2–36.4) and 56.3% (95% CI, 37.7–73.6), respectively. The median PFS in the dose-escalation phase was 6.7 months (95% CI, 3.5–9.2) for patients on the 28-day schedule and 4.1 months (95% CI, 2.8–6.1) for patients on the 21-day schedule (**Fig. 2A**).

In the phase II dose-expansion portion of the study, the confirmed ORR based on the investigator's assessment for patients was 19.5% (95% CI, 8.8–34.9), with 8 patients (19.5%) achieving PR (**Table 3**). The BOR was listed as unknown for 6 patients (14.6%). Median DOR was 10.3 months (95% CI, 4.1–not estimable). Overall, the majority of patients achieved disease response or stabilization, with a confirmed DCR of 70.7% (95% CI, 54.5–83.9). Each subject's response to treatment over the course of the study is displayed in swimmer plots in Supplementary Fig. S1. The median PFS was 3.7 months (95% CI, 3.5–5.6) and the median OS was 11.3 months (95% CI, 9.3–14.2), with an OS rate at 12 months of 45.0% (95% CI, 28.4–60.3; **Fig. 2B**).

Pharmacokinetic analysis

The following steady-state pharmacokinetic parameters from the dose escalation with its richer pharmacokinetic sampling are for the doses and regimen selected for the expansion (binimetinib 45 mg twice daily + ribociclib 200 mg once daily on the 28-day schedule) in 11 subjects. The binimetinib geometric mean (geometric %CV) area under the plasma concentration–time curve over the dosing interval (AUC_{tau}) and maximum serum concentration (C_{max}) at steady state were 2,250 (37.7%) hour*ng/mL and 441 (52.6%) ng/mL, respectively; the median (range) half-life ($t_{1/2}$) was 5.13 (3.20–6.70) hours, and the time to maximum serum concentration (T_{max}) was about 1.00 hour postdose. The ribociclib AUC_{tau} and C_{max} at steady state were 3,080 (63.2%) hour*ng/mL and 220 (76.5%) ng/mL, respectively; $t_{1/2}$ was 15.5 (13.9–20.8) hours, and the T_{max} was about 2.25 hours postdose. For the label dose of 600 mg ribociclib coadministered with binimetinib (21-day cycle), the ribociclib AUC_{tau} and C_{max} at steady state were 30,700 (46.4%) hour*ng/mL and 1,910 (38.5%) ng/mL, respectively. Ribociclib steady-state exposures increased greater than dose proportionally in the dose-escalation range of 200 to 600 mg once daily.

Table 3. Best overall response in the dose-escalation and dose-expansion phases as defined by RECIST version 1.1.

	Dose-escalation phase Ib		Dose-expansion phase II
	28-day schedule ***N* = 29**	**21-day schedule** ***N* = 32**	**28-day schedule[a]** ***N* = 41**
CR, *n* (%)	0	0	0
PR, *n* (%)	6 (20.7)	6 (18.8)	8 (19.5)
SD, *n* (%)	14 (48.3)	12 (37.5)	21 (51.2)
PD, *n* (%)	4 (13.8)	9 (28.1)	6 (14.6)
Unknown,[b] *n* (%)	5 (17.2)	5 (15.6)	6 (14.6)
Confirmed ORR, *n* (%)	6 (20.7)	6 (18.8)	8 (19.5)
(95% CI)	(8.0–39.7)	(7.2–36.4)	(8.8–34.9)
Confirmed DCR, *n* (%)	20 (69.0)	18 (56.3)	29 (70.7)
(95% CI)	(49.2–84.7)	(37.7–73.6)	(54.5–83.9)
Median PFS, months (95% CI)	6.7 (3.5–9.2)	4.1 (2.8–6.1)	3.7 (3.5–5.6)
Median DOR, months (95% CI)	NA	NA	10.3 (4.1–NE)

Abbreviations: NA, not available; NE, not estimable.

[a]Binimetinib twice daily on a continuous dosing schedule plus ribociclib once daily for 21 consecutive days followed by a 7-day planned break.

[b]Patients are categorized as unknown when they have no evaluable postbaseline scans.

