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PHASE II STUDIES

A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens

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Summary *Objectives* To assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) in patients with metastatic colorectal cancer who had failed one or two previous chemotherapeutic regimens that included oxaliplatin and/or irinotecan. *Methods* This was a Phase II, multicentre, open-label, randomised, two-arm, parallel-group study comparing AZD6244 with capecitabine monotherapy. Patients received either 100 mg twice daily oral AZD6244 free-base suspension every day or 1,250 mg/m^2 twice daily oral capecitabine, for 2 weeks, followed by a 1-week rest period, in 3-weekly cycles. The primary endpoint was the number of patients experiencing disease progression events. *Results* Sixty-nine patients were randomised in the study (34 and 35 patients in the AZD6244 and capecitabine groups, respectively). Disease progression events were experienced by 28 patients (~80%) in both the AZD6244 and capecitabine treatment groups. Median progression-free survival was 81 days and 88 days in the AZD6244 and capecitabine groups, respectively. Ten patients in the AZD6244 treatment arm had a best response of stable disease. For capecitabine, best response was a partial response in one patient, with stable disease in a further 15 patients. The most frequently observed adverse events reported with AZD6244 were acneiform dermatitis, diarrhoea, asthenia and peripheral oedema, compared with hand-foot syndrome, diarrhoea, nausea and abdominal pain with capecitabine. *Conclusions* AZD6244 showed similar efficacy to capecitabine in terms of the number of patients with a disease progression event and of progression-free survival. AZD6244 is currently undergoing evaluation in Phase II trials in combination with other chemotherapeutic agents.

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Introduction

The Ras/Raf/MEK/ERK signalling pathway, which regulates key cellular activities including proliferation, differentiation, development, inflammation, survival and migration, is frequently activated in human cancers, often as a result of activating mutations in BRAF or RAS genes [1]. In colorectal cancer (CRC), for example, oncogenic forms of RAS are found in up to 50% of cancers [1]. Mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) are central components of the Ras/Raf/MEK/ERK signalling pathway, where ERK1 and ERK2 are the only known substrates for MEK1/2. MEK1/2 are attractive targets for cancer therapy, because MEK inhibition has the potential to block inappropriate signal transduction, regardless of the upstream position of the oncogenic aberration [2, 3].

AZD6244 is a potent, selective, ATP-uncompetitive inhibitor of MEK1/2 that has demonstrated anti-tumour activity against a number of tumours in cell-based growth assays and in human tumour mouse xenograft models, including CRC [4, 5]. The clinical development of AZD6244 was further supported by a Phase I study which demonstrated that AZD6244 monotherapy has a manageable safety and tolerability profile with target inhibition demonstrated with continuous dosing at 100 mg twice daily (BID) [6].

These preclinical data supported the further evaluation of AZD6244 in metastatic CRC (mCRC) after failure of standard regimens including oxaliplatin and/or irinotecan. Indeed, there is a need for new, effective and well-tolerated treatments in the second- and third-line setting, despite recent and significant improvements in overall survival of up to 29 months in patients with mCRC treated in the first-line setting, due to utilization of new chemotherapeutics and targeted therapies such as bevacizumab or anti-epidermal growth factor receptor (EGFR) therapies [7].

After failure to standard treatments, capecitabine (Xeloda™) is considered as a palliative option in some centres, as it has shown clinical benefit as a first-line therapy in patients with mCRC in terms of tumour response [8, 9]. Capecitabine has also demonstrated disease stabilisation in a significant number of mCRC patients previously treated with 5-fluorouracil/ leucovorin-based regimens, including regimens containing oxaliplatin or irinotecan; however, limited clinical responses were observed [10].

Thus, to evaluate the efficacy and safety of AZD6244 in patients with mCRC who had failed one or two previous chemotherapeutic regimens that included irinotecan and/or oxaliplatin therapy, we conducted a randomised Phase II trial comparing AZD6244 with capecitabine monotherapy in this patient population.

Methods

Study objectives

The primary objective of the study was to assess the efficacy of AZD6244 versus capecitabine in the treatment of mCRC based on disease progression. The secondary objective was to assess the safety and tolerability of AZD6244 in the treatment of mCRC by review of adverse events (AEs) and laboratory parameters.

