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Phase I Pharmacokinetic and Pharmacodynamic Study of the Oral, Small-Molecule Mitogen-Activated Protein Kinase Kinase 1/2 Inhibitor AZD6244 (ARRY-142886) in Patients With Advanced Cancers

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Abstract

Purpose—To assess the tolerability, pharmacokinetics (PKs), and pharmacodynamics (PDs) of the mitogen-activated protein kinase kinase (MEK) 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancer.

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Patients and Methods—In part A, patients received escalating doses to determine the maximum-tolerated dose (MTD). In both parts, blood samples were collected to assess PK and PD parameters. In part B, patients were stratified by cancer type (melanoma *v* other) and randomly assigned to receive the MTD or 50% MTD. Biopsies were collected to determine inhibition of ERK phosphorylation, Ki-67 expression, and *BRAF, KRAS*, and *NRAS* mutations.

Results—Fifty-seven patients were enrolled. MTD in part A was 200 mg bid, but this dose was discontinued in part B because of toxicity. The 50% MTD (100 mg bid) was well tolerated. Rash was the most frequent and dose-limiting toxicity. Most other adverse events were grade 1 or 2. The PKs were less than dose proportional, with a median half-life of approximately 8 hours and inhibition of ERK phosphorylation in peripheral-blood mononuclear cells at all dose levels. Paired tumor biopsies demonstrated reduced ERK phosphorylation (geometric mean, 79%). Five of 20 patients demonstrated ≥ 50% inhibition of Ki-67 expression, and *RAF* or *RAS* mutations were detected in 10 of 26 assessable tumor samples. Nine patients had stable disease (SD) for ≥ 5 months, including two patients with SD for 19 (thyroid cancer) and 22 (uveal melanoma plus renal cancer) 28-day cycles.

Conclusion—AZD6244 was well tolerated with target inhibition demonstrated at the recommended phase II dose. PK analyses supported twice-daily dosing. Prolonged SD was seen in a variety of advanced cancers. Phase II studies are ongoing.

INTRODUCTION

Mitogen-activated protein kinase kinase (MEK or MAPK/ERK kinase) is a critical enzyme in the RAS/RAF/MEK/ERK pathway that regulates key cellular activities including proliferation, survival, and cell cycle regulation. This pathway is composed of a protein kinase cascade in which RAF, MEK, and ERK are in a sequential order.

MEK1/2 are attractive therapeutic targets because their only known substrates are ERK1/2. MEK inhibitors inhibit growth of human tumors in mouse xenografts[1–7] and leukemia cells in vitro.[8] Two other MEK inhibitors have been tested in clinical trials. CI-1040 showed insufficient antitumor activity to warrant further development,[9] and development of a second-generation MEK inhibitor, PD0325901,[10] has recently been discontinued.[11] AZD6244 is a potent, selective, adenosine triphosphate–uncompetitive inhibitor of MEK1/2, with an in vitro half maximal inhibitory concentration of 10 to 14 nmol/L against purified enzyme and no inhibition up to 10 μmol/L against numerous other serine/threonine and tyrosine kinases.[4] AZD6244 has excellent preclinical activity against many different tumors in cell-based growth assays and in human tumor mouse xenograft models, including colorectal,[4,6] pancreatic,[4] non–small-cell lung,[6] and hepatocellular cancer[5] and melanoma.[7]

Given this spectrum of preclinical activity[4] and the acceptable toxicology profile, a phase I study was undertaken to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AZD6244 in patients with advanced malignancies.

PATIENTS AND METHODS

Patient Selection

Eligibility criteria included patients aged ≥ 18 years with histologic or cytologic evidence of advanced cancer for which there was no curative or life-prolonging therapy; Eastern Cooperative Oncology Group performance status ≤ 2; prior radiation completed ≥ 3 weeks before study enrollment; life expectancy of ≥ 12 weeks; and adequate bone marrow (platelets ≥ 100,000/μL, absolute neutrophil count > 1,500/μL, and hemoglobin ≥ 9 g/dL), hepatic (total bilirubin ≤ 2.5× the upper limit of normal and AST ≤ 2.5× normal), and renal (serum creatinine ≤ 1.5× the upper limit of normal) function. In part B, patients were required to have a tumor that was safely accessible for biopsy. All patients gave written informed consent.

Experimental Treatment

This phase I, open-label, multiple-dose study assessed the safety, tolerability, PK, and PD of AZD6244 in patients with advanced solid malignancies. AZD6244 was formulated as an oral powder for reconstitution and supplied in dosing kits in 30-mL amber bottles. Antiemetic prophylaxis was not administered.

