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Phase 1b/2 Trial of Ribociclib + Binimetinib in Metastatic *NRAS*-Mutant Melanoma: Safety, Efficacy, and Recommended Phase 2 Dose

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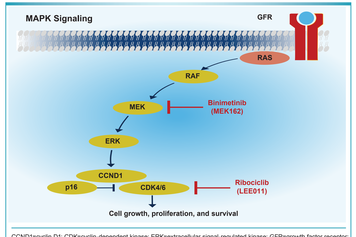
INTRODUCTION

- In addition to enhanced mitogen-activated protein kinase pathway signaling in *NRAS*-mutant melanoma, dysregulation in the cell cycle checkpoint is common.[1]
- Results of the phase 3 NEMO study demonstrated that the mitogen-activated protein kinase kinase (MEK) inhibitor binimetinib (BINI) improved progression-free survival (PFS) in patients with *NRAS*-mutant melanoma compared with dacarbazine.[2]
- Analyses of aberrant pathways in *NRAS*-mutant melanoma suggest that coinhibition of MEK and cyclin-dependent kinase 4 (CDK4) would be synergistic **(Figure 1)**.[3]

Figure 1. Ribociclib and Binimetinib Inhibitory Mechanisms*



CCND1=cyclin D1; CDK=cyclin-dependent kinase; ERK=extracellular signal-regulated kinase; GFR=growth factor receptor; MAPK=mitogen-activated protein kinase; MEK=mitogen-activated protein kinase kinase.
*p16 is a product of the *CDKN2A* gene.

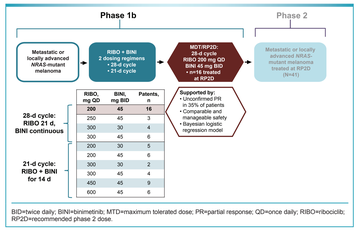
OBJECTIVE

Here we report data from an ongoing phase 1b/2 trial of the CDK4/6 inhibitor ribociclib (RIBO) in combination with BINI in patients with metastatic *NRAS*-mutant melanoma (clinicaltrials.gov: NCT01781572). The objective was to evaluate safety, pharmacokinetics (PK), efficacy, and pharmacodynamics in phase 1b patients receiving the recommended phase 2 dose (RP2D).

METHODS

- Study design **(Figure 2)**

Figure 2. Study Design



BID=twice daily; BINI=binimetinib; MTD=maximum tolerated dose; PR=partial response; QD=once daily; RIBO=ribociclib; RP2D=recommended phase 2 dose.

METHODS (continued)

- Multicenter, open-label, phase 1b/2 study in patients with locally advanced or metastatic *NRAS*-mutant melanoma
- A 28-day cycle of 200 mg oral RIBO once daily (QD) for 21 days + 45 mg oral BINI twice daily for 28 days was selected as the RP2D.
- RP2D selection was based on activity (unconfirmed response rate 35%), supported by comparable and manageable safety and the Bayesian logistic regression analysis.
- Patients included in the analysis received the RP2D in the phase 1b portion of the study as of April 4, 2017.
- Assessments
  - Safety was assessed by incidence and severity of adverse events (AEs).
  - PK parameters were analyzed using validated bioanalytical methods. Noncompartmental analysis was performed using Phoenix WinNonlin 7.0 (Certara, Princeton, NJ, USA).
  - For assessment of QT intervals, 3 electrocardiograms (ECGs) per patient were obtained predose on day 1 (baseline), and single ECGs were obtained at various time points including 2 and 4 hours postdose on days 1 and 21. The QT interval, corrected using Fridericia's formula (QTcF), was used to estimate the change in QTcF (ΔQTcF) by subtracting the baseline mean value.
  - Tumor assessments were made according to Response Evaluation Criteria in Solid Tumors version 1.1. Kaplan-Meier analysis was used to determine median PFS.
  - Genomic profiling was performed at Foundation Medicine Inc (Cambridge, MA, USA) by next-generation sequencing of archival or screening formalin-fixed paraffin-embedded tumor samples with the FoundationOne® panel. This panel uses hybrid capture and interrogates the full coding region of 315 cancer-related genes and select introns of 28 genes often rearranged in cancer.

RESULTS

- Patients
  - The phase 1b portion of the study enrolled 61 patients in 2 dosing regimens of RIBO + BINI in a 28-day cycle (5 cohorts including 29 total patients) and a 21-day cycle (6 cohorts including 32 total patients). Data presented here are from the 16 patients who received the RP2D in phase 1b (28-day cycle; **Figure 2**).
  - Baseline characteristics are listed in **Table 1**.

