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A first-in-human phase I study to evaluate the MEK1/2 inhibitor, cobimetinib, administered daily in patients with advanced solid tumors

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Summary

Objective—Cobimetinib, a MEK1/2 inhibitor, was administered to patients with advanced solid tumors to assess safety, pharmacokinetics, pharmacodynamics, and anti-tumor activity.

Methods—For dose-escalation, a 3 + 3 design was used. Oral cobimetinib was administered once daily on a 21-day on/7-day off (21/7) or a 14-day on/14-day off (14/14) schedule. Serial plasma

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Conflict of interest Lee S. Rosen, Patricia LoRusso, and Jonathan W. Goldman have received research funding from Genentech, Inc. Salim Yazji is a prior employee and current shareholder of Exelixis and is a current employee of Baxalta. Angela Shen is a prior employee of Exelixis and a current employee of Arvinas. Stuart Johnston is a shareholder and prior employee of Exelixis and a current employee of Nektar Therapeutics. Hsin-Ju Hsieh and Iris T. Chan are employees and shareholders of Roche. Branimir I. Sikic has received research funding from Exelixis, Genentech, Inc., Novartis, and Sanofi, and is a consultant for Novartis and Threshold Pharmaceuticals. Wen Wee Ma, Amy Weise, A. Dimitrios Colevas, and Alex Adjei declare that they have no potential conflicts of interest.

Research involving human participants All procedures performed involving human participants in the protocol were approved by Institutional Review Boards prior to patient recruitment and conducted in accordance International Conference on Harmonization E6 Guidelines for Good Clinical Practice.

Informed consent Informed consent was obtained from all individual participants included in the study.

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samples were collected for pharmacokinetic (PK) analysis on Day 1 and at steady state. In expansion stages, patients with RAS or RAF mutant tumors were treated at the maximum tolerated dose (MTD) of the 21/7 or 14/14 schedule.

Results—Ninety-seven patients received cobimetinib. In the 21/7 dose escalation, 36 patients enrolled in 8 cohorts (0.05 mg/kg–80 mg). Dose-limiting toxicities (DLTs) were Grade 4 hepatic encephalopathy, Grade 3 diarrhea, and Grade 3 rash. In the 14/14 dose escalation, 20 patients enrolled in 4 cohorts (60–125 mg). DLTs were Grade 3 rash and Grade 3 blurred vision associated with presence of reversible subretinal fluid. The MTD was 60 mg on 21/7 schedule and 100 mg on 14/14 schedule. Cobimetinib PK showed dose-proportional increases in exposure. The most frequent adverse events attributed to cobimetinib were diarrhea, rash, fatigue, edema, nausea, and vomiting. In patients treated at the 60-mg (21/7) or 100-mg (14/14) dose, one unconfirmed complete response and 6 confirmed partial responses were observed. All responses occurred in melanoma patients; 6 harbored the $BRAF^{V600E}$ mutation.

Conclusions—Cobimetinib is generally well tolerated and durable responses were observed in $BRAF^{V600E}$ mutant melanoma patients. Evaluation of cobimetinib in combination with other therapies is ongoing.

Keywords

Cobimetinib; Phase I; MEK inhibitor; BRAF; Melanoma

Introduction

The mitogen-activated protein kinase (MAPK) pathway, or RAS/RAF/MEK/ERK cascade, is a cell signaling pathway that is dysregulated in a variety of tumor types. Signal transduction via this pathway plays a major role in mediating cell growth, differentiation, and survival. In tumor cells, mutations of key upstream pathway components lead to aberrant signaling or constitutive pathway activation. Oncogenic activating mutations of KRAS and BRAF have been identified in approximately 20 % of cancers [1–6]. The role of these activating mutations in tumorigenesis has resulted in the development of antitumor agents that target key components of the MAPK pathway [7, 8].

The protein kinase MEK is a downstream effector and central component of the MAPK pathway. Inhibition of MEK is a strategy in the development of oncology therapeutics to control the growth of tumors that are dependent on aberrant MAPK pathway signaling [9–13], which leads to uncontrolled proliferation, invasion, metastasis, angiogenesis, and diminished apoptosis in tumor cells. MEK inhibitors have shown clinical activity as single agents in BRAF mutant and NRAS mutant tumors [14–16]. The MEK inhibitor, selumetinib, has shown single-agent clinical activity in serous carcinoma of ovary and peritoneum, biliary cancer, and thyroid cancer [17–19]. In addition, another MEK inhibitor, trametinib, is approved as a single agent for treatment of $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation-positive unresectable or metastatic melanoma.

Cobimetinib is a potent, selective, allosteric, orally administered MEK1/2 inhibitor that inhibits the phosphorylation of ERK1/2 in cell lines harboring KRAS or BRAF mutations

and has demonstrated dose-dependent tumor growth inhibition in colorectal carcinoma (CRC), melanoma, breast carcinoma, and lung carcinoma human xenograft tumor models [20–22].

The primary objectives of this study were to evaluate the safety and tolerability of cobimetinib administered orally in patients with advanced solid tumors and to determine the maximum tolerated dose (MTD) of cobimetinib when administered orally once daily on a 21-day on/7-day off (21/7) or a 14-day on/14-day off (14/14) dosing schedule.

Materials and methods

Patients

Eligible patients were age 18 years or older with histologically confirmed metastatic or unresectable solid tumors for which standard curative or palliative measures did not exist or were no longer effective. Key inclusion criteria were evaluable or measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, an Eastern Cooperative Oncology Group (ECOG) performance status <2 (Stage I) or performance status ≤2 (Stages IA, II, IIA), and adequate organ and bone marrow function. In addition, patients enrolled in the dose-expansion cohorts were also required to have RAS- or RAF-mutant tumors and fluorodeoxyglucose-positron emission tomography (FDGPET)-avid disease.

Study design

A Phase Ia, open label, dose-escalation study with a 3 + 3 design was conducted at 4 clinical sites in the United States (, ClinicalTrials.gov). Two dose-escalation stages were tested. In the first dose-escalation cohort (Stage I), patients were treated once daily with oral cobimetinib on Days 1–21 of a 28-day cycle (21/7) at the following dose levels: 0.05 mg/kg, 0.10 mg/kg, and 0.20 mg/kg in liquid dosage form and 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg in capsule formulation. After the MTD on the 21/7 schedule was identified, a second dose-escalation cohort was initiated (Stage IA), treating patients once daily with oral cobimetinib on Days 1–14 of a 28-day cycle (14/14) to evaluate if a dosing holiday of more than 7 days would enable longer-term dosing or a higher MTD (dose levels were 60 mg, 80 mg, 100 mg, and 125 mg in capsule formulation). Decisions to dose escalate were determined by the sponsor and study investigators, based upon all safety and pharmacokinetic (PK) data available after the last patient in a given cohort completed Cycle 1.

