Cancer Chemother Pharmacol (2011) 68:547–552
DOI 10.1007/s00280-011-1620-1

SHORT COMMUNICATION

Pilot study of PD-0325901 in previously treated patients with advanced melanoma, breast cancer, and colon cancer

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Received: 27 February 2011 / Accepted: 14 March 2011 / Published online: 24 April 2011

Abstract
Purpose To assess further the tolerability and preliminary antitumor activity of PD-0325901 in previously treated patients with advanced melanoma, breast cancer, and colon cancer.
Methods This pilot study evaluated PD-0325901 on an intermittent dosing schedule. PD-0325901 was administered orally at 20 mg twice daily (BID) for 21 consecutive days followed by 7 days of no treatment. This dose was not well tolerated and consequently changed to 15 mg BID.
Results Between October and December 2005, 13 patients with metastatic measurable disease were entered into the study (seven melanoma, three breast cancer, and three colon cancer). All patients had received prior systemic therapy and were treated with a total of 61 cycles of PD-0325901 (nine received an initial dose of 20 mg BID, four an initial dose of 15 mg BID). The study was terminated early because of an unexpected high incidence of musculoskeletal and neurological adverse events, including gait disturbance, memory impairment, confusion, mental status changes, mild to moderate visual disturbances, and muscular weakness including neck weakness ("dropped-head syndrome"). Other common toxicities were diarrhea, acneiform rash, fatigue, and nausea. There was no significant hematologic toxicity, and chemistry abnormalities were rare. One patient achieved a confirmed complete response, and five patients had stable disease.
Conclusions PD-0325901 can cause significant musculoskeletal, neurological, and ocular toxicity at doses $\geq$15 mg BID. Future studies with adaptive designs might evaluate doses $\leq$10 mg BID in tumor types with a high incidence of *Ras* and *Raf* mutations. ClinicalTrials.gov identifier NCT00147550.

Keywords PD-0325901 · MEK inhibitor · Pilot study · Neurological toxicity · Ocular toxicity

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Introduction

PD-0325901 is a second-generation, small-molecule inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal-related kinase (ERK) kinase (MEK) structurally related to CI-1040, the first MEK-targeted agent evaluated in clinical trials. Like CI-1040, PD-0325901 is exquisitely selective for its target as a result of the non-competitive nature of its inhibition of MEK [1]. Instead of competing with adenosine triphosphate (ATP) for the MgATP binding

site, PD-0325901 binds an inhibitor pocket adjacent to the MgATP binding site. Occupation of the inhibitor pocket locks the kinase into a catalytically inactive form [2]. The parent molecule, CI-1040, was well tolerated but was associated with insufficient efficacy to continue in development [3]. PD-0325901 has improved potency, metabolic stability, prolonged duration of target suppression, and higher oral bioavailability relative to CI-1040 [3].

In targeting MEK, PD-0325901 modulates the RAF–MEK–ERK pathway, a pathway central to cellular proliferation and survival [4]. MEK is central to the RAF–MEK–ERK pathway, ultimately relaying signals from a range of upstream transducers to downstream effectors via ERK [5]. MEK exists as two homologs, MEK1 and MEK2, both of which are attractive targets as they sequentially phosphorylate their only known substrates, ERK1 and ERK2 [6]. Inhibition of both MEK isoforms (MEK1 and MEK2) by PD-0325901, therefore, has the potential to block the aberrant signal transduction known to be constitutively active in a number of tumor types [7–9].

Here, we report results from an expanded cohort of patients from a first-in-human, phase I study further evaluating the safety, tolerability, and preliminary efficacy of PD-0325901 in patients with previously treated advanced melanoma, breast cancer, and colon cancer.

Materials and methods

The study enrolled patients with histologically or cytologically confirmed metastatic or inoperable non-ocular melanoma, colon cancer, or breast cancer. Patients were required to have at least one measurable lesion that had not been previously irradiated. Patients with breast or colon cancers were excluded if they had previously received more than two cytotoxic chemotherapy regimens for metastatic disease. Patients with melanoma were excluded if they had received more than one systemic therapy regimen (other than adjuvant therapy more than 6 months prior to enrollment). Other inclusion and exclusion criteria were the same as in the phase I portion [10]. The primary objective of this pilot study was to evaluate the feasibility of an intermittent dosing schedule of PD-0325901. Efficacy was assessed independently in each tumor type using Response Evaluation Criteria in Solid Tumors. Tumor measurements were conducted every 8 weeks. If the intermittent dosing schedule was well tolerated, then enrollment was to proceed to a phase II study with an optimized three-stage design [11]. A pre-specified number of objective or clinical benefit responses for each indication were to be observed to trigger recruitment of patients into the next stage of the phase II trial. The enrollment target for each indication in stage 1 was to be 20 patients.

