First-in-Class ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study

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ABSTRACT

Ulixertinib (BVD-S23) is an ERK1/2 kinase inhibitor with potent preclinical activity in BRAF- and RAS-mutant cell lines. In this multicenter phase I trial (NCT01781429), 135 patients were enrolled to an accelerated 3+3 dose-escalation cohort and six distinct dose-expansion cohorts. Dose escalation included 27 patients, dosed from 10 to 900 mg twice daily and established the recommended phase II dose (RP2D) of 600 mg twice daily. Ulixertinib exposure was dose proportional to the RP2D, which provided near-complete inhibition of ERK activity in whole blood. In the 108-patient expansion cohort, 32% of patients required dose reduction. The most common treatment-related adverse events were diarrhea (48%), fatigue (42%), nausea (41%), and dermatitis acniform (31%). Partial responses were seen in 3 of 18 (17%) patients dosed at or above maximum tolerated dose and in 11 of 81 (14%) evaluable patients in dose expansion. Responses occurred in patients with NRAS-, BRAF V600-, and non-V600 BRAF-mutant solid tumors.

SIGNIFICANCE: Here, we describe the first-in-human dose-escalation study of an ERK1/2 inhibitor for the treatment of patients with advanced solid tumors. Ulixertinib has an acceptable safety profile with favorable pharmacokinetics and has shown early evidence of clinical activity in NRAS- and BRAF V600- and non-V600-mutant solid-tumor malignancies. Cancer Discov; 8(2):1–12. © 2017 AACR.

INTRODUCTION

MAPK signaling via the RAS–RAF–MEK–ERK cascade plays a critical role in oncogenesis. As the terminal master kinase of this MAPK pathway, ERK1/2 influences cellular proliferation, differentiation, and survival through a variety of mechanisms (1). Aberrations of MAPK/ERK pathway components are ubiquitous across numerous cancer types. Mutations in RAS family genes (KRAS and NRAS) occur in approximately 30% of all human cancers (2), with KRAS mutations prevalent in pan-

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creative (>90%; ref. 3), biliary tract (3%-50%; ref. 4), colorectal (30%-50%; ref. 5), lung (25%-30%; ref. 6), ovarian (15%-39%; ref. 7), and endometrioid endometrial (18%; ref. 8) cancers, and NRAS mutations prevalent in melanoma (20%; ref. 9). Mutations in RAF family genes, most notably BRAF at codon V600, are frequent, particularly in malignant melanomas (50%; ref. 10), and in approximately 7% of a wide range of other cancers (11). Atypical BRAF alterations (non-V600) occur sporadically across numerous tumor types. Insight into the mechanism of action of such alterations is developing, with the understanding that BRAF V600 alterations can act as monomers to drive signaling, whereas specific atypical BRAF non-V600 alterations act in a dimer-dependent manner (12). Approved BRAF inhibitors ( vemurafenib and dabrafenib) are effective in BRAF V600-driven tumors, but have not been shown to be effective against BRAF non-V600 mutations. Mutations in MEK or ERK are rare, with reports for MEK mutations occurring in 5% to 8% of melanomas (10, 13), and ERK mutations occurring in cervical cancer (8; ref. 14) and head and neck squamous cell carcinoma (1.5%; ref. 15). Collectively, activating mutations of MAPK/ERK pathway components are frequent events in a range of cancer types. Therefore, downstream inhibition of ERK is an attractive therapeutic avenue to pursue.

Precedence for targeting the MAPK/ERK pathway has been established for treatment of BRAF V600–mutant melanoma and lung cancers, where combined BRAF and MEK inhibition is now standard of care following FDA approval of dabrafenib plus trametinib (16, 17) and vemurafenib plus cobimetinib (18). Furthermore, favorable phase III data have been described for encorafenib plus binimetinib (19). Initially, BRAF inhibitor monotherapy was shown to be effective (20), yet the addition of MEK inhibition not only attenuated BRAF inhibitor–associated toxicities but also improved overall response rates (ORR), progression-free survival (PFS), and overall survival (OS; refs. 16–18). The combination of BRAF/MEK inhibitor therapy now has been studied in a number of BRAF V600–mutant solid-tumor malignancies with varying results, ranging from melanoma-like outcomes in lung cancer.
Ulixertinib (BVD-523) is a highly potent, selective, reversible, ATP-competitive ERK1/2 inhibitor that has been shown to reduce tumor growth and induce tumor regression in BRAF- and RAS-mutant xenograft models. Furthermore, single-agent ulixertinib was found to inhibit tumor growth in human xenograft models that were cross-resistant to both BRAF and MEK inhibitors (38). Therefore, we undertook an open-label, first-in-human study (Clinicaltrials.gov identifier: NCT01781429) of oral ulixertinib to identify both the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D). Study aims also included assessment of the pharmacokinetic and pharmacodynamic properties of ulixertinib as well as preliminary efficacy in patients with genetic aberrations in BRAF, both at V600 and non-V600 positions, NRAS, and MEK.

