A Phase I Study of PF-04449913, an Oral Hedgehog Inhibitor, in Patients with Advanced Solid Tumors

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Abstract

Purpose: To estimate the maximum tolerated dose (MTD) of single-agent PF-04449913, and to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity in patients with advanced tumors.

Experimental Design: A 3+3 design was used in this open-label, multicenter, phase I study and dose escalation/de-escalation applied until identification of the MTD. PF-04449913 was orally administered once daily in continuous 28-day treatment cycles. The starting dose was 80 mg.

Results: A total of 23 patients were enrolled; 19 were evaluable for first-cycle dose-limiting toxicity (DLT). The first-cycle DLT rate at the 640 mg dose level was 33.3%, and the MTD was estimated to be 320 mg once daily. The recommended phase II dose was not determined. PF-04449913 was generally well tolerated at doses of 80 to 320 mg once daily. The most common treatment-related adverse events (AE) were grade 1–2 dysgeusia, fatigue, decreased appetite, nausea, dizziness, dehydration, and diarrhea. Treatment-related grade 3 AEs only occurred in patients receiving PF-04449913 640 mg once daily. No treatment-related grade 4–5 AEs were reported. Pharmacokinetic analysis indicated a generally dose-proportional kinetics with biphasic elimination, supporting once-daily dosing. PF-04449913 modulated hedgehog signaling at the dose levels tested, as demonstrated by >80% downregulation of GLI1 expression in the skin of treated patients. Eight patients (34.8%) achieved stable disease; none had complete or partial response. Three patients with disease progression at enrollment had prolonged disease stabilization (>6 months).


Introduction

The Hedgehog (Hh) signaling pathway is a key regulator of cell growth, self-renewal, patterning, and differentiation during embryogenesis, but is normally dormant in adult tissues (1, 2). The Hh pathway regulates the cell cycle (3) and processes as diverse as angiogenesis and myogenesis during development (4). In mammals, unbound patched-1 (PTCH1), the transmembrane receptor for Hh pathway ligands, acts as an inhibitor of the signal transducer Smoothened (SMO). When a Hh pathway ligand binds to PTCH1, this inhibition is relieved, allowing signaling via SMO and thereby facilitating the activation of the glioma-associated (GLI) transcription factors, the transcription of Hh target genes including GLI1 and MYC among others (5–7), and increased cell proliferation (8).

Aberrant Hh pathway activation via overexpression of the Hh ligand leading to autocrine and paracrine stimulation (6), inactivation or loss of function of PTCH1 (9, 10), or activating mutations in SMO (9) has been implicated in the pathogenesis of multiple cancers including B-cell malignancies (11), lung (12), liver (13), and pancreatic cancers (14–16), and in the development of bone metastases (8). Furthermore, aberrant Hh pathway activation has been associated with drug resistance in various hematologic (17, 18) and solid malignancies (19, 20). Several Hh signaling pathway inhibitors, many of them SMO inhibitors, have shown antitumor activity in xenograft models (21, 22). In addition, SMO inhibitors have demonstrated efficacy in a variety of solid tumors (23–26). Thus, SMO represents a promising therapeutic target for the inhibition of Hh signaling and treatment of a spectrum of malignancies.

PF-04449913 is a potent and selective Hh pathway inhibitor that acts by binding SMO and blocking signal transduction. In xenograft models of human colorectal and pancreatic cancer, treatment with PF-04449913 in combination with other antican-
cer agents resulted in 63% and 73% inhibition of tumor growth, respectively (27). Furthermore, PF-04449913 demonstrated preliminary antitumor activity in a phase I trial, when given as monotherapy in patients with acute myeloid leukemia and myelodysplastic syndrome (28).

This phase I study was designed to determine the maximum tolerated dose (MTD) of single-agent PF-04449913 when continuously administered to patients with advanced or metastatic solid tumors. Secondary objectives were to characterize the safety, tolerability, pharmacokinetics, pharmacodynamics,
Translational Relevance

Aberrant activation of the Hedgehog (Hh) pathway has been implicated in the pathogenesis of solid tumors and hematologic malignancies, and in the development of resistance to anticancer treatment. PF-04449913 is a potent and selective inhibitor of the Hh pathway with activity in preclinical models. In this first-in-human study, we estimated the maximum tolerated dose for daily, oral administration of PF-04449913, and evaluated the safety profile, tolerability, and preliminary antitumor activity in patients with advanced solid tumors. PF-04449913 was generally well tolerated and exhibited favorable pharmacokinetic properties, with evidence of Hh target pathway modulation. Eight patients (34.8%) achieved stable disease following treatment; prolonged disease stabilization (≥ 6 months) was observed in 3 patients with disease progression at study entry. These findings support further clinical development of PF-04449913 for patients with advanced malignancies.

and antitumor activity of PF-04449913 in this patient population.