During the dose-escalation stages, if a patient discontinued from the study prior to completing at least 75 % of the doses in the first 28-day cycle for reasons other than safety (e.g., withdrawal of consent, noncompliance), the patient was replaced. Patients who were replaced were not considered in dose-escalation decisions.

The dose-expansion stages (Stages II and IIA) further evaluated the safety, pharmacodynamic effects, and anti-tumor activity of cobimetinib at the MTDs of their respective dose-escalation stages in patients with FDG-PET-avid tumors and harboring a

BRAF, NRAS, or KRAS mutation. Study treatment continued until disease progression, unacceptable toxicity, or any other discontinuation criterion was met.

Study assessments

Safety—Physical examination, vital signs, electrocardiogram (ECG), clinical laboratory tests (hematology, serum chemistry, and urinalysis), and ECOG performance status were assessed at screening, during study treatment, and at the end of study visit. To monitor eye disorders reported during the study, the protocol was amended in February 2010 to include ophthalmologic examinations. The examinations were performed and interpreted by an ophthalmologist and included visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (SD-OCT).

Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0. The MTD of cobimetinib was defined as the highest dose level below the maximum administered dose (MAD) in which one or fewer of six patients experienced a dose-limiting toxicity (DLT), or the dose level at which no increase in plasma exposure was observed in two successive cohorts. A DLT was defined as a treatment-related adverse event occurring during Cycle 1, Days 1–28, and included Grade 3/4 nausea, vomiting and/or diarrhea despite maximal medical management, Grade 4 thrombocytopenia, Grade 4 neutropenia of $\geq$4 days duration, Grade 4 febrile neutropenia, or any AE of potential clinical significance.

For patients who experienced a DLT, study drug was held until the toxicity resolved; if there was a laboratory abnormality, study drug was held until abnormal laboratory values returned to within 10 % of the baseline value. A toxicity-related dose delay of more than 21 days required that the patient be withdrawn from study.

Pharmacokinetic analysis

Serial plasma samples for cobimetinib PK characterization were collected following the first dose (Day 1) and last dose (Day 21 or Day 14, respectively) in Cycle 1. Cobimetinib was quantified in plasma using a validated liquid chromatography-tandem mass spectrometry method (Advion Bioservices, Inc., Ithaca, NY). Plasma concentration-time data were analyzed via noncompartmental analysis methods using WinNonlin (version 5.2.1, Pharsight Corporation, Mountain View, CA). The following PK parameters were calculated: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve (AUC), and terminal elimination half-life ($t_{1/2}$) For Cycle 2 and higher, a PK blood sample was collected pre-dose on the first day of each subsequent cycle.

FDG-PET

In the dose-expansion stages, FDG uptake, as measured by PET, was evaluated as a pharmacodynamic marker and serial FDG-PET scans were collected at baseline, Cycle 1 Days 10–14 (steady state), and Cycle 1 Days 26–28 (trough) according to a standardized imaging protocol.

Scans were centrally collected and PETscan covariates were monitored throughout the study to ensure consistent data collection. The effect of cobimetinib on FDG uptake was assessed by an independent central reader based on the maximum standardized uptake value (SUV_{max}) of up to five tumor regions of interest [23, 24]. For each target lesion, the percent change from baseline (%CFB) in SUV_{max} was calculated and averaged over all target lesions to generate a mean percent change in SUV_{max} ($m\Delta SUV_{max}$). A partial metabolic response (mPR) was defined as a decrease of >20 % in $m\Delta SUV_{max}$ and no new lesions.

Tumor mutation analysis

Archival tissue samples were collected from patients in dose-escalation and dose-expansion cohorts to confirm or determine $BRAF^{V600}$, $NRAS^{Q61}$, or $KRAS^{G12/13}$ mutation status.

The mutation status of RAS, RAF, and PIK3CA genes in the archival or baseline samples of patients was detected using mutation-specific PCR at Esoterix, Inc. (Austin, TX) and MUT-MAP microfluidic chip-based multiplex PCR assays [25] at Genentech, Inc. (South San Francisco, CA) from genomic DNA isolated from formalin-fixed, paraffin-embedded samples.

Clinical activity

Tumor response was assessed using RECIST criteria [26] for all patients with measurable lesions using computerized tomography (CT) scan at screening and approximately every 8 weeks. Confirmation of complete response (CR) or partial response (PR) was obtained ≥4 weeks after the first documented response.

Statistical analysis

This report includes results based on the data cutoff of May 25, 2012. The analysis population consisted of all patients who received at least one dose of study drug. Descriptive summaries, such as means, medians, and proportions, are provided for demographics, disease characteristics, and safety data. The response was summarized using frequency counts and percentages. FDG-PET responses were summarized using frequency counts and percentages and were also tabulated against the RECIST responses. The median time-to-event outcome was estimated using the Kaplan-Meier method for the following events: onset of first occurrence of rash, diarrhea, and central serous retinopathy.

Results

Patients and exposure

Study enrollment occurred from May 2007 to November 2010. A total of 97 patients received cobimetinib. Patients with multiple solid tumor types were enrolled. The most common tumor types were CRC and melanoma (Table 1). We confirmed that 28 of 41 CRC patients harbored a KRAS mutation and that 6 melanoma patients had a $BRAF^{V600E}$ mutation. Patients had a median of 4 (range 0–13) prior systemic therapies. None of the patients enrolled received prior treatment with a MEK or BRAF inhibitor.

Patients completed a median of two cycles (range: 1–49) and the median time on treatment was 48 days (range: 1–1345). Ninety-seven patients received at least one dose of cobimetinib (Supplementary Fig. 1). Fifty-six patients were treated in the two dose-escalation stages. In dose escalation on the 21/7 dosing schedule, 36 patients received cobimetinib (Stage I). In dose escalation on the 14/14 dosing schedule, 20 patients were treated (Stage IA). Forty-one patients were treated in the dose-expansion stages; out of 21 patients enrolled, 20 received 60 mg cobimetinib on the 21/7 dosing schedule (Stage II) and out of 22 patients enrolled, 21 received 100 mg cobimetinib on the 14/14 dosing schedule (Stage IIA).

