Cancer Therapy: Clinical

Clinical Cancer Research

# A Phase II Study of PD-0325901, an Oral MEK Inhibitor, in Previously Treated Patients with Advanced Non–Small Cell Lung Cancer

Eric B. Haura[1], Alejandro D. Ricart[2], Timothy G. Larson[3], Philip J. Stella[4], Lyudmila Bazhenova[5], Vincent A. Miller[6], Roger B. Cohen[7], Peter D. Eisenberg[8], Paulina Selaru[2], Keith D. Wilner[2], and Shirish M. Gadgeel[9]

## Abstract

**Purpose:** To evaluate the efficacy of mitogen-activated protein kinase/extracellular signal-related kinase kinase inhibitor PD-0325901 in advanced non–small cell lung cancer patients who had experienced treatment failure after, or were refractory to, standard systemic therapy.

**Experimental Design:** This open-label, phase II study initially evaluated 15 mg PD-0325901 twice daily administered intermittently (3 weeks on/1 week off; schedule A). As this schedule was not well tolerated, a second schedule was introduced as follows: 5 days on/2 days off for 3 weeks, followed by 1 week off (schedule B). The primary end point was objective response.

**Results:** All patients had received prior systemic therapy (median of two regimens, including epidermal growth factor receptor inhibitors in 26%). Of 13 patients treated on schedule A, three discontinued due to adverse events (blurred vision, fatigue, and hallucinations, respectively). Twenty-one patients received schedule B. Main toxicities included diarrhea, fatigue, rash, vomiting, nausea, and reversible visual disturbances. Hematologic toxicity consisted mainly of mild-to-moderate anemia, without neutropenia. Chemistry abnormalities were rare. Mean (coefficient of variation) PD-0325901 trough plasma concentrations were 100 ng/mL (52%) and 173 ng/mL (73%) for schedules A and B, respectively, above the minimum target concentration established in preclinical studies (16.5 ng/mL). There were no objective responses. Seven patients had stable disease. Median (95% confidence interval) progression-free survival was 1.8 months (1.5-1.9) and overall survival was 7.8 months (4.5-13.9).

**Conclusions:** PD-0325901 did not meet its primary efficacy end point. Future studies should focus on PD-0325901 schedule, rational combination strategies, and enrichment of patient selection based on mode of action. *Clin Cancer Res; 16(8); 2450–7. ©2010 AACR.*

The RAS-RAF-mitogen-activated protein (MAP) kinase/extracellular signal-regulated kinase (ERK) kinase (MEK)-ERK signaling pathway is activated in many human tumors, mediating tumor growth, progression, and metastasis, and is therefore an attractive target for novel, molecularly targeted therapies (1, 2). Although MEK itself is not an oncogene product, it is the focus of many of the signal transduction pathways activated by known oncogenes (including BRAF and KRAS mutations) and tyrosine kinase receptors (1, 3). Thus, inhibition of MEK has the potential to prevent the subsequent downstream phosphorylation and activation of MAP kinase (to pMAPK/pERK) and consequently induce tumor regression and/or stasis in some contexts (1, 3).

Some progress has been made in the treatment of non–small cell lung cancer (NSCLC) in the past decade, with more options for adjuvant chemotherapy and concurrent chemoradiotherapy, and improved systemic therapy for first-line treatment of advanced disease (4–8). However, there is still a pressing need for new approaches to

**Authors' Affiliations:** [1]H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida; [2]Pfizer Global Research and Development, San Diego, California; [3]Hubert H. Humphrey Cancer Center-North Memorial Health Care, Robbinsdale, Minnesota; [4]St. Joseph Mercy Hospital, Ann Arbor, Michigan; [5]University of California at San Diego, San Diego, California; [6]Memorial Sloan-Kettering Cancer Center, New York, New York; [7]Fox Chase Cancer Center, Philadelphia, Pennsylvania; [8]California Cancer Care Inc., Greenbrae, California; and [9]Karmanos Cancer Institute, Detroit, Michigan

**Note:** Part of a Series: This article is being submitted as part of a two-part series; the second article documents a phase I study.

LoRusso PM, Krishnamurthi SS, Rinehart JJ, Nabell LM, Malburg L, Chapman PB, DePrimo SE, Bentivegna S, Wilner KD, Tan W, Ricart AD. Phase I pharmacokinetic and pharmacodynamic study of the oral MEK inhibitor PD-0325901 in patients with advanced cancers.

**Prior Presentation:** Presented in part at the American Association for Cancer Research-National Cancer Institute-European Organization for Research and Treatment of Cancer International Conference on Molecular Targets and Cancer Therapeutics, San Francisco, CA, USA, October 22 to 26, 2007.