Table 1. Baseline Demographics and Characteristics of Patients Receiving the RP2D (n=16)

Characteristic*	
Age, y, median (range)	62 (31–79)
Sex, female	8 (50)
ECOG performance status	
0	10 (63)
1	5 (31)
2	1 (6)
LDH > ULN	
Yes	8 (50)
No	8 (50)
Presence of liver/lung metastases	13 (81)
AJCC stage	
III	2 (13)
IV	14 (88)
Previous antineoplastic therapies	
0 or 1	9 (56)
2 or 3	6 (38)
≥4	1 (6)
Previous immunotherapy†	
Yes	11 (69)
No	1 (6)
Previous ipilimumab†	
Yes	7 (44)
No	5 (31)
Previous anti–PD-1/PD-L1†	
Yes	5 (31)
No	7 (44)

AJCC=American Joint Committee on Cancer; ECOG=Eastern Cooperative Oncology Group; LDH=lactate dehydrogenase; PD-1=programmed death 1; PD-L1=programmed death ligand 1; RP2D=recommended phase 2 dose; ULN=upper limit of normal.
*All data are n (%) unless otherwise noted.
†Not assessed, n=4.

- Median (range) duration of exposure was 5 (0–13) months.

RESULTS (continued)

- AEs are listed in **Table 2**.

Table 2. AEs in Patients Receiving the RP2D (n=16)*

	All Grades, n (%)	Grade 3/4, n (%)
Any AE	16 (100)	15 (94)
Increased creatine phosphokinase	10 (63)	1 (6)
Increased aspartate aminotransferase	8 (50)	4 (25)
Peripheral edema	7 (44)	0 (0)
Dermatitis acneiform	6 (38)	0 (0)
Diarrhea	6 (38)	0 (0)
Fatigue	6 (38)	0 (0)
Hyperphosphatemia	6 (38)	0 (0)
Hypoalbuminemia	6 (38)	1 (6)
Nausea	6 (38)	2 (13)
Rash	6 (38)	3 (19)
Increased alanine aminotransferase	5 (31)	4 (25)
Vomiting	4 (25)	2 (13)
Neutropenia	3 (19)	2 (13)
Hypophosphatemia	2 (13)	2 (13)

AE=adverse event; RP2D=recommended phase 2 dose.
*All-cause AEs (>35% in any treatment group) or grade 3/4 AEs (>12% in any treatment group).

- Observed PK parameters were similar to those previously reported for BINI and RIBO administered as monotherapy. There were no apparent drug-drug interactions **(Table 3)**.[4,5]

Table 3. PK Parameters for Patients Receiving the RP2D*

	RIBO	BINI
	n=15	n=15
Day 1 AUC, h·ng/mL	2180 (66.3)	1290 (46.2)
Day 1 C_{max}, ng/mL	229 (83.8)	349 (59.9)
	n=13	n=13
Steady-state AUC, h·ng/mL	3020 (62.4)	1800 (45.2)
Steady-state C_{max}, ng/mL	225 (79.8)	444 (56.8)
	n=13	n=12
R_{AUC}	1.34 (61.0)	1.57 (21.4)
RC_{max}	0.930 (61.6)	1.48 (36.5)

AUC=area under the curve; BINI=binimetinib; C_{max}=maximum serum concentration; PK=pharmacokinetic; R=calculable accumulation ratio; RIBO=ribociclib; RP2D=recommended phase 2 dose.
*Values are reported as geometric mean (geometric % coefficient of variation). The BINI AUC was AUC_{0-8h}, and the RIBO AUC was AUC_{0-24h}.

- Cardiac electrophysiology:
  - RIBO has been shown to prolong the QTc interval in a concentration-dependent manner, with an estimated change in QTcF from baseline (ΔQTcF) of 22.9 milliseconds (90% CI, 21.6–24.1) at the mean steady-state maximum serum concentration, which occurs 1–4 hours after a dose of 600 mg QD.[6]
  - ΔQTcF values were lower with RIBO 200 mg QD in this study. Mean (90% CI) values postdose on day 1 were 1.2 (−16.5–19.0) milliseconds at 2 hours and 1.5 (−17.3–20.4) milliseconds at 4 hours; values postdose on day 21 were 11.3 (−17.20–39.8) milliseconds at 2 hours and 10.7 (−23.2–44.5) milliseconds at 4 hours.
- Response
  - 4 patients (25%) had a partial response, with time to response ranging from 48–168 days **(Table 4)**.
  - Response duration for the 4 patients with confirmed response were 3.2†, 3.7†, 5.0, and 7.6† months, where † indicates censoring (2 patients for AEs, and 1 patient for clinical progression).