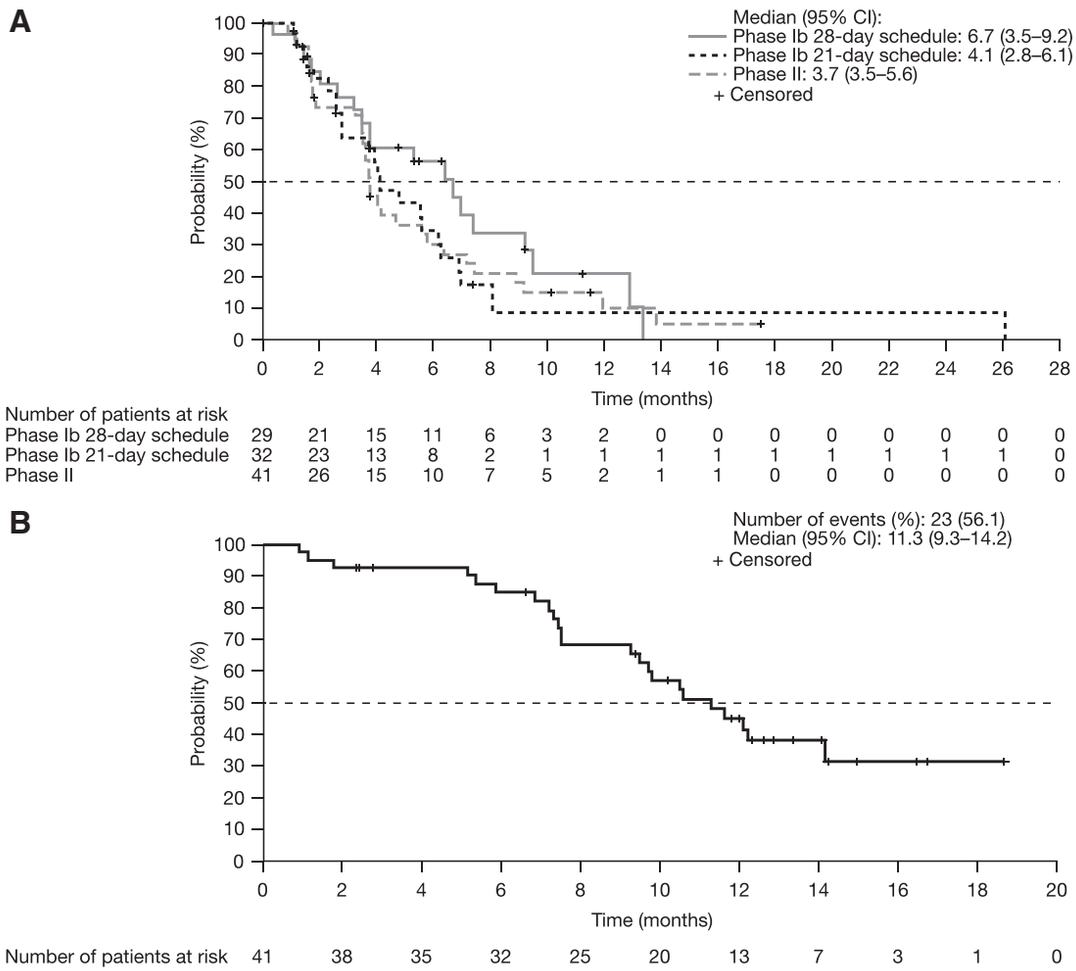


Figure 2.

Kaplan–Meier estimates of (**A**) PFS in phase Ib dose escalation and phase II dose expansion and (**B**) OS in phase II dose expansion. CI confidence interval; OS, overall survival; PFS, progression-free survival.

Biomarker analysis

On-treatment biopsies

Results from the 15 patients available (2 from phase Ib; 13 from phase II) for assessment of the change from baseline in pERK and pMEK protein activation are shown in Supplementary Fig. S2. As expected for MEK inhibition, median level of pERK numerically decreased under treatment, whereas median pMEK level remained unchanged. The results showed considerable variation between individual patients. There were no notable findings when comparing the 3 responders with the 12 nonresponders [mean change in pERK (SD) of −38 (143); mean change in pMEK of 3.5 (64)], though numbers were small.

Response rate of patients with alterations in cell-cycle regulators

Informative genomic analyses from baseline tumor samples were obtained from 80 patients. In 78 of those 80 patients, an *NRAS* alteration was confirmed (for a breakdown of the *NRAS* short mutations; see Supplementary Table S1 and Supplementary Table S2). A summary of all genomic alterations in patient tumors at baseline are presented in Supplementary Table S3 and Supplementary Fig. S3, including copy-number alterations, single-nucleotide variants, and gene rearrangements.