**Corresponding Author:** Eric B. Haura, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL. Phone: 813-903-6827; Fax: 813-903-6817; E-mail: eric.haura@moffitt.org.

**doi:** 10.1158/1078-0432.CCR-09-1920

## Translational Relevance

This is the first complete report of a disease-specific phase II study of a mitogen-activated protein kinase/extracellular signal-related kinase kinase (MEK) inhibitor in patients with advanced non–small cell lung cancer. PD-0325901 is a highly potent, oral, small-molecule inhibitor of MEK1 and MEK2. Our results are relevant to the future investigation of MEK inhibitors in non–small cell lung cancer, including identifying key toxicities and dosing issues. An intermittent PD-0325901 dose schedule was selected based on phase I data in patients with advanced tumors, but safety issues led to the revision of the dose schedule. Pharmacokinetic findings suggested that lower doses might have achieved target plasma concentrations. This study failed to achieve its primary objective as no antitumor activity of PD-0325901 was observed based on prespecified statistical criteria. We discuss why patient selection, mutation status, combination strategies with other pathway inhibitors, and the methods used to evaluate clinical response should be carefully considered when designing future trials of MEK inhibitors.

improve treatment outcomes. From a biological point of view, the inherent molecular heterogeneity of the disease has hampered efforts to improve outcomes in advanced NSCLC. For selected patients with incurable lung adenocarcinoma, the addition of bevacizumab to carboplatin/paclitaxel is a standard option in the United States (9). Remarkable effects have been achieved with erlotinib in selected groups of patients [such as nonsmokers and patients with activating mutations of the epidermal growth factor receptor (EGFR)] compared with best supportive care (10). Although second- and third-line therapies are available to patients, in nonselected patient populations, the gains in survival have been modest (11, 12).

The therapeutic potential of MEK inhibitors is being explored in a range of human tumors, including NSCLC. Although estimates vary, mutational activation of *KRAS* has been detected in up to ~25% of NSCLC samples (13–15) and ~2% in *BRAF* mutations (16). Activation of MAP kinase (also known as ERK1/2) has been shown to correlate positively with advanced tumor stage and the presence of lymph node metastases and thus tends to be associated with more aggressive NSCLC tumors (17). Consequently, MEK inhibition seems to be a rational therapeutic strategy for NSCLC and various preclinical findings have indicated that NSCLC cell lines, in particular those with *BRAF* mutations, are sensitive to MEK inhibitors (1, 18, 19).

PD-0325901 is a highly potent, selective, non-ATP–competitive, oral, small-molecule inhibitor of both MEK isoforms, MEK1 and MEK2. A phase I study of PD-0325901 in patients with advanced malignancies was done, in which the administration schedules tested were as follows: 1 mg once daily to 30 mg twice daily 3 weeks on treatment followed by 1 wk off, 10 to 20 mg twice daily continuous, and 10 mg twice daily 5 days on followed by 2 days off treatment.[10]

Fifteen milligrams twice daily was the highest dose with an acceptable incidence (<33%) of dose-limiting toxicity. However, the final phase II recommended dose has since been reconsidered due to the emergence of unexpected delayed toxicity.[10]

The primary objective of this phase II study was to determine the activity of PD-0325901 in patients with advanced NSCLC who had experienced treatment failure after, or were refractory to, standard systemic therapy, as measured by the objective response rate (ORR): complete response (CR) and partial response (PR). Secondary objectives of the study were to assess the safety profile of PD-0325901 in this patient population, determine the duration of progression-free survival (PFS) and overall survival (OS) following treatment, and evaluate the pharmacokinetics of PD-0325901 and their correlation with efficacy and safety parameters as appropriate.

## Patients and Methods

***Patient eligibility criteria.*** Patients had pathologically confirmed, progressive or recurrent, advanced-stage (IIIB with malignant pleural effusion or IV) NSCLC; had experienced treatment failure after at least one prior systemic therapy for advanced NSCLC; had measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST); had adequate organ and bone marrow function (absolute neutrophil count of ≥1,500/μL; had platelets of ≥100,000/μL; had bilirubin of ≤1.5 × upper limit of normal; had creatinine of ≤1.5 × upper limit of normal; had left ventricular ejection fraction of ≥50%); were ≥18 y of age; and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Patients were excluded if they had undergone a major surgical procedure or radiotherapy within 4 wk of study entry or systemic therapy within 2 wk of study entry. Exclusion criteria also included nontreated brain metastases, any significant ocular abnormality such as glaucoma or intraocular pressure of >21 mmHg, and active/uncontrolled infection or other serious medical conditions.