Patient selection

Patients aged ≥18 years were eligible for the study if they had histologically confirmed CRC, required treatment but had failed one or two previous chemotherapeutic regimens that must have included oxaliplatin and/or irinotecan, had World Health Organization performance status 0–2 and life expectancy >12 weeks, were suitable for treatment with capecitabine, and had adequate bone marrow reserve (platelets ≥100,000/μl, absolute neutrophil count ≥1,500/μl and haemoglobin ≥10 g/dl despite transfusion), hepatic (total bilirubin <1.5 × the upper limit of normal [ULN], alanine aminotransferase [ALT] and aspartate aminotransferase [AST] <2.5 × ULN irrespective of whether liver metastases were present) and renal (serum creatinine clearance >50 ml/min and serum creatinine <1.25 × ULN) function. Prior surgery and/or localised radiation were allowed. Exclusion criteria included previous therapy with an EGFR inhibitor, MEK inhibitor or capecitabine monotherapy. Prior capecitabine therapy was allowed if part of a combination regimen.

This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization/Good Clinical Practice. All patients gave written informed consent.

Study design

This was a Phase II, multicentre, open-label, randomised, two-arm, parallel-group study. From September 2006 to April 2007, patients were randomised 1:1 to receive either 100 mg BID oral AZD6244 free-base suspension every day or 1,250 mg/m^2 BID oral capecitabine, for 2 weeks, followed by a 1-week rest period, in 3-weekly cycles

(Fig. 1). The dose of AZD6244 administered in this study was based on safety and tolerability information from a Phase I study evaluating AZD6244 in patients with solid tumours [6].

AZD6244 dose interruptions and/or dose reductions (initially to 50 mg BID and then to 50 mg once daily) were permitted if any AE of grade 3 or higher, according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), or any intolerable AE occurred. Dose re-escalation was not permitted. Patients could continue to receive treatment until disease progression providing they continued to derive clinical benefit and in the absence of unacceptable toxicity. Patients who discontinued treatment were permitted to proceed with other treatments or participate in other studies at the discretion of the investigator.

Assessments

Tumour assessments were performed at screening and then per site clinical practice, with a mandatory assessment at the end of the study unless the patient had previously progressed. Disease progression was assessed using Response Evaluation Criteria In Solid Tumours (RECIST). Patients were evaluated for AEs during therapy and until 30 days after the last dose of study drug. AEs were graded according to the NCI CTCAE version 3.

Statistical analyses

The study was designed as a randomised exploratory study to quantify the level of risk entailed for further development [11]. The aim was to identify whether there was a clear signal of activity in mCRC. Disease progression event count has been shown to be an adequate assessment for Phase II decision making and has been presented as an alternative by Carroll [12], who demonstrated the high concordance in results obtained using an event count analysis and a log-rank test in a large randomised controlled trial. Thus, the study design adopted here removed, as far as possible, the need for regular assessments of disease status. The proportion of patients with a disease progression event occurring on or before the data cut-off point was compared between the two treatment groups using a logistic regression model with a complementary log–log function, and including a factor for treatment group. A progression event was defined as the earliest of (1) objective and/or clinical progression on or before the data cut-off point, as measured using RECIST criteria, or (2) death by any cause. The results were approximated as a hazard ratio (HR), reported with the corresponding confidence interval (CI) and *p*-value. The target number of patients with a disease progression event guided the timing of the data cut-off point. A total of 38 progression events would ensure this study had at least 80% power to detect a true HR of 0.50 at the two-sided 20% significance level. Therefore a minimum of 64 patients were required and the data cut-off was set for when 38 patients had progression events. As such, a result from this Phase II study would be considered statistically significant if the two-sided *p*-value was <0.2. The analysis was performed on an intent-to-treat (ITT) basis using the ITT analysis set. An additional analysis, taking into account the timing of a progression