RESULTS
Patient Characteristics

Between April 4, 2013, and March 6, 2017, a total of 135 patients at 12 sites were consented and enrolled into this study; 27 patients were enrolled in the dose-escalation portion and 108 patients enrolled in the cohort expansion portion (Fig. 1). All patients received at least one dose of study drug. Baseline demographics and disease characteristics are presented in Table 1. The median patient age across the study was 62 years. Fifty-two percent (14/27) and 64% (69/108) of patients were male, and 59% (16/27) and 68% (73/108) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 for the dose-escalation and cohort expansion phases of the study, respectively. Patients who had previously received BRAF and/or MEK therapy represented 41% (11/27) of those enrolled in dose escalation and 19% (21/108) in cohort expansion, or 24% (32/135) overall. Furthermore, 51% (69/135) of patients had received prior immunotherapy. Elevated lactate dehydrogenase (LDH) was present in 46% (43/93) of patients evaluated in screening.

In cohort expansion, 108 patients were enrolled to six cohorts: patients without prior MAPK-targeted therapy who had BRAF-mutant colorectal (17 enrolled/11 evaluable), lung (16/12), or other cancers (24/21), NRAS-mutant melanoma (22/18), or any tumor type with a MEK mutation (8/4), and patients with melanoma who had received prior BRAF and/or MEK inhibitor treatment and who were refractory to, intolerant of, or progressed on these treatments (21/15). A variety of specific BRAF and NRAS mutations were included, as were a number of different tumor types (Supplementary Table S1). Collectively, 91 patients with tumors harboring mutations in BRAF, 24 with NRAS, 9 with MEK, 5 with no mutation identified, and 6 with other mutations (5 KRAS and 1 GNAS) were enrolled.

Dose Escalation, Dose-Limiting Toxicities, MTD, and RP2D

Per protocol, 5 single-patient cohorts (from 10 through 150 mg twice daily) proceeded without evidence of a dose-limiting toxicity (DLT). The 300-mg twice daily cohort was expanded to more fully characterize ulixertinib exposures. One of 6 patients given 600 mg twice daily experienced a DLT of grade 3 rash. The 900-mg twice daily dose exceeded the MTD, with 1 patient experiencing grade 3 pruritus, grade 3 elevated aspartate aminotransferase, and grade 3 elevated alanine aminotransferase, and another patient experiencing grade 3 diarrhea, grade 3 vomiting, grade 3 dehydration, and grade 3 elevated creatinine (Supplementary Table S2). The subsequent intermediate dose of 750 mg twice daily also exceeded the MTD, with DLTs of...
Table 1. Clinical characteristics of patients at baseline, including cancer types, prior therapies, and enrollment

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>All patients (N = 135)</th>
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</thead>
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<tr>
<td>Age</td>
<td>62 (21–85) years</td>
</tr>
<tr>
<td>≥65 year</td>
<td>63 (47)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (61)</td>
</tr>
<tr>
<td>Female</td>
<td>52 (39)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45 (33)</td>
</tr>
<tr>
<td>1</td>
<td>90 (67)</td>
</tr>
<tr>
<td>Prior immune therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>69 (51)</td>
</tr>
<tr>
<td>No</td>
<td>66 (49)</td>
</tr>
<tr>
<td>Prior BRAFi/MEKi therapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 (24)</td>
</tr>
<tr>
<td>No</td>
<td>103 (76)</td>
</tr>
<tr>
<td>Pretreatment LDH, n (%)</td>
<td></td>
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<tr>
<td>Elevated</td>
<td>43 (32)</td>
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<tr>
<td>Not elevated</td>
<td>50 (37)</td>
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<tr>
<td>Not done</td>
<td>42 (31)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.83 (14.6–148.2)</td>
</tr>
<tr>
<td>Primary cancer type, n (%)</td>
<td></td>
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<tr>
<td>Melanoma</td>
<td>53 (39)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>26 (19)</td>
</tr>
<tr>
<td>Non-small cell lung</td>
<td>19 (14)</td>
</tr>
<tr>
<td>Papillary thyroid</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Prostate</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other*</td>
<td>21 (16)</td>
</tr>
<tr>
<td>Enrollment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Dose escalation</td>
<td>27 (20)</td>
</tr>
<tr>
<td>BRAF colorectal cohort</td>
<td>17 (13)</td>
</tr>
<tr>
<td>BRAF non-small cell lung cohort</td>
<td>16 (12)</td>
</tr>
<tr>
<td>BRAF melanoma cohort</td>
<td>21 (16)</td>
</tr>
<tr>
<td>BRAF other cancer cohort</td>
<td>24 (18)</td>
</tr>
<tr>
<td>NRAS melanoma cohort</td>
<td>22 (16)</td>
</tr>
<tr>
<td>MEK cancer cohort</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

