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Phase I, Open-Label, Dose-Escalation/ Dose-Expansion Study of Lifirafenib (BGB-283), an RAF Family Kinase Inhibitor, in Patients With Solid Tumors

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PURPOSE Lifirafenib is an investigational, reversible inhibitor of B-RAF^{V600E}, wild-type A-RAF, B-RAF, C-RAF, and EGFR. This first-in-human, phase I, dose-escalation/dose-expansion study evaluated the safety, tolerability, and efficacy of lifirafenib in patients with *B-RAF*- or *K-RAS/N-RAS*-mutated solid tumors.

METHODS During dose escalation, adult patients with histologically/cytologically confirmed advanced solid tumors received escalating doses of lifirafenib. Primary end points were safety/tolerability during dose escalation and objective response rate in preselected patients with *B-RAF* and *K-RAS/N-RAS* mutations during dose expansion.

RESULTS The maximum tolerated dose was established as 40 mg/d; dose-limiting toxicities included reversible thrombocytopenia and nonhematologic toxicity. Across the entire study, the most common grade ≥ 3 treatment-emergent adverse events were hypertension ($n = 23$; 17.6%) and fatigue ($n = 13$; 9.9%). One patient with *B-RAF*-mutated melanoma achieved complete response, and 8 patients with *B-RAF* mutations had confirmed objective responses: *B-RAF*^{V600E/K} melanoma ($n = 5$, including 1 patient treated with prior B-RAF/MEK inhibitor therapy), *B-RAF*^{V600E} thyroid cancer/papillary thyroid cancer (PTC; $n = 2$), and *B-RAF*^{V600E} low-grade serous ovarian cancer (LGSOC; $n = 1$). One patient with *B-RAF*-mutated non-small-cell lung cancer (NSCLC) had unconfirmed partial response (PR). Patients with *K-RAS*-mutated endometrial cancer and *K-RAS* codon 12-mutated NSCLC had confirmed PR ($n = 1$ each). No responses were seen in patients with *K-RAS/N-RAS*-mutated colorectal cancer ($n = 20$).

CONCLUSION Lifirafenib is a novel inhibitor of key RAF family kinases and EGFR, with an acceptable risk-benefit profile and antitumor activity in patients with *B-RAF*^{V600}-mutated solid tumors, including melanoma, PTC, and LGSOC, as well as *K-RAS*-mutated NSCLC and endometrial carcinoma. Future comparisons with first-generation B-RAF inhibitors and exploration of lifirafenib alone or as combination therapy in patients with selected RAS mutations who are resistant/refractory to first-generation B-RAF inhibitors are warranted.

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INTRODUCTION

The RAS-RAF-mitogen-activated protein kinase (MAPK) pathway plays a prominent role in tumorigenesis.¹ *K-RAS* mutations are common in pancreatic, colorectal, lung, and biliary tract tumors and occur in 15%–30% of endometrioid carcinomas.^{1,2} *H-RAS* mutations are common in salivary gland tumors¹; *N-RAS* mutations are frequent in melanomas. Among RAF serine/threonine kinases, *B-RAF* has the greatest inherent kinase activity.^{1,3} *B-RAF* mutations occur in approximately 50% of malignant melanomas,⁴ 40% of thyroid

carcinomas,³ between 2% and 38% of low-grade serous ovarian cancers (LGSOCs),⁵⁻⁸ and approximately 10% of metastatic colorectal cancers (CRCs).⁹ Despite this evident role in tumor biology, pursuit of RAS as a therapeutic target has proven difficult.¹⁰

First-generation *B-RAF* inhibitors have demonstrated clinical benefit in *B-RAF*^{V600E} metastatic melanoma^{11,12} but not as monotherapy in *B-RAF*^{V600E} CRC.^{13,14} Cutaneous squamous cell carcinoma (SCC) develops in 10%–26% of patients who receive B-RAF inhibitors,

including treatment-related keratoacanthomas that result from paradoxical MAPK signal activation.^{15,16} Most patients who receive these therapies develop resistance and ultimately experience relapse.¹⁷

In melanoma, resistance to first-generation B-RAF inhibitors stems from several mechanisms, including epidermal growth factor receptor (EGFR)-mediated reactivation of MAPK signaling,¹⁸ RAS-independent RAF kinase dimerization induced by *B-RAF*^{V600E} splice variants,^{19,20} AKT-dependent signaling pathways,^{17,21} and MAPK-redundant signaling pathways.^{17,22} In patients with *B-RAF*-mutated CRC, nonresponsiveness to first-generation B-RAF inhibitors is associated with EGFR-mediated reactivation of the MAPK pathway.¹⁴

Lifirafenib (BGB-283) is a novel, first-in-class, investigational RAF dimer inhibitor with potent, reversible inhibition of wild-type A-RAF, B-RAF, C-RAF, and *B-RAF*^{V600E} as well as EGFR^{15,23} and K-RAS.^{24,25} Preclinical studies have suggested that lifirafenib leads to a greater number of responses in *B-RAF*-mutated cancers than first-generation B-RAF inhibitors, including vemurafenib and dabrafenib.¹⁵ This study was designed to investigate safety/tolerability, examine pharmacokinetics (PK), establish the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) during dose escalation, and evaluate preliminary antitumor activity of lifirafenib in patients with tumors that harbor *B-RAF*, *N-RAS*, or *K-RAS* mutations.

METHODS

Study Design and Participants

This first-in-human, dose-escalation/dose-expansion, phase I study was conducted from November 20, 2013, to October 19, 2017, across 20 sites in Australia and New Zealand. Adult patients with histologically/cytologically confirmed advanced/metastatic solid tumors and an Eastern Cooperative Oncology Group performance status ≤ 1 were eligible if no effective standard therapy was available and they had locally assessed *B-RAF*, *N-RAS*, or *K-RAS* mutation-positive solid tumors or pancreatic cancer with unknown mutation status. Exclusion criteria included untreated leptomeningeal or brain metastases, major surgery within 28 days or radiotherapy within 14 days of enrollment, or unresolved toxicity grade > 1 from prior cancer therapy. All inclusion/exclusion criteria are presented in the Data Supplement (online only).

During dose escalation, patients were enrolled in successive dose-escalation cohorts of 3-6 patients each. Lifirafenib was administered on day 1 followed by a 2-day treatment-free period to allow for single-dose PK sample collection; on days 4-24, patients received once-daily lifirafenib. After cycle 1, patients received continuous treatment with once-daily lifirafenib in 21-day cycles. The first patient received 15 mg lifirafenib twice daily, but the dosing regimen was changed to 5 mg once daily after

reviewing the safety and PK profile in that patient. Subsequent dose escalation cohorts examined 5, 10, 20, 30, 40, 50, and 60 mg lifirafenib once daily. Because modeling and PK data suggested that discontinuous dosing regimens resulted in comparable or increased lifirafenib plasma concentrations versus continuous dosing schedules, an alternate 50-mg once-daily regimen on a week on/off cycle was examined ($n = 3$).