Part A was conducted to determine the maximum-tolerated dose (MTD) and used a standard three- to six-patient cohort design[12] evaluating doses of 50, 100, 200, and 300 mg bid. The incidence and severity of adverse events were evaluated and coded according to National Cancer Institute Common Terminology Criteria of Adverse Events (version 3). Response to therapy was monitored by modified Response Evaluation Criteria in Solid Tumors.[13] AZD6244-related dose-limiting toxicity (DLT) was defined as follows: any grade 4 toxicity (grade 4 neutropenia for > 7 days), grade 3 or 4 neutropenia with fever, grade 3 or 4 thrombocytopenia associated with bleeding (excluding patients receiving systemic anticoagulation), or any grade 3 or 4 nonhematologic toxicity. Grade 2 vomiting on 2 consecutive days despite optimal antiemetic therapy was considered dose limiting, as was any grade 2 toxicity lasting for more than 2 weeks or dosing interruption of more than 2 weeks for drug-related toxicity. 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). Each patient began the study with a single dose of AZD6244 on day 1, with assessment of adverse events on days 1, 2, and 3. If there were no DLTs through day 8, continuous bid dosing commenced. A cycle was defined as 28 days of twice-daily therapy.

In part B, patients were stratified by cancer type (melanoma *v* other) and randomly assigned to receive the MTD (200 mg bid) or 50% of the MTD dose (100 mg bid) to evaluate the dose that provided the best balance of safety/tolerability and PD effect for future clinical development. Tissue samples (tumor and normal skin) were obtained for PD assessments before dose and after 7 to 21 days of AZD6244 (day 15 ± 7 days). Patients must have taken the assigned dose uninterrupted for ≥ 7 days before the postdose biopsy.

Clinical Care of Patients

In the single-dose phase of part A, physical examinations, toxicity assessments, and laboratory analyses were conducted on days 1, 2, and 3. In the bid dosing phase, weekly assessments commenced on day 8 of the first 28-day cycle. ECG and PK assessments were conducted on day 22. In part B, assessments were conducted weekly in cycle 1 and every 28 days in subsequent cycles. Patients could continue on uninterrupted 28-day cycles of AZD6244 provided that there was no disease progression or unacceptable toxicity.

PD Analysis

Blood samples were collected on days 1 and 22 in part A and days 1 and 15 in part B before dose and 1 hour after dose for measurement of pERK levels by fluorescence-activated cell sorting analysis. Samples were treated ex vivo with 12-*O*-tetradecanoylphorbol-13-acetate for 10 minutes at 37°C within 1 hour of being drawn. ERK phosphorylation was preserved by immediate fixation of the cells with 1.2% methanol-free formaldehyde. Peripheral-blood mononuclear cells (PBMCs) were isolated, washed, and stored at −20°C. For analysis of ERK phosphorylation, cells were treated with an antibody to pERK, followed by a fluorescein isothiocyanate–conjugated secondary detection antibody and pERK quantitation by fluorescence-activated cell sorting analysis.

PK Analysis

Maximum observed plasma concentration (C_{max}) and median observed time to maximum plasma concentration values for each patient were derived from the plasma concentration-time profile, and the area under the time-concentration curve ($AUC_{0–24\ hours}$) was calculated using the linear trapezoidal rule (for details, see Appendix, online only).

Skin and Tumor Biopsy Sample Collection

Tissue samples (tumor and normal skin) were obtained for PD assessments before dose and after 7 to 21 days of AZD6244 (day 15 ± 7 days). The day 15 (± 7 days) postdose tumor and normal skin biopsies were collected 2 to 4 hours after dose on the same day as PK and PD assessments. Tumor biopsies (18-guage core needle) were taken using computed tomography or ultrasound scan guidance. Samples were fixed and stained with hematoxylin and eosin to confirm the diagnosis and the quality of the biopsy tissue. For optimal comparative biomarker studies, subsequent biopsies were taken from the same site as the screening biopsy. Skin biopsies were taken from the upper arm or buttocks using a 3- to 4-mm punch, using the same fixation method.

Immunohistochemistry

An indirect immunoperoxidase method, with antibodies against pERK1/2 or Ki-67, was used to evaluate pERK status and growth fraction (Ki-67) in situ. Negative and positive controls were included in each immunostained batch of slides. In all cases, these controls stained appropriately. Slides were scored, and representative microscopic fields were photographed. Nuclei and cytoplasm were scored for pERK by estimating the proportion of positive viable tumor cells multiplied by intensity of staining quantified on a 0 to 4+ scale. The proportion of tumor cell nuclei staining for Ki-67 was estimated by microscopic inspection in 10% increments. Only viable tumor was scored, with care taken to avoid necrotic areas of tumor.

Tumor DNA Mutation Analysis

Tumor tissue sections were isolated from paraffin-embedded sample blocks using a 1-mm array punch. Samples were washed and air dried, and DNA was extracted from fixed tissue. Analyses for *KRAS, NRAS*, and *BRAF* mutations were performed by established methods (see Appendix).

