Drug Substance(s)	AZD6244	**SYNOPSIS**	(For national authority use only)
Study Code	D1532C00011		
Date	14 January 2008		

A Phase II, Open, Randomised Study to Assess the Efficacy and Safety of AZD6244 vs capecitabine (Xeloda™) in Patients with Colorectal Cancer who have Failed One Or Two Prior Chemotherapeutic Regimens

Study dates		**Phase of development**
First patient enrolled	18 September 2006	Therapeutic exploratory (II)
Last patient enrolled	4 April 2007	

Objectives

The primary objective of this study was to assess the efficacy of AZD6244 versus capecitabine in the treatment of metastatic colorectal cancer by assessment of disease progression.

The secondary objective of the study was to assess the safety and tolerability of AZD6244 in the treatment of metastatic colorectal cancer by review of adverse events (AEs) and laboratory parameters.

Study design

This was a Phase II, open-label, randomised, 2-arm, parallel-group study in which patients were randomised in a 1:1 ratio to receive either:

- AZD6244 100 mg administered orally twice daily (BD) as the mix and drink formulation of AZD6244 free-base
- Capecitabine 1250 mg/m^2 administered orally BD for 2 weeks followed by a 1-week rest period in 3-weekly cycles.

The mix and drink formulation is an oral suspension of AZD6244 as the free-base for dispersion in an aqueous solution of sulphobutylether β-cyclodextrin (SBE-CD, Captisol®).

Target patient population and sample size

Patients in the target population were aged at least 18 years and required treatment for histologically confirmed colorectal cancer, but had failed one or two previous chemotherapeutic regimens (which included oxaliplatin and/or irinotecan). They were also suitable for treatment with capecitabine and had World Health Organization (WHO) performance status of 0–2 and life expectancy >12 weeks.

A total of 38 progression events would ensure the study had at least 80% power to detect a true hazard ratio (HR) of 0.50 at the 2-sided 20% significance level. Therefore, approximately 68 patients were required and a two-sided p-value of less than 0.2 was considered statistically significant in this Phase II study.

No events beyond the mandatory tumour assessment visit (MTAV; 27 June 2007 ± 3 days) were used in data analyses. The date of data cut-off for this study was 30 June 2007.

Duration of treatment

Patients continued to receive study treatment until objective and/or clinical progression, provided they were deriving clinical benefit, in the absence of unacceptable toxicity and provided the patient was willing to continue on study.

Patient population

Of 69 patients randomised (34 for AZD6244 and 35 for capecitabine; intention to treat [ITT] analysis set) a total of 68 received study treatment (34 in each treatment arm; evaluable for safety [EFS] analysis set). At the time of MTAV for each patient (27 June 2007 ± 3 days) 30 (88%) patients and 28 (80%) patients had discontinued AZD6244 and capecitabine, respectively. Approximately two-thirds of each group discontinued due to worsening of the condition under investigation.

Demographic and baseline characteristics were comparable between treatment groups: mean age was 62 versus 61 years, race was predominantly Caucasian (30 [88%] versus 30 [86%] patients) and 22 (65%) versus 17 (49%) patients were male, for AZD6244 and capecitabine respectively. Disease characteristics were also similar between treatment groups. Twenty-four (71%) versus 28 (80%) patients had received two previous chemotherapeutic regimens (the remainder had received 1 previous regimen), 23 (68%) versus 26 (74%) patients had advanced disease diagnosed at least 1 year prior to the start of the study, and 21 (62%) versus 27 (77%) patients had distant metastases (M1), for AZD6244 versus capecitabine respectively. This is representative of the target patient population.

Summary of efficacy results

The primary efficacy variable was number of progression events, with a progression event defined as the earliest of (i) objective disease progression as measured using Response Evaluation Criteria in Solid Tumours (RECIST) criteria and/or clinical progression on or before data cut-off or (ii) death from any cause. There was no significant difference between treatments in the number of patients with a disease progression event: 28 (82%) patients in the

AZD6244 group versus 28 (80%) patients in the capecitabine group, giving a HR of 1.08 (2-sided 80% confidence interval [CI]: 0.73, 1.58; p-value = 0.80; ITT analysis set, n=69).

Results were similar for an additional sensitivity analysis of progression-free survival (PFS), with median PFS of 81 days for AZD6244 and 88 days for capecitabine (HR=1.08; 80% CI 0.76 to 1.52; p=0.78; ITT analysis set, n=69).

Overall best response, in accordance with RECIST criteria, was stable disease (10 patients) for AZD6244, and partial response (1 patient) for capecitabine. A further 15 patients in the capecitabine group had stable disease. However, in both treatment groups, the majority of patients had best response of progressive disease.

Summary of safety results

At the data cut-off of 30 June 2007, median actual exposure to AZD6244 and capecitabine was 68.0 and 76.5 days, respectively.

The majority (97%) of patients experienced at least one AE, and most of these were judged to be related to study treatment. Dermatitis acneiform, diarrhoea, oedema peripheral, asthenia, nausea, anorexia and nasopharyngitis were the most common AEs reported with AZD6244 therapy. These events are consistent with the previously reported safety profile for AZD6244 and represent primarily CTCAE Grade 1 (mild) or 2 (moderate) events. Likewise, the AEs of palmar plantar erythrodysaesthesia syndrome, diarrhoea, nausea, and asthenia that were most commonly reported with capecitabine are consistent with the known safety profile for this drug.

A total of 10 (29%) patients in the AZD6244 group reported at least one AE of oedema, reported as a number of different preferred terms, compared with 3 (9%) patients in the capecitabine group. Similarly, rash was reported frequently (27 [79%] patients in the AZD6244 group) under a number of different preferred terms, although dermatitis acneiform was the most common (reported in 19 [56%] patients in the AZD6244 group). Dyspnoea was reported with AZD6244 only, in 6 (18%) of patients. The occurrence of these AEs is consistent with the previously reported safety profile of AZD6244.

A total 6 deaths were recorded prior to study termination (with study termination defined as being 30 days after the last dose of study treatment for each individual patient). Two deaths were in the AZD6244 group and 4 deaths were in the capecitabine group, with all but one attributed to worsening of the disease under investigation. Patient E0121003, a 71-year old woman in the AZD6244 treatment group, died following an AE of acute prerenal failure, which the investigator considered to be possibly related to AZD6244 treatment. SAEs were reported in 6 (18%) patients in each treatment group, and no specific SAE (ie, individual preferred term) was reported in more than 1 patient. A small number of patients from each treatment group experienced SAEs that were considered by the investigator to be related to study treatment (3 patients on AZD6244 and 1 on capecitabine).

Overall, no new safety concerns were identified for AZD6244 from the safety and laboratory results of this study.

For patients who continued to receive AZD6244 after the data cut-off of 30 June 2007, only SAE data will be collected. This data is not included in this report, but will be reported to Regulatory Authorities in accordance with standard pharmacovigilance procedures.