NOTE. Data are presented as N(%) unless indicated otherwise.
*Includes adenoid cystic, angiosarcoma, appendiceal, cecum, cholangiocarcinoma, gallbladder, gastrointestinal stromal tumor, mediastinal non-seminomatous germ cell tumor, mesothelioma, ovarian, pancreatic, salivary duct, small cell lung, squamous cell, thyroid, urachal, and vaginal.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic analyses of ulixertinib following a single dose and after achieving steady state in dose escalation are summarized in Fig. 2A and B. Generally, orally administered ulixertinib (taken without food) was slowly absorbed, reaching maximum concentration (Cmax) at approximately 2 to 4 hours, and then declining slowly thereafter. Plasma drug concentrations were measured as a function of time through a single dosing period (12 hours). As such, it was not possible to calculate an effective or terminal phase elimination rate. Ulixertinib pharmacokinetics were linear and dose proportional in terms of both Cmax (Supplementary Table S3) and area under the curve (AUC) when administered up to 600 mg twice daily on day 1 and at steady state (Fig. 2C and D, respectively). A further increase in exposure was not observed as the dose increased from 600 to 900 mg twice daily, although only a limited number of patients were treated at the higher dose levels. Minimal plasma accumulation of ulixertinib and its metabolites was observed at steady state at the lower (<75 mg twice daily) dose levels, whereas accumulation ranged from approximately 1.3- to 4.0-fold for the higher dose levels. The degree of inter-patient variability in plasma exposure to ulixertinib and its metabolites was moderate and considered clinically manageable. Urinary excretion of ulixertinib on day 1 and at steady state was negligible (<0.2% of the dose) and not dose-related within this very low percentage range. Individual renal clearance values ranged from 0.128 to 0.0895 L/hour (where n = 1 patient per dose level) and mean values ranged from 0.0149 to 0.0300 L/hour (where n ≥ 2 patients).

To confirm on-target and pathway inhibition by ulixertinib, we examined RSK1 phosphorylation as a target biomarker in patients’ whole-blood samples following oral dosing (assay provided in Methods). Samples collected from ulixertinib-treated patients displayed concentration-dependent inhibition of PMA-stimulated ERK activity (Fig. 2E), ranging from 0% ERK inhibition for patients dosed at 10 mg twice daily to 93% ± 8% ERK inhibition with dosing at 900 mg twice daily, when measured at trough. Near-complete (86% ± 12%) inhibition

diarrhea (48%), fatigue (42%), and nausea (42%; Table 2). No patients experienced a grade 4 or 5 treatment-related AE. Most events were grade 1 to 2, with treatment-related grade 3 events noted in 56 of 135 patients (41%). The most common grade 3 treatment-related events were rash (17% of patients, including maculopapular (n = 13), rash (n = 5), dermatitis acniform (n = 4), and erythematous (n = 1)), diarrhea (7%), anemia (4%), and fatigue (4%). AEs regardless of attribution leading to treatment interruptions occurred in 23 of 27 (85%) patients in dose escalation and 70 of 108 (65%) patients in cohort expansion, with gastrointestinal, and skin and subcutaneous disorders accounting for 20% and 15% of all dose interruptions, respectively. Median dose intensity for patients treated at RP2D was 89%. AEs leading to discontinuation regardless of attribution occurred in 26 of 135 (19%) patients, 3 in dose escalation (75, 300, and 900 mg twice daily) and 23 in cohort expansion. Twenty-five patients experienced a total of 38 treatment-related serious AEs (SAE); the only events occurring in multiple patients were diarrhea (n = 7), dehydration (n = 4), acute renal failure, anemia, increased blood creatinine, maculo-papular rash, nausea, and vomiting (n = 2 each).