All patients provided written informed consent and approval was obtained from the institutional review boards at each of the investigational centers participating in this study. The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki.

[10] LoRusso PM, Krishnamurthi SS, Rinehart JJ, Nabell LM, Malburg L, Chapman PB, DePrimo SE, Bentivegna S, Wilner KD, Tan W, Ricart AD. Phase I pharmacokinetic and pharmacodynamic study of the oral MEK inhibitor PD-0325901 in patients with advanced cancers. Clin Cancer Res, accepted for publication.

***Study design.*** This was a phase II, single-arm, multicenter, open-label study of two schedules of administration of PD-0325901, done at eight study centers in the United States between November 2005 and May 2007. PD-0325901 was initially administered orally with food twice daily (at 12-h intervals ± 2 h) at a starting dose of 15 mg twice daily on an intermittent schedule (3 wk on/1 wk off; schedule A). This schedule was not well tolerated. Consequently, the same dose (15 mg twice daily) was administered with additional breaks consisting of weekends "off treatment" (i.e., 5 d on/2 d off for 3 wk, followed by 1 wk off; schedule B). Each cycle was defined as 28 d. The dosing schedule was adjusted rather than reducing the administered dose because emerging data from the phase 1 trial (the later stages of which ran concurrently with the current trial report) suggested that continuous twice daily dosing was associated with delayed ocular toxicity (retinal vein occlusion after >3 mo of therapy in three patients). Thus, the introduction of treatment breaks was thought more likely to improve patient safety.

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Dose reductions were made for grade 3 or other intolerable drug-related toxicity. The predefined limit on the number of dose reductions for either schedule was three (dose level 1 was 10 mg twice daily; dose 2 was 5 mg twice daily; dose 3 was 3 mg twice daily). Study treatment continued until the occurrence of disease progression or unacceptable toxicity or until the investigator or patient made the decision to withdraw.

***Pretreatment and on-study assessments.*** A medical history was taken prestudy, and a physical examination, details of any concomitant medication, assessment of Eastern Cooperative Oncology Group performance status, and laboratory studies were done before treatment and every 4 wk. Laboratory studies included a complete blood count, prothrombin and partial thromboplastin times, electrolytes, blood urea nitrogen, serum creatinine, glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, lactate dehydrogenase, calcium, phosphorus, magnesium, total protein, albumin, B-type natriuretic peptide, creatine phosphokinase (muscle/muscle, muscle/brain, and brain/brain fractions), and urinalysis. Amylase was analyzed at screening only. Women of child-bearing potential had a pregnancy test before treatment; the result of which had to be negative.

Pretreatment assessments also included an electrocardiogram. In addition, multiple-gated acquisition scans and ophthalmic examinations were done at screening, and then after every other cycle or every cycle, respectively. Although preclinical data did not indicate a risk of QT/QTc prolongation or arrhythmia and a systematic electrocardiogram evaluation incorporated into the phase 1 study showed no evidence of QT/QTc effects, cardiovascular safety was closely monitored in this study (including assessment of B-type natriuretic peptide, creatine phosphokinase, baseline electrocardiogram, and regular multigated acquisition scans). This was due to reports that a small number of patients enrolled in trials of other MEK inhibitors developed noticeable decreases in ejection fraction of unknown relation to the study drug. Ophthalmic examinations were done at baseline and, following a protocol amendment, before each cycle. Ophthalmic examinations included best-corrected visual acuity, visual field examination (Amsler grid), intraocular pressure, external eye examination, and dilated funduscopy.

Relevant radiological assessments to evaluate all measurable and assessable sites of disease were conducted at baseline and radiological evaluation of disease status was repeated after every other cycle. Patients were able to continue treatment if they did not develop progressive disease or experience subjectively intolerable toxicity. Antitumor efficacy was evaluated by RECIST (20).

***Plasma pharmacokinetics sample collection and analysis.*** Blood samples for pharmacokinetic analysis were collected on days 1 and 15 (schedule A) or days 1 and 19 (schedule B) of cycles 1, 2, 3, 5, and 7, taken predose and 2 to 8 h postdose. The plasma concentration of PD-0325901 and its active carboxylic acid metabolite, PD-0315209, were determined using a validated liquid chromatography mass spectrometry method.

***Statistical analysis.*** The primary end point for this study was objective response by RECIST and was evaluated by the ORR. Secondary end points included duration of response, PFS, OS, safety profile of PD-0325901, and pharmacokinetic analysis. Based on a two-stage Simon Minimax design with an $\alpha$ level of 10% and 90% power, 60 patients (39 in stage 1 and an additional 21 in stage 2) were required to test the null hypothesis that the true ORR was ≤5% versus the alternative hypothesis that the true ORR was ≥15%. At least two confirmed objective responses were needed in stage 1 to allow the expansion of the trial to stage 2. At the end of the study, at least six confirmed objective responses were needed to reject the null hypothesis.

