Phase I Pharmacokinetic and Pharmacodynamic Study of the Oral MAPK/ERK Kinase Inhibitor PD-0325901 in Patients with Advanced Cancers

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Abstract

Purpose: To determine tolerability, pharmacokinetics, and pharmacodynamics of PD-0325901, a highly potent, selective, oral mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase 1/2 inhibitor in advanced cancer patients.

Experimental Design: Sixty-six patients received PD-0325901 at doses from 1 mg once daily to 30 mg twice daily (BID). Cycles were 28 days; three administration schedules were evaluated. Pharmacokinetic parameters were assessed and tumor biopsies were done to evaluate pharmacodynamics.

Results: Common adverse events were rash, diarrhea, fatigue, nausea, and visual disturbances including retinal vein occlusion (RVO; n = 3). Neurotoxicity was frequent in patients receiving ≥15 mg BID. The maximum tolerated dose, 15 mg BID continuously, was associated with late-onset RVO outside the dose-limiting toxicity window. An alternative dose and schedule, 10 mg BID 5 days on/2 days off, was therefore expanded; one RVO event occurred. Three of 48 evaluable patients with melanoma achieved confirmed partial responses; 10 had stable disease ≥4 months. PD-0325901 exposure was generally dose proportional. Doses ≥22 mg BID consistently caused ≥60% suppression of phosphorylated ERK in melanoma. Fifteen patients showed significant decreases (≥50%) in Ki-67.

Conclusions: PD-0325901 showed preliminary clinical activity. The maximum tolerated dose, based on first cycle dose-limiting toxicities, was 15 mg BID continuously. However, 10 and 15 mg BID continuous dosing and 10 mg BID 5 days on/2 days off schedules were associated with delayed development of RVO; thus, further enrollment to this trial was stopped. Intermittent dose scheduling between 2 and 10 mg BID should be explored to identify a recommended dose with long-term PD-0325901 use. Clin Cancer Res; 16(6): 1924–37. ©2010 AACR.

The RAS–mitogen-activated protein kinase (MAPK) pathway has emerged as a critical signaling network involved in the regulation of cell growth and survival. The RAS-MAPK cascade mediates proliferative and antiapoptotic signaling from growth factors and oncogenic factors (such as gain-of-function RAS and RAF mutant phenotypes) that promote tumor growth, progression, and metastasis. The RAS-MAPK pathway is constitutively active in several solid tumor types (1–4).

MAPK/extracellular signal-regulated kinase (ERK) kinase (MEK) occupies a pivotal position in the RAS-MAPK pathway and serves as a focal point for several mitogenic signaling pathways activated by known oncogenes (e.g., BRAF, ErbB, and RAS; refs. 5–7). Although MEK has not been identified as an oncogene itself, constitutively active MEK has been shown in >30% of primary tumor cell lines tested (including colon, lung, breast, pancreas, ovary, and kidney; ref. 2). Constitutively active MEK shows transforming ability and has resulted in highly tumorigenic cell lines in vitro (6, 7). MEK is a dual-specificity kinase and phosphorylates its only known substrates, ERK1/2 (MAPK), on both a tyrosine and threonine residue.
Preclinically, MEK inhibition has been shown to lead to growth abrogation in tumors driven by mutant BRAF, NRAS, and KRAS alleles, implicating MEK as a critical downstream effector for various signaling intermediates of the same pathway (5, 8). The tight selectivity of MEK and its importance within the RAS-MAPK cascade has resulted in its emergence as a rational target for directed clinical therapy.

CI-1040 was the first MEK inhibitor to show in vivo activity and the first to be tested clinically in cancer patients (1, 9, 10). CI-1040 was generally well tolerated but failed to show sufficient anticancer activity to warrant further development and was unable to reach targeted drug concentrations (1, 11). Therefore, PD-0325901, a derivative of CI-1040 with a high degree of structural similarity, was subsequently developed as a more potent MEK inhibitor with greater systemic exposure (12). PD-0325901 is an orally administered, non–ATP-competitive, potent, and selective small-molecule inhibitor of both MEK isoforms (MEK1/MEK2). PD-0325901 acts by preventing phosphorylation and subsequent activation of ERK (pERK), which acts as a pharmacodynamic (PD) marker for assessment of MEK inhibition. Although structurally similar to CI-1040, PD-0325901 showed several pharmacologic improvements over its predecessor, including a 50-fold greater potency against MEK, longer pERK suppression, increased metabolic stability, and better solubility (1). PD-0325901 has an apparent inhibition equilibrium constant (K_{i,app}) of ~1 nmol/L in vitro versus activated MEK1 and MEK2 and has been shown to inhibit tumor growth in six of seven human tumor xenograft models (1, 12).

Studies in rats showed dose-dependent decreases in pERK following single oral administration (13). Primary PD-0325901 toxicities in preclinical studies were to the gastrointestinal tract, skin, cornea, central nervous system, liver, gallbladder, bone, and systemic mineralization. The preclinical findings for PD-0325901, including acceptable toxicity profile in animal models and preclinical efficacy in vitro and in vivo, were considered to hold promise for the use of the compound as a therapeutic agent. One of the major species resulting from metabolism of PD-0325901 is the carboxylic acid metabolite PD-0315209. This metabolite showed comparable efficacy to the parent compound when assayed against purified MEK1. However, PD-0315209 was found to be significantly less effective than PD-0325901 at reducing ERK phosphorylation in tumor cells and in a PD assay using C26 tumor-bearing mice. PD-0325901 is administered as the R-isomer; however, the S-enantiomer PD-0326116 has been detected in vivo studies.