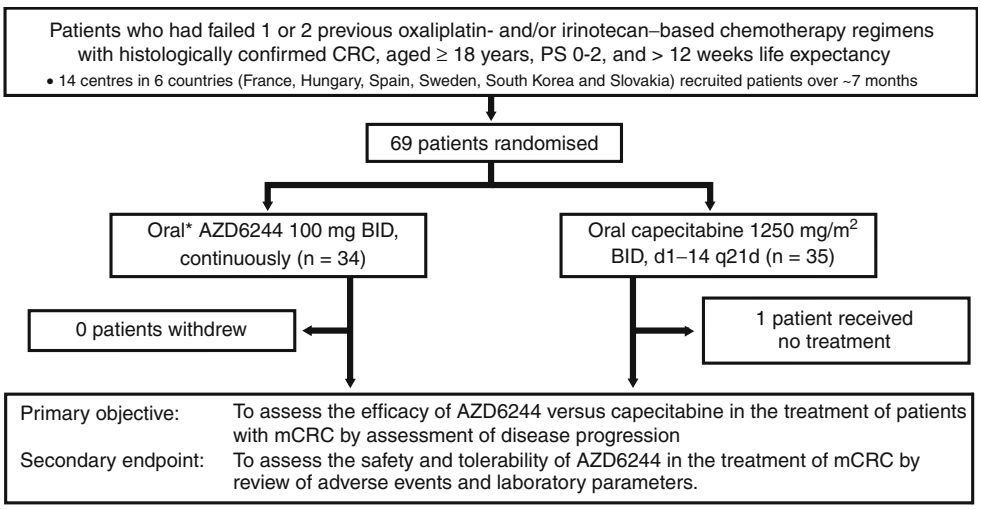

Fig. 1 AZD6244 versus capecitabine study design

BID, twice daily; CRC, colorectal cancer; mCRC, metastatic CRC; PS, performance status; q21d, every 21 days

Patients continued to receive treatment until objective and/or clinical progression, providing they were deriving clinical benefit, in the absence of unacceptable toxicity and provided the patient was willing to continue the study.
*Free-base oral suspension formulation.

event (as assessed by the investigator), was also performed in support of the progression event count analysis.

Results

Demographics and patient characteristics

A total of 69 patients were randomised in the study (34 and 35 patients to the AZD6244 and capecitabine treatment groups, respectively) and comprised the ITT population. One patient randomised to capecitabine was found to be ineligible and was withdrawn prior to study drug administration and excluded from the evaluable for safety (EFS) analysis. The two treatment groups were comparable for demographic and baseline characteristics (Table 1).

Table 1 Patient demographics and disease characteristics (ITT population)

Characteristic	Number of patients (%)	
	AZD6244, n=34	Capecitabine, n=35
Age (years)		
Mean (SD)	61.6 (9.83)	60.7 (9.73)
Median (range)	61.5 (38–81)	60.0 (39–80)
Sex		
Male	22 (65)	17 (49)
Female	12 (35)	18 (51)
Race		
Caucasian	30 (88)	30 (86)
Oriental	4 (12)	5 (14)
Number of previous chemotherapeutic regimens		
1	10 (29)	7 (20)
2	24 (71)	28 (80)
Local radiation	7 (21)	8 (23)
Time since diagnosis of advanced disease[a]		
<1 year	11 (32)	9 (26)
≥1 year	23 (68)	26 (74)
Was recurrence local?		
No	29 (85)	28 (80)
Yes	5 (15)	7 (20)
Was recurrence regional?		
No	23 (68)	20 (57)
Yes	11 (32)	15 (43)
Distant metastases		
M0	9 (26)	4 (11)
M1	21 (62)	27 (77)
MX	4 (12)	4 (11)

SD standard deviation

[a] Advanced disease = stage IV, Duke's D or TNM M1

Efficacy

For the primary efficacy variable of the number of patients with a progression event, there was no significant difference between treatment groups. In the AZD6244 group, 82% of patients (n=28) had a disease progression event, compared with 80% of patients (n=28) in the capecitabine group (ITT analysis set; Table 2).

