Drug Substance(s)	ZD6474	**SYNOPSIS**	(For national authority use only)
Study Code	D4200C00038		
Date	21 February 2007		

A Phase I, Open-Label Study to Assess the Safety and Tolerability of ZD6474 in Combination with Irinotecan, 5-Fluorouracil and Leucovorin (FOLFIRI) as First- or Second-Line Therapy in Patients with Metastatic Colorectal Adenocarcinoma

Study centre(s)

This was a multi-centre study. Approximately 20 patients with histologically-confirmed metastatic colorectal adenocarcinoma were planned to be recruited from 2 sites in the UK and 2 sites in Spain. Additional centres were to be added, if necessary, in order to ensure adequate patient numbers were available for the study.

Regulatory and ethics approval for the study was obtained in the UK. However, the Spanish ethics committee was only willing to approve the study with 3 patients at each dose level, which AZ did not consider would provide sufficient tolearability and pharmacokinetic data, so approval was sought and obtained from regulatory and ethics committees for 2 sites in Belgium. Twelve patients were recruited from the UK and 9 from Belgium.

Study dates		**Phase of development**
First patient enrolled	18 August 2005	Clinical pharmacology (I)
Last patient completed	N/A (addendum report to follow)	
Data cut-off date	05 May 2006	

End of study was defined as the date the last patient ceases treatment with ZD6474 and completes all associated follow up assessments.

Nomenclature

The collective name for irinotecan, 5-fluorouracil (5-FU), and leucovorin is 'FOLFIRI'. For ease, this chemotherapy regimen will be referred to as FOLFIRI throughout this report when referring to the combination of all three medications.

Objectives

The primary objective of the study was to establish the safety and tolerability of AstraZeneca ZD6474 when co-administered with irinotecan, 5-FU and leucovorin (FOLFIRI), to patients with metastatic colorectal adenocarcinoma, by assessment of adverse events (AEs), vital signs, clinical chemistry, haematology, urinalysis, electrocardiogram (ECG) and physical examination.

The secondary objectives of the study were:

1. To investigate the pharmacokinetics of ZD6474, irinotecan and 5-FU when co-administered to patients with metastatic colorectal adenocarcinoma, by assessment of appropriate pharmacokinetic parameters

2. To make a preliminary assessment of the efficacy of ZD6474 and FOLFIRI when co-administered to patients with metastatic colorectal adenocarcinoma, as measured by an objective response rate based on radiological and clinical tumour assessments using the Response Evaluation Criteria in Solid Tumours (RECIST)

The exploratory objectives of this study were:

1. To determine EGFR mutational status and the mutational status of other candidate genes (to be determined) by the collection of paraffin-embedded tumour tissue for DNA extraction and banking

2. To determine the mutational status of target genes and genotyping data of absorption, distribution, metabolism and excretion (ADME) genes, by the collection of a blood sample for DNA extraction storage and analysis

Study design

This was a Phase I, multi-centre, open-label, ascending-dose study, to establish the safety and tolerability of once-daily oral doses of ZD6474 when co-administered with standard 14-day treatment cycles of FOLFIRI to patients with metastatic colorectal adenocarcinoma.

An initial cohort of up to 10 patients was to receive 100 mg ZD6474. Following safety review of these patients, if less than 2 patients experienced dose-limiting toxicity (DLT) related to ZD6474, a second cohort of up to 10 patients was to receive 300 mg ZD6474. If 300 mg was not tolerated, an intermediate dose of 200 mg could be investigated in up to 10 additional patients.

Target patient population and sample size

Approximately 20 patients with histologically-confirmed metastatic colorectal adenocarcinoma, who had measurable disease and were eligible for first- or second-line chemotherapy were to be enrolled into the study. Patients with recurrent disease could have received 5-FU-based adjuvant therapy.