On the basis of the preclinical findings, a phase I study of oral PD-0325901 was undertaken in patients with advanced solid tumors. The primary objectives of the study were to (a) determine the maximum tolerated dose (MTD) and recommended phase II dose and schedule of PD-0325901; (b) determine the safety profile including dose-limiting toxicities (DLT) of PD-0325901; (c) characterize the pharmacokinetics (PK) of PD-0325901 and its metabolite, PD-0315209, including the effect of food on bioavailability; and (d) seek preliminary evidence of antitumor activity. Secondary objectives included (a) assessing the effect of PD-0325901 on a PD biomarker of MEK inhibition (pERK) for proof of mechanism and (b) exploring potential correlations between PK, PD, antitumor response, and mutations in the RAS-MAPK pathway.

Materials and Methods

Patient selection. Eligibility criteria included adult patients with histologically or cytologically documented advanced breast cancer, colorectal cancer, non–small cell lung cancer (NSCLC), or nonocular melanoma refractory to standard therapy or for whom no standard therapy existed. RAS-MAPK pathway is constitutively active in a proportion of these tumor types, giving a more homogenous population for interpretation of biomarkers and mutation analysis. Initially, all participants enrolled were required to provide one pretreatment and one posttreatment tumor biopsy. Following implementation of a protocol amendment, patients were recommended to provide tumor biopsies. Participants were required to have Eastern Cooperative Oncology Group performance status of ≤2 and adequate bone marrow (absolute neutrophil count ≥1,500/μL, platelets ≥100,000/μL, hemoglobin ≥9 g/dL), hepatic (bilirubin ≤2× upper limit of normal...
(ULN), aspartate aminotransferase or alanine aminotransferase <3 ULN, or <5 ULN if liver metastases), and renal (creatinine ≤1.5× ULN) functions. Participants were required to have a left ventricular ejection fraction ≥50% as assessed by miltigated acquisition scan.

Radiation or cytotoxic therapy within 4 wk of study entry was not permitted. Participants with a history of congestive heart failure, active brain metastases, or other serious medical conditions were excluded. After two cases of retinal vein occlusion (RVO), a protocol amendment also excluded patients with glaucoma, intraocular pressure ≥21 mmHg, or any other significant abnormality on ophthalmic examination (by an ophthalmologist). Pregnant women were not eligible for enrollment, and patients of reproductive age were requested to practice birth control while on treatment. Institutional review board approval of the protocol and consent form was obtained at each participating site, and all participants gave written informed consent before study entry.

**Study design.** PD-0325901 (Pfizer, Inc.) was administered orally on one of three schedules: intermittent (3 wk on treatment/1 wk off), continuous [daily (QD)], and continuous with breaks (5 d on/2 d off treatment). Each cycle consisted of 28 d and at least three patients were treated per cohort. The initial starting dose of PD-0325901, supported by preclinical toxicity data, was 1 mg QD with a 3 wk on/1 wk off schedule. The administration schedule then transitioned to twice daily (BID) dosing in the second cohort, as BID dosing was predicted to sustain target suppression more completely throughout the dosing interval. Cohort 2 received 1 mg BID, with subsequent dose escalation in subsequent cohorts. Per protocol, once the MTD for the 3 wk on/1 wk off (3/1) schedule was determined, continuous QD dosing was tested with dosing through the off week. The protocol also made provision for exploration of additional schedules, such as the eventual 5 d on/2 d off schedule tested, due to observed toxicities. Patients received treatment until disease progression or unacceptable toxicity.

Dose escalation was based on cycle 1 (28 d) toxicity (see definition of DLT below). Dose escalation occurred when all patients enrolled in the preceding cohort had completed one cycle of therapy without experiencing DLT. DLT was defined as any of the following during the first cycle of therapy: grade 4 hematologic toxicity, grade ≥3 nonhematologic treatment-related toxicity not controlled by maximal treatment (e.g., nausea, vomiting, and diarrhea), and any PD-0325901–related toxicity resulting in treatment delay exceeding 21 d. Patients experiencing DLT had treatment interrupted until toxicity returned to grade ≤1. Resumption of PD-0325901 was at the next lower dose level tested. Patients receiving <75% of the PD-0325901 dose or discontinuing from the study before completion of the DLT observation window for reasons other than treatment-related toxicity were to be replaced. Adverse events (AE) were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 3.0.

Patients were to continue treatment at their initially assigned dose level for at least two cycles. They might then be treated at the next higher dose level proven to be safe if they experienced no drug-related toxicity of grade ≥2. If one patient experienced DLT, up to three additional patients were to be enrolled to that dose level. The MTD was defined as one dose level below that which induced DLT in more than one third of patients (at least two of a maximum of six). Patients received therapy until disease progression, unacceptable toxicity, or investigator/patient decision to withdraw study consent.

**Pretreatment and follow-up studies.** Safety evaluations included physical examination, assessment of Eastern Cooperative Oncology Group performance status, vital signs, review of concomitant medications, toxicity assessment, and routine laboratories at baseline and before each cycle. Because of the potential for ocular toxicity (11), an ophthalmic examination including best-corrected visual acuity, visual field examination (Amsler grid), intraocular pressure, external eye exam, and dilated funduscopy was done at baseline and before each cycle, following a protocol amendment. Weekly laboratory assessments were done on days 8, 15, and 21 during cycle 1. Cardiac function studies included creatinine phosphokinase and B-type natriuretic peptide and multigated acquisition at baseline and every 1 to 2 mo, respectively. Tumor measurements for the assessment of efficacy were done at screening and every two cycles. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors. For patients with a complete or

<table>
<thead>
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<th>Characteristic</th>
<th>n = 66</th>
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<td>Gender, n (%)</td>
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<td>Median (range) age (y)</td>
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<td>2 (3)</td>
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<tr>
<td>Tumor type, n (%)</td>
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<tr>
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<td>7 (11)</td>
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<tr>
<td>NSCLC</td>
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<tr>
<td>Colorectal cancer</td>
<td>4 (6)</td>
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<tr>
<td>Received prior systemic therapy, n (%)</td>
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<tr>
<td>Median no. therapies (range)</td>
<td>4 (0-14)</td>
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<tr>
<td>Dosing schedule, n (%)</td>
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<td>Intermittent</td>
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<tr>
<td>Continuous</td>
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<tr>
<td>Continuous with breaks</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Median no. PD-0325901 cycles/patient</td>
<td>3 (1-9)</td>
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</tbody>
</table>

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
partial response (PR), a confirmatory tumor assessment was
done at least 4 wk after the response was noted.