Dose-limiting toxicities

Six patients experienced DLTs, four on the 21/7 dosing schedule and two on the 14/14 dosing schedule (Supplementary Table 1). On the 21/7 dosing schedule, at the 40-mg dose level, a 71-year-old patient with metastatic duodenal adenocarcinoma to the liver and a prior history of jaundice predating enrollment experienced Grade 4 hepatic encephalopathy and Grade 3 elevated ammonia, which resolved following lactulose therapy, routine supportive care, and discontinuation of study drug. At the 60-mg dose level, one of six patients experienced Grade 3 rash that improved with skin toxicity management, drug holiday, and dose reduction. At the 80-mg dose level, there were two DLTs—one patient experienced Grade 3 diarrhea despite treatment with anti-diarrheal medications, and one patient experienced a Grade 3 rash. On the 14/14 dosing schedule, at the 125-mg dose level, the two DLTs were Grade 3 rash and Grade 3 blurred vision associated with central serous retinopathy, a reversible, subretinal fluid accumulation. All DLTs were reversible with supportive care, study drug interruption, and/or dose reduction.

The cobimetinib MTD on the 21/7 dosing schedule was 60 mg once daily and the MTD on the 14/14 dosing schedule was 100 mg once daily.

Common adverse events

Eighty-seven (90 %) patients experienced at least one treatment-related AE. Overall, the most frequent AEs (occurring in ≥20 % patients) attributed to cobimetinib by the investigator were diarrhea, rash, fatigue, edema (including peripheral, periorbital, and facial), nausea, and vomiting (Table 2). Of those AEs reported as treatment-related, 72 % were Grade 1–2 (data not shown). Diarrhea and rash were the most frequently reported treatment-related Grade 3 or higher AEs, which were reversible with study drug interruption, dose reduction, or supportive care.

Separated by cohort, in the 21/7 dosing schedule the most frequent AEs (occurring in ≥20 % patients) attributed to cobimetinib by the investigator were diarrhea, rash, fatigue, and edema. In the 14/14 dosing schedule, the most frequent AEs (occurring in ≥20 % patients) were the same as those reported on the 21/7 dosing schedule but also included nausea, vomiting, eye disorders, and abdominal pain.

In patients that received the MTD during dose-escalation or dose-expansion stages on the 21/7 or 14/14 dose schedule, the incidence of rash and edema were similar, 67 % and 34 %, respectively. In general, the incidence of frequently reported drug-related AEs was higher on

the 14/14 schedule (MTD 100-mg dose) when compared to the 21/7 schedule (MTD 60-mg dose).

Skin adverse events

Skin rash, especially acneiform rash, is an adverse event observed with cobimetinib and other MEK inhibitors [15, 27–30]. In this study, the incidence of treatment-related rash was 54 %, of which the large majority (94 %) was Grade 1 or 2 in severity. The median onset of rash was 12 days (range 6–245) with a median rash duration of 20 days (range 1–332). Skin adverse events were managed with topical agents, study drug interruption, or dose reduction. A total of four (4 %) patients had dose reductions due to treatment-related rash: two at 100 mg (14/14, MTD) and one each at 80 mg (21/7) and 125 mg (14/14).

Ocular adverse events

Six patients experienced Grade ≥2 visual disturbances, including three with blurred vision, one with "eye disorder" (not otherwise specified) and two with central serous retino- pathy (CSR), a reversible fluid accumulation between layers of the retina. Two patients at 125 mg (14/14) and one patient at 100 mg (14/14) experienced CSR, which was confirmed by ophthalmology examination. Of the three patients with documented CSR, all cases resolved with study drug interruption and dose reduction ($n = 2$) or study drug discontinuation ($n = 1$).

Creatine phosphokinase, skeletal muscle isozyme (CPK-MM) elevation

One patient at the 100-mg dose level (14/14 schedule) had Grade 3 CPK-MM elevation. The patient was asymptomatic and without clinical or laboratory evidence for myocardial injury or rhabdomyolysis. The patient continued on study at the same dose and schedule without sequellae.

Adverse events leading to dose reduction/interruption, or discontinuation

Twenty-four (25 %) patients experienced treatment-related AEs that led to dose reductions or interruption. Six of 24 patients had both dose interruptions followed by dose reductions due to study-related AEs. Eleven patients experienced treatment-related AEs leading to dose reduction. Rash ($n = 4$) was the most common cause of dose reduction. Diarrhea ($n = 5$) was the most common cause of dose interruptions. On the 21/7 dosing schedule, all dose reductions and dose interruptions due to related AEs occurred at dose levels ≥40 mg.

Six patients experienced treatment-related AEs that led to permanent discontinuation of study drug. These AEs were hepatic encephalopathy, diarrhea, edema, atrial fibrillation, blurred vision, and cardiorespiratory arrest.

Serious adverse events (SAE) and deaths

Overall, 41 (42 %) patients experienced at least one SAE, regardless of causality, including eleven (11 %) patients with at least one SAE attributed to the study drug. The most frequently reported SAEs, regardless of causality, were gastrointestinal disorders, occurring in 14 % patients. The most commonly reported SAEs related to the study drug were diarrhea ($n = 2$), fatigue ($n = 2$), and cardiac disorders ($n = 2$). Two patients experienced

cardiovascular SAEs; one patient had Grade 3 atrial fibrillation (60 mg, 21/7) and another patient had Grade 5 cardiorespiratory arrest (125 mg, 14/14; detailed below) attributed to the study drug.

Two deaths were attributed to the study drug by the investigator. A patient with breast cancer and a history of pleural effusion requiring drainage experienced Grade 5 cardiorespiratory arrest 12 days after the start of study drug treatment (125 mg, 14/14). A patient with melanoma that had metastasis to the bone and lung was hospitalized for respiratory distress and altered mental status after 31 days on study drug; eight days after hospitalization, the patient experienced Grade 5 fatal respiratory distress (60 mg, 21/7). For both deaths, the other possible contributing factors included the patients' underlying malignancy. All of the other 12 deaths reported while on study were due to disease progression.