In total, 24 patients were enrolled in the study, but 3 of these were screening failures, so 21 patients received study medication (11 patients in the 100-mg ZD6474 cohort, and 10 patients in 300-mg cohort). For the Safety Monitoring Committee (SMC) review meetings, 6 patients per cohort were required to be evaluable for safety; evaluable patients were to have completed at least 6 weeks of treatment with ZD6474 in combination with at least 3 cycles of FOLFIRI treatment (and were to have had the associated safety assessments), or were to have experienced a DLT prior to completion of this dosing regimen.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Once daily oral doses of ZD6474 (100 mg or 300 mg) in combination with standard 14-day treatment cycles of FOLFIRI (Day 1 irinotecan 180 mg/m^2 given intravenously over 90 minutes and leucovorin 400 mg/m^2 given intravenously over 2 hours simultaneously, immediately followed by 5-FU 400 mg/mg^2 bolus given over 2 to 4 minutes, followed by 5-FU 2400 mg/m^2 given as a 46-48 hour infusion). The components of FOLFIRI were sourced locally. The following batches of ZD6474 were used in this study: PO10033341 (100 mg), PO10037724 (100 mg), PO10041786 (100 mg), PO10047896 (100 mg), PO10033270 (300 mg), PO10033278 (300 mg), PO10033345 (300 mg), PO10037729 (300 mg).

Duration of treatment

ZD6474 was to be taken for at least 6 weeks (in combination with at least 3 cycles of FOLFIRI). After this period, patients could continue daily oral dosing of ZD6474 in combination with FOLFIRI, or could remain on ZD6474 alone, assuming they did not meet a withdrawal criterion, (including disease progression), were free from intolerable toxicity, and, in the investigator's opinion, were receiving some benefit from the therapy.

Variables

- **Safety**

  The safety variables were the primary outcome variables for the study:
  AEs, haematology, clinical chemistry, urinalysis, ECG, physical examination, vital signs

- **Pharmacokinetic**

  – **ZD6474**
  Pre-dose plasma concentrations
  Maximum (peak) steady state drug concentration in plasma during dosing interval ($C_{ss, max}$)
  Time to reach peak or maximum concentration or maximum response following drug administration (t_{max})
  Area under the plasma concentration-time curve during any dosing interval at steady state (AUC_{ss})
  Total body clearance of drug from plasma after oral dosing (CL/F)

  – **Irintocecan and SN-38**:
  Maximum plasma (peak) drug concentration after single dose administration (C_{max})
  Half-life($t_{1/2}$)
  Area under plasma concentration-time curve from zero to infinity(AUC)
  Area under plasma concentration-time curve from zero to time t ($AUC_{(0-t)}$)

  Irinotecan only
  Total body clearance of drug from plasma (CL)
  Volume of distribution (apparent) at steady state (V_{ss})

  – **5-FU**:
  $t_{1/2}$, CL, V_{ss}, amount of drug in the body at steady state (A_{ss}), steady state drug concentration in plasma during constant infusion (C_{ss})

Efficacy

A preliminary assessment of the efficacy of ZD6474 and FOLFIRI when co-administered to patients with metastatic colorectal adenocarcinoma was to be made using Response Evaluation Criteria in Solid Tumours (RECIST) to assess objective tumour response rates and determine a patient's best overall tumour response rate.

In addition, blood samples were to be collected for analysis of CEA (pharmacodynamic/efficacy variable).

- **Pharmacogenetic**

  Optional blood sample and archival tumour tissue samples for retrospective genotyping of known genes of the vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) system and other genes that may be involved in the response and/or toxicity to ZD6474

Statistical methods

There was to be no formal statistical analysis of the safety data. All data was to be listed and summarised.

There was to be no formal statistical analysis of a pharmacokinetic interaction between ZD6474 and FOLFIRI. This was to be assessed by comparison of the summary statistics for the derived pharmacokinetic variables alone and when given in combination, and by comparison of the intra-patient measures of exposure alone and when given in combination with chemotherapy.

There was to be no formal statistical analysis of the objective response data. Objective response data was to be listed and summarised.

There was to be no formal statistical analysis of the pharmacogenetic data. The results of any genotyping that was performed was not to form part of the Clinical Study Report (CSR).

Patient population

In total, 24 patients were enrolled in this study. Three of these patients did not fulfil eligibility criteria, so only 21 patients were dosed in this study.