Safety and Adverse Events

Investigator-assessed treatment-related adverse events (AE) of any grade were noted in 125 of 135 patients (93%) treated, whereas 105 of 115 patients (91%) treated at the RP2D had a treatment-related AE. Study wide, the most common treatment-related AEs were rash (76%, predominantly acniform), grade 3 rash and grade 2 diarrhea in 1 patient and grade 2 hypotenion, grade 2 anemia, and grade 1 elevated creatinine in another patient, which delayed cycle 2 dosing. Therefore, the MTD and RP2D were determined to be 600 mg twice daily.
of ERK activity was observed throughout the entire dosing period at RP2D. Ulixertinib exposures in cohort-expansion patients dosed at the RP2D were Cmax 1.15 and 2.12 μg/mL and AUC0-12 8.07 and 19.93 μg*h/mL after the first dose and at steady state, respectively (Fig. 2F).

Antitumor Effects

Tumor response to ulixertinib was assessed in 25 and 81 evaluable patients from the dose-escalation and expansion cohorts, respectively, using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Per protocol, evaluable patients were defined as those who completed two cycles of treatment. Although no patient achieved a complete response, 14 partial responses were observed in 101 evaluable patients were defined as those who completed two cycles of treatment. Although no patient achieved a complete response, 14 partial responses were observed in 101 evaluable patients who were dosed at 600 mg twice daily or greater (3 in cohort expansion, 53 patients with melanoma were classified by their kinase activity (12, 40). Of note, central nervous system (CNS) responses were seen in a patient with BRAFV600E–mutant glioblastoma multiforme.

Dose-Escalation Cohorts

In dose escalation, 3 of 25 (12%) evaluable patients (all with melanoma harboring BRAF V600M mutations) achieved partial responses (PR). These 3 patients, who were BRAF/MEK therapy naïve, intolerant, or refractory, had response durations of 4.2, 12.4, and 24.9 months, respectively (Fig. 3A and B). Figure 3C shows computed tomography (CT) scans of one of the responders, who had progressed on prior vemurafenib and subsequent dabrafenib treatment and maintained a PR for 24.9 months. Noteworthy, this patient’s PR was first observed after 13.5 months of treatment, whereas total time on study exceeded 38.4 months (ongoing at data cutoff).

Additionally, 6 patients had stable disease for more than 6 months. Figure 3B depicts the time to PR and the duration of response in this study population. One patient with bronchioalveolar non–small cell lung cancer (not enough tissue for molecular profiling) was on treatment for >26.2 months with stable disease. Twenty-six of 27 patients (96%) discontinued treatment due to progressive disease (85%, 23/27) or other reasons (11%, 3/27; 1 drug-related and 2 unrelated AEs). The mean duration of ulixertinib treatment before discontinuation was 6.6 months.

Dose-Expansion Cohorts

In dose expansion, the tumor response and duration on study for each cohort are depicted in Fig. 4A and B, respectively. PRs were seen in 11 of 81 (14%) evaluable patients, including 3 of 18 with NRAS-mutant melanoma, 3 of 12 with BRAF-mutant lung cancer (2 with V600E and 1 with L597Q), 1 of 15 with BRAF/MEK inhibitor–refractory BRAF V600E–mutant melanoma, and 4 of 21 with other BRAF-mutant cancers. These include one each of BRAF L485W gallbladder cancer (Fig. 5A), BRAF V600E glioblastoma multiforme (Fig. 5B), BRAF G469A head and neck cancer, and BRAF G469A small-bowel cancer. Of these patients, two of the responses lasted greater than 4.9 months. The maximal tumor responses for patients with BRAF non-V600 mutations (n = 28) are shown in Fig. 4C and are classified by their kinase activity (12, 40). Of note, central nervous system (CNS) responses were seen in a patient with BRAF V600E–mutant lung cancer with metastases, and another with BRAF V600E–mutant glioblastoma multiforme.

Based on the preclinical data, it was expected that ulixertinib would have activity in patients with melanoma harboring mutations in the MAPK pathway (39). In all (including dose escalation and expansion), 53 patients with melanoma were

Table 2. Patients with AEs that occurred in ≥10% (possibly related or related) including combined rash events and combined ocular events

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>&lt;300 mg b.i.d. (n = 5)</th>
<th>300 mg b.i.d. (n = 4)</th>
<th>600 mg (n = 115)</th>
<th>&gt;600 mg b.i.d. (n = 11)</th>
<th>Total (N = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined rashb</td>
<td>3 (60)</td>
<td>0 (0)</td>
<td>3 (25)</td>
<td>0 (0)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (100)</td>
<td>1 (25)</td>
<td>4 (38)</td>
<td>7 (6)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (60)</td>
<td>1 (25)</td>
<td>4 (38)</td>
<td>2 (2)</td>
<td>6 (54)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (60)</td>
<td>2 (50)</td>
<td>4 (38)</td>
<td>2 (2)</td>
<td>6 (54)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>28 (24)</td>
<td>0 (0)</td>
<td>6 (54)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0)</td>
<td>1 (25)</td>
<td>27 (23)</td>
<td>1 (&lt;1)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>1 (25)</td>
<td>18 (16)</td>
<td>1 (&lt;1)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Combined ocular</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>14 (12)</td>
<td>1 (&lt;1)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>eventsb</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>12 (10)</td>
<td>1 (&lt;1)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>6 (5)</td>
<td>5 (4)</td>
<td>6 (54)</td>
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<tr>
<td>Anemia</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>6 (5)</td>
<td>4 (36)</td>
<td>6 (54)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (8)</td>
<td>1 (&lt;1)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>10 (9)</td>
<td>0 (0)</td>
<td>2 (18)</td>
</tr>
</tbody>
</table>