PK analysis. Each patient participated in the PK evaluation
of PD-0325901, PD-0326116, and PD-0315209. Serial
blood samples were collected after an 8-h fast on day 1
(single dose) and day 21 (multiple dose) of cycle 1. Subjects
on the continuous with breaks schedule had blood
samples collected on day 19, instead of day 21. In the
QD cohort, blood samples were drawn before dose and
1, 2, 3, 4, 6, 8, 12, and 24 h after dose. Twenty-four-hour
samples were not collected for the BID cohorts. Urine samples
were collected from 0 to 6, 6 to 12, and 12 to 24 h af-
after dose on day 21 of cycle 1 for QD administration and
0 to 6 and 6 to 12 h after dose for BID administration. Plas-
ma and urine samples were stored at −20°C until analysis.

Plasma and urine samples were assayed using
validated chiral analytic methods for concentrations of
PD-0325901 (R-enantiomer), PD-0326116 (S-enantiomer), and
PD-0315209 (carboxylic acid metabolite). PD-0325901,
PD-0326116, PD-0315209, and internal standards, [3H3]
PD-0325901 and [3H3]PD-0315209, were isolated from
EDTA human plasma or human urine by liquid/liquid ex-
traction. Analysis was by liquid chromatography-tandem
mass spectrometry in the negative ion mode using multi-
ple reaction monitoring. This assay required a 0.200 mL
aliquot of plasma or a 0.100 mL aliquot of urine. Samples
were quantified by applying a 1/concentration2 weighted
quadratic regression analysis. For the plasma matrix,
the range of quantitation for all three analytes was 0.100
to 1,000 ng/mL, and the value for below the limit of
quantification was 1.00 ng/mL. For urine, the range of
quantitation was 1.00 to 1,000 ng/mL, and the value for
below the limit of quantification was 1.00 ng/mL.

Plasma PKs were evaluated by a noncompartmental meth-
method using WinNonlin version 4.1.b (Pharsight Corp.). The
following PK parameters were determined: peak concentra-
tion (Cmax), time to Cmax (Tmax), last measurable observed
plasma concentration (Clast), area under concentration-
time curve from time 0 to end of dosing interval (AUC0−τ),
terminal plasma half-life (t1/2), and accumulation ratio (cal-
culated by the ratio of AUC0−τ on day 21 of cycle 1 to AU
0−τ on day 1 of cycle 1). Urine data were analyzed using
Microsoft Excel 2002. The amount of PD-0325901 and its metabolites
excreted in urine over a dosing interval was estimated by cal-
culating the product of urine concentration and volume. The
percentage of the dose recovered in urine as parent drug
and metabolites was calculated as the total amount recovered
in urine divided by the dose, with the adjustment of metabolites
to PD-0325901 equivalents.

PD analysis. PD markers of MEK1/2 activity (pERK),
AKT signaling cascade [phosphorylated AKT (pAKT)],
and cell proliferation (Ki-67) in tumor biopsies were assessed
before drug administration and after 14 d of
PD-0325901 treatment (day 15 of cycle 1) by semiquanti-
tative immunohistochemistry done at Oncotech. Posttreat-
ment tumor biopsies were obtained 2 to 4 h after dosing
to determine the extent of pERK suppression at a time con-
sistent with the Cmax. For optimal comparison, subsequent
biopsies were taken from the same site as the baseline bi-
opsy whenever possible.

Samples were fixed and stained with H&E for review of
pathologic diagnosis and tissue morphology and integrity
to determine acceptability for immunohistochemical staining. Indirect immunoperoxidase (with antibodies against pERK1/2 and pAKT) and immunobiotinylated methods (with antibodies against Ki-67) were used. Negative and positive controls were included in each immunostained batch of slides. The percentage of stained cells was multiplied by intensity of staining (quantified on a 0 to 3+ scale) to obtain a final semiquantitative Histo-score (H-score).

**Tumor DNA mutation analysis.** Three 10-μm sections were cut from each of the 43 available patient tumor samples. Following overnight lysis incubation with proteinase K at 55°C, genomic DNA was extracted with Qiagen DNeasy spin columns following the Animal Tissues protocol. Tumor tissue mutation screening was done at Transgenomic, Inc. using WAVE System technology and was carried out for BRAF, NRAS, and KRAS somatic mutations in gene regions known to contain activating mutations. These genomic regions included BRAF exons 11 and 15, NRAS exons 1 and 2, and KRAS exons 1 and 2. Any mutations detected were verified by standard di-deoxynucleotide sequencing.

**Statistical evaluation.** H-scores, graphs, averages, and SDs were calculated using Microsoft Excel 2003. ANOVA t tests were done using GraphPad InStat version 3.05 and GraphPad Prism version 4.03 (GraphPad Software). Baseline-scaled ratios were calculated for each evaluable pair of biopsies (postdose/predose value). Because the data were treated as being multiplicative, geometric means were calculated to obtain an overall mean level of inhibition. Safety data were summarized using descriptive statistics. Differences in progression-free survival (PFS) between patients who had BRAF mutation at baseline and those who did not were assessed using log-rank test, as were differences between patients with and without ≥60% pERK reduction and skin rash.