Patients and Methods

Patients

All eligible patients had histologically or cytologically confirmed locally advanced or metastatic solid tumors (including basal cell carcinoma, small cell, or non–small-cell lung cancer, pancreatic cancer, melanoma, hepatocellular carcinoma, cervical cancer, and soft tissue- or cartilage-derived sarcoma) that were resistant to standard therapy, or for which no standard therapy exists or standard therapy would be inappropriate. Other key inclusion criteria were Eastern Cooperative Oncology Group performance status of 0 or 1 at screening and adequate bone marrow, renal function, and liver function (total serum bilirubin ≤ 1.5 × upper level of normal (ULN), unless the patient had Gilbert syndrome; aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN or ≤ 5 × ULN if there was liver involvement secondary to a tumor). Key exclusion criteria were symptomatic brain metastases, prior treatment with a Hh pathway inhibitor, current (or within 6 months) significant cardiovascular disease or QTcF (QTc using Fridericia’s formula) more than 470 milliseconds (ms), active and clinically significant infections, current or anticipated use of drugs known to be moderate or strong cytochrome P450 3A4 inhibitors, strong cytochrome P450 3A4 inducers, cytochrome P450 3A4 substrates with narrow therapeutic indices, or strong P-glycoprotein inducers/inhibitors.

Study design and treatment

A standard 3 + 3 design was used in this open-label, multicenter, phase 1, dose-finding study. A dose escalation/de-escalation design was applied in four patient cohorts until identification of the MTD. The MTD was defined as the highest dose administered below the dose resulting in ≥ 33% of patients experiencing dose-limiting toxicities (DLT). The MTD would be declared the recommended phase II dose (RP2D), if long-term administration was proven clinically feasible in a larger number of patients. The study was approved by the Institutional Review Boards and complied with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent. The study was registered at ClinicalTrials.gov (ID: NCT01286467).

PF-04449913 was self-administered orally once daily in the morning as monotherapy in continuous 28-day treatment cycles. The starting dose was 80 mg based on the results of a phase I trial in patients with hematologic malignancies (NCT00953758; ref. 28). In cycle 1 only, patients received treatment for 25 days followed by 3 days of rest to allow for adequate sample collection for pharmacokinetic analyses. In cycle 2 and beyond, PF-04449913 was administered continuously. PF-04449913 treatment continued for up to 12 months or until occurrence of disease progression, patient withdrawal, or unacceptable toxicity. Patients experiencing a DLT during the first treatment cycle were assigned to a lower dose if treatment with study drug was to be continued. After the first cycle, dose reductions were allowed on the basis of patients’ individual tolerability. No additional anticancer therapy was permitted during the study.

Assessments

DLT and safety

The criteria for DLT, the primary endpoint, occurring during cycle 1 and attributable to PF-04449913 included hematologic DLTs such as grade 4 neutropenia lasting for ≥ 7 days, febrile neutropenia defined as grade ≥ 3 neutropenia and a body temperature ≥ 38.5°C, grade ≥ 3 neutropenic infection, grade ≥ 3 thrombocytopenia with bleeding, and grade 4 thrombocytopenia lasting for ≥ 7 days, and nonhematologic DLTs such as grade ≥ 3 adverse events (AE) that had been maximally treated (e.g., nausea, vomiting, diarrhea) or failure to deliver ≥ 80% of planned doses owing to treatment-related AEs. Patients were evaluable for DLT if no major treatment deviation occurred during cycle 1.