Alterations in *CDK4*, *CCND1*, and *CDKN2A*, whose gene products act in the G_1 cell-cycle checkpoint, are of interest for response to the CDK4/6 inhibitor ribociclib. Indeed, the response rate in patients with coalterations of cell-cycle regulators in *NRAS*-mutant melanoma was higher than in patients without such alterations, with an ORR of 32.5% (95% CI, 20.1–48.0; 13/40) and 10% (95% CI, 4.0–23.1; 4/40), respectively (**Fig. 3**). *Post hoc* testing revealed a significant difference between the ORRs of those with coalterations of cell-cycle regulators and those without these alterations (difference $P < 0.014$, χ^2 test).

Discussion

This multicenter, open-label, dose-finding, and dose-escalation study was designed to estimate the MTD and/or RP2D for the combination of binimetinib and ribociclib in patients with histologically or cytologically confirmed locally advanced or metastatic *NRAS*-mutant melanoma. The dose-escalation part of the study was followed by a dose expansion at the RP2D to assess the clinical efficacy and to

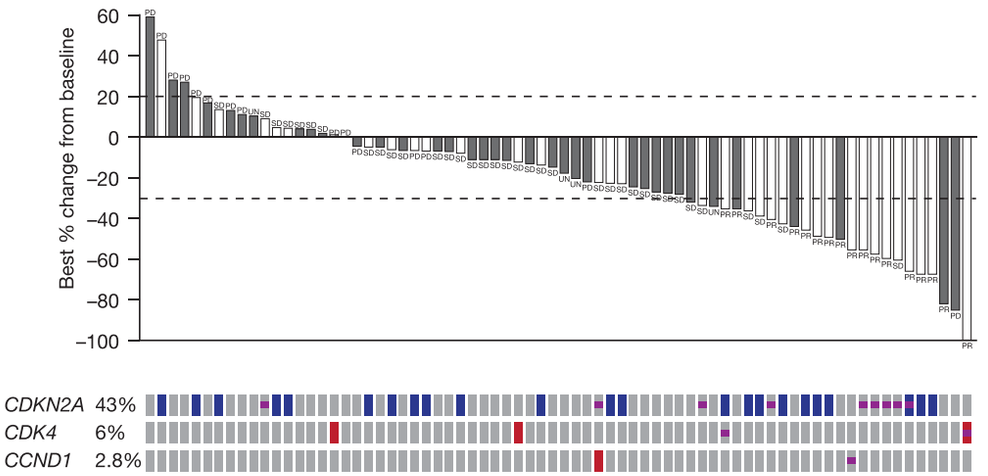


Figure 3.

Tumor change from baseline by presence of cell-cycle alterations. Waterfall plot of best change from baseline (%) tumor in evaluable patients (top). Dark gray bars = no cell-cycle gene alterations; light gray bars = cell-cycle gene alterations. Oncoprint of cell-cycle gene alteration (16) by patient (bottom). Red rectangles are amplification, blue rectangles are loss of copy, and purple squares are short variants. The biomarker analysis set consisted of all patients who provided a biomarker sample for DNA sequencing and had at least one reported result, even if the result was that no gene alteration was found. PD, progressive disease; PR, partial response; SD, stable disease; UN, unknown.

further assess the safety of the drug combination. In the dose-escalation part of the study, the 45 mg binimetinib twice daily + ribociclib 200 mg once daily treatment arm on a 28-day schedule was selected as the RP2D based on the ORR and the AE profile; this combination dose and schedule had a manageable toxicity profile and was clinically feasible. The median PFS in the expansion phase (3.7 months) is comparable with the median PFS seen in the NEMO trial (11). However, caution should be taken making direct comparisons between clinical trials, for example the patient population of the NEMO trial had ECOG scores and pretreatment conditions that differ from the patient population of the current phase Ib/II study.

For both binimetinib and ribociclib, the observed pharmacokinetics were similar to historical pharmacokinetics data from monotherapy trials, supporting a lack of drug–drug interaction (ref. 14; data on file, Pfizer). For ribociclib, the label dose is 600 mg once daily and the pharmacokinetics is greater than dose proportional. Therefore, ribociclib exposures at the RP2D of 200 mg once daily were much lower than those expected for the label dose, with an AUC_{tau} about 10% that of the label dose.