Pharmacokinetics

Cobimetinib PK was characterized following oral administration after single and multiple dosing in all cohorts. As shown in Supplementary Fig. 2, cobimetinib is absorbed with a median t_{max} of one to three hours. Exposure increased with increasing doses and was dose-proportional from 0.05 mg/kg (approximately 3.5 mg for a 70-kg adult) to 100 mg (clinically relevant dose range). The cobimetinib mean terminal half-life across all doses following administration was 49 h (range: 23 to 80 h). Following daily oral administration, the cobimetinib accumulation ratio was approximately two-fold from 24 h to steady state, which is consistent with its half-life and the dosing interval of 24 h. Based on the half-life of cobimetinib, steady-state was expected to be achieved in approximately 10 days. Table 3 provides a summary of cobimetinib PK following administration at the MTD on the two schedules.

FDG-PET

A total of 30 patients in Stages II and IIA had baseline, Day 14, and Day 28 measures of SUV_{max}. At the Cycle 1 Day 10–14 PET scan, metabolic response rates (on drug) were 47 % (8 of 17) at the 60-mg (21/7) MTD, and 61 % (11 of 18) at the 100-mg (14/14) MTD. At the Cycle 1 Day 26–28 (off-drug) PET scan, the metabolic response rates were comparable between the two dosing cohorts, 31 % (5 of 16; 60 mg, 21/7) and 33 % (5 of 15; 100 mg, 14/14) (Fig. 1).

Anti-tumor activity

Of 74 patients with measurable disease, six confirmed partial responses (cPR) and one unconfirmed complete response (uCR) that was a cPR, were observed. All responses were in melanoma patients treated at the 60-mg (21/7) or 100-mg (14/14) MTDs; 50 % of the 14 melanoma patients enrolled were responders (Fig. 2). Of these seven responders, six were patients positive for the $BRAF^{V600E}$ mutation. These responses were durable with a median time on cobimetinib of 280 days (range 42–721+ days). In addition, prolonged stable disease (SD) of five months or greater was observed in five patients with the following tumor types (Fig. 2): carcinoid (47+ months), non-small cell lung cancer (NSCLC; 13 months), adenoid cystic carcinoma (7 months), esophageal (6 months), and sarcoma (5 months). Of the 28 patients with KRAS-mutant colorectal cancer, there were no responses.

An example of a confirmed partial response observed using CT and PET imaging in a patient with $BRAF^{V600E}$ mutant melanoma who received 60-mg cobimetinib (21/7) is presented in Fig. 3.

Discussion

In this study, cobimetinib MTDs were established for two dosing schedules. The MTD on the 21/7 dosing schedule was 60 mg. With a one-week longer dosing holiday (14/14 schedule), a higher MTD of 100 mg was achieved. Establishing two MTDs for cobimetinib may allow greater flexibility in determining the appropriate dose and schedule for specific cobimetinib combinations with other anti-cancer agents. The common AEs (occurring in ≥20 % patients) observed on both dosing schedules were diarrhea, rash, fatigue, edema, vomiting, and nausea. These common AEs were manageable and similar to those observed with other MEK inhibitors [15, 27–30].

Central serous retinopathy has been observed with cobimetinib and other MEK inhibitors and is considered a class effect with this class of drugs [15, 27–30]. It is characterized by reversible, bilateral central vision abnormalities (i.e., blurred vision; seeing halos or spots) and associated with reversible subretinal fluid found on SD-OCT examination. Three (5 %) of 56 patients treated at either MTD had Grade ≥2 CSR. All visual adverse events were reversible and resolved within one week of stopping study drug. There were no reports of retinal vein occlusion in this study. For patients receiving cobimetinib, it is recommended that ophthalmological evaluations be performed at regular intervals and at any time the patient reports a change in their vision.

Asymptomatic, reversible skeletal muscle isozyme elevations have been observed with cobimetinib and other MEK inhibitors [15, 27, 29, 30]. There is limited information as to the frequency of CPK-MM elevations in patients receiving cobimetinib monotherapy, because CPK-MM testing was not a part of the routine safety laboratory assessments at the time this study was conducted. One patient at the 100-mg dose level (14/14 schedule) had CPK-MM elevations. CPK elevations have been observed in the clinical trials of cobimetinib combined with vemurafenib [31, 32].

Decreases in cardiac function have been reported with other MEK inhibitors [27, 33–35]. Monitoring for left ventricular ejection fraction (LVEF) was not part of routine assessments for drugs in this class at the time the study was conducted. No events of symptomatic decreases in LVEF were reported in this study.

Patients with RAS or RAF mutant tumors treated with cobimetinib at the 60-mg 21/7 and 100-mg 14/14 MTDs showed evidence of pharmacodynamic responses by FDGPET. FDG-PET partial metabolic responses were observed in many patients with KRAS-mutant colorectal cancer, but were generally not sustained during the dosing holiday and did not correlate with any RECIST radiographic responses (Fig. 2). If, in larger populations, it remains true that the response to drug seen on FDG-PET is different when tested while on drug as opposed to off, clinicians might consider carefully the timing of scans to assess maximal drug benefit. In contrast to colorectal cancer patients, FDG-PET partial metabolic

responses in $BRAF^{V600E}$ mutant melanoma patients were deeper, sustained during the 7- or 14-day dosing holiday at trough cobimetinib levels, and also correlated with RECIST radiographic responses.

Durable objective responses were observed in melanoma patients when cobimetinib was administered at the MTD on either the 21/7 or 14/14 dosing schedule. Of the 14 melanoma patients, there were seven objective responses: three PRs were observed at 60 mg on the 21/7 dosing schedule, and three PRs and one uCR (which was a cPR) were observed at the 100 mg 14/14 dosing schedule. Of the seven objective responses, six were patients positive for the $BRAF^{V600E}$ mutation. The mutation status of one patient with an objective response was unknown. As observed with other MEK inhibitors, there were no responses observed in patients with the KRAS-mutant colorectal cancer [29, 36].