Statistical Evaluation

Safety data were summarized using appropriate descriptive statistics. Baseline scaled ratios were calculated for each assessable pair of biopsies (corresponding to the postdose/predose value). Because the data were treated as being multiplicative, geometric means (gmean) were calculated to give an overall mean level of inhibition, and corresponding CIs were calculated for these mean levels of inhibition.

Correlations of markers between tumor and skin samples were assessed using the Spearman rank correlation coefficient. Differences in time on study between patients who had an oncogene mutation at baseline and those who did not were assessed using a Wilcoxon signed rank test, as were differences in biomarker inhibition between patients with and without the mutation.

RESULTS

Fifty-seven patients (35% malignant melanoma; Table 1) received a total of 184 assessable cycles of therapy across four dose levels. The median number of cycles administered per patient was two (range, one to 22 cycles). Other baseline patient characteristics are listed in Table 1.

Toxicity

The toxic effects of AZD6244 are listed in Table 2 and Table 3.

Hematologic toxicity—Minimal hematologic toxicity was seen with AZD6244.

Rash—Rash was the most frequent toxicity and DLT, occurring in 74% of all patients, and precluded dose escalation greater than 300 mg bid. The rash was dose dependent, erythematous, and maculopapular, occurring predominantly on the torso. Resolution typically occurred with dosing interruption and/or dose reduction. In part B, an increase in frequency and severity of this rash led to selection of 100 mg bid as the tolerable phase II dose. Of the 43 episodes of skin rash, 34 were of maximum grade 1 or 2, and nine were grade 3 or 4.

GI toxicity—Mild to moderate diarrhea was the principal GI toxicity (56% of patients). Abdominal examination during the diarrhea episodes was benign. Diarrhea resolved promptly with loperamide therapy and/or drug discontinuation. In addition to diarrhea, nausea (n = 25) and vomiting (n = 14) were observed, which resolved quickly and completely with antiemetic therapy.

Edema—Mild to moderate edema occurred in 19 of 57 patients, whereas severe edema occurred in one patient with pre-existing abdominal distension from ascites.

Fatigue—Fatigue was dependent on dose and duration of treatment and mild to moderate in 20 of 22 patients. It was reversible with dose reduction and/or interruption.

Other toxicities—Mild to moderate reversible ALT and AST elevation occurred in 14% and 14% of patients, respectively. Blurred vision, which was transient and reversible, occurred in 12% of patients. These events were all grade 1 or 2. Eight patients (14%) experienced serious adverse events, including hypoxia, pneumonitis, bradycardia, renal insufficiency, and exfoliative dermatitis.

Dose reductions and study discontinuation—Seven patients (12%) required dose reductions for treatment-related toxicity, 24 patients (42%) required drug holidays of up to 2 weeks, and eight patients (14%) discontinued treatment for drug-related toxicity. On the basis of these results, the MTD and recommended dose of AZD6244 as an oral powder for reconstitution formulation for subsequent clinical testing is 100 mg bid.

PK

After a single dose of AZD6244, the median terminal half-life was 8.3 hours. C_{max} increased with increasing dose (Table 4 and Table 5). The mean area under the plasma concentration-time curve (AUC_{inf}) after single doses of AZD6244 also increased with increasing dose. Similarly, the steady-state AUC over the 12-hour dosing interval ($AUC_{0–12}$ hours) increased to a maximum at 200 mg bid. In part B, the median observed time to maximum plasma concentration was 1 hour after dose. The mean single-dose C_{max} values for the 100-mg and 200-mg cohorts were similar to the respective steady-state (day 15) C_{max} values. In both parts, the single-dose and steady-state AUC values increased with increasing dose in a less than dose-proportional manner (Table 4 and Table 5). In part B, however, it is likely that the median terminal half-life (4.7 hours) is an underestimate because of the shorter PK sampling schedule, which ended at 12 hours after dose (before the evening dose).

PD

Inhibition of ERK phosphorylation in PBMCs—Inhibition of ERK phosphorylation has been proposed as a PD biomarker of MEK inhibitor activity.[14] We initially measured inhibition of ERK phosphorylation in lymphocytes from 12-*O*-tetradecanoylphorbol-13-acetate-treated whole blood as a surrogate for tumor tissue (Appendix Table A1, online only). Up to 100% inhibition of ERK phosphorylation was seen 1 hour after the first dose, indicating rapid distribution and activity of AZD6244 in the bloodstream. Importantly, up to 90% inhibition of ERK phosphorylation (gmean = 51%) was seen in the trough samples on day 15 or 22, indicating that target inhibition was maintained throughout the bid dosing regimen.