Safety evaluations included physical examination, vital signs, 12-lead electrocardiograms, and clinical laboratory tests. Vital sign assessments and clinical laboratory tests were performed at screening and at regular intervals during cycle 1 (days 1, 8, 15, 25), on days 1 and 15 of cycles 2 to 8, on day 1 of subsequent cycles, and at study completion. Physical examinations and 12-lead electrocardiograms were performed at screening, on days 1, 15, 25 of cycle 1, on day 1 of subsequent cycles, and at study completion. AEs were assessed for severity and relationship to treatment and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Pharmacokinetics and pharmacodynamics

Serial plasma samples were collected from each patient to determine the pharmacokinetics of PF-04449913 after a single dose (cycle 1, day 1) and at steady state (cycle 1, day 25). Plasma specimens were stored at approximately − 10 to − 30°C until analysis. Plasma samples were analyzed for PF-04449913 concentrations at Covance Bioanalytical Services, LLC using a validated, sensitive, and specific high-performance liquid chromatography/tandem mass spectrometric method. The lower limit of quantification of plasma PF-04449913 was 0.2 ng/mL. The pharmacokinetic parameters included maximum observed plasma concentration (Cmax), time to first occurrence of Cmax (Tmax), area under the plasma concentration–time profile from zero to time tau (24 hours; AUC0–tau), terminal plasma elimination half-life (t1/2), apparent oral clearance (CL/F), apparent volume of
distribution \( (V_z/F) \), minimum plasma concentration \( (C_{min}) \), average concentration \( (C_{avg}) \), and accumulation ratio \( (R_{ac}) \). Pharmacokinetic parameters were calculated for each patient and each treatment using a noncompartmental analysis of plasma concentration–time data.

Pharmacodynamic parameters included normal skin biopsies, tumor biopsies, and blood samples collected at screening and on day 15 of cycle 1 for determination of treatment-related changes in Hh pathway-regulated gene expression and cytokine levels, respectively. Changes in expression of Hh pathway-related genes in skin biopsies were measured using validated custom TaqMan low-density array cards run on the Applied Biosystems ViiATM 7 system (Life Technologies). Genes analyzed included \( GLI1, GLI2, GLI3, HHIP, FOXM1, PTCH1, PTCH2, CDK5R1, MYCN, SMAD4, CCNE1, SUFU, CCND1, CCND2, GSK3B, SFRP1, \) and \( BCL2 \). Measurements of 13 cytokines in blood samples were performed by Aushon Biosystems using the Searchlight Multiplex ELISA platform. Cytokines analyzed included fibroblast growth factor beta, IFN\( y \), insulin growth factor binding protein-3, IL2, IL6, IL8, IL10, monocyte chemotactic protein-1, stem cell factor, stromal-derived factor-1, TGF\( \beta \), TNF\( \alpha \), and VEGF.

### Antitumor activity

Tumor assessments were performed by computed tomography at screening, on day 1 of alternate treatment cycles (e.g., at 8-week intervals), and at study completion. Objective tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors version 1.1.

### Statistical analyses

Study sample size was estimated empirically, based on the occurrence of DLTs during dose escalation. Safety, efficacy, pharmacokinetic, and pharmacodynamic data were summarized using descriptive statistics.

## Results

### Patient characteristics and treatment

The baseline characteristics of the 23 patients enrolled in this study are listed in Table 1. Median age was 61 years; 14 patients were male and 9 female; and all had Eastern Cooperative Oncology Group performance status 0 or 1 at study entry. More than 90% of patients had measurable disease at baseline, had undergone prior surgery, and had received prior systemic treatment. The majority (69.6%) had also received prior radiotherapy. Seven patients had pancreatic cancer, three had chondrosarcoma, two had lung cancer (small cell and non–small cell), one patient each had adenocarcinoma of the cervix, basal cell carcinoma, malignant hepatocellular carcinoma, malignant melanoma, or other soft tissue- or cartilage-derived sarcoma.

Four patients each received PF-04449913 at 80 and 160 mg once daily (Table 2). One patient in the 160 mg once-daily cohort did not receive 80% of the planned PF-04449913 dose for reasons not related to study treatment toxicities and so was not evaluable for first-cycle DLT occurrence; this patient was replaced per protocol. Seven patients received 320 mg once daily (one was not evaluable for first-cycle DLT) and 8 patients received 640 mg once daily (two were not evaluable for first-cycle DLT). Patients received a median of 2 cycles of treatment (range, 1–14 cycles) in the 80, 320, and 640 mg once-daily cohorts and 1.5 cycles in the 160 mg once-daily cohort. The mean relative dose received by patients was 98.6%, 93.7%, 96.5%, and 67.8% for the 80, 160, 320, and 640 mg once-daily cohorts, respectively. All patients discontinued study treatment, primarily owing to disease progression (43.5%).