Efficacy and safety analyses included all patients who received at least one dose of study medication. The number and proportion of patients who achieved an objective response (CR or PR) was to be summarized along with the corresponding exact two-sided 95% confidence interval, calculated using the F distribution. PFS, duration of response, and OS were to be summarized using the Kaplan-Meier method, with the median event time and a two-sided 95% confidence interval for the median provided for each of these end points.

## Results

***Patient characteristics.*** The baseline demographic and clinical characteristics of all patients in the study are summarized in Table 1. Overall, 34 patients were enrolled, 13 patients on the initial schedule (schedule A, 3 weeks on/1 week off) and 21 on the revised schedule (schedule B, 5 days on/2 days off for 3 weeks, followed by 1 week off). In total, 27 patients were exsmokers or current smokers and

**Table 1.** Baseline demographic and clinical characteristics

| | Schedule A (*n* = 13) | Schedule B (*n* = 21) |
|---|---|---|
| Gender, *n* (%) | | |
| Male | 8 (62) | 10 (48) |
| Female | 5 (38) | 11 (52) |
| Mean (range) age, y | 62 (47-81) | 63 (36-82) |
| ECOG performance status, *n* (%) | | |
| 0 | 6 (46) | 10 (48) |
| 1 | 7 (54) | 11 (52) |
| Smoking status, *n* (%) | | |
| Current smoker | 1 (8) | 2 (10) |
| Exsmoker | 9 (69) | 15 (71) |
| Never smoked | 3 (23) | 4 (19) |
| Histology, *n* (%) | | |
| Adenocarcinoma | 5 (38) | 15 (71) |
| Squamous cell carcinoma | 3 (23) | 3 (14) |
| Large cell carcinoma/unclassified | 5 (38) | 3 (14) |
| Median (range) number of prior systemic therapies | 2 (1-4) | 2 (1-4) |
| Patients receiving at least one prior EGFR inhibitor, *n* (%) | 4 (31) | 5 (24) |

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

the majority of patients (*n* = 30, 88%) were Caucasian; no patients of Asian ethnicity were enrolled onto the study. All patients had received prior systemic therapy, with a median of two regimens (range, 1-4), and 26% had received EGFR tyrosine kinase inhibitors.

***Exposure to study treatment.*** Three of the patients on schedule A discontinued the study early (during cycle 1) due to treatment-related adverse events (blurred vision, fatigue, and hallucinations; *n* = 1 each). The high rate of adverse events led to the discontinuation of schedule A after 13 patients were enrolled. Patients already receiving treatment were switched to schedule B and the remaining study patients were assigned to schedule B. Patients received a median of one cycle of treatment on schedule A and two cycles on schedule B (Table 2).

The dose of PD-0325901 was reduced in four patients on schedule A (31%) and five patients on schedule B (24%, Table 2). A slightly greater percentage of patients discontinued treatment on schedule A due to a PD-0325901–related adverse event (23%) compared with schedule B (19%; Table 2). Emerging safety data from the phase I study of PD-0325901 indicated that doses of PD-0325901 that is ≥10 mg twice daily

**Table 2.** Summary of study drug exposure, dose reductions, and reasons for discontinuation

| | Schedule A (*n* = 13) | Schedule B (*n* = 21) |
|---|---|---|
| Total number of cycles | 22 | 48 |
| Median (range) number of cycles | 1 (1-5) | 2 (1-10) |
| Patients with dose reductions, *n* (%) | | |
| None | 9 (69) | 16 (76) |
| Any | 4 (31) | 5 (24) |
| ≥2 | 2 (15) | 0 |
| Reasons for discontinuation, *n* (%) | | |
| Death* | 2 (15) | 0 |
| AEs related to study drug | 3 (23) | 4 (19) |
| AEs unrelated to study drug | 1 (8) | 2 (10) |
| Consent withdrawn | 1 (8) | 2 (10) |
| Progressive disease | 6 (46) | 13 (62) |

Abbreviation: AE, adverse event.
*Both deaths were due to progressive disease.