During dose expansion, patients with *B-RAF* and *K-RAS/N-RAS* mutations received lifirafenib 30 mg/d (RP2D) administered in 21-day cycles; patients could have melanoma (treatment naïve or resistant to B-RAF/MEK inhibitor therapy), CRC, non-small-cell lung cancer (NSCLC), thyroid cancer, endometrial cancer, pancreatic cancer, or other solid tumors. For both phases, patients continued treatment until unacceptable toxicity or patient withdrawal. Treatment beyond progression was permitted in patients who derived clinical benefit. Criteria for dose reductions/interruptions and treatment discontinuation are outlined in the Data Supplement.

End Points and Assessments

The primary end point during dose escalation was safety and tolerability, including dose-limiting toxicity (DLT) assessments and treatment-emergent adverse events (TEAEs). Adverse events (AEs) were graded by severity and evaluated by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Secondary end points included PK parameters from blood plasma samples obtained at prespecified time points, objective response rates (ORRs; complete response [CR] + partial response [PR]) and stable disease (SD) on the basis of RECIST version 1.1, progression-free survival (PFS), duration of response (DoR), and duration of SD. Exploratory end points included 18F-fluorodeoxyglucose (FDG) uptake using FDG positron emission tomography-computed tomography (FDG-PET-CT) scans at screening and on cycle 2, day 1 (± 3 days).

The primary end point during dose expansion was investigator-assessed ORR. Secondary end points included PFS, DoR, duration of SD, disease control rate (DCR), clinical benefit rate (CR + PR + durable SD [SD ≥ 24 weeks]), safety/tolerability, and steady-state predose lifirafenib plasma concentration at prespecified time points.

Statistical Analysis

Dose escalation sample size was determined by dose levels and emerging toxicities; 30 patients were required to establish the RP2D and schedule. Expansion cohorts were to include ≤ 20 patients (total: up to 200 patients); enrollment in some arms stopped early because of difficulties in patient recruitment. Descriptive statistics summarized continuous and categorical variables; Kaplan-Meier estimators summarized time-to-event variables. The safety analysis set consisted of patients who received ≤ 1 dose of lifirafenib.

The DLT analysis set included patients who experienced DLTs (or patients who received $\geq 80\%$ of planned lifirafenib doses) during cycle 1.

Study Oversight

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the requirements of public registration of clinical trials. The protocol was approved by site-specific institutional review boards. Written informed consent was obtained from each patient at enrollment.

RESULTS

Patient Disposition

During dose escalation ($n = 35$), 31 patients received once-daily lifirafenib (5 mg, $n = 3$; 10 mg, $n = 3$; 20 mg, $n = 3$; 30 mg, $n = 3$; 40 mg, $n = 10$; 50 mg, $n = 6$; 60 mg, $n = 3$). Four patients received alternate lifirafenib dosing regimens (15 mg twice daily, $n = 1$; 50 mg/d on a week on/off schedule, $n = 3$). All 35 patients were included in the safety analysis set; 31 patients comprised the DLT analysis set. Reasons for treatment discontinuation included disease progression ($n = 24$), AEs ($n = 5$), investigator/sponsor decision ($n = 1$), and other (transition to lifirafenib compassionate use [thyroid cancer, $n = 2$; melanoma, $n = 1$]; clinical progression, $n = 1$; DLT, $n = 1$). During dose expansion ($n = 96$), reasons for treatment discontinuation included disease progression ($n = 57$), AEs ($n = 19$), withdrawal of consent ($n = 4$), investigator/sponsor decision ($n = 3$), death ($n = 2$), and other (transition to lifirafenib compassionate use [melanoma, $n = 2$; thyroid cancer, CRC, NSCLC, and LGSOC, $n = 1$ each], clinical progression, $n = 5$; noncompliance, $n = 1$). Across the entire study, 11 patients were treated > 2 weeks beyond progression (*B-RAF*, $n = 7$; *K-RAS*, $n = 4$); mean duration of treatment beyond progression was 157 days (range, 41-420 days) for patients with *B-RAF* mutations and 215 days (range, 100-256 days) for those with *K-RAS* mutations.

Demographic and Baseline Characteristics

Demographic and baseline characteristics are listed in Table 1. Patients were heavily pretreated, with approximately 50% receiving ≥ 3 lines of anticancer therapy and $\geq 75\%$ having prior anticancer surgery (dose escalation, 77.1%; dose expansion, 87.5%). Twelve patients with *B-RAF* mutations received prior B-RAF inhibitor treatment. During dose escalation, 31.4% of patients harbored *B-RAF* mutations, and 57.1% harbored *K-RAS* mutations; similar proportions of patients harbored *B-RAF* (43.8%) or *K-RAS* (40.6%) mutations during dose expansion.

Safety and Tolerability

During dose escalation, the most frequent TEAEs were fatigue ($n = 24$; 68.6%) and dermatitis acneiform ($n = 15$; 42.9%; Table 2). Five patients (14.3%) experienced TEAEs that led to discontinuation. Treatment-related TEAEs were

TABLE 1. Demographic and Baseline Characteristics During Dose Escalation and Dose Expansion

Characteristic	Dose Escalation, No. (%)	Dose Expansion, No. (%)
No. of patients	35	96
Median age, years (range)	59 (33-77)	63 (20-82)
Sex		
Male	22 (62.9)	56 (58.3)
Female	13 (37.1)	40 (41.7)
ECOG PS		
0	12 (34.3)	33 (34.4)
1	23 (65.7)	63 (65.6)
Type of solid tumor		
Colorectal cancer	13 (37.1)	34 (35.4)
Non-small-cell lung cancer	9 (25.7)	10 (10.4)
Melanoma	5 (14.3)	18 (18.8)
Cholangiocarcinoma	2 (5.7)	0 (0.0)
Thyroid ^a	3 (8.6)	3 (3.1)
Endometrial	2 (5.7)	5 (5.2)
Ovarian	1 (2.9)	1 (1.0)
Pancreatic	0 (0.0)	18 (18.8)
Other	0 (0.0)	7 (7.3)
Tumor stage		
III	4 (11.4)	15 (15.6)
IV	31 (88.6)	80 (83.3)
Mutation type ^b		
<i>B-RAF</i>	11 (31.4)	42 (43.8)
<i>B-RAF</i> ^{V600}	7 (20.0)	40 (41.7)
Other <i>B-RAF</i> mutation	2 (5.7)	2 (2.1)
Unspecified <i>B-RAF</i> mutation	2 (5.7)	0 (0.0)
<i>K-RAS</i>	20 (57.1)	39 (40.6)
<i>N-RAS</i>	4 (11.4)	3 (3.1)
Missing	1 (2.9)	12 (12.5)
Lines of prior anticancer drug therapy		
1	5 (14.3)	18 (18.8)
2	7 (20.0)	22 (22.9)
≥ 3	18 (51.4)	47 (49.0)
Prior B-RAF inhibitor treatment	0 (0.0)	12 (12.5)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

^aIncluded 1 patient in the dose-escalation phase and 3 patients in the dose-expansion phase with papillary thyroid cancer.