All 21 patients were Caucasian. In the 100-mg cohort, there were 5 male and 6 female patients. The mean age was 52 years (range: 33 to 72 years), the mean weight was 79.8 kg (range: 60 to 115 kg), and mean BMI 28.1 kg/m^2 (range: 21 to 41 kg/m^2). In the 300-mg cohort, there were 7 male and 3 female patients. The mean age was 54 years (range 37 to 71 years), the mean weight was 72.6 kg [range: 50 to 107 kg], and mean BMI 24.9 kg/m^2 (range: 19 to 36 kg/m^2).

Some of the demographic characteristics of the patients in this study were not well balanced between the 2 cohorts. There was a slight difference in the sex distribution between the 2 cohorts, but this was not anticipated to affect the safety and tolerability results of the study. However, the 100-mg cohort had 4 first-line patients and 7 second-line patients, while the 300-mg cohort had 1 first-line and 9 second-line patients, and as a result, the 300-mg patients tended to have more extensive disease than the 100-mg patients.

Eleven patients received once-daily oral doses of ZD6474 100 mg in combination with standard 14-day treatment cycles of FOLFIRI. Less than 2 patients experienced dose-limiting toxicity (DLT) that was considered to be possibly related to ZD6474, so a second cohort of

10 patients were enrolled and received once-daily oral doses of ZD6474 300 mg in combination with standard 14-day treatment cycles of FOLFIRI. Less than 2 patients experienced DLT in the 300-mg cohort, so a third cohort to investigate a 200-mg dose was not required.

Table S1 gives a summary of patient status at the time of data cut-off (05 May 2006).

Table S1 Summary of patient status at data cut-off

Patient status at data cut-off [a]	**Number of patients (%)**		
	100 mg cohort (n=11)	**300 mg cohort (n=10)**	**Total (n=21)**
Evaluable for safety review by SMC [b]	6 (54.5)	6 (60.0)	12 (57.1)
Evaluable for PK at data cut-off	11 (100.0) [c]	6 (60.0) [c]	17 (81.0) [c]
Completed 60-day safety follow-up at data cut-off [d]	2 (18.2)	0 (0.0)	2 (9.5)
Ongoing in study at data cut-off	9 (81.8)	10 (100.0)	19 (90.5)
Ongoing on ZD6474 alone	0 (0.0)	0 (0.0)	0 (0.0)
Ongoing on combination treatment	6 (54.5)	8 (80.0)	14 (66.7)
Ongoing for follow-up [e]	3 (27.3)	2 (20.0)	5 (23.8)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)

[a] Note that rows are not mutually exclusive (eg, patient may be ongoing on ZD6474 but may also have been evaluable for safety review/PK at data cut-off)

[b] A patient who was evaluable for safety review by the Safety Monitoring Committee was defined as having completed at least 6 weeks of treatment with ZD6474 and at least 3 cycles of FOLFIRI treatment, including associated safety assessments, or having experienced a DLT prior to this. One evaluable patient (in the 300-mg cohort) experienced a DLT.

[c] The figures presented here represent the the number of patients who were evaluable for PK for at least 1 analyte.

[d] This category includes patients who have died during treatment. In this category, 1 patient (Patient 3 Centre 1 [E0001997] died of haematemesis, and 1 patient (Patient 1 Centre 1 [E0001999]) completed follow-up.

[e] Patients off all treatment or ongoing on FOLFIRI, and ongoing for safety and efficacy follow-up.

Data derived from Tables 11.1.1, 11.1.2 and 11.1.4.

At data cut-off, 9 patients continued in the 100-mg cohort (6 receiving combination treatment, and 3 ongoing for safety and efficacy follow-up [with 1 of these 3 patients ongoing on FOLFIRI alone]) and 10 patients in the 300-mg cohort (8 receiving combination treatment, and 2 ongoing for safety and efficacy follow-up [with 1 of these 2 patients ongoing on FOLFIRI alone]). Safety and efficacy data for patients ongoing in the study after data cut-off will be collected and reported in an addendum report.