**Table 3.** Best response to treatment (evaluated by RECIST)

| | Schedule A (*n* = 13) | Schedule B (*n* = 21) |
|---|---|---|
| CR, *n* | 0 | 0 |
| PR, *n* | 0 | 0 |
| SD, *n* (%) | 2 (15) | 5 (24) |
| Progressive disease, *n* (%) | 6 (46) | 10 (48) |
| Not evaluable, *n* (%) | 5 (38) | 6 (29) |
| Disease-control rate (CR + PR + SD), *n* (%) | 2 (15) | 5 (24) |

could produce late ocular toxicity in the form of retinal vein occlusion.[10] Thus, further enrollment into this study was suspended during stage 1 and no patients remain on the study.

***Efficacy.*** There were no objective responses during the study (Table 3). Of the eight patients with posttreatment imaging on schedule A, two had stable disease (SD). Of the patients on schedule B, 6 patients had early symptomatic deterioration and/or significant toxicity; thus, only 15 patients had tumor reevaluation. Of these, five patients had SD, the longest lasting 10 months with a maximum 25% reduction in tumor size. Combining data from patients on both schedules, median PFS was 1.8 (95% confidence interval, 1.5-1.9) months (Fig. 1) and median OS was 7.8 months (95% confidence interval, 4.5-13.9; Fig. 2).

***Toxicity.*** All patients who received at least one dose of PD-0325901 were analyzed for safety. Table 4 summarizes treatment-related adverse events reported in ≥10% of patients on either schedule. The most common treatment-related toxicities (incidence in schedule A/incidence in schedule B) were diarrhea (54%/76%), fatigue (31%/48%), rash (46%/33%), vomiting (38%/33%), and nausea (38%/29%). Of note, there was a substantial decrease in the incidence of visual disturbance with schedule B, although neurologic events were similar between schedules. Visual symptoms comprised of blurred vision, halo vision, photopsia, and diplopia. Two patients (10%) had pulmonary embolism (associated with deep-vein thrombosis in one case) and one patient (5%) had grade 2 congestive heart failure on schedule B, all of which were considered related to study treatment. The patient with congestive heart failure presented on day 9 of cycle 1 and was resolved after permanent discontinuation of study drug and supportive therapy on day 31. No significant myelosuppression was observed on either schedule. Hematologic toxicity consisted mainly of mild-to-moderate anemia, without any neutropenia or leukopenia. Chemistry abnormalities were rare, and seldom grade ≥3.

A 47-year-old male patient on schedule A developed severe shortness of breath during the third week of cycle 1. Radiographic evaluation showed diffuse interstitial infiltrates in the lungs. Congestive heart failure was ruled out by echocardiogram. The treating physician reported pneumonia and progressive disease, and the patient was treated with broad-spectrum antibiotics and antifungals without improvement. The patient died due to multiple organ system failure in hospice. Another patient on schedule A, a 64-year-old male with a medical history of adrenal insufficiency, experienced severe weakness during cycle 1 in the context of progressive disease. He died due to worsening adrenal failure. Three patients died within 28 days of their last PD-0325901 dose due to adverse events deemed not to be related to study drug (aspiration pneumonia, aspiration with respiratory failure, and respiratory arrest).

***Pharmacokinetics.*** On day 15 (schedule A) or day 19 (schedule B) of cycle 1, the mean (coefficient of variation) trough plasma concentrations of PD-0325901 and its metabolite PD-0315209 were 100 ng/mL (52%) and 250 ng/mL (58%), respectively, for schedule A (*n* = 11)

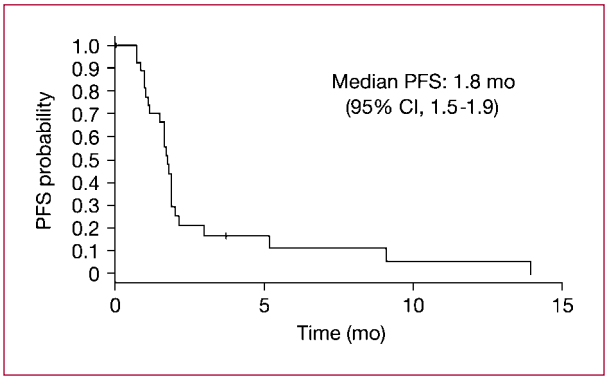


**Fig. 1.** Kaplan-Meier plot for PFS. 95% CI, 95% confidence interval.

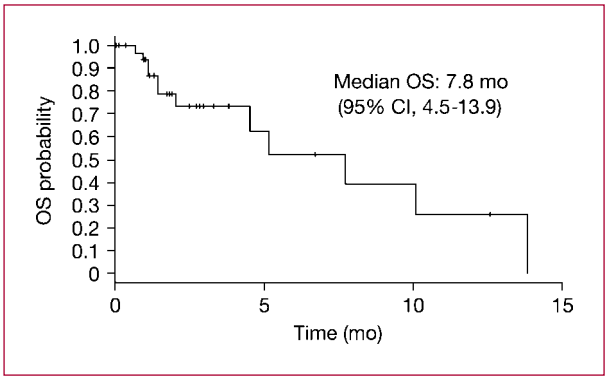


**Fig. 2.** Kaplan-Meier plot for OS.

**Table 4.** Summary of treatment-related, nonhematologic adverse events and all-causality hematologic and chemistry abnormalities occurring with a frequency of ≥10% in either schedule (maximum grade, all cycles)