### DLT and safety

Of the 23 patients enrolled, 19 patients were evaluable for DLT (Table 2). None of the patients receiving PF-04449913 at the 80, 160, and 320 mg once-daily dose levels experienced DLTs. One patient among the first three receiving the 640 mg once-daily dose did not receive at least 80% of the planned dose in cycle 1 owing to treatment-related grade 2 fatigue, dehydration, dizziness, and hypotension, meeting the DLT definition. This cohort was expanded to include three additional patients, of whom one experienced a DLT of treatment-related grade 3 nausea, vomiting, and dehydration in cycle 1. As the observed first-cycle DLT rate at the 640 mg once-daily dose level was 33.3% (2 of 6 treated patients) the MTD was estimated to be 320 mg once daily based on the 3+3 study design. Cohort expansion at the MTD to further characterize the safety of this dose level and to determine the RP2D in this patient population did not occur because of a sponsor’s decision not related to safety concerns.
All patients experienced at least one treatment-emergent AE (Supplementary Table S). The most frequently reported AEs were dysgeusia (65.2%), fatigue (56.5%), decreased appetite (43.5%), diarrhea (43.5%), nausea (39.1%), dehydration (34.8%), dizziness (34.8%), vomiting (26.1%), muscle spasms (26.1%), and alopecia (26.1%). Ten (43.5%) patients experienced grade 3 AEs and one (4.3%) patient had grade 4 upper abdominal pain. Three patients with disease progression died on study: two with pancreatic cancer and one with sarcoma and grade 5 dyspnea. None of the deaths was attributed to study treatment. Grade 3 QTc interval prolongation was reported as an AE in two patients. One patient in the 320 mg once-daily cohort developed a postbaseline QTcF interval of 61.7 ms 2 hours postdose on day 15; this patient, in the 640 mg once-daily cohort, developed an increase in QTcF interval of 542 ms with an increase of 132 ms over baseline at the end of treatment assessment on day 54. This patient did not receive treatment on day 54 and dosing was discontinued owing to disease progression. This patient had no missed doses over the course of treatment and had no other QTcF prolongation event reported. The other patient in the 640 mg once-daily cohort had absolute QTcF values of more than 500 ms on study days 1 and 45 (range, 501–512 ms); however, absolute QTcF values were less than 500 ms. None of these QTc interval prolongation AEs were considered treatment-related by the investigator. Finally, one patient, in the 640 mg once-daily cohort, developed an increase in QTcF interval of 61.7 ms 2 hours postdose on day 15; this increase was not reported as an AE because no grade change from baseline occurred.

Treatment-related AEs were reported for 20 of 23 patients (87.0%) on study (Table 3). The most frequent treatment-related AEs were dysgeusia (65.2%), fatigue (52.2%), nausea (43.4%), decreased appetite (34.8%), dizziness (30.4%), diarrhea (26.1%), dehydration (26.1%), vomiting (21.7%), muscle spasms (21.7%), and alopecia (21.7%). Most of the treatment-related AEs were grade 1 or 2 in severity; grade 3 treatment-related AEs were observed in 5 patients and included fatigue, decreased appetite, dizziness, dehydration, increased alanine aminotransferase, and increased aspartate aminotransferase. None of the patients receiving the MTD (320 mg once daily) or a lower dose of PF-04449913 experienced a treatment-related grade 3 AE. There were no treatment-related grade 4 or 5 AEs. The most common hematologic laboratory abnormalities were anemia (82.6%) and lymphopenia (65.2%); they were mostly grade 1 or 2 in severity. The only hematologic abnormality ≥grade 3 was lymphopenia reported in 4 (17.4%) patients.

Treatment-related AEs led to study drug discontinuation in 7 (30.4%) patients; 1, 2, and 4 patients in the 160, 320, and 640 mg once-daily cohorts, respectively. AEs leading to permanent discontinuations in 2 or more patients included dehydration, fatigue, nausea, and vomiting. Temporary discontinuations due to treatment-related AEs occurred in 4 (17.4%) patients. AEs leading to temporary discontinuation were: hyperbilirubinemia, increased ALT, AST, and blood alkaline phosphatase (n = 1); diarrhea (n = 1); constipation, gastroesophageal reflux disease (GERD), nausea, and vomiting (n = 1); diarrhea, nausea, malaise, dehydration, presyncope, and syncope (n = 1). Dose reductions due to treatment-related AEs occurred in 2 (8.7%) patients. AEs leading to dose reduction included decreased appetite (n = 1); GERD, dehydration, dizziness, dysgeusia, and orthostatic hypotension (n = 1).