In this Phase Ia study, cobimetinib was generally well-tolerated in patients with advanced solid tumors with MTDs of 60 mg (21/7) once daily and 100 mg (14/14) once daily. The AEs attributed to cobimetinib observed were manageable, reversible, and similar to those of other MEK inhibitors, and will be further characterized in currently ongoing studies. Because cobimetinib anti-tumor activity shows encouraging signs in $BRAF^{V600E}$ mutant melanoma patients, combination therapy with cobimetinib has potential to improve efficacy of other therapies and delay the acquired resistance that is associated with MEK pathway activation. Cobimetinib was recently approved for use in combination with vemurafenib for the treatment of adult patients with unresectable or meta-static melanoma with a $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation and is also currently being evaluated in combination with other targeted agents, immunotherapy, and standard chemotherapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Davies H, Bignell GR, Cox C, et al. (2002) Mutations of the BRAF gene in human cancer. Nature 417:949–954. doi:10.1111/ced.12015 [PubMed: 12068308]
2. Allen LF, Sebolt-Leopold J, Meyer MB (2003) CI-1040 (PD184352), a targeted signal transduction inhibitor of MEK (MAPKK). Semin Oncol 30(5 Suppl 16):105–116 [PubMed: 14613031]
3. Malumbres M, Barbacid M (2003) RAS oncogenes: the first 30 years. Nat Rev Cancer 3:459–65. Erratum in: Nat Rev Cancer 3:708 [PubMed: 12778136]
4. Bamford S, Dawson E, Forbes S, et al. (2004) The COSMIC (Catalogue of Somatic Mutations in Cancer) database and website. Br J Cancer 91:355–358 [PubMed: 15188009]
5. Karnoub A, Weinberg RA (2008) Ras oncogenes: split personalities. Nat Rev Mol Cell Biol 9:517–531. doi:10.1038/nrm2438 [PubMed: 18568040]

6. Hoeflich KP, Merchant M, Orr C, et al. (2012) Intermittent administration of MEK inhibitor GDC-0973 plus PI3K inhibitor GDC-0941 triggers robust apoptosis and tumor growth inhibition. Cancer Res 72:210–219. doi:10.1158/0008-5472.CAN-11-1515 [PubMed: 22084396]
7. McCubrey JA, Steelman LS, Chappell WH, et al. (2012) Advances in targeting signal transduction pathways. Oncotarget 3:1505–1521 [PubMed: 23455493]
8. Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D (2013) MEK and the inhibitors: from bench to bedside. J Hematol Oncol 6:27. doi:10.1186/1756-8722-6-27 [PubMed: 23587417]
9. Wellbrock C, Karasarides M, Marais R (2004) The RAF proteins take centre stage. Nat Rev Mol Cell Biol 5:875–885 [PubMed: 15520807]
10. Solit DB, Garraway LA, Pratilas CA, et al. (2006) BRAF mutation predicts sensitivity to MEK inhibition. Nature 439:358–362 [PubMed: 16273091]
11. Roberts PJ, Der CJ (2007) Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 26:3291–3310 [PubMed: 17496923]
12. Hoeflich KP, O'Brien C, Boyd Z, et al. (2009) In vivo antitumor activity of MEK and phosphatidylinositol 3-kinase inhibitors in basal-like breast cancer models. Clin Cancer Res 15:4649–4664. doi:10.1158/1078-0432.CCR-09-0317 [PubMed: 19567590]
13. Hatzivassiliou G, Haling JR, Chen H, et al. (2013) Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. Nature 501:232–236. doi:10.1038/nature12441 [PubMed: 23934108]
14. Kim KB, Kefford R, Pavlick AC, et al. (2013) Phase II study of the MEK1/MEK2 inhibitor Trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol 31:482–489. doi:10.1200/JCO.2012.43.5966 [PubMed: 23248257]
15. Falchook GS, Lewis KD, Infante JR, et al. (2012) Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol 13:782–789. doi:10.1016/S1470-2045(12)70269-3 [PubMed: 22805292]
16. Ascierto PA, Schadendorf D, Berking C, et al. (2013) MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol 14:249–256. doi:10.1016/S1470-2045(13)70024-X [PubMed: 23414587]
17. Farley J, Brady WE, Vathipadiekal V, et al. (2013) Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 14:134–140. doi:10.1016/S1470-2045(12)70572-7 [PubMed: 23261356]
18. Bekaii-Saab T, Phelps MA, Li X, et al. (2011) Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. J Clin Oncol 29:2357–2363. doi:10.1200/JCO.2010.33.9473 [PubMed: 21519026]
19. Ho AL, Grewal RK, Leboeuf R, et al. (2013) Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med 368: 623–632. doi:10.1056/NEJMoa1209288 [PubMed: 23406027]
20. Rosen L, LoRusso P, Ma WW et al. (2011) A first-in-human Phase 1 study to evaluate the MEK1/2 inhibitor GDC-0973 administered daily in patients with advanced solid tumors [abstract]. In: Proceedings of the 102nd Annual Meeting of the American Association for Cancer Research; 2011 Apr 2–6; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 71(8 Suppl):Abstract nr 4716. doi:10.1158/1538-7445.AM2011-4716
21. Wong H, Choo EF, Alicke B, et al. (2012) Antitumor activity of target and cytotoxic agents in murine subcutaneous tumor models correlates with clinical response. Clin Cancer Res 18:3846–3855. doi:10.1158/1078-0432.CCR-12-0738 [PubMed: 22648270]
22. Choo EF, Belvin M, Boggs J, et al. (2012) Preclinical disposition of gdc-0973 and prospective and retrospective analysis of human dose and efficacy predictions. Drug Metab Dispos 40:919–927. doi:10.1124/dmd.111.043778 [PubMed: 22315332]
23. Young H, Baum R, Cremerius U et al.; European Organization for Research and Treatment of cancer (EORTC) PET study group (1999) measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. Eur J Cancer 35:1773–82 [PubMed: 10673991]