Median progression-free survival (PFS) in the ITT population was 81 days for AZD6244 and 88 days for capecitabine (HR 1.08; two-sided 80% CI=0.76, 1.52), with no statistically significant difference between treatment groups (Fig. 2). However, since the majority of patients were treated until progression, and given that the protocol did not require regular tumour assessments, it is possible that an interim scan may have identified patients with disease progression at an earlier time point.

In the ITT population, the investigators' assessment of best overall response according to RECIST criteria for AZD6244 was stable disease, recorded in 10 patients (Table 3). The best response with capecitabine was partial response in a single patient, with a further 15 patients having best response of stable disease. In both treatment groups, the majority of patients had a best response of progressive disease. However, given that the protocol did not require regular tumour assessments, it is possible that an interim scan may have identified patients who had a better tumour response than that reported here. Additionally patients were not required to have measurable disease at baseline.

Safety and tolerability

The median total exposure to AZD6244 and capecitabine was 71 days and 80 days, respectively. In both treatment groups, the difference between the total and actual exposure was small (data not shown), indicating a low frequency of dose interruptions.

The most frequently reported AEs were consistent with the treatments, the underlying disease and the co-morbid conditions typically experienced by this patient population. The number of patients experiencing an AE was comparable between the two treatment arms (33 patients [97%] in both groups; EFS analysis set) and the majority were of mild to moderate severity. The most common all-causality AEs reported with AZD6244 were acneiform dermatitis, diarrhoea, asthenia and peripheral oedema (Table 4). The most frequently observed AEs with capecitabine were hand-foot syndrome (HFS), diarrhoea, nausea and abdominal pain. Approximately one-third of patients with any AE reported events of CTCAE grade 3 in each treatment group, and most of these specific AEs occurred in only one patient. Only two patients had CTCAE grade 4 events (one

Table 2 Hazard ratio between treatment groups of the number of patients with a disease progression event (ITT analysis set)

Treatment group	*n*	Number of patients with an event (%)	Comparison between groups			
			HR[a]	80% CI	95% CI	*p*-value
AZD6244	34	28 (82)	1.08	0.73, 1.58	0.60, 1.94	0.80
Capecitabine	35	28 (80)				

[a] Analysed using a logistic regression model with a complementary log–log function with a factor for treatment group. A hazard ratio <1 would indicate a lower risk of disease progression with AZD6244, compared with capecitabine

case of anuria in the AZD6244 arm and one case of colonic obstruction with capecitabine), neither of which was judged by the investigator to be treatment related.

A total of six deaths were recorded prior to study termination (30 days after the last dose of study treatment for an individual patient). Two deaths were recorded in the AZD6244 group compared with four in the capecitabine group, with all but one attributed to worsening of the disease under investigation. One patient in the AZD6244 group died following a serious AE (SAE) of acute prerenal failure. The patient was a 71-year-old female with metastatic colorectal cancer and concurrent Type 2 diabetes mellitus and hyperthyroidism. Six days after starting AZD6244 she had signs of hypotension, hypoperfusion and dehydration. A clinical diagnosis of acute prerenal failure was made, and the patient was treated with rehydration measures by emergency physicians, initially at home then after hospital admission. She deteriorated rapidly, dying about 12 h after admission early on day 8 of the study. The investigator considered the prerenal failure to be possibly related to study treatment.

Overall, each treatment group experienced 11 SAEs in a total of six patients, but no specific SAEs were reported in more than one patient. Of these, SAEs possibly related to study treatment were experienced by three patients receiving AZD6244 (supraventricular/ventricular extrasystoles, asthenia and acute prerenal failure) and by one patient receiving capecitabine (renal failure).

Dose reductions and treatment discontinuations

Most patients (88% and 82% in the AZD6244 and capecitabine treatment groups, respectively) discontinued therapy prior to the data cut-off, primarily because of worsening of the condition under investigation (65% and 69%, respectively). Six patients (18%) in the AZD6244 group and three patients (9%) in the capecitabine group discontinued because of an AE. In the AZD6244 treatment arm, four patients required a dose reduction because of causally related AEs but did not permanently discontinue treatment and three patients required dose interruption (causally related in one patient) without the need for dose reduction or treatment discontinuation.