**Results**

Sixty-six patients (Table 1) were treated with a total of 209 cycles of PD-0325901. Six patients received <75% of the planned doses of PD-0325901 due to a nontreatment-related AE that prompted early treatment interruption or discontinuation [intestinal obstruction (n = 1), spinal cord compression (n = 1), progressive disease (n = 3), and one patient withdrew consent]. These patients were not considered assessable for tolerability of any dose level and were replaced. All but four patients had received prior systemic therapy with a median of four therapies (range, 0-14; Table 1). Patients received a median of three (range, 1-9) cycles of PD-0325901. Four patients required dose reduction for toxicity and seven patients discontinued therapy due to treatment-related AEs.

Dose escalation began with the intermittent schedule and continued through the 30 mg BID dose, where DLTs were observed in two of six patients (Table 2). Assessment of continuous dosing was initiated at 20 mg BID.

### Table 3. Most common treatment-related AEs (maximum grade, all cycles)

<table>
<thead>
<tr>
<th>AE</th>
<th>Total no. patients with events</th>
<th>PD-0325901 schedules and dose levels (no. patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 mg QD (n = 4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All G≥3</td>
</tr>
<tr>
<td>Rash</td>
<td>52</td>
<td>—</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17</td>
<td>—</td>
</tr>
<tr>
<td>Balance and gait disorders*</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>—</td>
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<tr>
<td>Visual disturbance</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>6</td>
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*Includes ataxia, dizziness, and gait disturbance.
In addition, 20 mg BID 3 weeks on/1 week off was further assessed in an independent pilot study. This companion study was terminated prematurely, however, due to an unexpected high incidence of musculoskeletal and neurologic AEs. The formal MTD on the continuous dosing schedule was 15 mg BID.

The dose and schedule for expansion to explore the recommended phase II dose was 10 mg BID 5 days on/2 days off. This was based on the observation of significant ocular toxicity (RVO) that occurred after cycle 1 at doses of PD-0325901 of 15 mg BID (continuous) and 10 mg BID (continuous). Of note, one patient had RVO after nine cycles of therapy on 10 mg BID on the 5 days on/2 days off schedule. As a result of the ocular toxicity, enrollment discontinued.

**Toxicity.** The most common AEs considered to be at least possibly related to treatment with PD-0325901 were rash, diarrhea, fatigue, nausea, and visual disturbances/eye disorders (Table 3). Rash was the most common AE; this was dose dependent and a frequent DLT during the dose escalation. Rash was erythematous and maculopapular in nature, mainly on the face, upper body, and arms. Severe grades usually resolved with temporal treatment interruption and subsequent dose reduction and/or supportive care. Diarrhea was the principal gastrointestinal toxicity, severe only in one patient, and typically resolved with symptomatic treatment (including loperamide in some cases). Fatigue incidence and intensity increased with dose and was reversible on drug discontinuation. Hematologic and nonhematologic laboratory abnormalities were mainly of grade 1/2 severity. Grade 4 events comprised lymphopenia (4.8%), neutropenia (3.2%), anemia (1.6%), and increased levels of aspartate aminotransferase (1.6%).

**Neurologic and ocular toxicity.** Acute neurotoxicity (visual disturbance, balance, and gait disorders) was common in patients receiving ≥15 mg BID, regardless of schedule (Table 3). In contrast to the neurotoxic effects observed, all episodes of RVO presented quite late, after 13, 15, and 36 weeks of therapy. A retrospective analysis of relevant visual episodes found predisposing factors for retinopathy (hypertension, diabetes, hypercholesterolemia, and glaucoma) in all patients with RVO but no correlation with cumulative PD-0325901 dose.

**Pharmacokinetics.** Plasma PK profiles and parameters for PD-0325901 following oral administration in the fasted state are presented in Fig. 1A and B and Table 4. After oral administration on an empty stomach, PD-0325901 was absorbed rapidly, with peak plasma concentrations occurring within 1 to 2 hours after dosing. Plasma concentrations declined with an average t\(_{1/2}\) of 7.8 hours (range, 5-18 hours across dosing cohorts). Estimates of t\(_{1/2}\) should, however, be interpreted with caution because samples were not collected beyond 12 hours after BID dosing. In general, both C\(_{max}\) and AUC\(_{0-7}\) increased proportionally with the doses tested in this study (1 mg QD/BID to 30 mg BID).

Following multiple oral BID dosing, PD-0325901 AUC\(_{0-7}\) on day 21 was slightly higher than that on day 1. The accumulation ratio ranged from 1.3 to 1.9. The coefficient of variation on day 21 was 15% to 50% for

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**Table 3. Most common treatment-related AEs (maximum grade, all cycles) (Cont’d)**

<table>
<thead>
<tr>
<th>PD-0325901 schedules and dose levels (no. patients)</th>
<th>Intermittent</th>
<th>Continuous</th>
<th>With breaks</th>
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<td>All G(_2)3</td>
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<td>15 mg BID (n = 6)</td>
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AUC₀₋τ and 12% to 73% for Cₘₐₓ across the different PD-0325901 dosing schedules. The variability in AUC₀₋τ and Cₘₐₓ on day 1 was generally lower than that on day 21. The plasma PK parameters of the carboxylic acid metabolite, PD-0315209, are summarized in Fig. 1C and D and Table 4. The mean ratios of PD-0315209 to PD-0325901 plasma AUC₀₋τ values ranged from approximately 61% to 166% following repeat dosing.

Fig. 1. Plasma concentration-time plot (semi-log scale) under fasted conditions of PD-0325901 on cycle 1 day 1 (A), PD-0325901 on cycle 1 day 21 (B).
PD-0315209 plasma AUC₀₋₇ and Cₘ₃₃ generally increased with dose. The t₁/₂ of PD-0315209 seemed to be longer than that of the parent drug. Following multiple BID dosing, the day 21 AUC of PD-0315209 increased 3-fold on average compared with day 1.