Abbreviation: b.i.d., twice daily.

*a Combined rash includes preferred terms of dermatitis acneiform (1), acne (1), skin exfoliation (2), and any term containing rash (81).

*b Combined ocular events includes preferred terms of halo vision (1), photophobia (2), retinal detachment (1), retinal vein occlusion (1), retinopathy (1), vision blurred (6), visual impairment (10), and vitreous floaters (1). Note that retinal vein occlusion event (grade 3) occurred after study and resolved with drug cessation.

Combined molecular profiling (n = 28) are shown in Fig. 4C and are classified by their kinase activity (12, 40). Of note, central nervous system (CNS) responses were seen in a patient with BRAF V600E–mutant lung cancer with metastases, and another with BRAF V600E–mutant glioblastoma multiforme.

Based on the preclinical data, it was expected that ulixertinib would have activity in patients with melanoma harboring mutations in the MAPK pathway (39). In all (including dose escalation and expansion), 53 patients with melanoma were
Figure 2. Pharmacokinetics and pharmacodynamics of ulixertinib. Plasma concentrations of ulixertinib as a function of time and dose level following dosing on day 1 (A) and at steady state (B). AUC as a function of dose level following dosing on day 1 (C) and at steady state (D). The data for dose levels 10 to 150 mg twice daily (b.i.d.) represent a single patient at each dose level. Plasma levels and pharmacodynamic effects of ulixertinib are shown as a function of the dose level (E). Ulixertinib plasma levels from patients dosed with 600 mg/kg, twice daily, are shown at day 1 and steady state (F).

treated with ulixertinib, and 40 were eligible for response evaluation per RECIST v1.1. In 19 such patients with BRAF-mutant melanoma previously treated with a BRAF and/or MEK inhibitor, 3 (15%) achieved a PR, 6 had stable disease, and 10 had progressive disease as a best response. In the patients with a PR, the time from last MAPK-targeted therapy was 21, 26, and 169 days, respectively. In patients with stable disease, this number ranged from 19 to 713 days; however, all but one commenced therapy within 6 weeks of the last dose of these targeted therapies. Seventeen patients with NRAS-mutated melanoma were evaluable for response. Three patients (18%) achieved a PR, 6 had stable disease, and 8 had disease progression as best response. Additionally, 3 other patients with melanoma harboring BRAF mutations, who had not received prior targeted therapy, were treated. One of 2 patients with a BRAF V600 mutation responded, and the 1 patient with a BRAF fusion had stable disease.

DISCUSSION

We report results from a first-in-human study evaluating the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of ulixertinib in 135 patients with advanced solid tumors. In the dose-escalation portion of this study,
Figure 3. Dose-escalation patient response. Individual patient’s target lesion response (A) and time on study (B) are shown as a function of initial dose level. C, A representative sustained partial tumor response in a melanoma patient that was refractory to prior BRAF inhibitor therapy. Horizontal red line in A depicts RECIST v1.1 partial response threshold. b.i.d., twice daily.
Figure 4. Cohort expansion patient response. Target lesion responses (A) and time on study (B), grouped by cohort, are shown for each evaluable patient initially dosed with 600 mg of ulixertinib twice daily in the expansion phase of the study. Specific genetic mutations are also indicated (A, B). C, Tumor response data for patients with atypical (non-V600) BRAF mutations, with specific mutations indicated. Data are further discriminated by color based on the literature-reported MAPK pathway activity, as indicated by pERK levels. CRC, colorectal cancer; NSCLC, non–small cell lung cancer.
oral treatment with ulixertinib resulted in both radiographic responses by RECIST v1.1 (3 PRs) and prolonged disease stabilization in some patients, many with tumor alterations consistent with MAPK activation (BRAF, KRAS, NRAS). Drug exposures increased linearly with increasing doses up to 600 mg twice daily, which provided near-complete 24/7 inhibition of ERK substrate (RSK1) phosphorylation in an ex vivo whole-blood assay. Furthermore, toxicities associated with ulixertinib were consistent with preclinical models and were manageable when administered up to its MTD and RP2D, determined to be 600 mg twice daily.