| Adverse event | Schedule A (*n* = 13) | | | Schedule B (*n* = 21) | | |
|---|---|---|---|---|---|---|
| | Grade 1/2, *n* (%) | Grade 3, *n* (%) | Grade 4, *n* (%) | Grade 1/2, *n* (%) | Grade 3, *n* (%) | Grade 4, *n* (%) |
| **Nonhematologic, treatment related*** | | | | | | |
| Diarrhea | 6 (46) | 1 (8) | 0 | 14 (67) | 1 (5) | 1 (5) |
| Fatigue | 4 (31) | 0 | 0 | 8 (38) | 2 (10) | 0 |
| Rash | 5 (38) | 1 (8) | 0 | 7 (33) | 0 | 0 |
| Vomiting | 5 (38) | 0 | 0 | 7 (33) | 0 | 0 |
| Nausea | 5 (38) | 0 | 0 | 6 (29) | 0 | 0 |
| Dermatitis acneiform | 1 (8) | 0 | 0 | 7 (33) | 0 | 0 |
| Confusional state | 3 (23) | 1 (8) | 0 | 3 (14) | 1 (5) | 0 |
| Vision blurred | 5 (38) | 0 | 0 | 1 (5) | 0 | 0 |
| Peripheral edema | 2 (15) | 0 | 0 | 4 (19) | 0 | 0 |
| Facial edema | 2 (15) | 0 | 0 | 4 (19) | 0 | 0 |
| Visual disturbance | 4 (31) | 0 | 0 | 1 (5) | 0 | 0 |
| Dry mouth | 2 (15) | 0 | 0 | 3 (14) | 0 | 0 |
| Dyspnea | 2 (15) | 1 (8) | 0 | 1 (5) | 1 (5) | 0 |
| Dizziness | 1 (8) | 0 | 0 | 3 (14) | 0 | 0 |
| Dehydration | 0 | 0 | 0 | 0 | 2 (10) | 1 (5) |
| Constipation | 0 | 0 | 0 | 3 (14) | 0 | 0 |
| Myalgia | 1 (8) | 0 | 0 | 2 (10) | 0 | 0 |
| Asthenia | 1 (8) | 0 | 0 | 2 (10) | 0 | 0 |
| Weight gain | 1 (8) | 0 | 0 | 2 (10) | 0 | 0 |
| Headache | 1 (8) | 0 | 0 | 2 (10) | 0 | 0 |
| Hallucination | 1 (8) | 1 (8) | 0 | 1 (5) | 0 | 0 |
| Dyspepsia | 2 (15) | 0 | 0 | 1 (5) | 0 | 0 |
| Diplopia | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Abdominal pain | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Upper abdominal pain | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Agitation | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Cough | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Dry skin | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Pruritus | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Erythematous rash | 0 | 0 | 0 | 2 (10) | 0 | 0 |
| Epistaxis | 2 (15) | 0 | 0 | 0 | 0 | 0 |
| **Hematologic and chemistry abnormalities, all causality†** | | | | | | |
| Anemia | 6 (46) | 0 | 0 | 10 (48) | 0 | 0 |
| Lymphopenia | 3 (23) | 3 (23) | 1 (8) | 5 (24) | 3 (14) | 0 |
| Hypoalbuminemia | 6 (46) | 0 | 0 | 9 (43) | 0 | 0 |
| Hyperglycemia | 3 (23) | 0 | 0 | 9 (43) | 1 (5) | 0 |
| Alkaline phosphatase | 3 (23) | 1 (8) | 0 | 6 (29) | 0 | 0 |
| Hyponatremia | 2 (15) | 1 (8) | 0 | 5 (24) | 0 | 0 |
| Hypocalcemia | 2 (15) | 0 | 1 (8) | 4 (19) | 0 | 0 |
| Hypokalemia | 2 (15) | 0 | 0 | 3 (14) | 0 | 0 |
| AST | 2 (15) | 0 | 0 | 1 (5) | 1 (5) | 0 |
| ALT | 2 (15) | 0 | 0 | 1 (5) | 1 (5) | 0 |
| Thrombocytopenia | 1 (8) | 0 | 0 | 2 (10) | 0 | 0 |
| Hypophosphatemia | 0 | 0 | 0 | 2 (10) | 0 | 0 |

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

*Treatment related.