PD-0325901 was administered as purified R-enantiomer. To evaluate the in vivo interconversion from R-enantiomer...
Table 4. Plasma PK parameters of (A) PD-0325901 and (B) PD-0315209 on days 1 and 21 of cycle 1 (C1D1 and C1D21) under fasting conditions

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Day No. patients</th>
<th>Mean (CV%)</th>
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<tr>
<td>1 QD intermittent</td>
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<td>19.9 (22) 1.01 (1.00-1.08)</td>
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<td></td>
<td>21 4</td>
<td>22.3 (42) 1.96 (1.00-3.97)</td>
<td>143 (18)</td>
<td>14 (7)†</td>
</tr>
<tr>
<td>1 BID intermittent</td>
<td>1 2</td>
<td>25.7 1.00</td>
<td>83.8</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>21 2</td>
<td>41.1 1.00</td>
<td>169</td>
<td>—</td>
</tr>
<tr>
<td>2 BID intermittent</td>
<td>1 0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>21 4</td>
<td>152 (30) 1.00 (0.98-1.02)</td>
<td>578 (48)</td>
<td>16 (63)†</td>
</tr>
<tr>
<td>4 BID intermittent</td>
<td>1 2</td>
<td>111 2.00</td>
<td>405</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>21 2</td>
<td>198 0.98</td>
<td>691</td>
<td>5.5</td>
</tr>
<tr>
<td>8 BID intermittent</td>
<td>1 1</td>
<td>510 1.00</td>
<td>1,410</td>
<td>—</td>
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<tr>
<td>15 BID intermittent</td>
<td>1 3</td>
<td>642 (28) 1.00 (1.00-1.05)</td>
<td>2,273 (34)</td>
<td>6.5 (34)</td>
</tr>
<tr>
<td></td>
<td>21 3</td>
<td>706 (73) 1.02 (1.00-1.18)</td>
<td>2,840 (50)</td>
<td>8.7†‡</td>
</tr>
<tr>
<td>20 BID intermittent</td>
<td>1 1</td>
<td>839 1.00</td>
<td>2,140</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>21 3</td>
<td>766 (12) 2.00 (1.00-2.00)</td>
<td>3,497 (46)</td>
<td>7.7 (34)</td>
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<tr>
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<td>1 1</td>
<td>535 1.02</td>
<td>2,220</td>
<td>—</td>
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<td></td>
<td>21 1</td>
<td>734 1.00</td>
<td>2,720</td>
<td>18.4</td>
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<tr>
<td>30 BID intermittent</td>
<td>1 6</td>
<td>1,508 (31) 1.01 (0.98-2.00)</td>
<td>4,687 (35)</td>
<td>4.8 (27)</td>
</tr>
<tr>
<td></td>
<td>21 2</td>
<td>1,640 2.00</td>
<td>6,215</td>
<td>4.7</td>
</tr>
<tr>
<td>20 BID continuous</td>
<td>1 6</td>
<td>814 (32) 1.00 (1.00-3.00)</td>
<td>2,425 (18)</td>
<td>4.8 (31)§</td>
</tr>
<tr>
<td></td>
<td>21 6</td>
<td>972 (48) 1.00 (1.00-3.00)</td>
<td>3,235 (15)</td>
<td>4.6 (25)†</td>
</tr>
<tr>
<td>15 BID continuous</td>
<td>1 6</td>
<td>740 (29) 1.00 (1.00-2.00)</td>
<td>2,130 (27)</td>
<td>7.3 (48)</td>
</tr>
<tr>
<td></td>
<td>21 6</td>
<td>839 (34) 1.02 (1.00-1.08)</td>
<td>3,062 (22)</td>
<td>5.2 (27)</td>
</tr>
<tr>
<td>10 BID continuous</td>
<td>1 6</td>
<td>479 (29) 1.00 (1.00-2.07)</td>
<td>1,219 (34)</td>
<td>13.6 (57)</td>
</tr>
<tr>
<td></td>
<td>21 6</td>
<td>462 (60) 1.17 (1.00-4.00)</td>
<td>1,883 (38)</td>
<td>7.3 (53)</td>
</tr>
<tr>
<td>10 BID continuous with breaks*</td>
<td>1 13</td>
<td>385 (33) 1.00 (1.00-3.00)</td>
<td>1,325 (25)‖</td>
<td>6.5 (42)‖</td>
</tr>
<tr>
<td></td>
<td>21 8</td>
<td>445 (46) 1.04 (1.00-4.00)</td>
<td>1,883 (28)§§</td>
<td>6.1 (37)‖</td>
</tr>
<tr>
<td>Overall</td>
<td>1</td>
<td>1.00 (0.98-3.00)</td>
<td>7.8 (63)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>1.00 (0.98-11.8)</td>
<td>7.8 (64)</td>
<td>—</td>
</tr>
<tr>
<td>B. PD-0315209</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mg QD intermittent</td>
<td>1 4</td>
<td>2.99 (39) 2.51 (1.02-24.4)</td>
<td>55.2 (56)</td>
<td>29 (28)§</td>
</tr>
<tr>
<td></td>
<td>21 4</td>
<td>5.98 (43) 5.00 (2.08-7.92)</td>
<td>109 (54)</td>
<td>24 (23)‡</td>
</tr>
<tr>
<td>1 mg BID intermittent</td>
<td>1 2</td>
<td>34.2 12.00</td>
<td>97.0</td>
<td>24.9</td>
</tr>
<tr>
<td></td>
<td>21 2</td>
<td>15.4 1.00</td>
<td>140</td>
<td>—</td>
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<td>2 mg BID intermittent</td>
<td>1 0</td>
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<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>21 4</td>
<td>54.3 (47) 1.01 (0.98-4.02)</td>
<td>495 (54)</td>
<td>35 (63)‡</td>
</tr>
<tr>
<td>4 mg BID intermittent</td>
<td>1 2</td>
<td>38.7 3.02</td>
<td>364</td>
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<td></td>
<td>21 2</td>
<td>134 2.98</td>
<td>1,088</td>
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<td>8 mg BID intermittent</td>
<td>1 1</td>
<td>85.8</td>
<td>2.90</td>
<td>819</td>
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<tr>
<td>15 mg BID intermittent</td>
<td>1 3</td>
<td>169 (31) 3.03 (1.05-4.00)</td>
<td>1,090§</td>
<td>37§</td>
</tr>
<tr>
<td></td>
<td>21 3</td>
<td>405 (58) 3.05 (2.00-6.00)</td>
<td>4,177 (53)</td>
<td>28§</td>
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<tr>
<td>20 mg BID intermittent</td>
<td>1 1</td>
<td>132 1.00</td>
<td>1,120</td>
<td>56.4</td>
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<tr>
<td></td>
<td>21 3</td>
<td>306 (43) 4.00 (2.00-4.02)</td>
<td>2,950 (47)</td>
<td>11§</td>
</tr>
<tr>
<td>20 mg BID intermittent†</td>
<td>1 1</td>
<td>114 1.02</td>
<td>437</td>
<td>—</td>
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<td>21 1</td>
<td>170 2.83</td>
<td>1,650</td>
<td>16.3</td>
</tr>
<tr>
<td>30 mg BID intermittent</td>
<td>1 6</td>
<td>278 (15) 2.51 (1.00-8.00)</td>
<td>2,353 (27)</td>
<td>14 (34)‖</td>
</tr>
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<td></td>
<td>21 2</td>
<td>604 2.98</td>
<td>5,785</td>
<td>12§</td>
</tr>
<tr>
<td>20 mg BID continuous</td>
<td>1 6</td>
<td>147 (27) 2.00 (1.00-4.00)</td>
<td>1,185 (24)</td>
<td>12 (34)</td>
</tr>
<tr>
<td></td>
<td>21 6</td>
<td>342 (28) 2.00 (1.00-3.03)</td>
<td>2,973 (25)</td>
<td>29 (121)‡‡</td>
</tr>
</tbody>
</table>