PD-0325901 was administered orally initially at a dose of 20 mg twice daily (BID) on an intermittent schedule comprising therapy for 3 weeks of a 4-week cycle (21 consecutive days of therapy followed by 7 days of no treatment). This dose had been selected for expansion and further assessment after achieving the maximum administered dose at 30 mg BID in the dose-escalation portion of the phase I study [10]. However, this dose was not well tolerated and was, therefore, reduced to 15 mg BID. Treatment cycles were repeated until disease progression, unacceptable toxicity, or investigator/patient decision to withdraw.

Physical examinations, including a 12-lead electrocardiogram and laboratory tests, were conducted at screening, initiation of therapy, and every 4 weeks thereafter. An opthalmologic examination was carried out at screening and at 4 weekly intervals after treatment commenced. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, and were monitored throughout the study period until at least 4 weeks after the last dose of study drug. AEs were followed until resolution or stabilization. Safety analysis included all patients who received at least one dose of study drug. 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.

Results

Between October and December 2005, 13 patients with metastatic measurable disease (median age, 60 years; range, 34–81) were enrolled into the study. Of these, seven had melanoma (regionally metastatic in three), three had breast cancer, and three had colon cancer. All patients had received prior systemic therapy. Baseline characteristics are presented in Table 1. Overall, a total of 61 cycles of PD-0325901 were administered, with a median of three cycles per patient (range, 1–28+ cycles). Nine patients initially received PD-0325901 20 mg BID and four patients initially received PD-0325901 15 mg BID. At the end of the study, one patient remained on therapy and 12 patients had discontinued therapy, three due to progressive disease, seven due to AEs considered to be treatment related (20 mg BID, $n = 6$; 15 mg BID, $n = 1$), one due to non-compliance, and one patient died as a result of metastatic colon cancer.

Toxicity

No treatment-related AEs of grade 4 or 5 severity were reported during the study. The most frequently occurring

Table 1 Patient characteristics

Characteristics	$N = 13$
Median (range) age, years	59.8 (34–81)
Sex, *n* (%)	
Male	7 (53.8)
Female	6 (46.2)
Primary tumor site, *n*	
Melanoma	7
Breast	3
Colon	3

treatment-related AEs are presented in Table 2. These included diarrhea, rash, fatigue, and nausea. Diarrhea was mild and satisfactorily treated with supportive therapy (e.g., oral fluid replacement and antidiarrheal agents). Acneiform rash was typically mild to moderate and reversible; mainly on the face, upper body, and arms. Treatment-related musculoskeletal and neurological AEs in the cohort initially treated at 20 mg BID comprised gait disturbance, memory impairment, confusion, mental status changes, mild to moderate visual disturbances, and muscular weakness including neck weakness ("dropped-head syndrome"). One of the patients with neck weakness had an electromyography suggesting inflammatory myopathy with elevated creatinine phosphokinase, which returned to normal after PD-0325901 discontinuation. The high rate of AEs led to the discontinuation of this dose. Consequently, patients receiving clinical benefit were allowed to continue study therapy at the discretion of the treating physician at a reduced dose of 15 mg BID. Patients subsequently enrolled into the study received an initial dose of 15 mg BID. Nevertheless, some neurological AEs presented at this new dose, including an ischemic optic neuropathy of grade 3 severity. At this point, the study was terminated early because of an unexpected high incidence of musculoskeletal and neurological AEs. These events were reversible upon discontinuation of PD-0325901 in most of the patients, although in four patients events were not completely resolved at last follow up. The maximum tolerated dose and the recommended phase II dose were further evaluated in the phase I study [10] at lower doses. Hematological toxicity and chemistry abnormalities were rare.