Inhibition of ERK phosphorylation and Ki-67 labeling index in tumor biopsies—After documenting target inhibition in a surrogate tissue in part A, paired tumor samples were collected before treatment and after at least 7 continuous days of treatment and evaluated for inhibition of ERK phosphorylation by immunohistochemistry. We also evaluated drug effects on downstream signaling events by examining the reduction in the Ki-67 labeling index, a marker of cell proliferation. Figure 1 shows representative immunohistochemistry photomicrographs. Twenty of the 24 paired biopsies were assessable, with 19 having detectable pretreatment pERK expression and all 20 having detectable pretreatment Ki-67 expression. Strong inhibition of ERK phosphorylation was seen with a gmean inhibition of 79% (90% CI, 50% to 91%; Fig 2A). Ki-67 labeling was reduced in post-treatment tumor samples but not as consistently as pERK, the primary proof-of-mechanism biomarker. Nine of 20 samples showed some reduction, with ≥ 50% reduction in five samples (Fig 2B). The skin biopsies were generally uninformative because of variable and minimal baseline levels of pERK.

DNA Mutation Analysis

Activating mutations in the *RAS* genes (*KRAS* and *NRAS*) and in the *BRAF* gene have been reported to identify tumors that may be sensitive to MEK inhibition.[6,15] Therefore, the presence of specific mutations in these genes was evaluated in tumor samples from this study. Appendix Table A2 (online only) lists these data. Of the 26 patients with samples assessable for mutational status, 10 had a single mutation in *KRAS* (n = 5), *NRAS* (n = 4), or *BRAF* (n = 1).

The average length of time on study for patients carrying mutations (median, 3.5 months; range, 1 to 6 months) was greater than for those without a mutation (median, 2 months; range, 1 to 4 months). There is no statistical evidence of effect ($P = .30$ by Wilcoxon signed rank test) in this small sample. Four of the 10 patients with a mutation had tumor biopsies assessable for the pERK assay, which showed strong inhibition of ERK phosphorylation (100%, 100%, 83%, and 25%). These four patients, plus one other patient with a mutation, had tissue assessable for Ki-67 labeling and showed a strong labeling index (100%, 97%, 92%, 88%, and 33%). Possibly because of the small numbers in the study, there was no significant difference between biomarker knockdown for those patients with mutation versus those without mutation or with unknown mutation status (pERK: $P = .13$; Ki-67: $P = .13$). Of note, three patients showing the strongest reduction in Ki-67 labeling were all mutation positive.

Antitumor Activity

Figure 3 summarizes tumor responses by Response Evaluation Criteria in Solid Tumors. Nineteen patients (33%) had stable disease (SD) at the end of cycle 2, and nine patients (16%) had SD for ≥ 5 months. One patient with medullary thyroid cancer experienced SD for 19 cycles, whereas one patient with both uveal melanoma and renal cell carcinoma had SD for 22 cycles.

DISCUSSION

AZD6244 is a potent and selective MEK1/2 inhibitor that has shown excellent preclinical activity in a range of tumor models[4] with an acceptable toxicology profile, and this phase I study demonstrates that AZD6244 is well tolerated up to 100 mg bid. In part A, the MTD was 200 mg bid, but because of an increase in the frequency and severity of rash in part B, the lower dose level (50% of the MTD; 100 mg bid) was recommended as the tolerable phase II dose. The most common treatment-related toxicities observed with AZD6244 were rash, diarrhea, nausea, and fatigue, which are consistent with those observed for PD0325901 and CI-1040.[9,10,16] Seven patients developed transient and reversible blurred vision while receiving AZD6244, an adverse effect also observed with PD0325901 and CI-1040.[9,10,16] Five of these ocular events were observed at doses greater than the recommended phase II dose. When conducted, ophthalmologic examinations were unrevealing in regard to etiology. Rigorous physical examination and laboratory tests did not identify any other significant toxicities observed with other MEK inhibitors, including syncope and neurotoxicity.[16,17]

Despite a growing clinical literature on MEK inhibitors, there is only limited evidence to date that MEK can be inhibited consistently in patient tumors at tolerable inhibitor doses. In addition, it is unclear whether such inhibition correlates with clinical outcome and whether MEK inhibition in surrogate tissues corresponds to MEK inhibition in tumors. Accordingly, we determined whether tolerable doses of AZD6244 would inhibit MEK in PBMCs, skin, and patient tumors. Skin biopsies were generally uninformative because of the variable and minimal baseline levels of pERK. We observed a dose-dependent inhibition of ERK phosphorylation in PBMCs, as well as consistent inhibition of ERK phosphorylation when comparing pre- and post-treatment tumor biopsies, but there were insufficient data to suggest a correlation between surrogate tumor tissue PD. We also demonstrated inhibition of Ki-67 in patient tumors, but again, there were insufficient data to conclude whether PBMC samples are suitable surrogate tissues for tumor samples. Because activating mutations in *NRAS*, *KRAS*, and *BRAF* genes correlate in preclinical studies with sensitivity to MEK inhibitors, mutational analysis of these genes was performed in 26 available tumors. In this small sample size, there was a nonsignificant trend towards delayed progression on study in patients with mutations compared with wild-type tumors.