24. Binns DS, Pirzkall A, Yu W et al.; OSI3926g Study Team (2011) Compliance with PET acquisition protocols for therapeutic monitoring of erlotinib therapy in an international trial for patients with non-small cell lung cancer. Eur J Nucl Med Mol Imaging 38:642. doi:10.1007/s00259-010-1665-0 [PubMed: 21207024]
25. Patel R, Tsan A, Tam R, et al. (2012) Mutation scanning using MUT-MAP, a high-throughput, microfluidic chip-based, multi-analyte panel. PLoS One 7:e51153. doi:10.1371/journal. pone. 0051153 [PubMed: 23284662]
26. Therasse P, Arbuck SG, Eisenhauer EA et al.; European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–16 [PubMed: 10655437]
27. LoRusso PM, Adjei AA, Varterasian M, et al. (2005) Phase I and pharmacodynamic study of the oral MEK inhibitor CI-1040 in patients with advanced malignancies. J Clin Oncol 23:5281–5293 [PubMed: 16009947]
28. Martinez-Garcia M, Banerji U, Albanell J, et al. (2012) First-inhuman, phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of RO5126766, a first-in-class dual MEK/RAF inhibitor in patients with solid tumors. Clin Cancer Res 18:4806–4819 [PubMed: 22761467]
29. Infante JR, Fecher LA, Falchook GS, et al. (2012) Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 13:773–781. doi:10.1016/S1470-2045(12)70270-X [PubMed: 22805291]
30. Honda K, Yamamoto N, Nokihara H, et al. (2013) Phase I and pharmacokinetic/pharmacodynamic study of RO5126766, a first-in-class dual Raf/MEK inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 72:577–584. doi:10.1007/s00280-013-2228-4 [PubMed: 23860959]
31. Ribas A, Gonzalez R, Pavlick A, et al. (2014) Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. Lancet Oncol 15:954–965. doi:10.1016/S1470-2045(14)70301-8 [PubMed: 25037139]
32. Larkin J, Ascierto PA, Dréno B, et al. (2014) Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 371:1867–1876. doi:10.1056/NEJMoa1408868 [PubMed: 25265494]
33. Flaherty KT, Robert C, Hersey P et al.; METRIC Study Group (2012) Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 367:107–14. doi:10.1056/NEJMoa1203421 [PubMed: 22663011]
34. Catalanotti F, Solit DB, Pulitzer MP, et al. (2013) Phase II trial of MEK inhibitor selumetinib (AZD6244, ARRY-142886) in patients with BRAFV600E/K-mutated melanoma. Clin Cancer Res 19: 2257–2264. doi:10.1158/1078-0432.CCR-12-3476 [PubMed: 23444215]
35. Weekes CD, Von Hoff DD, Adjei AA, et al. (2013) Multicenter phase I trial of the mitogen-activated protein kinase 1/2 inhibitor BAY 86–9766 in patients with advanced cancer. Clin Cancer Res 19:1232–1243. doi:10.1158/1078-0432.CCR-12-3529 [PubMed: 23434733]
36. Bennouna J, Lang I, Valladares-Ayerbes M, et al. (2011) A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens. Investig New Drugs 29: 1021–1028. doi:10.1007/s10637-010-9392-8 [PubMed: 20127139]

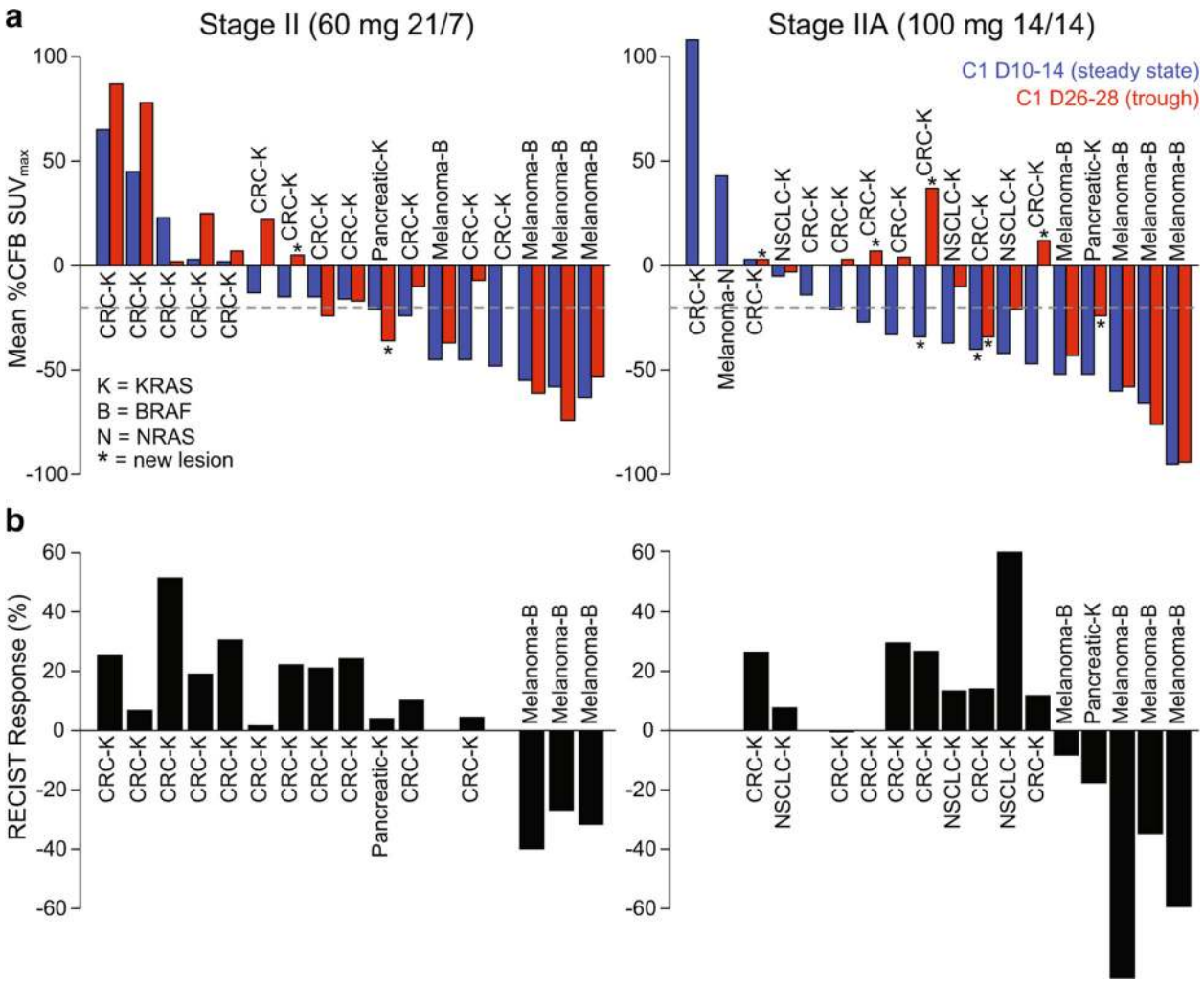

Fig. 1.