Laboratory and clinical parameters

For most haematological and clinical chemistry parameters, no clinically relevant changes were apparent between

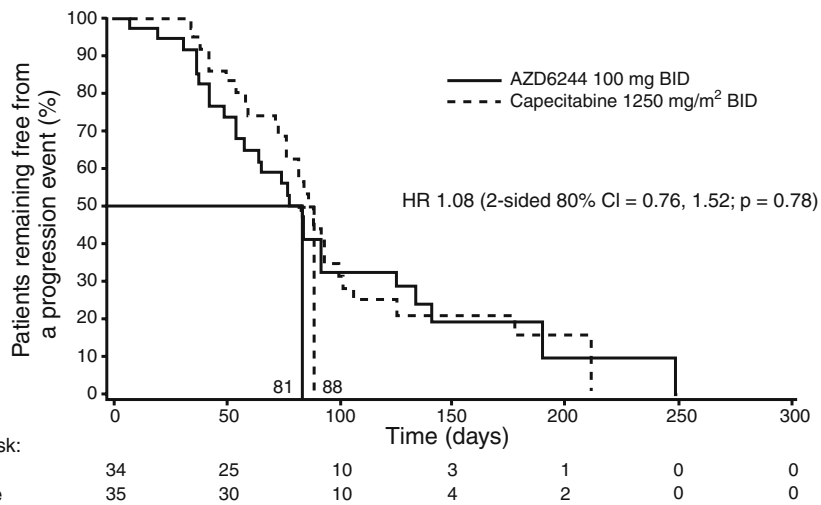

Fig. 2 Comparison of progression-free survival for AZD6244 and capecitabine treatment groups (ITT analysis set)

*Since the protocol did not require regular tumour assessments, the time to progression was not robust and may have been overestimated for some patients

Table 3 Investigator's overall best response in accordance with RECIST criteria (ITT analysis set)[a]

Treatment group	*n*	Number of patients (%)				
		Complete response	Partial response	Stable disease	Progressive disease	Not evaluable
AZD6244	34	0	0	10 (29)	21 (62)	3 (9)
Capecitabine	35	0	1 (3)	15 (43)	18 (51)	1 (3)

[a] Since the protocol did not require regular tumour assessments, it is possible that an interim scan may have identified patients who had a better tumour response than that reported here. Additionally, patients were not required to have measurable disease at baseline

AZD6244 and capecitabine. However, the following observations were made based on worst finding on treatment: decreases in haemoglobin of CTCAE grade 1/2 were reported in 16 patients (47%) in the AZD6244 group compared with 10 patients (30%) in the capecitabine treatment arm; approximately twice as many patients on AZD6244 had an increase in ALT or AST of 1–2 CTCAE grades from baseline compared with capecitabine (36% versus 18% for ALT and 45% versus 21% for AST), the majority of these increases for both AZD6244 and capecitabine were from CTCAE grade 0 to CTCAE grade 1 and for AZD6244 resulted in a small increase in mean values during the first few weeks of treatment; many patients had elevated alkaline phosphatase (ALP) at the start of the study and more patients in the AZD6244 group had a further increase in ALP of 1 CTCAE grade compared with those in the capecitabine group (48% versus 15% of patients, respectively); more patients had an increase in bilirubin on capecitabine versus AZD6244 (41% versus 9% of patients, respectively), the majority of which were of 1–2 CTCAE grades from CTCAE grade 0; more patients had a fall in albumin of CTCAE grade 1/2 in the AZD6244 group compared with capecitabine (30% versus 6% of patients, respectively); and there was suggestion of a small increase in phosphate levels for AZD6244, as indicated by the highest value on treatment compared with baseline. Overall, no new safety concerns were identified for AZD6244 from the haematology and clinical chemistry results.