(Continued on the following page)
to S-enantiomer (PD-0326116), PD-0326116 concentrations were also determined in the current study. Mean S-to-R ratios for AUC₀–τ on day 21 ranged from 0.01613 to 0.03890 across the doses administered, indicating a minor conversion from R-isomer to S-isomer. PD-0325901 excretion as unchanged drug in urine ranged from mean values of 1.63% to 5.98%. Urinary excretion of PD-0315209 and PD-0326116 was minimal, generally accounting for <1% of the dose.

**Pharmacodynamics.** A total of 33 patients had matched, evaluable pretreatment and posttreatment specimens, 24 of whom had melanoma. In melanoma patients, PD-0325901 treatment resulted in a significant decrease in pERK expression relative to baseline (Fig. 2A; Table 5). Analysis of two sections per tumor sample gave rise to mean H-scores of 91 and 25 at baseline and day 15, respectively (P = 0.0023; n = 23; first set of sections), and 94 versus 19 at baseline and day 15, respectively (P = 0.0003; n = 23; second set of sections). A significant difference was also shown between pretreatment and posttreatment specimens in Ki-67 expression (Fig. 2B), with a mean H-score of 96 versus 58, respectively (P = 0.0019; n = 24). On the other hand, there was no significant difference in pAKT expression, with a pretreatment mean H-score of 135 compared with a posttreatment H-score of 151 on day 15 (n = 24). These relationships did not achieve significance in breast, colon, or lung cancer, possibly due to the small sample size. However, in patients with melanoma, the pAKT H-score showed an inverse correlation with the pERK H-score (P = 0.0001) and Ki-67 H-score (P = 0.0002). Doses of PD-0325901 ≥2 mg BID, the dose level at which the plasma concentration of PD-0325901 exceeded the minimum level (16.5-53.5 ng/mL) consistent with target inhibition based on xenograft mouse models,

**Somatic mutation screening.** Of the 43 patients with samples assessable for mutational status, 23 had BRAF, KRAS, or NRAS mutations. KRAS mutations (exon 1 or 2) were found in two of two colorectal cancer and one of five NSCLC cases. NRAS mutations (exon 1 or 2) were found in 6 of 29 melanoma and 1 of 5 NSCLC cases. BRAF mutations (exon 15; V600E) were found in 15 of 29 melanoma cases.

**Antitumor activity.** Fifty-eight patients were evaluable for efficacy. There were three confirmed PRs, all in patients with melanoma (Table 5). Twenty-three patients had stable disease (SD) after two cycles of therapy (21 melanoma and 2 NSCLC); 10 patients with melanoma still had SD after four cycles (two patients achieved tumor regression >30% on one occasion).

**Exploratory analyses of biomarkers and clinical activity.** An exploratory analysis was done to determine any
correlations between changes in tumor size and levels of pERK, as well as BRAF mutational status. Genotyping results were available for two of the patients with a PR: one patient had a BRAF V600E mutation and one had a Gln61Lys mutation in NRAS. However, it was not possible to determine any overall correlation between these two variables: changes in tumor size and genotype. An exploratory Kaplan-Meier analysis compared PD markers with PFS. This revealed no significant difference in the probability of PFS between patients with and without BRAF V600E mutations (13.3 weeks versus 12 weeks, respectively) in melanoma patients, although the total patient numbers were small. Patients with reductions from baseline levels of pERK of ≥60% showed numerically longer PFS, but stratification of PFS according to the observed decrease in pERK from baseline (≥60% and <60%) revealed no significant associations (Fig. 2C). Patients who experienced a rash during treatment with PD-0325901 showed a trend toward higher probability of PFS (P = 0.105; Fig. 2D).