†All causes; includes random glucose in some tests.

and 173 ng/mL (73%) and 285 ng/mL (76%), respectively, for schedule B ($n$ = 10). Such levels were sustained on day 15/19 of cycle 2. There were too few evaluable concentration values for a meaningful comparison between cycles 3 and 5.

## Discussion

To our knowledge, the present study of PD-0325901 is the first complete report of a phase II study of a MEK inhibitor specifically in patients with advanced NSCLC. The primary objective of this study was not met according to a prespecified criterion. Six or more confirmed objective responses were to be observed to reject the null hypothesis that the true probability of response was ≤5%. No objective responses were observed in this heavily pretreated population; thus, the alternative hypothesis that the true probability of response was ≥15% was rejected. The lack of response, coupled with the safety issues in this and a phase I study of PD-0325901, in which development of retinal vein occlusion was observed,[10] prompted a decision to terminate this study during stage 1. Toxicity, patient enrichment strategies, choice of end points, and rational combination strategies for MEK inhibitors merit further discussion.

Visual disturbances, diarrhea, fatigue, and rash were common treatment-related adverse events during the study and led to treatment discontinuation in some patients. Optical neuropathy and retinal vein occlusion have been reported with continuous dosing of PD-0325901[10] but were not observed in this study, which used intermittent schedules that included at least 1 week off treatment. It will be important to refine the dosing regimen of PD-0325901 further to minimize toxicity. The mean trough concentrations of PD-0325901 in this study were far above the $IC_{50}$ based on tumor xenograft mouse models (range, 16.5-53.5 ng/mL)[11] and were also above the plasma drug concentration required for 90% pERK suppression in normal lung tissue in rats (99 ng/mL; ref. 21). Therefore, a PD-0325901 dose lower than 15 mg twice daily might be both effective and more tolerable, given that minimum target concentrations (determined in animal models) were achieved at doses of ≥2 mg twice daily in a phase I study of PD-0325901.[10]

It will clearly be important to understand the determinants of efficacy for the future development of MEK inhibitors for NSCLC. Genetic markers (*BRAF* and *KRAS* mutations) may also contribute to treatment outcome, as *BRAF*-mutant tumor cells are exquisitely sensitive to MEK inhibition compared with RAS-mutant and RAS/*BRAF*-wild-type cell lines (1, 18). Tumor histology may also be able to enrich for patients sensitive to MEK inhibitors, as has been suggested for the anti-insulin–like growth factor type 1 receptor antibody, figitumumab being more active in squamous cell carcinoma and pemetrexed showing more activity in adenocarcinoma histology (22, 23). In addition, linking genomic data to drug sensitivity could establish which NSCLC patient subsets are likely to be responsive to MEK inhibition (24).

It could be argued that objective responses to MEK may be unlikely based on the cell cycle arrest mechanism and thus end points such as disease control or PFS may have been a better choice. Targeted agents may prolong survival without achieving high proportions of objective responses (25). Thus, future studies should focus more clearly on end point measurements and consider alternative strategies such as examining positron emission tomography imaging with tracers such as 3′-deoxy-3′-[18F]-fluoro-L-thymidine that can assess inhibition of tumor proliferation (26).

Despite the lack of tumor responses in our study, some consideration should be made for combination strategies with other pathway inhibitors. Preclinical studies have shown that cells without isolated *BRAF* mutations (which account for the majority of NSCLC) MEK inhibition is unlikely to result in growth arrest, despite effective ERK inhibition (13, 14, 27). Growth factor signaling pathways are highly redundant and are found in network arrays (28) and this redundancy may allow cells to resist single pathway inhibition. Notably, RAS and phosphoinositide 3-kinase/AKT pathways intersect at various points and dual inhibition of MEK and phosphoinositide 3-kinase was recently shown to shrink KRAS-driven tumors in a mouse model of lung cancer (29). Thus, clinical studies exploring MEK inhibition in combination with direct or indirect phosphoinositide 3-kinase/AKT inhibitors or EGFR tyrosine kinase inhibitors are warranted. In addition, linking genomic data to drug sensitivity could establish which NSCLC patient subsets are likely to be responsive to MEK inhibition (24).