AZD6244 displayed less than dose-proportional PK with increasing C_{max} and AUC as doses increased from 50 to 300 mg bid. There was a high degree of interpatient variability, which is not surprising for an oral agent. No food effect study was performed, and no guidance for food intake was given except for PK assessments that were performed in the fasting state (1 hour before and 2 hours after dosing). The PK profile supports a bid dosing scheme that results in exposures that adequately inhibit the drug target.

The best clinical response was SD that lasted for 5 or more months in nine patients. Two patients maintained SD for 19 and 22 cycles. One patient with malignant melanoma had a 70% tumor shrinkage after three cycles of AZD6244 but developed symptomatic brain metastases before confirmatory scans could be performed. This patient had an *NRAS* mutation and showed 100% inhibition of ERK phosphorylation and 97% inhibition of Ki-67. Thus, the present phase I study provides preliminary evidence of antineoplastic activity in humans.

In summary, this study establishes that the MEK inhibitor AZD6244 has a manageable safety and tolerability profile and identifies a suitable dose for subsequent clinical trials (100 mg orally, twice daily continuously) that results in target inhibition. Although this study demonstrates that the MEK1/2 target can be safely inhibited in vivo in humans, our data also suggest that target inhibition may be necessary but not sufficient for antineoplastic activity.

These findings support future clinical development of AZD6244, and phase II studies are in progress.

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Appendix

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

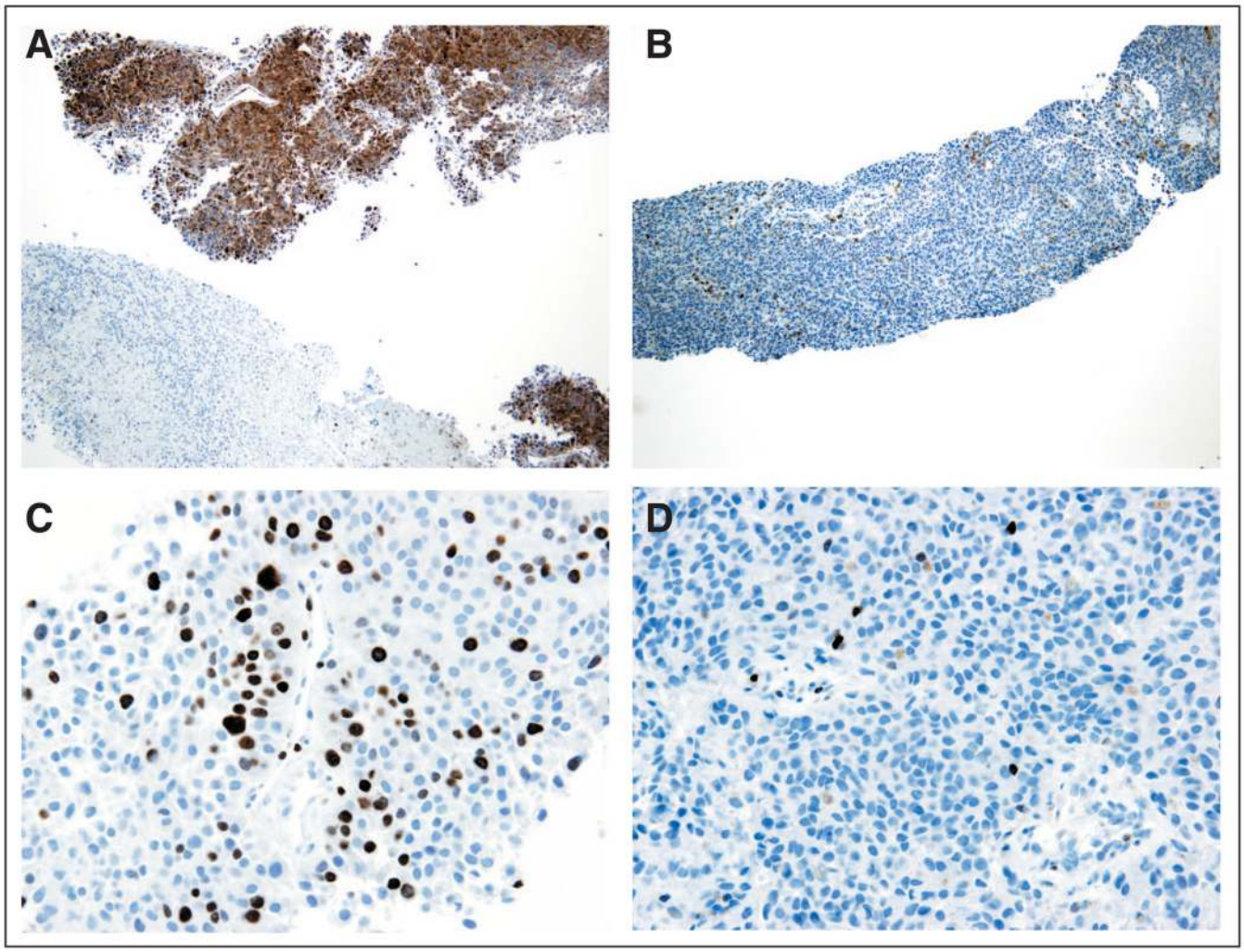

Fig 1.