Pharmacodynamic response by FDG-PET (**a**) and corresponding cobimetinib anti-tumor responses (**b**) in dose-expansion patients with a post-baseline tumor assessment. *Dashed lines* in (**a**) indicate a 20 % decrease of SUV_{max}. Eight patients (4 in Stage II and 4 in Stage IIA) were not evaluable for FDG-PET response. C cycle, *D* day

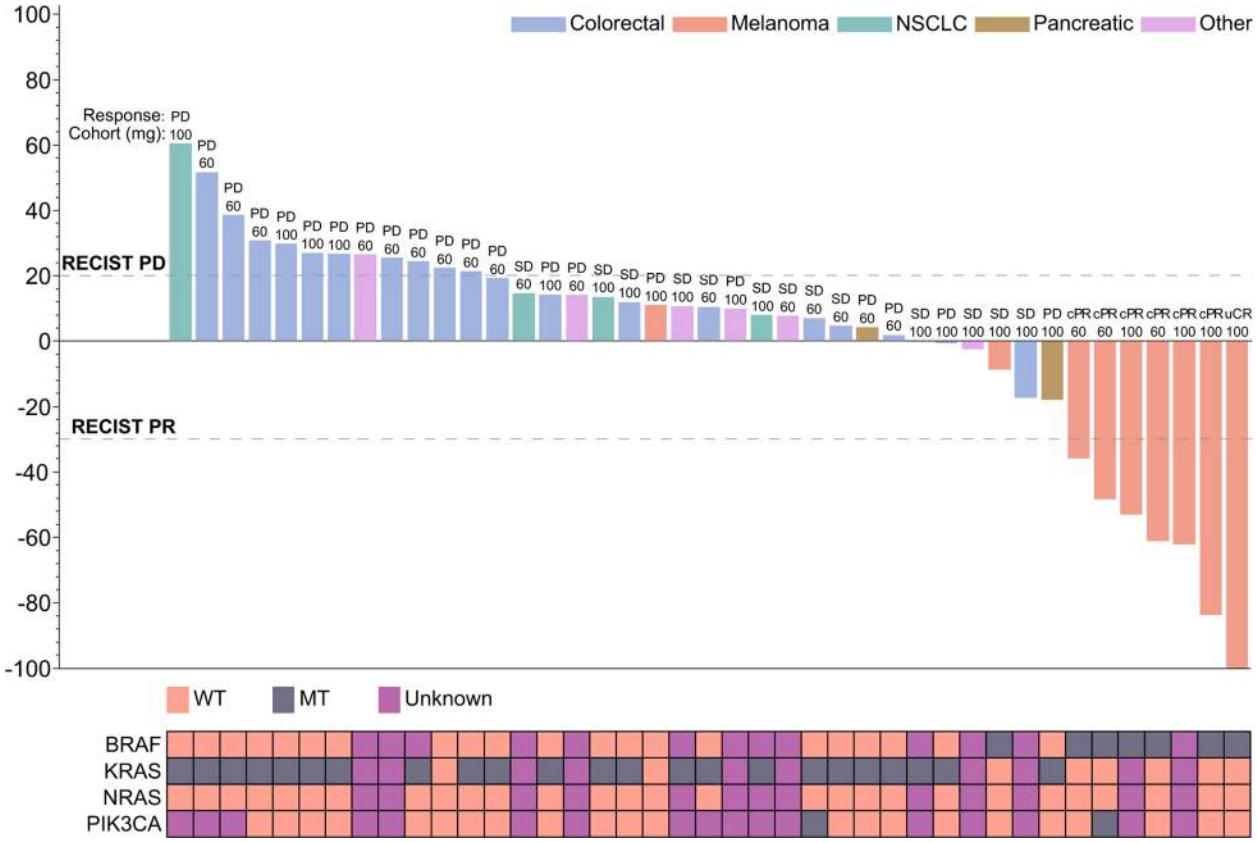

Fig. 2.

Cobimetinib best anti-tumor responses, as measured by RECIST criteria in patients treated at the MTDs. Dashed lines indicate the RECIST progressive disease (PD) cutoff of 20 % and the RECIST partial response (PR) cutoff of - 30 %, respectively. Individual patient mutation profiles are provided underneath the graph. *cPR* confirmed partial response, *MT* mutant, *SD* stable disease, *uCR* unconfirmed complete response, *WT* wild type

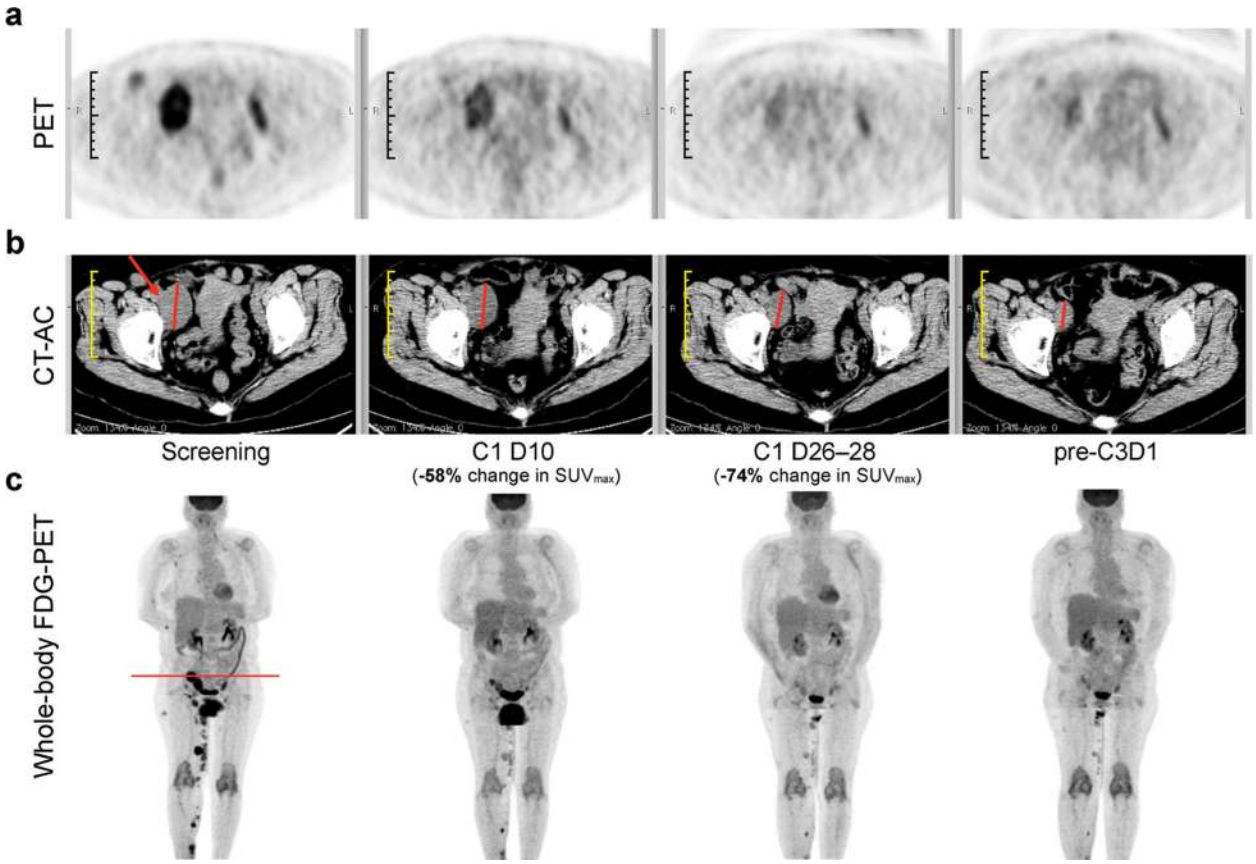

Fig. 3.