Discussion

This multicentre, randomised, open-label Phase II study showed that AZD6244 has similar clinical benefits to capecitabine in patients with mCRC who had failed one or two previous chemotherapy regimens that included the current mCRC standard of care therapeutic agents oxaliplatin and/or irinotecan. There were no significant differ-

Table 4 Number of patients with the most commonly reported (≥10% of patients) all-causality adverse events by CTCAE grade (EFS analysis set)

Preferred term	Number of patients (%)			
	AZD6244, *n*=34		Capecitabine, *n*=34	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Acneiform dermatitis	16 (47)	3 (9)	1 (3)	0
Diarrhoea	13 (38)	2 (6)	9 (26)	0
Asthenia	8 (24)	2 (6)	8 (24)	1 (3)
Peripheral oedema	9 (26)	0	3 (9)	0
Nausea	4 (12)	1 (3)	9 (26)	0
Anorexia	5 (15)	0	6 (18)	0
Nasopharyngitis	5 (15)	0	2 (6)	0
Constipation	2 (6)	2 (6)	4 (12)	0
Fatigue	4 (12)	0	4 (12)	0
Upper abdominal pain	4 (12)	0	3 (9)	0
Exertional dyspnoea	4 (12)	0	0	0
Abdominal pain	3 (9)	0	7 (21)	0
Stomatitis	3 (9)	0	5 (15)	0
Vomiting	2 (6)	1 (3)	4 (12)	0
Hand-foot syndrome	0	0	14 (41)	5 (15)

ences between AZD6244 and capecitabine in terms of the number of disease progression events and the sensitivity analysis of PFS.

In this study, AZD6244 and capecitabine achieved a median PFS of 81 and 88 days, respectively. Disease stabilisation was achieved in 29% and 46% of patients in the AZD6244 and capecitabine groups, respectively. This is consistent with a previous study evaluating capecitabine in mCRC patients refractory to 5-FU/LV regimens, of which 82% and 45% of patients had previously been treated with oxaliplatin- and irinotecan-based regimens, respectively [10]. This study, in which patients had previously been treated with up to four chemotherapy regimens, similarly found that capecitabine achieved few clinical responses (2% partial response), with a high proportion of patients (53%) achieving disease stabilisation, and the median time to progression was 61 days [10].

In the present study, a similar number of AEs were experienced by patients in each treatment arm, although there were some differences in the profile of AEs reported. Asthenia and diarrhoea were commonly associated with both treatments and, in addition, frequently reported AEs associated with AZD6244 included acneiform dermatitis and peripheral oedema. These AEs are consistent with those reported in a Phase I study evaluating AZD6244 in solid tumours [6]. The AE profile of capecitabine, consisting predominantly of HFS and nausea in addition to asthenia and diarrhoea, was also consistent with the previously reported safety profile of this drug [13–15]. Some variation was observed between the two treatment arms in terms of the clinical chemistry parameters, with AZD6244 associated with a two-fold increase in the number of patients with a mild to moderate rise in ALT or AST at some time during the study compared with capecitabine. This resulted in a small rise in mean values during the first few weeks of treatment, which was consistent with the findings of the earlier Phase I study [6]. AZD6244 was generally well tolerated, as indicated by the low number of dose reductions/interruptions and treatment withdrawals. One death resulting from acute prerenal failure in the AZD6244 treatment arm was considered by the investigator to be possibly related to treatment. However, no other cases of this condition and no clinically significant changes in renal function have been reported in AZD6244 clinical studies to date [6, 16, 17]. Overall, no new safety concerns were identified for AZD6244 from the safety and laboratory results of this study.

This study used a free-base suspension ('mix-and-drink') formulation of AZD6244; however, a solid oral capsule formulation has been developed to enable more convenient dosing of AZD6244. In a Phase I study comparing the free-base suspension with the capsule, the new formulation was shown to be a viable successor to the free-base suspension based on its pharmacokinetic and safety profiles [18, 19]. Combination regimens using the new formulation are currently being evaluated in Phase II clinical trials.

Conclusion

In conclusion, the results of this study indicate that AZD6244 is a well-tolerated treatment option with comparable efficacy to capecitabine, as demonstrated by the number of patients with disease progression events and by PFS, for the treatment of second- and third-line CRC. AZD6244 is currently undergoing further clinical development in Phase II trials in combination with other chemotherapeutic agents in various tumour types. In these trials, and in the development of other targeted therapies in the near future, a key element will be the tailoring of treatments to the molecular signature of the tumour, requiring the identification of biomarkers that are predictors of response for these new agents.

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