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A phase I dose-finding, safety and tolerability study of AZD8330 in patients with advanced malignancies

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Abstract ***Objective:*** This is the first clinical study of the MEK1/2 inhibitor AZD8330 (ARRY-424704). This phase I study defined the maximum tolerated dose (MTD) and assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of AZD8330 in patients with advanced malignancies.

Methods: Patients with refractory cancer or cancer with no standard therapy received either once-daily (OD) or twice-daily (BID) oral AZD8330 on day 1 followed by a 7-day washout period and continuous dosing from day 8. The starting dose was 0.5 mg with dose escalations in subsequent cohorts until a non-tolerated dose was reached.

Results: Eighty-two patients received AZD8330 across 11 cohorts. The most frequent AZD8330-related adverse events were acneiform dermatitis (13/82, 16%), fatigue (11/82, 13%), diarrhoea (11/82, 13%) and vomiting (9/82, 11%). Four patients experienced dose-limiting toxicities: mental status changes (40 mg OD; 2/9 patients and 60 mg OD; 1/3) and rash (20 mg BID; 1/9). The MTD was defined as 20 mg BID. AZD8330 exposure increased approximately proportionally with dose across the dose range 0.5–60 mg OD. Dose-dependent modulation of phosphorylated ERK in peripheral blood mononuclear cells (PBMCs) was observed at doses $\geqslant 3$ mg. One patient had a partial response and thirty-two (39%) had stable disease, with a duration >3 months in 22 patients, assessed by Response Evaluation Criteria in Solid Tumors.

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Conclusion: AZD8330 has a manageable toxicity profile at the MTD of 20 mg BID, and target inhibition was confirmed in PBMCs. One patient with malignant melanoma had a partial response.

1. Introduction

MAPK ERK kinase (MEK) 1 and 2 are essential enzymes in the Ras/Raf/MEK/ERK protein kinase pathway that regulate cellular proliferation. Deregulation of this pathway occurs frequently in a variety of tumours and promotes cell survival and tumour growth. The only known substrates of MEK1/2 are the extracellular signal-regulated kinases ERK1 and ERK2; MEK inhibition is therefore an attractive therapeutic target in cancer.

Several MEK inhibitors are currently being investigated clinically in various tumour types.[1–5] AZD8330 (ARRY-424704) is a potent, selective, uncompetitive MEK1/2 inhibitor, with a half-maximum inhibitory concentration (IC_{50}) of 7 nM.[6] In tumour xenograft models, AZD8330 demonstrated dose-dependent tumour growth inhibition of approximately 90% at tolerated doses (1.0 mg/kg once daily [OD]).[6] These preclinical results suggest that AZD8330 may provide effective tumour growth inhibition with a favourable tolerability profile.

This is the first clinical study of AZD8330, designed to determine its safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile in patients with advanced malignancies.

2. Patients and methods

2.1. Patients

Eligible patients were $\geqslant$18 years of age, with a confirmed diagnosis of cancer refractory to standard therapy or for which no standard therapy exists. Other inclusion criteria included a World Health Organization performance status of 0–2 and adequate renal, hepatic and cardiac function.

2.2. Trial design

This was an open-label, phase I dose-escalation study conducted in two centres in the USA and one centre in Norway (NCT00454090). Enrolment was from March 2007 to April 2010. All patients provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki.

2.3. Interventions

Eligible patients in each cohort (of six to nine evaluable patients) received either an OD or twice-daily (BID) dose of AZD8330 (AstraZeneca, Alderley Park, Cheshire, UK) on day 1 followed by a 7-day washout period and continuous OD or BID dosing, respectively, from day 8. Patients were not permitted food 2 h preceding and 1 h following dosing. The starting dose of AZD8330 was 0.5 mg; subsequent cohorts received an increased dose of AZD8330 determined by the Safety Review Committee (SRC), until a non-tolerated dose was reached. A non-tolerated dose was defined as the dose at which $\geqslant$2/6 patients in a cohort experienced a dose-limiting toxicity (DLT) within 35 days of commencing treatment. Patients remained on treatment until disease progression and for as long as they continued to derive clinical benefit. All patients were followed until withdrawal of consent or the end of the study (6 months following first treatment dose).

2.4. End-points

The primary objective of the study was to assess the safety and tolerability of AZD8330. Secondary objectives were: to determine the PK profile of AZD8330 following both single and multiple dosing, to investigate the effect of AZD8330 on pERK in peripheral blood mononuclear cells (PBMCs) and to explore relationships between PK and PD parameters. Assessment of AZD8330 efficacy was an exploratory end-point.

2.5. Safety

All adverse events (AEs) were recorded from the time of informed consent until 30 days after study treatment was discontinued, using Common Terminology Criteria for Adverse Events (CTCAE) version 3. General safety monitoring information is provided in the Supplementary section. AEs were followed to resolution where possible.

A DLT was defined as any CTCAE grade $\geqslant$3 AE unrelated to underlying disease; continuous dose interruption for >2 weeks for any toxicity considered to be possibly related to AZD8330; or any toxicity considered to be clinically significant by the investigator, within 35 days of first dose. The maximum tolerated dose (MTD) was defined as the last dose tested below the non-tolerated dose in six evaluable patients.

2.6. PK analysis

Serial venous blood samples (2 mL) were taken predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10 (for 0.5–1.5 mg only),