Cobimetinib anti-tumor activity in $BRAF^{V600E}$ mutant melanoma, imaged using (**a**) PET, (**b**) CT-AC, and (**c**) FDG-PET. (**a**), (**b**) *Black* and *yellow* scale bars, 1 cm/tick. (**b**) *Red arrow* indicates the tumor; *red lines* indicate the diameter of the tumor. (**c**) *Red line* shows the location of the scanned cross-section. *C* cycle, *CT-AC* computed tomography-attenuation correction, *D* day

Table 1

Patient demographics and disease characteristics

	All Patients (*N* = 97)
Age in years, median (range)	60 (30–82)
Gender, n (%)	
Male	47 (48 %)
Female	50 (52 %)
ECOG status, n (%)	
0	20 (20 %)
1	72 (74 %)
2	5 (5 %)
No. of prior systemic therapies, median (range)	4 (0–13)
Primary cancer diagnosis, n (%)	
Colorectal	41 (42 %)
Melanoma	12 (12%)
Ocular melanoma	2 (2 %)
Pancreatic	6 (6 %)
NSCLC	6 (6 %)
Ovarian	5 (5 %)
Head or neck	5 (5 %)
Unknown primary	2 (2 %)
Gastric	2 (2 %)
Adenoid cystic	2 (2 %)
Other[a]	14 (14 %)

[a]Includes bladder, bone, breast, carcinoid, cervical, cholangiocarcinoma, leiomyosarcoma, neuroendocrine, prostate, sarcoma, schwannoma, small bowel, testicular, and esophageal

Table 2

Cobimetinib-related AEs occurring in ≥10 % of patients

	All patients n (%)		21/7 schedule n (%)				14/14 schedule n(%)			
	N = 97		All (*n* = 56)		60 mg, MTD (*n* = 27)		All (*n* = 41)		100 mg, MTD (*n* = 29)	
	All Grades	≥Grade 3	All Grades	≥Grade 3	All Grades	≥Grade 3	All Grades	≥Grade 3	All Grades	≥Grade 3
Diarrhea	59 (61 %)	7 (7 %)	27 (48 %)	2 (4 %)	15 (56 %)	0	32 (78 %)	5 (12 %)	23 (79 %)	4 (14 %)
Rash[a]	53 (54 %)	6 (6 %)	27 (48 %)	2 (4 %)	18 (67 %)	1 (4 %)	26 (63 %)	4 (10 %)	19 (66 %)	3 (10 %)
Fatigue	37 (38 %)	5 (5 %)	17 (30 %)	3 (5 %)	9 (33 %)	3 (11%)	20 (49 %)	2 (5 %)	19 (66 %)	2 (7 %)
Edema[b]	28 (29 %)	0	14 (25 %)	0	9 (33 %)	0	14 (34 %)	0	10(34 %)	0
Nausea	25 (26 %)	0	10 (18 %)	0	6 (22 %)	0	15 (37 %)	0	12 (41 %)	0
Vomiting	22 (23 %)	0	5 (9 %)	0	3 (11 %)	0	17 (42 %)	0	14 (48 %)	0
Eye disorders[c]	17 (18%)	1 (1 %)	5 (9 %)	0	4 (15 %)	0	12 (29 %)	1 (2 %)	7 (24 %)	1 (3 %)
Abdominal pain[d]	12 (12 %)	1 (1 %)	1 (2 %)	0	0	0	11 (27 %)	1 (2 %)	10 (35 %)	1 (3 %)
Stomatitis	11 (11%)	0	6 (11 %)	0	3 (11 %)	0	5 (12 %)	0	3 (10 %)	0
Dry skin	11 (11 %)	0	7 (13 %)	0	2 (7 %)	0	4 (10 %)	0	3 (10 %)	0

[a] Includes rash, dermatitis acneiform, rash pruritic, rash generalized, dermatitis, exfoliative rash, rash erythematous and rash maculo-papular

[b] Includes peripheral edema, periorbital edema, edema, and facial edema

[c] Includes abnormal eye sensation, retinal edema, photopsia, blurred vision, central serous retinopathy, vitreous floaters, and eye disorder (not otherwise specified)

[d] Includes abdominal pain upper or lower, abdominal discomfort, and abdominal tenderness

Table 3

Steady-state cobimetinib PK summary following administration of 60 mg dose (21/7) or 100-mg dose (14/14)

	Geometric Mean (SD) (%CV)			
PK Parameter	**n**	**60 mg (21/7)**	**n**	**100 mg (14/14)**
tmax (h)[a]	39	2.4 (1.0–23.75)	18	3 (1.5–6.0)
$C_{max,ss}$ (ng/mL)	39	273 (60)	18	649 (54)
$AUC_{0–24,ss}$ (ng•h/mL)	37	4340 (61)	18	10,800 (59)
R_{acc}	22	2.4 (44)	18	2.6 (51)
$t_{1/2}$ (h)[b]	19	43.6 (23.1–69.6)	13	54.0 (45.3–71.1)
CL/F (L/h)	37	13.8 (61)	18	14.8 (92)

$AUC_{0–24,ss}$ area under the plasma concentration-time profile over a 24-h sampling interval, *$C_{max,ss}$* maximum observed plasma concentration at steady-state, *CL/F* apparent plasma clearance, *CV* coefficient of variation, *R_{acc}* accumulation ratio (ratio of Day 21 $AUC_{0–24}$/Day 1 $AUC_{0–24}$), *h* hour, *$t_{1/2}$* elimination half-life, *t_{max}* time to C_{max}

[a] Median (range)

[b] Geometric mean (range)