^bOne patient in the 60-mg dose-escalation cohort had both *B-RAF* and *N-RAS* mutations. One dose-expansion patient with colorectal cancer had both codon 12 and codon 13 *K-RAS* mutations.

TABLE 2. Incidence of Treatment-Emergent Adverse Events That Occurred in More Than 10% of Patients in Either Phase

Treatment-Emergent Adverse Event	Dose Escalation (n = 35), No. (%)		Dose Expansion (n = 96), No. (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	24 (68.6)	4 (11.4)	47 (49.0)	9 (9.4)
Acneiform dermatitis	15 (42.9)	0 (0.0)	17 (17.7)	0 (0.0)
Decreased appetite	14 (40.0)	2 (5.7)	35 (36.5)	0 (0.0)
Constipation	14 (40.0)	2 (5.7)	26 (27.1)	0 (0.0)
Thrombocytopenia	14 (40.0)	5 (14.3)	22 (22.9)	7 (7.3)
Vomiting	14 (40.0)	0 (0.0)	19 (19.8)	1 (1.0)
Nausea	13 (37.1)	1 (2.9)	33 (34.4)	1 (1.0)
Dysphonia	11 (31.4)	0 (0.0)	31 (32.3)	1 (1.0)
Hypertension	11 (31.4)	7 (20.0)	23 (24.0)	16 (16.7)
Palmoplantar erythrodysesthesia syndrome	11 (31.4)	2 (5.7)	20 (20.8)	1 (1.0)
Diarrhea	9 (25.7)	1 (2.9)	32 (33.3)	0 (0.0)
Back pain	9 (25.7)	0 (0.0)	22 (22.9)	2 (2.1)
Pyrexia	8 (22.9)	1 (2.9)	23 (24.0)	6 (6.3)
Abdominal pain	8 (22.9)	0 (0.0)	21 (21.9)	4 (4.2)
Muscle spasms	8 (22.9)	0 (0.0)	12 (12.5)	0 (0.0)
Weight decrease	8 (22.9)	1 (2.9)	12 (12.5)	1 (1.0)
ALT increase	8 (22.9)	3 (8.6)	10 (10.4)	2 (2.1)
Headache	7 (20.0)	0 (0.0)	18 (18.8)	2 (2.1)
Arthralgia	7 (20.0)	0 (0.0)	16 (16.7)	1 (1.0)
Oropharyngeal pain	7 (20.0)	0 (0.0)	10 (10.4)	0 (0.0)
Hypophosphatemia	7 (20.0)	0 (0.0)	8 (8.3)	2 (2.1)
Pain in extremity	7 (20.0)	0 (0.0)	9 (9.4)	0 (0.0)
Hypokalemia	6 (17.1)	0 (0.0)	15 (15.6)	3 (3.1)
Cough	6 (17.1)	0 (0.0)	15 (15.6)	0 (0.0)
Insomnia	6 (17.1)	0 (0.0)	12 (12.5)	0 (0.0)
Anemia	6 (17.1)	3 (8.6)	10 (10.4)	5 (5.2)
Gastroesophageal reflux disease	6 (17.1)	0 (0.0)	4 (4.2)	0 (0.0)
Musculoskeletal chest pain	6 (17.1)	0 (0.0)	7 (7.3)	0 (0.0)
Pruritus	6 (17.1)	0 (0.0)	7 (7.3)	0 (0.0)
γ-Glutamyl transferase increase	6 (17.1)	4 (11.4)	4 (4.2)	4 (4.2)
Oral candidiasis	6 (17.1)	0 (0.0)	12 (12.5)	0 (0.0)
Upper respiratory tract infection	6 (17.1)	0 (0.0)	5 (5.2)	0 (0.0)
Rash	5 (14.3)	0 (0.0)	23 (24.0)	0 (0.0)
Dyspnea	4 (11.4)	1 (2.9)	15 (15.6)	4 (4.2)
Chills	4 (11.4)	0 (0.0)	9 (9.4)	0 (0.0)
Dry mouth	5 (14.3)	0 (0.0)	9 (9.4)	0 (0.0)
Abdominal pain, upper	4 (11.4)	0 (0.0)	8 (8.3)	2 (2.1)
Myalgia	4 (11.4)	0 (0.0)	10 (10.4)	0 (0.0)
Palmoplantar keratoderma	5 (14.3)	0 (0.0)	1 (1.0)	0 (0.0)
Photosensitivity reaction	5 (14.3)	0 (0.0)	5 (5.2)	0 (0.0)
Skin hypertrophy	4 (11.4)	0 (0.0)	1 (1.0)	0 (0.0)
Skin lesion	4 (11.4)	0 (0.0)	4 (4.2)	0 (0.0)

(continued on following page)

TABLE 2. Incidence of Treatment-Emergent Adverse Events That Occurred in More Than 10% of Patients in Either Phase (continued)

Treatment-Emergent Adverse Event	Dose Escalation (n = 35), No. (%)		Dose Expansion (n = 96), No. (%)	
	Any Grade	Grade $\geq$ 3	Any Grade	Grade $\geq$ 3
Increased AST	5 (14.3)	2 (5.7)	10 (10.4)	1 (1.0)
ECG QT prolonged	4 (11.4)	0 (0.0)	5 (5.2)	2 (2.1)
Urinary tract infection	4 (11.4)	0 (0.0)	10 (10.4)	1 (1.0)
Hypomagnesemia	4 (11.4)	0 (0.0)	7 (7.3)	0 (0.0)
Neutropenia	4 (11.4)	0 (0.0)	4 (4.2)	2 (2.1)
Hypotension	4 (11.4)	0 (0.0)	5 (5.2)	2 (2.1)
Dysgeusia	5 (14.3)	0 (0.0)	6 (6.3)	0 (0.0)
Lethargy	4 (11.4)	0 (0.0)	8 (8.3)	0 (0.0)
Glossodynia	3 (8.6)	0 (0.0)	11 (11.5)	0 (0.0)
Dry skin	2 (5.7)	0 (0.0)	10 (10.4)	0 (0.0)
Hyperkeratosis	3 (8.6)	0 (0.0)	10 (10.4)	0 (0.0)
Dizziness	3 (8.6)	0 (0.0)	10 (10.4)	0 (0.0)