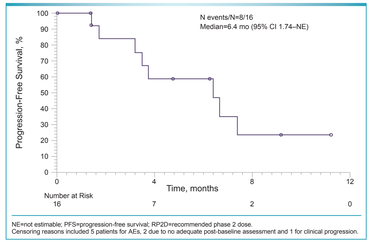
Table 4. Confirmed Response Rates in Patients Receiving the RP2D (n=16)

	n (%)
Complete response	0 (0)
Partial response	4 (25)
Stable disease	7 (44)
Progressive disease	3 (19)
Not evaluable	2 (13)
Disease control rate*	11 (69)

RP2D=recommended phase 2 dose.
*Complete response + partial response + stable disease.

- Median PFS is shown in **Figure 3**.

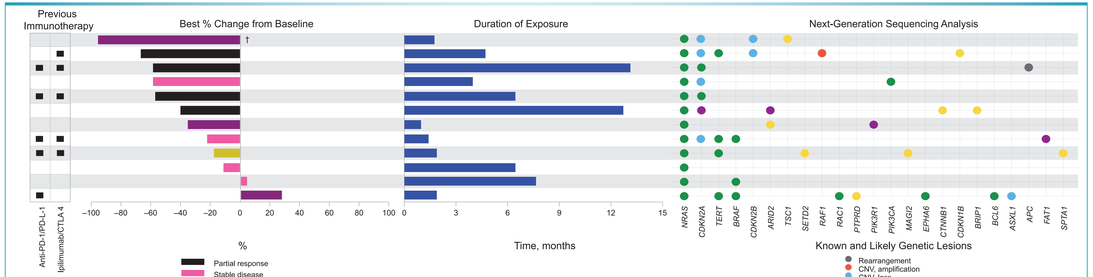
Figure 3. Kaplan-Meier Estimates of PFS in Patients Receiving the RP2D (n=16)



NE=not estimable; PFS=progression-free survival; RP2D=recommended phase 2 dose.
Censoring reasons included 5 patients for AEs, 2 due to no adequate post-baseline assessment and 1 for clinical progression.

- Genomic profiling
  - Genomic profiling data were available from 12 patients (Foundation Medicine panel) with clinical outcomes **(Figure 4)**.
  - Concurrent *CDKN2A* alterations were observed in 7/12 (58%) patients and 4/4 (100%) patients with a partial response. All of the *CDKN2A* alterations were known inactivating mutations.
  - Concurrent promoter mutations in the telomerase (*TERT*) gene were observed in 4/12 (33%) patients. This observation supports recent findings of the high prevalence of *TERT* promoter mutations in melanoma.[7-9]
  - Concurrent *BRAF* non-V600 mutations were observed in 3/12 (25%) patients.

Figure 4. Genetic Landscape of *NRAS*-Mutant Melanoma in Patients Receiving the RP2D (n=12)*



CNV=copy number variant; CTLA4=cytotoxic T-lymphocyte–associated protein 4; PD-1=programmed death 1; PD-L1=programmed death ligand 1; RP2D=recommended phase 2 dose; SV=structural variant.
*Of the n=16 RP2D patients, 14 had postbaseline tumor assessment, and of these, 12 had biomarker data available. Of the 2 who did not have biomarker data, 1 patient had stable disease with a best % change from baseline of −27.1% and the other had stable disease with a best % change from baseline of −8.1%.
†Patient had tumor shrinkage in their original tumors. However, due to new tumors patient was classified as having progressive disease.

CONCLUSIONS

- RIBO + BINI at the selected RP2D exhibited favorable efficacy and a manageable safety profile in patients (n=16) with metastatic *NRAS*-mutant melanoma.
- AEs were generally consistent with those reported with BINI monotherapy in the NEMO study or with RIBO monotherapy.[2,6] Liver test abnormalities were also increased; these have previously been observed with RIBO and BINI treatment.[2,6]
- No drug-drug interactions were observed between RIBO and BINI.
- Genomic profiling analysis of this cohort of patients with *NRAS*-mutant melanoma found that *CDKN2A* and *TERT* mutations were the most frequent additional aberrations, which is consistent with previous reports in melanoma.
- 41 patients have been enrolled in the ongoing phase 2 portion of the study.

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Conflicts of Interest

- Martin Schuler: Honoraria from Alexion, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Lilly, MSD, Novartis, and Roche. Consultant/advisory role for AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, Novartis, and Roche. Research funding received from BMS, Boehringer Ingelheim, Amgen, BMS, GSK, Merck MSD, Novartis, Pierre-Fabre, and Roche. Hospital Essen. No other relationships to disclose.
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- Viviana Bozón: Employment during the past 2 years at Array BioPharma and Takeda. Stock or other ownership, Array BioPharma and Takeda. Patents, royalties/other intellectual property: Takeda.
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Available at: www.arraybiopharma.com

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