In summary, no objective responses were observed with PD-0325901 in patients with NSCLC. Patient selection in future trials of MEK inhibitors should be refined based on clinical and genetic determinants, and the end point used to assess antitumor activity should be carefully chosen. Further evaluation using a lower dose of PD-0325901 on the intermittent schedule may be warranted in selected patients with BRAF mutations or in other tumor contexts in which downstream signaling is reliant on MEK for tumor maintenance.

### Disclosure of Potential Conflicts of Interest

R.B. Cohen, commercial research grant, Pfizer (paid to Fox Chase Cancer Center for the trial itself). P.D. Eisenberg, commercial research grant, Pfizer. A.D. Ricart, P. Selaru, and K.D. Wilner, employment, Pfizer. P. Selaru, K.D. Wilner, stockholders, Pfizer. E. Haura, commercial research grant, Bristol Myers Squibb; filed patent for biomarkers of dasatinib. The other authors have disclosed no potential conflicts of interest.

### Grant Support

Medical writing support was provided by Christine Arris at ACUMED (Tytherington, UK) and was funded by Pfizer, Inc. The study was funded by Pfizer, Inc.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 07/22/2009; revised 12/01/2009; accepted 12/10/2009; published OnlineFirst 03/23/2010.

[11] Pfizer. Investigator's Brochure: PD 0325901. September 2006.

## References


1. Solit DB, Garraway LA, Pratilas CA, et al. BRAF mutation predicts sensitivity to MEK inhibition. Nature 2006;439:358–62.
2. Sebolt-Leopold JS, Herrera R. Targeting the mitogen-activated protein kinase cascade to treat cancer. Nat Rev Cancer 2004;4: 937–47.
3. Ji H, Wang Z, Perera SA, et al. Mutations in BRAF and KRAS converge on activation of the mitogen-activated protein kinase pathway in lung cancer mouse models. Cancer Res 2007;67:4933–9.
4. Arriagada R, Bergman B, Dunant A, Le CT, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351–60.
5. Curran WJ, Scott CB, Langer CJ, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III nsclc: RTOG 9410 [abstract]. Proc Am Soc Clin Oncol 2003;22 Suppl:621.
6. Scagliotti GV, De MF, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002;20:4285–91.
7. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.
8. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589–97.
9. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542–50.
10. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353:123–32.
11. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22: 1589–97.
12. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.
13. Brose MS, Volpe P, Feldman M, et al. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res 2002;62:6997–7000.
14. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949–54.
15. Kwiatkowski DJ, Harpole DH, Jr., Godleski J, et al. Molecular pathologic substaging in 244 stage I non-small-cell lung cancer patients: clinical implications. J Clin Oncol 1998;16:2468–77.
16. Pratilas CA, Hanrahan AJ, Halilovic E, et al. Genetic predictors of MEK dependence in non-small cell lung cancer. Cancer Res 2008; 68:9375–83.
17. Vicent S, Lopez-Picazo JM, Toledo G, et al. ERK1/2 is activated in non-small-cell lung cancer and associated with advanced tumours. Br J Cancer 2004;90:1047–52.
18. Pratilas CA, Halilovic E, Sawai A, Grbovic-Huezo O, Rosen N, Solit DB. BRAF mutation predicts MEK-dependence in non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2007;25 Suppl:570s.
19. Brognard J, Dennis PA. Variable apoptotic response of NSCLC cells to inhibition of the MEK/ERK pathway by small molecules or dominant negative mutants. Cell Death Differ 2002;9:893–904.
20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
21. Brown AP, Carlson TC, Loi CM, Graziano MJ. Pharmacodynamic and toxicokinetic evaluation of the novel MEK inhibitor, PD0325901, in the rat following oral and intravenous administration. Cancer Chemother Pharmacol 2007;59:671–9.
22. Scagliotti GV, Parikh P, von PJ, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–51.
23. Karp DD, Paz-Ares LG, Novello S, et al. Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer. J Clin Oncol 2009;27:2516–22.
24. Bild AH, Yao G, Chang JT, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 2006;439: 353–7.
25. Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. J Clin Oncol 2004;22:4442–5.
26. Ullrich RT, Zander T, Neumaier B, et al. Early detection of erlotinib treatment response in NSCLC by 3′-deoxy-3′-[F]-fluoro-L-thymidine ([F]FLT) positron emission tomography (PET). PLoS One 2008;3: e3908.
27. Naoki K, Chen TH, Richards WG, Sugarbaker DJ, Meyerson M. Missense mutations of the BRAF gene in human lung adenocarcinoma. Cancer Res 2002;62:7001–3.
28. Rowinsky EK. Signal events: cell signal transduction and its inhibition in cancer. Oncologist 2003;8 Suppl 3:5–17.
29. Engelman JA, Chen L, Tan X, et al. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med 2008;14:1351–6.