Immunostains of pre- and post-treatment melanoma specimens from the same patient. (A) Before dose, tumor cells are reactive to anti-pERK antibody (brown staining; magnification, ×100). (B) After dose, cells are unreactive to same anti-pERK antibody (magnification, ×100). (C) Before dose, variable nuclear Ki-67 labeling (approximately 30% positive nuclei; magnification, ×400). (D) After dose, marked reduction in nuclear Ki-67 labeling (< 1% positive nuclei; magnification, ×400)

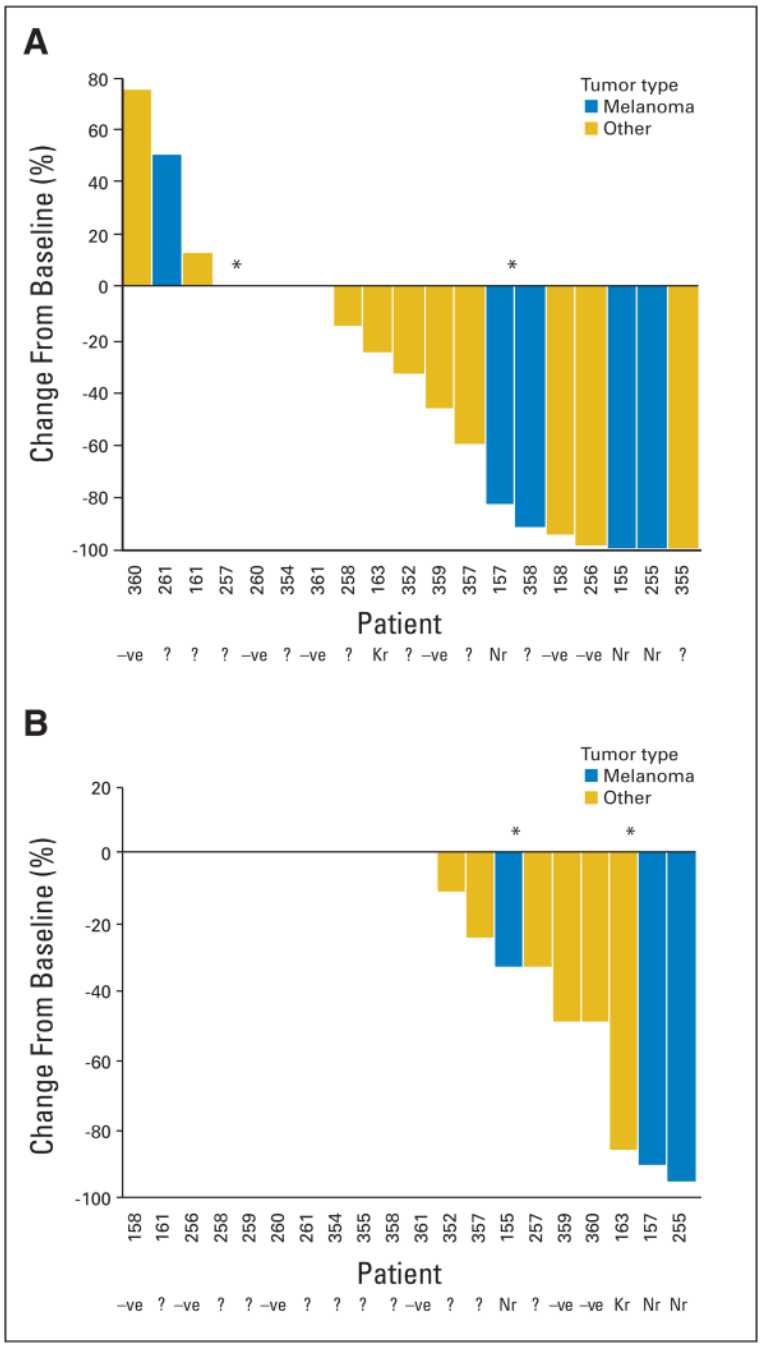

Fig 2.

Percent change from baseline at day 15 (± 7 days) in (A) tumor cell nuclei H-score for pERK and (B) proportion of tumor cell nuclei staining for Ki-67. Patients received 100 mg bid or 200 mg bid (denoted by *).