### Pharmacokinetics and pharmacodynamics

PF-04449913 was absorbed rapidly (time to first occurrence of $C_{\text{max}}$ approximately 2 hours across all doses) and eliminated slowly in a biexponential manner ($t_{1/2}$ approximately 20 hours; Table 4). A generally dose-proportional increase in $C_{\text{max}}$ and area under the plasma concentration–time profile from zero to time tau (24 hours) at steady state (Fig. 1) of PF-04449913 was observed across the dose range evaluated. Moderate accumulation of PF-04449913 occurred at steady state (median accumulation ratio, 1.35–1.75), consistent with the observed $t_{1/2}$.

Of the 17 Hh pathway genes evaluated in normal skin biopsies from 15 patients, only GLI1 showed consistent downregulation in all evaluable patient samples (Fig 2A). Exploratory pharmacokinetic/pharmacodynamic analyses demonstrated that >$50\%$ GLI1 inhibition was achieved at steady state across all PF-04449913 doses (Fig 2B). Pathway modulation in tumor tissue could not be assessed due to the fact that tumor samples were available from only one patient in this study. No consistent changes were detected following treatment with PF-04449913, at all doses evaluated, in the blood levels of the 13 cytokines assayed (data not shown).

<table>
<thead>
<tr>
<th>Dose level (mg once daily)</th>
<th>DLTs by dose level</th>
<th>Patients with DLTs (n)</th>
<th>DLTs</th>
<th>any AE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>4/4</td>
<td>0</td>
<td>None</td>
<td>87.0</td>
</tr>
<tr>
<td>160</td>
<td>3/4</td>
<td>0</td>
<td>None</td>
<td>87.0</td>
</tr>
<tr>
<td>320</td>
<td>6/7</td>
<td>0</td>
<td>None</td>
<td>87.0</td>
</tr>
<tr>
<td>640</td>
<td>6/8</td>
<td>2</td>
<td>1 Patient unable to receive 80% of planned dose owing to 2 grade 2 fatigue, dehydration, dizziness, and hypotension and 1 Patient with grade 3 nausea, vomiting, and dehydration</td>
<td>87.0</td>
</tr>
</tbody>
</table>

### Table 3. Treatment-related AEs experienced by ≥5% of patients

<table>
<thead>
<tr>
<th>AEs</th>
<th>All grades $^\text{a}$, n (%)</th>
<th>Grade 3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>20 (87.0)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>15 (65.2)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (52.2)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (34.8)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (34.8)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (30.4)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (26.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>6 (26.1)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (21.7)</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5 (21.7)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (21.7)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2 (8.7)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (8.7)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Alkaline phosphate increased</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase,*

$^{a}$None of the patients experienced a treatment-related grade 4 or 5 AE.
Antitumor activity

Eight (34.8%) patients achieved stable disease as best overall response. None achieved a complete or partial response. Eight patients had objective disease progression. Response could not be determined in 4 patients.

Prolonged disease stabilization of ≥6 months was observed in 3 patients, all with progressive disease before enrollment; (i) a 27-year-old woman with desmoplastic small round cell tumor and prior progression in the liver and in the peritoneum, previously treated with cyclophosphamide/doxorubicin/vincristine alternating with ifosfamide/etoposide for eight cycles followed by liposomal doxorubicin for 10 cycles, who had stable disease for approximately 7 months on PF-04449913 80 mg once daily; (ii) a 72-year-old man with locally advanced pancreatic cancer and metastases to the lung and mediastinal/aortocaval lymph nodes, previously treated with capecitabine/radiotherapy and gemcitabine for 18 months followed by capecitabine monotherapy upon disease progression, who had stable disease for approximately 11 months on PF-04449913 160 mg once daily; and (iii) a 49-year-old man with extraskeletal myxoid chondrosarcoma in the thigh with lung metastases, previously treated with radiation, who had stable disease for approximately 11 months on PF-04449913 640 mg once daily, at which time one lung nodule progressed and was resected; other nodules remained stable on treatment.