Ulixertinib was successfully administered in six cohorts of patients with NRAS, BRAF, and MEK mutations at the RP2D, which demonstrated unique and encouraging clinical activity. Tumor regression and/or stabilization of disease was seen in every dose cohort, and partial responses were seen in patients with a variety of solid-tumor malignancies with mutations in BRAF V600E/K, non-V600 BRAF, and NRAS. In particular, non-V600 BRAF mutations, including L485W, L597Q, and G469A across a variety of solid tumors, were shown to be clinically actionable for the first time, with durable objective responses. This study provides the first clinical evidence that dimer-dependent atypical BRAF non-V600 mutations may be actionable by downstream ERK inhibition, highlighting an important new therapeutic target for future drug development in solid tumors. Furthermore, the CNS activity of ulixertinib was clinically demonstrated by the objective responses achieved in glioblastoma multiforme and lung cancer with brain metastases.

Ulixertinib was generally well tolerated, with manageable and reversible toxicity. The most common AEs were rash (most commonly acneiform), fatigue, and gastrointestinal AEs, including nausea, vomiting, and diarrhea. The safety profile of ulixertinib is consistent with its selective inhibition of the MAPK pathway; the AE profile overlaps considerably with MEK inhibitor experience (41). However, toxicities associated with any targeted therapy may include dependence on both the specific mechanism and the degree of target inhibition, as well as any off-target effects.

Durable responses by RAF and MEK inhibitors are often limited by intrinsic and eventual acquired resistance, with a common feature often involving reactivation of the ERK pathway (25–31, 38). Thus, ERK inhibition with ulixertinib alone or in combination with other MAPK signaling pathway inhibitors may have the potential to delay the development of resistance to existing therapies and to benefit a broader patient population (42). The ability of ERK inhibitors, including ulixertinib, to retain their potency in BRAF- and MEK-resistant cell lines provides preclinical evidence for their use in patients with acquired resistance to standard of care (BRAF/MEK inhibitor combination therapy; refs. 34, 35, 39).

Importantly, in this study, 9 of 19 patients with BRAF-mutant melanoma previously treated with MAPK inhibitor therapy had either a PR or stable disease, including a patient with a PR while receiving ulixertinib whose cancer had progressed after experiencing stable disease when treated initially with a BRAF inhibitor ( vemurafenib) and subsequently with dabrafenib. This patient remained on study for a total of 38.4 months as of the cutoff date of this publication. Based in part on the antitumor effects observed in this patient, the FDA has designated as a Fast Track development program the investigation of ulixertinib for the treatment of patients with unresectable or metastatic BRAF V600E/K or MEK inhibitor(s). One potential explanation for this activity in patients with BRAF-mutant melanoma previously treated with MAPK pathway–targeted therapy is repopulation of the tumor following a break in treatment (43). However, in 2 of the 3 PRs and 5 of the 6 patients with stable disease, ulixertinib commenced within 6 weeks of the last BRAF and/or MEK inhibitor dose, with the majority treated within 4 weeks.
In summary, we report initial data from the phase I study evaluating ulixertinib, a first-in-class ERK inhibitor, as a treatment for patients with advanced cancers. Continuous, twice-daily oral treatment with ulixertinib resulted in antitumor effects in subsets of patients with a variety of solid-tumor types, including patients either naive to or having progressed on available MAPK pathway–targeted therapies. Ulixertinib generally was well tolerated in this population of patients with advanced cancer, and toxicities were manageable; the MTD and RP2D were 600 mg twice daily. Ulixertinib exposures increased linearly up to the RP2D, and robust pharmacodynamic effects were evident at this dose level. The preliminary efficacy shown in a variety of molecularly defined cohorts, hallmarked by MAPK activating alterations, supports the ongoing development of ulixertinib as a single agent as well as in combination.

**METHODS**

**Patients**

Between April 4, 2013, and March 6, 2017, a total of 135 patients at 12 sites were consented and enrolled into the study, after local Institutional Review Board approval. All participants provided informed consent prior to initiation of any study procedures. Patients ages ≥18 years were eligible for participation if they had incurable, histologically confirmed metastatic or advanced-stage malignant tumors; an ECOG PS of 0 or 1; adequate renal, hepatic, bone marrow, and cardiac function; and a life expectancy ≥3 months. Patients may have received up to two prior lines of chemotherapy for their metastatic disease. Exclusion criteria were known uncontrolled brain metastases; gastrointestinal conditions that could impair absorption of the investigational drug; patients who had prior treatment with the investigational drug within 21 days or 5 half-lives of the drug, whichever was shorter; patients with known uncontrolled nonmelanoma skin cancer; patients who had brain metastases; patients with known serous cystadenoma or cystadenocarcinoma of the ovary; patients who had a prior malignancy that had relapsed or metastasized or was not in complete remission for ≥1 year; patients with a known contraindication to the investigational drug; patients who had a confirmed positive pregnancy test; and patients who were pregnant or breast-feeding.