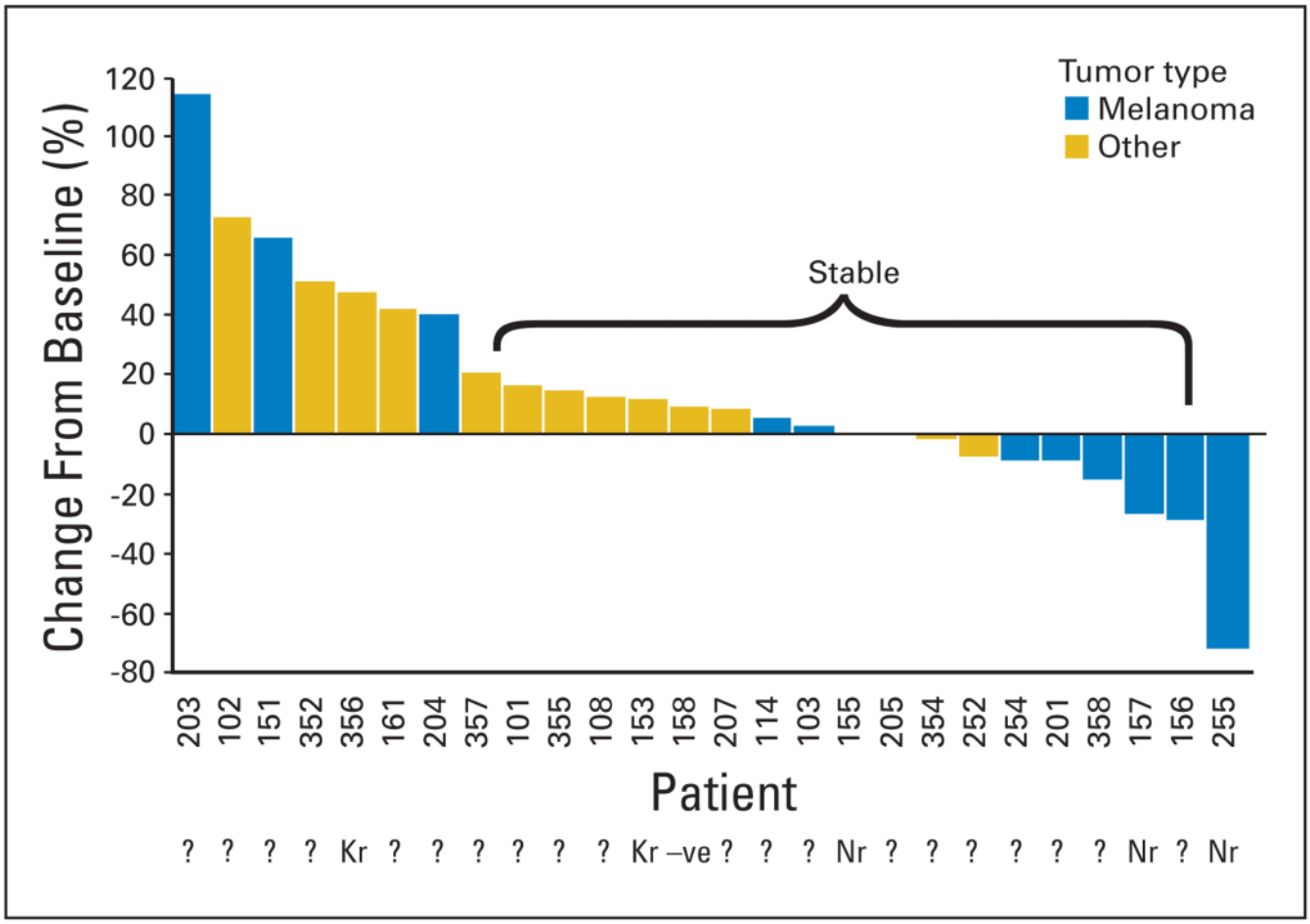

Fig 3.
Best percent change from baseline in target lesion size for patients who have at least postbaseline efficacy assessment.

Table 1

Patient Characteristics

	All Patients in Safety Population					
	Part A (n = 23)		Part B (n = 34)		Total (N = 57)	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Sex						
Male	13	56.5	20	58.8	33	57.9
Female	10	43.5	14	41.2	24	42.1
Age, years						
Median	58		60		59	
Range	29–78		34–84		29–84	
Race						
White	21	91.3	33	97.1	54	94.7
African American	1	4.3	1	2.9	2	3.5
Asian	1	4.3	0	0	1	1.8
ECOG performance status at screening						
0	9	39.1	13	38.2	22	38.6
1	14	60.9	20	58.8	34	59.6
2	0	0	1	2.9	1	1.8
No. of metastatic sites						
1	6	26.1	6	17.6	12	21.1
2		39.1		26.5	18	31.6
≥ 3	8	34.8	19	55.9	27	47.3
Prior anticancer treatments						
Surgery	21	91.3	32	94.1	53	93.0