predominantly grades 1-2. The most common grade $\geq$ 3 treatment-related TEAEs during dose escalation were thrombocytopenia (14.3%), hypertension (11.4%), and fatigue (11.4%; Data Supplement). Among patients eligible for DLT assessment (n = 31), 6 experienced reversible DLTs, 5 of which occurred at doses $\geq$ 40 mg/d (Data Supplement). Observed DLTs included grade 3 increased ALT (n = 1) and grade 4 thrombocytopenia (n = 5); thrombocytopenia typically occurred within 2-3 weeks of initial dosing. Comprehensive investigations (including bone marrow biopsies) in the first 2 patients with thrombocytopenia revealed normal bone marrow morphology and reserve, which suggested a peripheral cause. Patients were treated with platelet transfusion (n = 1) or prednisolone administration (n = 4) and withholding of lifirafenib; platelet counts recovered within 6-20 days. Grade $\geq$ 3 TEAEs (including DLTs) occurred in 26 patients (74.3%), with more patients reporting grade $\geq$ 3 TEAEs in the 40, 50, and 60 mg/d cohorts (61.5%) versus lower-dose cohorts (38.5%). Grade $\geq$ 3 TEAEs that occurred in patients who received $\geq$ 40 mg/d are listed in the Data Supplement. The MTD was established at 40 mg/d. Eighty percent (4 of 5 patients) of dose-limiting thrombocytopenia occurred in patients who received 40 and 60 mg/d (n = 2 each), and 70% of patients treated with 40 mg/d had dose interruptions/reductions as a result of drug toxicity, typically between days 13 and 28 of cycle 1. On the basis of these data, the RP2D was established at 30 mg/d.

Of 96 patients who received lifirafenib during dose expansion, the most commonly reported TEAEs were fatigue (n = 47; 49%) and decreased appetite (n = 35; 36.5%; Table 2). During the entire study, cutaneous SCC or keratoacanthoma was not reported. Grade $\geq$ 3 TEAEs occurred in 68 patients (70.8%), and serious TEAEs occurred in 56 patients (58.3%). TEAEs led to discontinuation in 19 patients (19.8%), most commonly fatigue (n = 5) and

thrombocytopenia (n = 2; Data Supplement). Fifty patients (52%) experienced AEs that led to a dose adjustment, which resulted in a median relative dose intensity of 95.0%. Four patients (4.2%) experienced 6 TEAEs considered unrelated to treatment that led to death: pericardial effusion, sepsis, pleural effusion, intracranial hemorrhage, intestinal perforation as a result of disease progression, and small intestinal obstruction (n = 1 each). During dose expansion, the most common grade $\geq$ 3 treatment-related AEs were hypertension (8.3%) and fatigue (7.3%); 2 patients discontinued because of treatment-related grade $\geq$ 3 thrombocytopenia.

Antitumor Activity

Patients with *B-RAF* and *K-RAS* mutations from both phases had responses (Table 3). Among patients with *B-RAF* mutations, 8 (15.1%) of 53 achieved PR, including 1 patient with melanoma who received prior RAF inhibitor therapy, and 27 (50.9%) of 53 had SD; time to response and DoR of patients with select tumors are shown in Figure 1. During dose escalation, 1 patient with *B-RAF*-mutated melanoma (40 mg/d) achieved CR (Data Supplement). Across the entire study, 5 of 23 patients with *B-RAF*^{V600} melanoma achieved confirmed PR, including 4 treatment-naïve patients and 1 who progressed after 6 months of prior B-RAF inhibitor therapy (Fig 1; Data Supplement). Confirmed PRs occurred in patients with *B-RAF*-mutated thyroid cancer/PTC (n = 2) and *B-RAF*^{V600E} LGSOC (n = 1). One patient with *B-RAF*-mutated NSCLC achieved unconfirmed PR.

Across the entire study, 2 patients with *K-RAS* mutations (endometrial cancer [20 mg/d] and codon 12-mutated NSCLC [30 mg/d], n = 1 each) had confirmed responses, which resulted in an ORR of 3.4%; 32 patients (54.2%) with *K-RAS* mutations had SD (Fig 2). Twelve patients with *K-RAS*- or *N-RAS*-mutated CRC had SD

TABLE 3. Patient Responses by Mutation Status

Response	<i>B-RAF</i> ^{mut} , No. (%)	<i>K-RAS</i> ^{mut} / <i>N-RAS</i> ^{mut} , No. (%)
No. of patients	53	66
Best overall response (confirmed)		
CR	1 (1.9)	0
PR ^a	8 (15.1)	2 (3.0)
SD	27 (50.9)	33 (50.0)
PD	8 (15.1)	16 (24.2)
NE/missing	9 (17.0)	15 (22.7)
Objective response rate (CR + PR)	9 (17.0)	2 (3.0)
Disease control rate (CR + PR + SD)	36 (67.9)	35 (53.0)

NOTE. Twelve patients with *B-RAF*^{V600} had received prior B-RAF inhibitor treatment: 10 had melanoma, 1 had CRC, and 1 had adenocarcinoma with unknown primary origin.

Abbreviations: CR, complete response; mut, mutated; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

^aIncludes 1 patient in the 60-mg dose-escalation cohort with both *B-RAF* and *N-RAS* mutations.

(Data Supplement); 5 patients with *K-RAS*-mutated endometrial cancer (codon 12 mutated, *n* = 4; codon 2 mutated, *n* = 1) and 2 patients with *K-RAS*-mutated NSCLC (codon 12 mutated and *K-RAS* G13D, *n* = 1 each) had SD (Data Supplement). Median DoR was 31.7 months (95% CI, 6.8 to 31.7 months) during dose escalation and 11.1 months (95% CI, 1.9 months to not reached) during dose expansion. Median duration of SD during dose expansion was 4.1 months (95% CI, 3.5 to 4.9 months). Duration of treatment was > 1 year for several patients with *B-RAF* (*n* = 10) and *K-RAS* mutations (*n* = 5).

PK Outcomes

Systemic exposure increased from 5 to 50 mg on cycle 1, day 1, and cycle 2, day 1 (Data Supplement). Although not powered to assess proportionality, the log-log regression model accounted for > 80% of the observed variation from 10 to 60 mg for cycle 1, day 1. Lifirafenib was rapidly absorbed, with a median time to reach maximum plasma concentration of 3 hours. The accumulation ratio for maximum serum concentration (*C*_{max}), area under the plasma concentration curve from 0-9 hours (*AUC*₀₋₉), and *AUC*₀₋₂₄ estimated from cycle 2, day 1/cycle 1, day 1, was similar from 10 to 50 mg (Data Supplement). Average accumulation ranged from 3.3- to 6.1-fold for *C*_{max} and 3.6- to 7.6-fold for *AUC*₀₋₉ and *AUC*₀₋₂₄. Three patients had measurable terminal half-life (range, 15-59 hours); terminal half-life estimates should be interpreted with caution because samples were not collected beyond 72 hours after dosing.