Efficacy

One patient with advanced melanoma achieved a confirmed complete response. This patient had received interferon alpha as adjuvant therapy before enrollment in the study. A further five patients had stable disease after two cycles of therapy.

Pharmacokinetics

The plasma trough concentrations of PD-0325901 and its metabolite, PD-0315209, were evaluated. On day 15 of cycle 1, the respective mean (coefficient of variation, %) plasma trough concentrations of PD-0325901 and PD-0315209 were 158 and 188 ng/mL for the 15 mg BID group ($n = 2$) and 181 ng/mL (90.8%) and 211 ng/mL (60.8%) for the 20 mg BID group ($n = 5$). Such levels were sustained on day 15 of cycles 2–4.

Discussion

This report describes the tolerability and preliminary antitumor activity of an intermittent dosing schedule of the oral MEK inhibitor, PD-0325901, in patients with advanced melanoma, breast cancer, and colon cancer. Both doses of PD-0325901, 20 mg BID and 15 mg BID, were found to be unsuitable for a formal phase II evaluation. The incidence of musculoskeletal and neurological AEs at these doses was unexpectedly high.

Typical toxicities of this mechanistic class include diarrhea, acneiform rash, nausea, and fatigue. These toxicities were frequently reported in the current study, as well as in phase I and II studies of the structurally related MEK inhibitor CI-1040 [1, 3] and in phase I and II studies of the structurally distinct non-ATP-competitive MEK inhibitor, AZD6244 [12–17]. Similar AEs have been observed in phase I studies of the oral MEK1/2 inhibitors, AS703026 and GSK1120212, with diarrhea, rash/skin reactions, nausea, and asthenia/fatigue all commonly reported [18, 19]; nausea, vomiting, and diarrhea were also among the most frequently reported AEs in a phase I study of the intravenously administered MEK1 and MEK kinase-1 inhibitor, E6201 [20].

Visual disturbances, quite frequently occurring AEs in this study, are not without precedent in MEK inhibitors. Visual disturbances, typically transient blurring and altered light perception, were reported for 9% of patients receiving CI-1040 in a phase II trial. These visual effects resolved, usually within 24 h, when treatment was interrupted and did not recur when treatment was resumed [3]. Similarly, grade 1 or 2 blurred vision that was transient and reversible was documented at the higher dose levels in a phase I study of AZD6244 [12]. However, visual disturbances were not among the most frequently reported AEs in a phase I trial of the solid, oral formulation, or in phase II studies of AZD6244 [13–16]. Transient visual disturbances (abnormal color perception, blurred vision, and visual field defects) were also reported at the highest dose level in a phase I study of AS703026 [18], and central serous retinopathy was a dose-limiting toxicity in a phase I study of

Table 2 Treatment-related adverse events occurring with a frequency of at least 15% of the study population (maximum grade, all cycles)

Adverse events,[a,b] *n*	15 mg (*N* = 4)		20 mg (*N* = 9)	
	Grade 3	All grades	Grade 3	All grades
Diarrhea	0	3	0	7
Rash	0	4	0	6
Chromatopsia	0	0	0	7
Dermatitis acneiform	0	2	1	3
Halo vision	0	2	0	3
Nausea	0	2	0	3
Vomiting	0	0	0	5
Fatigue	0	2	0	3
Edema peripheral	0	1	0	4
Pruritus	0	1	0	4
Pain in extremity	0	0	0	4
Vision blurred	0	1	0	2
Gait disturbance	0	0	1	2
Muscular weakness	0	0	1	2
Confusion	0	1	0	2
Alopecia	0	2	0	1
Anemia	0	1	0	1
Extraocular muscle paresis	0	0	0	2
Visual disturbance	0	1	0	1
Abdominal pain	0	0	0	2
Constipation	0	0	0	2
Stomatitis	0	1	0	1
Infection[c]	0	1	0	1
Neck pain	0	0	0	2
Dizziness	0	0	0	2
Dysarthria	0	0	0	2
Depression	0	1	0	1
Insomnia	0	0	0	2
Dysphonia	0	1	0	1
Dry skin	0	1	0	1
Erythema	0	0	0	2
Periorbital edema	0	1	0	1

[a] There were no adverse events of grade 4 or 5 severity

[b] Grade 3 events occurring in ≤15% of the study population comprised abscess limb, abscess neck, syncope, cyanopsia, optic nerve ischemic neuropathy, subcutaneous abscess, hypokalemia, psychotic disorder, and hypoxia

[c] Upper respiratory tract

GSK1120212 [19]. It is notable that PD-0325901 was related to a case of optic ischemic neuropathy in the present study. The association of these particular AEs with agents extremely specific for MEK inhibition suggests that visual disturbances may be a mechanistic class effect.