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	All Patients in Safety Population					
	Part A (n = 23)		Part B (n = 34)		Total (N = 57)	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Radiation	13	56.5	25	73.5	38	66.7
Chemotherapy regimens	22	95.7	30	88.2	52	91.2
0	1	4.3	4	11.8	5	8.8
1	7	30.4	6	17.6	13	22.8
≥ 2	15	65.2	24	70.6	39	68.4
Cancer types						
Melanoma					20	35.1
Breast					10	17.5
Colorectal					5	8.8
Other*					22	38.6

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*Two patients each: non–small-cell lung cancer, hepatocellular, head and neck, sarcoma, thyroid, gastroesophageal junction; one each: lung squamous cell carcinoma, adenoid cystic, mesothelioma, renal cell, pancreatic, ovarian, bronchoalveolar, bladder, thymus, and leiomyosarcoma.

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Table 2

Treatment-Related Adverse Events*

	AZD6244 bid Dose (No. of patients)								
	50 mg (n = 3)		100 mg (n = 31)		200 mg (n = 15)		300 mg (n = 8)		Total No. of Patients (N = 57)
Adverse Event	**Grade 1–2**	**Grade 3–4**	**Grade 1–2**	**Grade 3–4**	**Grade 1–2**	**Grade 3–4**	**Grade 1–2**	**Grade 3–4**	
Any event	3		30		14		7		54
Rash†	2	0	21	3	8	4	3	2	43
Diarrhea	2	0	16	0	12	0	2	1	33
Nausea	0	0	13	1	8	0	3	0	25
Fatigue	2	0	8	1	8	1	2	0	22
Peripheral edema	1	0	9	1	6	0	2	0	19
Vomiting	0	0	7	0	5	0	2	0	14
ALT elevation	0	1	4	0	4	0	0	0	9
AST elevation	1	0	2	1	5	0	0	0	9
Blurred vision	0	0	2	0	2	0	3	0	7

*Data include treatment-related adverse events with an onset date on or after the day 1 single dose in part A or the first dose in Part B.

†Rash includes the following Medical Dictionary for Regulatory Activities preferred terms: Dermatitis Acneiform, Rash, Rash Erythematous, Rash Maculo-papular, and Rash Pruritic.

Table 3

Dose-Limiting Toxicities in Cycle 1

Dose-Limiting Toxicity	AZD6244 Dose (No. of patients)			Total No. of Patients
	100mg	200mg	300 mg	
Total	31	15	8	54
Rash	2	3	2	7
Hypoxia	1*	1	—	2
Diarrhea	—	—	1	1
T-wave inversion	1*	—	—	1

* Occurred in same patient.

Table 4

Pharmacokinetic Parameters for AZD6244 on Days 1 (single dose) and 22 (bid dosing)

C_{max} (ng/mL)				T_{max} (h)				AUC* (ng • h/mL)				$t_{1/2}$ (h)			
Day 1		Day 22		Day 1		Day 22		Day 1		Day 22		Day 1		Day 22	
Geometric Mean	CV	Geometric Mean	CV	Median	Range	Median	Range	Geometric Mean	CV	Geometric Mean	CV	Median	Range	Median	Range
528	64	528	40	3	1–3	1	1–1	3,581	18	2,193	57	6.7	6.6–8.7	—	—
486	75	718	63	1	1–4	1	1–1	2,929	23	2,365	78	11.1	7.6–24.0	—	—
781	93	1,010	116	1	1–4	1	1–1	4,900	112	2,960	145	6.1	4.5–28.3	—	—
952	74	—	—	1	1–4	—	—	6,488	63	—	—	14.5	7.1–19.4	—	—

erved plasma concentration; T_{max}, time to maximum plasma concentration; AUC, area under the concentration-time curve; $t_{1/2}$, terminal half-life; CV, coefficient

2 hours after dose, except for the day 1, which are AUC_{inf} values.

Table 5

Pharmacokinetic Parameters for AZD6244 on Days 1 (single dose) and 15 (bid dosing)

C_{max} (ng/mL)				T_{max} (h)				AUC* (ng • h/mL)				$t_{1/2}$ (h)			
Day 1		Day 15		Day 1		Day 15		Day 1		Day 15		Day 1		Day 15	
Geometric Mean	CV	Geometric Mean	CV	Median	Range	Median	Range	Geometric Mean	CV	Geometric Mean	CV	Median	Range	Median	Range
807	68	895	52	1	1–8	1	1–4	3,124	43	5,006	47	4.5	2.2–10.5	—	—
933	61	952	38	2	1–4	1	1–2	5,234	42	6,944	27	5.4	3.5–6.6	—	—

erved plasma concentration; T_{max}, time to maximum plasma concentration; AUC, area under the concentration-time curve; $t_{1/2}$, terminal half-life; CV, coefficient

12 hours after dose.

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