Discussion

In this first-in-human study, PD-0325901 inhibited MEK (as measured by pERK levels) at a broad range of doses and showed preliminary antitumor activity in previously treated patients with advanced melanoma. Doses ≥2 mg BID, the dose level at which the plasma concentration of PD-0325901 exceeded the target inhibition based on xenograft mouse models (16.5-53.5 ng/mL), consistently caused >60% suppression of pERK in melanoma samples from patients. There was also a significant decrease in Ki-67 expression (a proliferation marker) in patients with melanoma (≥50% reduction in 15 of 24 posttreatment samples). As shown in the pioneering study by Solit et al. (5), effective pERK inhibition does not always correlate with the desired end-biological effect. Of note, Ki-67 has recently been postulated as a biomarker associated with better correlation with biological activity (e.g., growth inhibition) than pERK (14).

Fig. 2. PD and exploratory analyses. A, waterfall plot of % change from baseline (pretreatment) to day 15 (posttreatment) in pERK. Mutations: B, BRAF; K, KRAS; N, NRAS; n, negative; u, unknown. *, melanoma patients. B, waterfall plot of % change from baseline (pretreatment) to day 15 (posttreatment) in Ki-67. *, breast patient; f, melanoma patients. CRC, colorectal cancer. C, Kaplan-Meier analysis of PFS in patients with pERK decrease ≥60% versus <60%. D, Kaplan-Meier analysis of PFS in patients with or without rash.
The main DLT associated with PD-0325901 was rash. PD-0325901 was dose escalated until DLT was observed in two patients receiving 30 mg BID on the 3 weeks on/1 week off intermittent schedule. The most frequently reported treatment-related AEs on all treatment schedules were rash, diarrhea, fatigue, nausea, and visual disturbances/eye disorders, a toxicity profile consistent with those observed for other MEK inhibitors (10, 11, 15). Seven patients developed transient and reversible blurred vision while receiving PD-0325901, an AE also reported with CI-1040 and AZD6244 (11, 15). Unexpectedly, neurotoxicity was common in patients receiving PD-0325901 at doses ≥15 mg BID in this study and also in an additional pilot study. This toxicity generally presented early during treatment. One patient who was escalated from the original dose of 4 to 20 mg BID experienced optic neuropathy. The formal MTD on the continuous schedule was found to be 15 mg BID. However, as the study progressed, long-term ophthalmic AEs, specifically RVO, manifested in patients receiving PD-0325901 on the continuous schedule. Notably, two patients on the continuous schedule were diagnosed with RVO after 3.5 and 4 months of therapy. Consequently, 10 mg BID continuous with breaks (5 days on/2 days off) dosing was evaluated and further expanded. Long-term administration of PD-0325901 on the 5 days on/2 days off schedule was, however, also associated with RVO, with one patient experiencing RVO after 9 months of therapy, and as a result, further enrollment was stopped.

The relationship of the retinal toxicity to PD-0325901 is supported by the reversibility of ophthalmologic AEs on treatment discontinuation. Of note, expert retrospective review of fundus photographs revealed progressive findings in the retina of the last patient before the overt clinical presentation. Visual disturbances in general were more common at doses ≥15 mg BID, and RVO only presented after repeated cycles of therapy on the continuous schedules. Furthermore, at doses ≥4 mg BID in this study, mean maximum plasma concentrations of PD-0325901

---

### Table 5. Patients who had confirmed PR or SD after four cycles of therapy

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Dose†</th>
<th>Response</th>
<th>Reason for discontinuation</th>
<th>Cycles of therapy</th>
<th>Mutations‡</th>
<th>pERK change (%)</th>
<th>Ki-67 change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2–20 mg BID intermittent</td>
<td>SD</td>
<td>PD</td>
<td>9</td>
<td>No</td>
<td>−95</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2–8 mg BID intermittent</td>
<td>SD</td>
<td>Other§</td>
<td>4</td>
<td>No</td>
<td>−100</td>
<td>−87</td>
</tr>
<tr>
<td>3</td>
<td>4–20 mg BID intermittent</td>
<td>SD</td>
<td>AE (optic neuropathy)</td>
<td>7</td>
<td>BRAF V600E</td>
<td>−76</td>
<td>−85</td>
</tr>
<tr>
<td>4</td>
<td>20 mg BID intermittent</td>
<td>PR</td>
<td>AE</td>
<td>5</td>
<td>BRAF V600E</td>
<td>−100</td>
<td>−100</td>
</tr>
<tr>
<td>5</td>
<td>30–10 mg BID intermittent</td>
<td>SD (35% ↓)</td>
<td>AE</td>
<td>9</td>
<td>No</td>
<td>0</td>
<td>−63</td>
</tr>
<tr>
<td>6</td>
<td>20–15 mg BID continuous</td>
<td>SD (37% ↓)</td>
<td>PD</td>
<td>6</td>
<td>BRAF V600E</td>
<td>−100</td>
<td>−75</td>
</tr>
<tr>
<td>7</td>
<td>20–15 mg BID continuous</td>
<td>PR</td>
<td>PD and AE (donut vision)</td>
<td>8</td>
<td>NRAS Gln61Lys</td>
<td>−100</td>
<td>+39</td>
</tr>
<tr>
<td>8</td>
<td>15–10 mg BID continuous</td>
<td>SD</td>
<td>PD</td>
<td>6</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td>15 mg BID continuous</td>
<td>SD</td>
<td>PD</td>
<td>6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>10 mg BID continuous</td>
<td>SD</td>
<td>PD</td>
<td>4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>11</td>
<td>10 mg BID 5 d on/2 d off</td>
<td>SD</td>
<td>AE (RVO)</td>
<td>9</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>12</td>
<td>10 mg BID 5 d on/2 d off</td>
<td>PR</td>
<td>PD</td>
<td>6</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>13</td>
<td>10 mg BID 5 d on/2 d off</td>
<td>SD</td>
<td>Other∥</td>
<td>4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: N/A, not available; PD, progressive disease.