**Study Design and Objectives**

This was an open-label, phase I study to assess the safety, pharmacokinetics, and pharmacodynamics of escalating doses of ulixertinib in a capsule formulation in patients with advanced malignancies. The dosing regimen combined both accelerated titration and standard cohort 3 + 3 dose-escalation schema, which were used jointly to identify the MTD and RP2D of ulixertinib in patients with advanced solid tumors. One to 6 patients per treatment cohort were assigned to receive sequentially higher oral doses of ulixertinib administered twice daily (12-hour intervals) continuously in 21-day cycles at the following doses: 10 mg (n = 1); 20 mg (n = 1); 40 mg (n = 1); 75 mg (n = 1); 150 mg (n = 1); 300 mg (n = 4); 600 mg (n = 7); 900 mg (n = 7); and 750 mg (n = 4). In the cohort-expansion phase, patients were enrolled to one of six cohorts until at least 15 patients per cohort were expected to be evaluable for response to therapy. The six cohorts were reduced from up to 100% to a maximum of 50% when fewer than 2 of 6 patients assigned to that cohort had experienced ulixertinib-related DLTs in the first 21 days of treatment that resulted in grade 4 or higher hematologic toxicity for >1 day; grade 3 hematologic toxicity with complications (e.g., thrombocytopenia with bleeding); grade 3 or higher nonhematologic toxicity, except untreated nausea, vomiting, constipation, pain, and rash (these become DLTs if the AE persisted despite adequate treatment); or a treatment interruption exceeding 3 days in cycle 1 (or the inability to be in cycle 2 for >7 days) due to ulixertinib-related toxicity.

**MTD, DLT, and RP2D**

MTD was defined as the highest dose cohort at which ≤33% of patients experienced ulixertinib-related DLTs in the first 21 days of treatment. DLT was defined as a ulixertinib-related toxicity in the first 21 days of treatment that resulted in a grade 4 or higher hematologic toxicity for >1 day; grade 3 hematologic toxicity with complications (e.g., thrombocytopenia with bleeding); grade 3 or higher nonhematologic toxicity, except untreated nausea, vomiting, constipation, pain, and rash (these become DLTs if the AE persisted despite adequate treatment); or a treatment interruption exceeding 3 days in cycle 1 (or the inability to be in cycle 2 for >7 days) due to ulixertinib-related toxicity.

The RP2D could be as high as the MTD and was determined in discussion with the clinical investigators, medical monitor, and sponsor. Observations related to pharmacokinetics, pharmacodynamics, and any cumulative toxicity observed after multiple cycles were included in the rationale supporting the RP2D.

**Safety Assessments**

Patients who received ulixertinib and experienced any untoward medical occurrence had their AE defined as per the MedDRA coding dictionary, regardless of causal relationship with test article. The AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Grading Scale, version 4.03. Investigators assessed the relationship of AEs to study drug as either unrelated, possibly related, or related, and followed up until event resolution or stabilization or the AE was judged to no longer be clinically significant. An SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity or a congenital anomaly/birth defect.

Safety evaluations were conducted at baseline, on days 8, 15, 22, 29, 36, and 43, and, in patients who continued treatment, every 3 weeks or if clinically indicated thereafter. Each evaluation included a physical examination and clinical laboratory studies. Electrocardiograms were repeated if clinically significant and at the discretion of the investigator. Holter monitoring (12 ± 2 hours) was performed in a subset of patients in cycle 1, at day 1 and day 15 (PK sampling
days) and Holter ECG analyses were conducted by BioClinica. An ophthalmologic assessment was also conducted at screening, at the end of study, and at other visits by an ophthalmologist if clinically indicated.