FDG-PET-CT Scans

During dose escalation, 34 patients (including those who received lifirafenib 15 mg twice weekly or 50 mg once daily on a week on/off cycle) had tumor imaging on cycle 2, day 1. FDG-PET-CT scans showed no FDG uptake in 1 patient, low FDG uptake in 1 patient, moderate FDG uptake in 10 patients, and high FDG uptake in 15 patients (7 patients were missing postbaseline results). Complete metabolic reduction was observed in 1 patient with a *B-RAF* mutation who received 40 mg/d; 11 patients had partial metabolic reduction per European Organization for Research and Treatment of Cancer criteria.²⁶ Decreases in maximum and average standardized uptake volumes, indicative of significant pharmacodynamic activity, were generally observed at lifirafenib doses ≥ 30 mg. At cycle 2, day 1, changes in FDG uptake from baseline were observed in 9 patients, including 7 (20.6%) who changed from high to moderate uptake, 1 (2.9%) who changed from high to low uptake, and 1 (2.9%) who changed from low to no uptake. All patients with confirmed clinical responses (*n* = 3; 8.6%) had FDG-PET-CT responses, but not all patients with FDG-PET-CT responses had clinical responses (6 had SD). Among patients who received once-daily lifirafenib (*n* = 31), FDG-PET-CT responses were observed in patients with *B-RAF*, *K-RAS*, and *N-RAS* mutations (Fig 3).

DISCUSSION

This first-in-human dose-escalation/dose-expansion study evaluated lifirafenib, a novel investigational oral RAF family kinase inhibitor, in patients with *B-RAF*-, *K-RAS*-, or *N-RAS*-mutated solid tumors. The MTD was determined as 40 mg once daily; DLTs included reversible thrombocytopenia and increased ALT.

Lifirafenib had an acceptable risk-benefit profile. The dose-escalation phase suggested that once-daily lifirafenib was better tolerated at doses ≤ 30 mg than ≥ 40 mg, irrespective of schedule. Treatment-related dermatologic toxicities were observed, but cutaneous SCCs and keratoacanthomas reported with other B-RAF inhibitor treatments²⁷ were not. Treatment-related thrombocytopenia and hypertension were manageable and likely stemmed from off-target inhibition of kinases other than B-RAF, including EGFR and PDGF. A prior report demonstrated that lifirafenib inhibited additional kinases, including EGFR, DDR1, DDR2, EPHA3, FLT3, VEGFR2, ABL1, RET, EPHA7, EPHB2, MNK2, and ZAK, with half-maximal inhibitory concentrations (*IC*₅₀s) within 10-fold of that for B-RAF^{V600E}.¹⁵ With an *IC*₅₀ of 108 nM, inhibition of VEGFR2 by lifirafenib could potentially account for the clinically observed hypertension in our study and was similar to off-target effects of other kinase inhibitor therapies.^{15,28} The precise mechanism of thrombocytopenia remains unclear but seems dose related because a higher proportion of patients experienced thrombocytopenia at doses

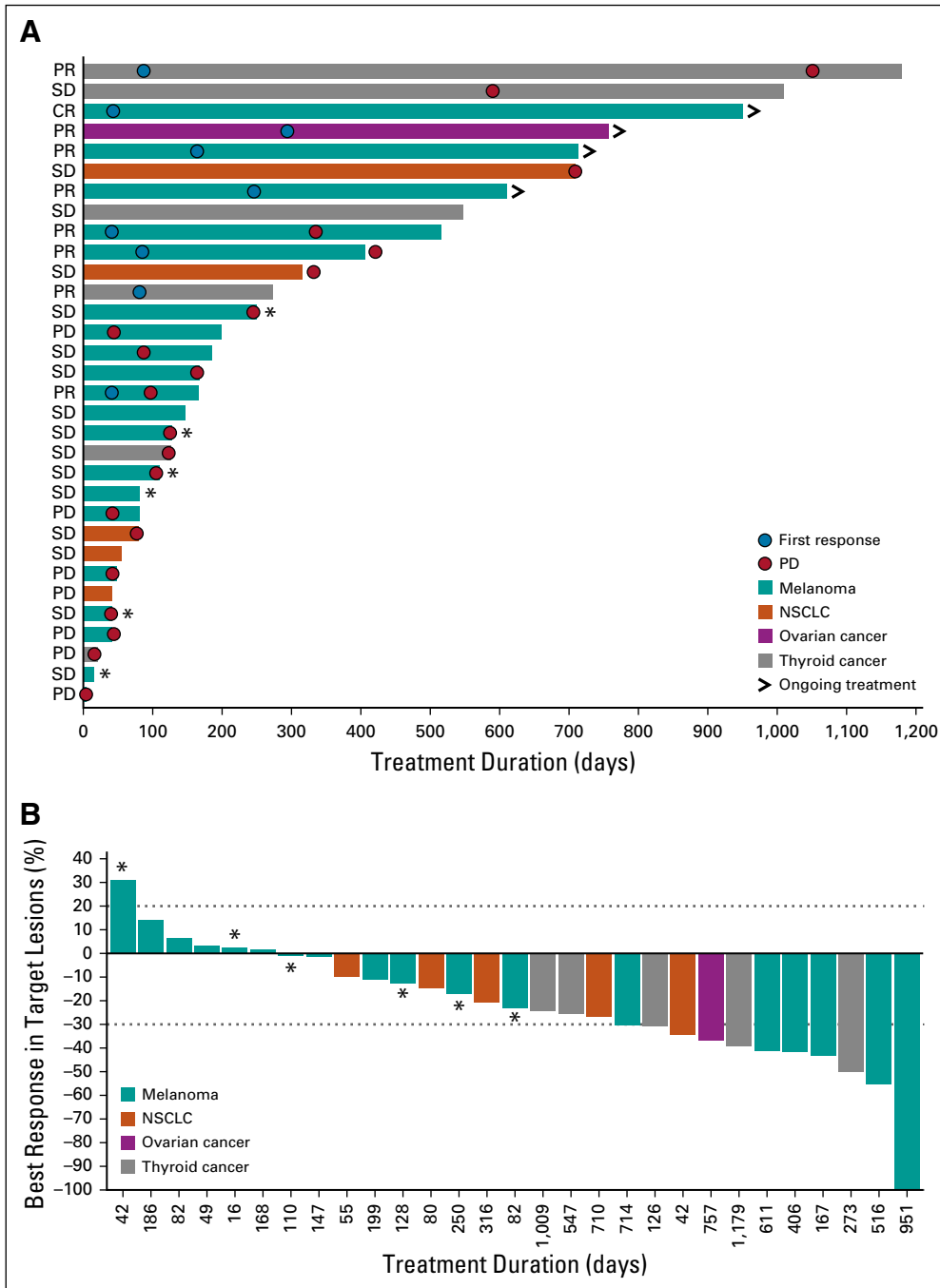


FIG 1. (A and B) Responses in patients with *B-RAF*-mutated cancers (both phases). (>) Ongoing treatment indicates ongoing response at time of data cutoff. An additional 6 patients not included in this figure had prior *B-RAF* inhibitor treatment (4 had melanoma, 1 had colorectal cancer, and 1 had adenocarcinoma with unknown primary origin). (*) Patients who received prior *B-RAF/MEK* inhibitor treatment. CR, complete response; NSCLC, non-small-cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