*All patients listed had melanoma.
†Original assigned dose→(dose escalated up/reduced down to) final dose.
‡As detected by Transgenomic, Inc. using WAVE System technology to screen selected gene regions.
§Patient withdrew consent.
∥Insufficient clinical response (did not meet PD according to Response Evaluation Criteria in Solid Tumors). Patient and investigator decided to switch therapy.
at steady state were above 99 ng/mL, consistent with 90% pERK suppression in normal lung tissue in preclinical models (13), raising the possibility that visual AEs arise as a result of prolonged and/or high levels of pERK suppression. It is also conceivable that patient predisposition may also play a role in the presentation of visual AEs. Retrospective analysis revealed preexisting factors for retinopathy in all patients who developed RVO (such as hypertension, diabetes, hypercholesterolemia, and glaucoma). The physiopathology of ocular toxicity is currently not well understood, and preclinical safety studies conducted before this study did not identify retinal damage. Ocular toxicity associated with PD-0325901 administration has recently been investigated preclinically. In rabbits, intravitreal injection of PD-0325901 resulted in RVO, hemorrhage, and leakage similar to that observed in humans in the current study (16). Rats receiving oral PD-0325901 did not manifest clinical symptoms of RVO, but patterns of retinal gene expression suggested an increased oxidative stress and inflammatory response, endothelium and blood-retinal barrier damage, and prothrombotic effects (16).

The optimal dose of PD-0325901 should produce acceptable inhibition of MEK in the tumor, and such inhibition may be achieved well below the MTD, unlike standard cytotoxic agents, which are generally administered at the MTD. Results of this study indicate that a biologically active dose and schedule for PD-0325901 should be identified between 2 and 10 mg BID with a specifically designed dose efficacy study. Such a study would ideally be conducted in patients with advanced melanoma, and would measure PK and biological activity in tumor and/or surrogate tissues. As no data about the PD effects of PD-0325901 in humans were available at the time of study initiation, the widest possible range of doses and schedules was evaluated. Evidence of clinical activity was observed over the range of 4 to 30 mg BID in patients with melanoma. Cutaneous rash is frequently observed with most epidermal growth factor receptor inhibitors (17, 18)—epidermal growth factor receptor signals upstream of MEK—and rash was detected in ~70% of patients treated in this study. Patients who experienced rash during treatment with PD-0325901 showed a trend toward a higher probability of PFS (rash, 14.4 versus no rash, 7.8 weeks; log-rank P = 0.105; hazard ratio, 0.583; 95% confidence interval, 0.303-1.12), indicating that rash is a potential clinical PD biomarker of PD-0325901 antitumor activity. It was not possible to draw any definitive conclusions about correlations between the mutational status of tumors and clinical benefit with PD-0325901 treatment in this phase I study. The range of doses, small sample size, the possibility of off-target effects, and variety of tumor types included are all potential confounding factors. Although limited, the results suggest potential for PD-0325901, either as monotherapy or in combination with other targeted agents, for treatment of patients with BRAF mutant tumors. Treatment of RAS mutant tumors may also be explored, preferentially in combination with AKT signaling cascade inhibitors.

In conclusion, in this phase I study, PD-0325901 showed preliminary evidence of activity in pretreated patients with melanoma. Continuous dosing regimens were, however, associated with RVO. Clinical predisposing factors for retinopathy may increase the risk of RVO, but prospective evaluation is required to confirm this observation. Although the dose/schedule further expanded, 10 mg BID 5 days on/2 days off, was safe according to conventional standards (DLT during cycle 1), the occurrence of late ocular toxicity prevented a clear definition of a recommended phase II dose for future studies. A further evaluation of PD-0325901 should consider comparison of doses ≤10 mg BID on an intermittent schedule to define the optimal biological dose.

Disclosure of Potential Conflicts of Interest

P.M. LoRusso: commercial research grant from AstraZeneca, Ariad, Pfizer, Genentech, Sanofi-Aventis, Endocyte, Array, BioPharma, Boehringer Ingelheim Pharmaceuticals, GlaxoSmithKline, Euelxix, BMS, Takeda, Merck, Synta Pharmaceuticals, Geron, Eisai, Allos, Myeligen, I3 Pharma, Hana Biosciences, Abbott Laboratories, Curis, Inc., Millenium Pharmaceuticals, Boston Biomedical, Novartis, Afinigen, MedImmune, Amgen, and NIH received honoraria from speakers bureaus from Genentech, GlaxoSmithKline, and Sanofi; been compensated for consultancy/advisory boards for Abraxis, AstraZeneca, Bristol-Myers Squibb, Eisai, Genentech, GlaxoSmithKline, the NCI, Novartis, Pfizer, Sanofi, Syndax, and Takeda; sat on a scientific review committee for the NCI; sat on a data safety monitoring committee for Syndax; S.S. Krishnamurthi: owns stock in Pfizer; S.E. DePrimo: Pfizer employee at the time of the work and owns stock in Pfizer; S. Benitevuga, K.D. Wilner, and W. Tan: employees of Pfizer and own stock in Pfizer; A.D. Ricart: employee of Pfizer

Acknowledgments

We thank Paulina Selaru and other Pfizer colleagues for their contribution toward generation of these data; Scott Boerner (Karmanos Cancer Institute) for valuable assistance; and PGRD colleagues at Legacy Ann Arbor for their contributions to this study at the initial stage, including D. Miller, S.S. Menon, L.R. Whitfield, S. Sadis, M.B. Meyer, and J. Leopold. Medical writing support was provided by Christine Arris at ACUMED (Tytherington, UK) and was funded by Pfizer Inc.

Grant Support

Pfizer, Inc.

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Received 07/22/2009; revised 01/08/2010; accepted 01/11/2010; published OnlineFirst 03/09/2010.

References

Clinical Cancer Research

Phase I Pharmacokinetic and Pharmacodynamic Study of the Oral MAPK/ERK Kinase Inhibitor PD-0325901 in Patients with Advanced Cancers


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