Discussion

The Hh pathway has a well-defined role in tumor maintenance and growth, and the potential therapeutic value of Hh pathway inhibitors has been demonstrated in tumors with mutations leading to pathway activation, for example, PTCH1 mutations in basal cell carcinomas. However, although reports suggest the involvement of Hh ligands in a spectrum of other solid tumors (12–16), including several types evaluated in this study, the precise role of Hh ligands in these malignancies remains unclear. Consequently, the therapeutic value of Hh pathway inhibitors for patients with solid tumors requires further evaluation.

The main objectives for this open-label, dose-finding, phase I trial were to evaluate the safety and tolerability of the SMO inhibitor PF-04449913 administered orally once daily to patients with advanced or metastatic solid tumors, to establish the MTD in this patient population, and to determine the RP2D. DLTs were experienced in the first cycle by 2 patients receiving PF-04449913 640 mg once daily and the MTD was therefore estimated to be 320 mg once daily. The RP2D could not be determined in this study owing to lack of enrollment of an MTD expansion cohort. On the basis of the findings of another study, the RP2D for continuous daily administration of PF-04449913 has been set at 100 mg once daily. This determination was based primarily on the observation that coadministration of PF-04449913 with strong CYP3A4 inhibitors resulted in a 140% higher AUC\text{\textsuperscript{0 → ∞}} and 40% higher C\textsubscript{max} compared with PF-04449913 alone (29).

PF-04449913 was generally well tolerated at doses from 80 mg to 320 mg once daily in these patients. The most common treatment-related AEs were grade 1–2 dysgeusia, fatigue, decreased appetite, nausea, dizziness, dehydration, and diarrhea, in line with the safety profile expected for this
drug class (23, 30, 31). Treatment-related grade 3 AEs only occurred in patients receiving the highest dose of PF-04449913 evaluated, 640 mg once daily, which exceeded the MTD of 320 mg once daily established in this study. Although grade 3 QTc prolongation was reported for 2 patients (one patient in the 320 and 640 mg once-daily cohorts, respectively), neither of these AEs was considered to be treatment related by the investigator as in one case (320 mg once-daily dose level), PF-04449913 was not administered on the day when the instrumental QTc prolongation occurred and in the other case (640 mg once-daily dose level), it was attributed to an underlying cardiac abnormality. There were no significant QTc changes in any patient receiving the lower doses of PF-04449913 (80–160 mg once daily). Treatment with PF-04449913 was not associated with clinically significant hematologic toxicity at the dose levels tested; the only grade 3 or higher hematologic laboratory abnormality was lymphopenia, observed in 17.4% of patients.

The pharmacokinetic profile observed for PF-04449913 indicated generally dose-proportional kinetics with biphasic elimination for the range of doses tested. This profile supports once-daily dosing of PF-04449913 in future clinical trials.

The marked (more than 80%) downregulation of GLI1 expression in the surrogate tissue of PF-04449913–treated patients indicated that PF-04449913 modulated Hh signaling (i.e., its targeted molecular pathway), at the dose levels tested. Although no objective tumor responses were observed in this dose-escalation study, prolonged stable disease, lasting approximately 7 to 11 months, was reported in three patients. Of note, each of these patients had progression of their previously treated disease before enrollment in this study. Taken together, the safety, pharmacokinetic, pharmacodynamic, and efficacy

Figure 2.

A, changes in GLI1 gene expression at day 15 of cycle 1 versus baseline in normal skin biopsies. Bars represent individual patients; dose groups are indicated above the figure. B, changes in GLI1 gene expression in normal skin versus PF-04449913 exposure at steady state by dose. AUC\textsubscript{tau}, area under the plasma concentration–time curve from time zero to tau (24 hours).
data reported here support further clinical investigation of PF-04449913 in patients with solid tumors. The details of the development strategy are currently under evaluation, but the studies are likely to include an “enrichment” step, based upon direct evidence of pathway overactivity or the presence of genetic markers suggesting overactivity.

**Disclosure of Potential Conflicts of Interest**

W.A. Messersmith reports receiving a commercial research grant from Pfizer. M.N. Shaik has ownership interest (including patents) in Pfizer. R. Cesari and R. Courtney are employees of Pfizer. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.J. Wagner, W.A. Messersmith, M.N. Shaik, S. Li, X. Zheng, K.R. McLachlan, R. Courtney, W.J. Levin, A.B. El-Khoueiry

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.J. Wagner, W.J. Levin

Study supervision: A.J. Wagner, M.N. Shaik, R. Cesari, W.J. Levin

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**References**


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