≥ 40 versus ≤ 30 mg/d. Thrombocytopenia resolved rapidly with drug interruption, and although steroids were initiated on the basis of an assumed peripheral (possibly immune-mediated) mechanism, the specific impact this intervention had remains unclear. A more direct kinase-mediated effect, particularly given lifirafenib's novel kinase inhibition profile, remains possible and warrants additional exploration. Kinases, including EGFR and PDGF, have individually, but rarely, been implicated in platelet dysfunction,²⁹⁻³¹ and the effect of collectively inhibiting these kinases is unclear. Of note, thrombocytopenia was

manageable at or below the RP2D and did not recur with ongoing dosing in patients who continued treatment. Additional exploration of alternate dose schedules and underlying causative mechanisms remains an important priority in the ongoing development of lifirafenib.

Lifirafenib was rapidly absorbed, and systemic exposure increased during cycles 1 and 2 from 10 to 50 mg/d. During dose escalation, FDG-PET-CT scans were used as a surrogate marker of MAPK pathway inhibition to define optimal biologic dosing.³² Partial/complete metabolic reductions by FDG-PET-CT scan were observed in 12 of 34 patients,

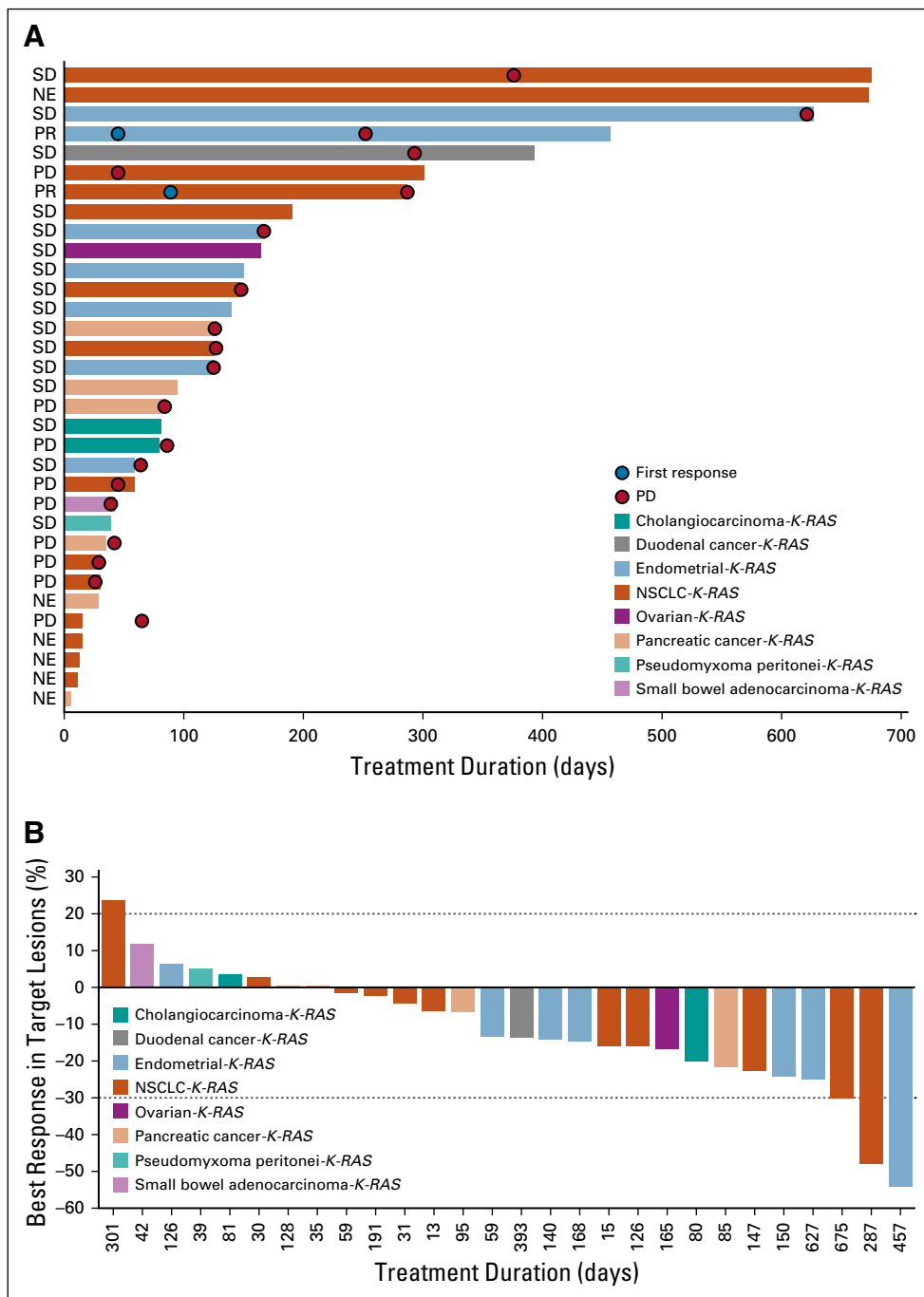


FIG 2. (A and B) Responses in patients with *K-RAS*-mutated cancers (excluding colorectal cancer; both phases). NE, not evaluable; NSCLC, non-small-cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.

including 11 who received ≥ 30 mg/d lifirafenib, which suggests significant pharmacodynamic activity at doses ≥ 30 mg/d. The accumulation ratio was similar from 10–50 mg/d. On the basis of the safety/tolerability, antitumor activity, PK profile, and pharmacodynamic activity, the RP2D was established at 30 mg/d.

While the overall antitumor activity of lifirafenib was modest, antitumor activity was observed in patients with *B-RAF*-mutated solid tumors, including melanoma, thyroid cancer, and LGSOC. Limited information with regard to pharmacodynamic markers of response and/or resistance

were collected; detailed genetic information for responders/nonresponders (beyond underlying *B-RAF* and *K-RAS* mutations) was unavailable for most patients. Additional investigation may be needed to understand the underlying mechanism of response and resistance to this novel agent and to inform future treatment decisions and/or trial design. During dose expansion, 4 of 7 patients with *B-RAF*^{V600}-mutated melanoma who had not received prior *B-RAF*/MEK inhibitor therapy had confirmed PR (ORR, 57.1%; DCR, 85.7%). Because 2 patients with responses and no PD transferred to a compassionate use program, DoR was not