**Pharmacokinetic Analysis**

The pharmacokinetic population consisted of patients who received at least 1 dose of ulixertinib and had evaluable pharmacokinetic data for plasma and/or urine. Blood samples were collected prior to dosing, and then at 0.5 (± 5 minutes), 1 (± 5 minutes), 2 (± 10 minutes), 4 (± 10 minutes), 6 (± 10 minutes), 8 (± 10 minutes), and 12 (± 2 hours) hours on day 1 (visit 2; baseline/initiation of treatment) and day 15 (visit 4; at steady state). On day 22, prior to dose administration, a final blood sample was collected for pharmacokinetic analyses. Urine samples were collected pre-dose and at the 1- to 6-hour and 6- to 12- (± 2) hour intervals post-dose on days 1 and 15. Plasma and urine samples were analyzed for ulixertinib and metabolites using validated LC/MS-MS methods. Standard pharmacokinetic parameters were obtained using Phoenix WinNonlin (Pharsight) with a noncompartmental method. Pharmacokinetic Analysis

Relationship between dose and exposure was calculated using standard least-squares regression analysis.

**Pharmacodynamic Confirmation of Target Inhibition by Ulixertinib**

ERK inhibition by ulixertinib was determined by measuring pRSK/RSK as a target biomarker in human whole-blood samples obtained from patients who had received ulixertinib during the phase 1 study. To establish a ulixertinib-dependent RSK1-phosphorylation calibration curve, healthy donor blood was treated with serial dilutions of ulixertinib (DMSO control) for 2 to 3 hours followed by stimulation with 100 nmol/L PMA for 20 minutes at room temperature. Peripheral blood mononuclear cells were isolated, lysed, and flash-frozen prior to measurement of pRSK and total RSK by ELISA (PathScan).

A plot of the pRSK/RSK ratio as a function of ulixertinib concentration was used as a standard curve for determination of ERK activity. Maximum (100%) inhibition was defined as the pRSK/RSK value obtained in the presence of 10 μmol/L ulixertinib: Baseline inhibition was defined as the pRSK/RSK value obtained in untreated and unstimulated blood. The EC_{50} for ulixertinib was determined to be ~200 ng/mL.

Patient samples were evaluated using this methodology, with each patient serving as their own control for maximal and minimal stimulation. Pre- and post-ulixertinib treatment samples were collected at day 1 and steady state.

**Antitumor Response**

Tumor measurements based on physical examination occurred at baseline and on the first day of each treatment cycle. CT and other assessments were made every 2 to 3 cycles. Findings were assessed in accordance with RECIST v1.1: Complete response was defined as disappearance of all target lesions; PR was defined as a ≥30% decrease in the sum of the longest diameters of target lesions, taking baseline measurements as reference; stable disease was defined as being of neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the baseline measurement. CT scans were performed per routine site protocols and assessed by site radiologists; no central read assessments were included in this analysis.

**Disclosure of Potential Conflicts of Interest**

R.J. Sullivan reports receiving a commercial research grant from Merck and is a consultant/advisory board member Merck and Novartis. J.R. Infante is Vice President of Early Development at Johnson & John-son and is a consultant/advisory board member for BioMed Valley. F. Janku reports receiving commercial research grants from BioMed Valley Discoveries, Novartis, and Plexxikon, has ownership interest (including patents) in Provitagen, and is a consultant/advisory board member for Novartis. G.I. Shapiro reports receiving commercial research grants from Pfizer, Lilly, and Merck/EMD Serono, and is a consultant/advisory board member for Pfizer, Lilly, G1 Therapeutics, Roche, Vertex Pharmaceuticals, and Merck/EMD Serono. A.W. Tolcher is a consultant/advisory board member for Asana and Astex. A. Wang-Gillam is a consultant/advisory board member for Pfizer, Merrimack, Ipsen, Newlink, Jacobio, and Repugene. M. Sznol is a consultant/advisory board member for Novartis, Genentech/Roche, and Pierre-Fabre. R.D. Carvajal is a consultant/advisory board member for Bristol-Myers Squibb, Janssen, Iconic Therapeutics, Merck, Roche/Genentech, Aura Biosciences, Chimeron, and Rgenix. S.P. Patel has received honoraria from the speakers bureaus of Bristol-Myers Squibb and Merck, has ownership interest (including patents) in Proventus, and is a consultant/advisory board member for Amgen, Castle Biosciences, Genentech, and Incyte. M. Varterasian is a consultant/advisory board member for BioMed Valley Discoveries. D.M. Hyman reports receiving commercial research grants from AstraZeneca, Puma Biotechnology, and Loxo Oncology, and is a consultant/advisory board member for CytoMx, Atara Biotherapeutics, Boehringer Ingelheim, Chugai, and AstraZeneca. B.T. Li is a consultant/advisory board member for Genentech. No potential conflicts of interest were disclosed by the other authors.

**Authors’ Contributions**


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.J. Sullivan, J.R. Infante, M.E. Lacouture, S.P. Patel, C.M. Emery, A.L. Groover, S. Saha, D.J. Welsch, B.T. Li.


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