The RAF–MEK–ERK pathway is involved in neural development and cardiac function, and its dysregulation may contribute to pathophysiological processes [21]. The "dropped-head syndrome" (or "isolated neck extensor myopathy") is a rare neuromuscular syndrome characterized by a predominant weakness of the neck extensor muscles and, to the best of our knowledge, it has not been frequently related to pharmacological treatment [22–25]. To date, published reports of the clinical experience with AZD6244 have detailed the most frequently occurring AEs. Neurologic effects, other than visual disturbances, and musculoskeletal effects have not been noted. Transient ataxia has, however, been reported for CI-1040 [3]. This raises the possibility that, rather than being mechanistic effects, these non-visual neurological AEs and musculoskeletal

effects result from the particular pharmacophore (CI-1040 and PD-0325901 are structural analogs). It will be of interest to see if full publication of ongoing trials will reveal similar toxicities, thereby suggesting a class rather than a pharmacophore effect. Of note, dizziness has been recently reported with a novel solid oral dosage form of AZD6244 [13], and dizziness, dysarthria, and ataxia with E6201 [20]. This opens the possibility of neuromuscular effects with more potent forms of MEK inhibitors (one complete response was reported by Agarwal et al. [13]). The mechanisms of these toxicities are currently unknown. Although still limited, there is evidence for a regulatory role of the RAS–MAPK pathway in neural and muscular physiology [26–31]. The plasma trough concentrations of PD-0325901 were far above the median effective concentrations based on tumor-bearing and human tumor xenograft mouse models (range, 16.5–53.5 ng/mL; Pfizer, Investigator's Brochure: PD 0325901. September 2006). In contrast, 99 ng/mL is the plasma drug level required for 90% pERK suppression in normal rat tissue [32]. These preclinical data suggest that doses $\geq$15 mg BID in patients might significantly inhibit the RAS–MAPK pathway in normal tissues, exceeding the risk/benefit ratio.

One patient with melanoma achieved a confirmed complete response, and five patients achieved stable disease. In a study of AZD6244, conducted in patients with advanced melanoma, subanalysis of immature survival data by BRAF status hinted at higher efficacy in BRAF-positive patients [15]. These data coupled with the responses observed in refractory advanced melanoma in the phase I portion of the current study emphasize the importance of patient selection for MEK inhibitors [10]. Further clinical data may be obtained in the near future from other highly selective inhibitors of MEK, including AS703026, GSK1120212, E6201, and XL518 [18–20, 33].

If these toxicities prove to be a class effect, then the therapeutic dose may be determined by titrating efficacy against toxicity. The toxicities that lead to the early termination of the current trial were detected at PD-0325901 doses of 15 mg BID and above. The preliminary anticancer activity reported with MEK inhibitors suggests that these agents might be developed in difficult-to-treat disease, such as advanced melanoma and pancreatic cancer. It may therefore be of interest to carry out future studies with adaptive designs to evaluate PD-0325901 doses of 10 mg BID or less in tumor types with a high incidence of *Ras* and *Raf* mutations. It will, however, be necessary to manage drug-related toxicities appropriately.

Acknowledgments We would like to thank all of the participating patients and their families, as well as the network of investigators, research nurses, study coordinators, and operations staff. Medical writing assistance was provided by Christine Arris of ACUMED® (Tytherington, UK), and was funded by Pfizer Inc. This study was sponsored by Pfizer Inc.

Conflicts of interest PDB's institution (The Angeles Clinic) received research funding from Pfizer for the trial itself. GAD has nothing to disclose. DB's institution (Sharp Clinical Oncology Research) receives research funding from Pfizer for participating in the trial. CHR received research funding from Pfizer for the trial itself, and his institution (Sharp Clinical Oncology Research) has received a commercial research grant from Merck for a clinical trial. CRG has performed a consultant/advisory role for Pfizer. ADR is an employee of Pfizer and owns stock in Pfizer.

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