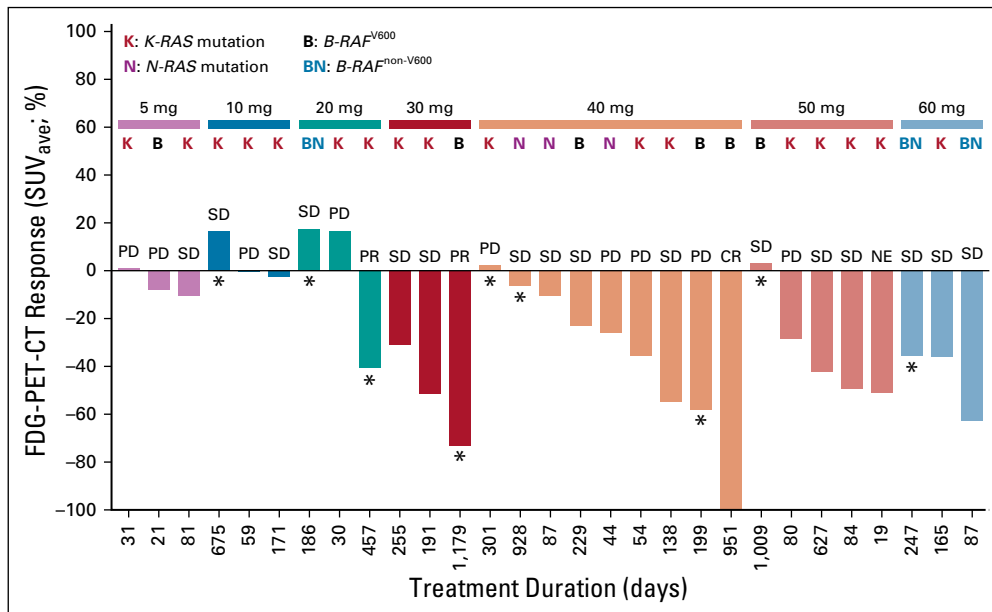


FIG 3. Responses across lifirafenib dose cohorts by ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) analysis. Two patients were missing a post-baseline PET scan. (*) Patients who were treated beyond progression. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SUV_{ave} , average standardized uptake volume.

reached. One of 3 patients with $B\text{-RAF}^{\text{V600}}$ -mutated thyroid cancer had confirmed PR (ORR, 33.3%; DCR, 100%; Data Supplement), comparable to reported clinical activities for first-generation B-RAF inhibitors, such as vemurafenib and dabrafenib, which demonstrated an ORR of 48% and 50% (DCR, 91%), respectively, in patients with $B\text{-RAF}$ -mutated melanoma.^{12,33} Importantly, antitumor activity was observed in $K\text{-RAS}$ -mutant cancers, including NSCLC and endometrial carcinoma (Data Supplement), with prolonged disease control. In contrast, lifirafenib had limited clinical activity in patients with $K\text{-RAS}$ -mutated CRC or pancreatic cancer. This observation was unlikely due to differences in $K\text{-RAS}$ mutations between NSCLC and CRC or pancreatic cancer because these results were similar to phase I results of a novel RAF/MEK inhibitor, RO5126766, that showed promise in $K\text{-RAS}$ -mutated NSCLC and endometrial/ovarian cancers but not in $K\text{-RAS}$ -mutated CRC.^{34,35} This suggests that oncogenic $K\text{-RAS}$ may be context dependent, potentially requiring different approaches on the basis of tumor types. Two novel investigational $K\text{-RAS}^{\text{G12C}}$ covalent inhibitors, AMG 510 and MRTX849, recently demonstrated preliminary antitumor activity in $K\text{-RAS}$ -mutant tumors.^{36,37}

Albeit early, the data showed promising efficacy signals and may represent a breakthrough in treatment of $K\text{-RAS}$ -mutant tumors. However, targeting only $K\text{-RAS}^{\text{G12C}}$ mutations limits the utility of these new therapies, resulting in a continued unmet medical need for tumors with oncogenic $K\text{-RAS}$ mutations beyond $K\text{-RAS}^{\text{G12C}}$.

In summary, lifirafenib demonstrated an acceptable risk-benefit profile given the safety results and responses in patients with $B\text{-RAF}$ -mutated melanoma, thyroid cancer, and LGSOC and $K\text{-RAS}$ -mutated NSCLC and endometrial cancer. Our findings suggest that lifirafenib could potentially benefit patients with MAPK pathway-associated kinase alterations beyond $B\text{-RAF}^{\text{V600}}$ mutations, including activated $K\text{-RAS}$. Additional investigation of the safety/efficacy of lifirafenib as monotherapy or in combination is warranted, especially in $K\text{-RAS}$ -mutated solid tumor malignancies other than CRC; a phase I/II trial of lifirafenib in combination with a MEK inhibitor in patients with $B\text{-RAF}$ - and RAS -mutant tumors (ClinicalTrials.gov identifier: [NCT03905148](https://clinicaltrials.gov/ct2/show/study/NCT03905148)) has recently commenced enrollment.

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DATA SHARING STATEMENT

Upon request, and subject to certain criteria, conditions, and exceptions, BeiGene will provide access to individual de-identified participant data from BeiGene-sponsored global interventional clinical studies conducted for medicines (1) for indications that have been approved or (2) in programs that have been terminated. BeiGene will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data requests may be submitted to medicalinformation@beigene.com.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Santarap L, Lippman SM, El-Naggar AK: Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. *Expert Opin Ther Targets* 16:103-119, 2012
- Okuda T, Sekizawa A, Purwosunu Y, et al: Genetics of endometrial cancers. *Obstet Gynecol Int* 2010:984013, 2010
- Durrant DE, Morrison DK: Targeting the Raf kinases in human cancer: The Raf dimer dilemma. *Br J Cancer* 118:3-8, 2018
- Long GV, Menzies AM, Nagrial AM, et al: Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 29:1239-1246, 2011
- Bösmüller H, Fischer A, Pham DL, et al: Detection of the BRAF V600E mutation in serous ovarian tumors: A comparative analysis of immunohistochemistry with a mutation-specific monoclonal antibody and allele-specific PCR. *Hum Pathol* 44:329-335, 2013
- Singer G, Oldt R III, Cohen Y, et al: Mutations in BRAF and KRAS characterize the development of low-grade ovarian serous carcinoma. *J Natl Cancer Inst* 95:484-486, 2003
- Jones S, Wang TL, Kurman RJ, et al: Low-grade serous carcinomas of the ovary contain very few point mutations. *J Pathol* 226:413-420, 2012
- Wong KK, Tsang YT, Deavers MT, et al: BRAF mutation is rare in advanced-stage low-grade ovarian serous carcinomas. *Am J Pathol* 177:1611-1617, 2010
- Strickler JH, Wu C, Bekaii-Saab T: Targeting BRAF in metastatic colorectal cancer: Maximizing molecular approaches. *Cancer Treat Rev* 60:109-119, 2017
- Stephen AG, Esposito D, Bagni RK, et al: Dragging ras back in the ring. *Cancer Cell* 25:272-281, 2014
- Chapman PB, Robert C, Larkin J, et al: Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: Final overall survival results of the randomized BRIM-3 study. *Ann Oncol* 28:2581-2587, 2017
- Hauschild A, Grob JJ, Demidov LV, et al: Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 380:358-365, 2012
- Kopetz S, Desai J, Chan E, et al: PLX4032 in metastatic colorectal cancer patients with mutant BRAF tumors. *J Clin Oncol* 28, 2010 (suppl; abstr 3534)
- Corcoran RB, Ebi H, Turke AB, et al: EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov* 2:227-235, 2012
- Tang Z, Yuan X, Du R, et al: BGB-283, a novel RAF kinase and EGFR inhibitor, displays potent antitumor activity in BRAF-mutated colorectal cancers. *Mol Cancer Ther* 14:2187-2197, 2015
- Anforth R, Menzies A, Byth K, et al: Factors influencing the development of cutaneous squamous cell carcinoma in patients on BRAF inhibitor therapy. *J Am Acad Dermatol* 72:809-815.e1, 2015