The combination of binimetinib and ribociclib was clinically active in patients with locally advanced or metastatic melanoma with documented *NRAS* alteration. AEs were generally consistent with those reported when using binimetinib and ribociclib as single agents.

In an effort to improve upon the clinical efficacy, combinations of MEK inhibition with targeting RAF, ERK, EGFR–PI3K–AKT, and CDK4/6 is an active area of research (17). Hence, the selection of a combination of MEK + CDK4/6 inhibitors that are regulators of the G_1–S cell-cycle checkpoint is a rational choice for further research. This combination was shown to inhibit synergistically the growth of *NRAS*-mutant melanoma cell lines (8, 18). Despite limited patient numbers, the efficacy data from our study suggest that combining MEK + CDK4/6 inhibition may be clinically more active in patients with *NRAS*-mutant melanoma with concurrent genetic alterations in cell-cycle regulators than MEK inhibition alone. As most of the patients had received prior immunotherapies, mostly targeting PD-1/PD-L1 and/or CTLA-4, an interaction with subsequent response to binimetinib/ribociclib could not be established (Supplementary Fig. S4).

In this study, target inhibition was observed in several of the 15 assessed patients with pretreatment and on-treatment tumor biopsies showing a decrease in pERK activation with pMEK activation unchanged after treatment with ribociclib + binimetinib. Most interestingly, the *post hoc* analyses revealed significantly higher response rates in patients with *NRAS*-mutant melanoma also harboring somatic alterations in genes encoding regulators of the G_1 cell-cycle checkpoint (such as *CDKN2A*, *CDK4*, or *CCND1)*. This observation suggests that the inhibition of CDK4/6 may be relevant to the antitumor effects in these *NRAS*-mutant melanomas. Selection of patients with *NRAS*-mutant melanoma by somatic comutations may lead to enhanced antitumor effects of combination therapy with MEK and CDK4/6 inhibitor–based regimens. Furthermore, this combination may have additional benefits following immune checkpoint inhibitors when given simultaneously. Results in preclinical settings have demonstrated enhanced immune antitumor effects for both CDK4/6 inhibitors and MEK inhibitors in combination with inhibitors of programmed cell death protein 1 or ligand 1 (anti-PD-1/PD-L1). There are now a number of clinical trials including CDK4/6 inhibitors or MEK inhibitors in combination with anti-PD-1/PD-L1.

In summary, the dose and schedule of the regimen chosen for evaluation in the dose-expansion phase, binimetinib 45 mg twice daily (continuous) + ribociclib 200 mg once daily (21 days on/7 days off) on the 28-day schedule, was generally well tolerated and exhibited a modest response rate for pretreated patients with locally advanced or metastatic melanoma with documented *NRAS* alteration. In patients with melanomas harboring *NRAS* mutations and comutations of genes acting in the D-cyclin-CDK4/6-INK4a-Rb pathway at the G_1 cell-cycle checkpoint, the response rate was improved. Clinical development of combined targeting strategies in *NRAS*-mutant melanoma should consider this lead.

Authors' Disclosures

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Authors' Contributions

M. Schuler: Supervision, investigation, writing–review and editing. **L. Zimmer:** Supervision, investigation, writing–review and editing. **K.B. Kim:** Investigation, writing–review and editing. **J.A. Sosman:** Conceptualization, supervision, investigation, writing–original draft, writing–review and editing. **P.A. Ascierto:** Investigation, writing–review and editing. **M.A. Postow:** Investigation, writing–review and editing. **F.Y.F.L. De Vos:** Investigation, writing–review and editing. **C.M.L. van Herpen:** Investigation, writing–review and editing. **M.S. Carlino:** Investigation, writing–review and editing. **D.B. Johnson:** Investigation, writing–review and editing. **C. Berking:** Investigation, writing–review and editing. **M.B. Reddy:** Supervision, investigation, writing–review and editing. **A.S. Harney:** Conceptualization, resources, data curation, formal analysis, investigation, methodology, project administration, writing–review and editing. **J.D. Berlin:** Supervision, investigation, writing–review and editing. **R.N. Amaria:** Supervision, investigation, writing–review and editing.

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