17. Shi H, Moriceau G, Kong X, et al: Melanoma whole-exome sequencing identifies (V600E)B-RAF amplification-mediated acquired B-RAF inhibitor resistance. *Nat Commun* 3:724, 2012
18. Girotti MR, Pedersen M, Sanchez-Laorden B, et al: Inhibiting EGF receptor or SRC family kinase signaling overcomes BRAF inhibitor resistance in melanoma. *Cancer Discov* 3:158-167, 2013
19. Poulikakos PI, Persaud Y, Janakiraman M, et al: RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). *Nature* 480:387-390, 2011
20. Rizos H, Menzies AM, Pupo GM, et al: BRAF inhibitor resistance mechanisms in metastatic melanoma: Spectrum and clinical impact. *Clin Cancer Res* 20:1965-1977, 2014
21. Mao M, Tian F, Mariadason JM, et al: Resistance to BRAF inhibition in BRAF-mutant colon cancer can be overcome with PI3K inhibition or demethylating agents. *Clin Cancer Res* 19:657-667, 2013
22. Temraz S, Mukherji D, Shamseddine A: Dual inhibition of MEK and PI3K pathway in KRAS and BRAF mutated colorectal cancers. *Int J Mol Sci* 16:22976-22988, 2015
23. Tang Z, Liu Y, Jiang B, et al: BGB-283: A novel RAF dimer inhibitor, displays potent antitumor activity in HCC patient derived xenograft models. *Cancer Res* 76, 2016 (suppl; abstr 1230)
24. Desai J, Markman B, Sandhu SK, et al: Updated safety, efficacy, and pharmacokinetics (PK) results from the phase I study of BGB-A317, an antiprogrammed death-1 (PD-1) mAb in patients (pts) with advanced solid tumors. Presented at 31st Ann Meet Soc Immunother Cancer, National Harbor, MD, November 9–13, 2016
25. Hao H, Muniz-Medina VM, Mehta H, et al: Context-dependent roles of mutant B-Raf signaling in melanoma and colorectal carcinoma cell growth. *Mol Cancer Ther* 6:2220-2229, 2007
26. Young H, Baum R, Cremerius U, et al: Measurement of clinical and subclinical tumour response using [¹⁸F]-fluorodeoxyglucose and positron emission tomography: Review and 1999 EORTC recommendations. *Eur J Cancer* 35:1773-1782, 1999
27. Wu JH, Cohen DN, Rady PL, et al: BRAF inhibitor-associated cutaneous squamous cell carcinoma: New mechanistic insight, emerging evidence for viral involvement and perspectives on clinical management. *Br J Dermatol* 177:914-923, 2017
28. Robinson ES, Khankin EV, Karumanchi SA, et al: Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: Mechanisms and potential use as a biomarker. *Semin Nephrol* 30:591-601, 2010
29. Cao H, Bhuyan AAM, Umbach AT, et al: Inhibitory effect of afatinib on platelet activation and apoptosis. *Cell Physiol Biochem* 43:2264-2276, 2017
30. Ohnishi H, Yamaguchi K, Shimada S, et al: A new approach to the treatment of atherosclerosis and trapidil as an antagonist to platelet-derived growth factor. *Life Sci* 28:1641-1646, 1981
31. Ohnishi H, Kosuzume H, Hayashi Y, et al: Effects of trapidil on thromboxane A₂-induced aggregation of platelets, ischemic changes in heart and biosynthesis of thromboxane A₂. *Prostaglandins Med* 6:269-281, 1981
32. McArthur GA, Puzanov I, Amaravadi R, et al: Marked, homogeneous, and early [¹⁸F]fluorodeoxyglucose-positron emission tomography responses to vemurafenib in BRAF-mutant advanced melanoma. *J Clin Oncol* 30:1628-1634, 2012
33. Chapman PB, Hauschild A, Robert C, et al: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 364:2507-2516, 2011
34. Harris SJ, Luken MJ, Perez DR, et al: Updated efficacy and safety results from the phase I study of intermittent dosing of the dual MEK/RAF inhibitor, RO5126766 in patients (pts) with RAS/RAF mutated advanced solid tumours. *J Clin Oncol* 34, 2016 (suppl; abstr 2582)
35. Chenard-Poirier M, Kaiser M, Boyd K, et al: Results from the biomarker-driven basket trial of RO5126766 (CH5127566), a potent RAF/MEK inhibitor, in RAS- or RAF-mutated malignancies including multiple myeloma. *J Clin Oncol* 35, 2017 (suppl; abstr 2506)
36. Canon J, Rex K, Saiki AY, et al: The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* 575:217-223, 2019
37. Hallin J, Engstrom LD, Hargis L, et al: The KRAS^{G12C} inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. *Cancer Discov* 10:54-71, 2020



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase I, Open-Label, Dose-Escalation/Dose-Expansion Study of Lifirafenib (BGB-283), an RAF Family Kinase Inhibitor, in Patients With Solid Tumors

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Employment: BeiGene, BeiGene (I)

Leadership: MapKure

Stock and Other Ownership Interests: BeiGene, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Regeneron Pharmaceuticals, Incyte, Merck, Clovis Oncology, Adaptimmune, Rigel, Arrowhead Pharmaceuticals, AbbVie, AstraZeneca

Patents, Royalties, Other Intellectual Property: Multiple patents obtained as BeiGene employee, multiple patents awarded as BeiGene employee (I)

Travel, Accommodations, Expenses: BeiGene, BeiGene (I)

Benjamin Solomon

Honoraria: Bristol-Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Roche, Genentech, Pfizer

Consulting or Advisory Role: Bristol-Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Pfizer (Inst), Roche, Genentech, Loxo Oncology

Research Funding: Pfizer (Inst)

Patents, Royalties, Other Intellectual Property: Royalties from Veristrat (Biodesix), UpToDate

No other potential conflicts of interest were reported.