Table S2 gives a summary of patients who discontinued study treatment before data cut-off.

Table S2 Summary of patients who discontinued study treatment before data cut-off

Patient status at data cut-off [a]	Number of patients (%)		
	100 mg cohort (n=11)	300 mg cohort (n=10)	Total (n=21)
Patients ongoing study at data cut-off	9 (81.8)	10 (100.0)	19 (90.5)
Patients who completed the study [b]	2 (18.2)	0 (0.0)	2 (9.5)
Patients who discontinued ZD6474 prior to data cut-off	5 (45.5)	2 (20.0)	7 (33.3)
Adverse event	1 (9.1)	1 (10.0)	2 (9.5)
Disease progression	4 (36.4)	1 (10.0)	5 (23.8)
Patients who discontinued FOLFIRI prior to data cut-off	4 (36.4)	1 (10.0)	5 (23.8)
Disease progression	4 (36.4)	1 (10.0)	5 (23.8)

[a] Note that rows are not mutually exclusive
[b] This category includes all evaluable and non-evaluable patients who had completed follow-up prior to data cut-off

Data from all 21 dosed patients were included in the data listings. Data from all 21 patients who received at least one dose of ZD6474 were included in the safety summary. These patients also provided the efficacy data. All patients with valid PK data were included in the PK summary for each analyte. All 11 patients were included in the summary of AEs for ZD6474 100-mg dose. All 10 patients were included in the summary of AEs for ZD6474 300-mg dose.

Summary of safety results

Both 100 mg and 300 mg ZD6474 had an acceptable tolerability profile when given in combination with FOLFIRI. One DLT was recorded in this study in the 300-mg cohort. This patient (with a history of controlled hypertension, but who, in retrospect, appeared to be borderline hypertensive at study entry) experienced a DLT of hypertension. As only 1 of the patients who were evaluable for safety review by the SMC experienced a DLT, the protocol definition of a tolerable dose was met in both cohorts.

All 21 patients dosed in this study experienced one or more AEs. A total of 20 (95%) patients experienced an AE that was considered by the investigator or AstraZeneca physician to be related to ZD6474 (11 and 9 patients in the 100-mg and 300-mg cohorts, respectively). The most frequently reported AEs (in >20% of patients) were diarrhoea (95%), nausea (57%), vomiting (38%), abdominal pain (38%), dyspepsia (33%), constipation (29%), stomatitis (24%), headache (38%), lethargy (33%), alopecia (43%), erythema (33%), rash (33%), pruritis (24%), fatigue (48%), nasopharyngitis (24%), neutropenia (33%), and insomnia (29%). The most commonly reported ZD6474-related AEs (in >20% of patients) were diarrhoea (52%), lethargy (29%) and rash (24%). ZD6474-related AEs seen in this study were consistent with the expected safety profile of ZD6474.

The most commonly-experienced CTCAE grade 3 or 4 AEs (in >1 patient) were neutropenia (19%, all grade 3), hypertension (14%, all grade 3), catheter-related complication/thrombosis (10%, both grade 3), and pulmonary embolism (10%, both grade 4).

One patient died as a result of an AE (100-mg cohort; haematemesis). This event was not considered by the investigator to be causally related to ZD6474. A total of 3 patients (14%) had at least 1 SAE (excluding SAEs with outcome of death) prior to data cut-off. Nine SAEs occurred in these 3 patients who were all in the 100-mg cohort. Four of these SAEs were assessed as being causally related to ZD6474 (all in the same patient: pulmonary embolism, and 3 events of rash in 3 body areas concurrently).

Two (10%) patients experienced AEs leading to discontinuation of ZD6474. One patient in the 100-mg cohort experienced rash in 3 body areas concurrently, and 1 patient in the 300-mg cohort experienced hypertension. Both conditions were considered to be related to ZD6474. Two patients experienced OAEs in this study. One patient in the 100-mg cohort experienced diarrhoea and abdominal cramps concurrently (not related to ZD6474 treatment), and 1 patient in the 300-mg cohort experienced catheter-related complication (thrombus formation; considered to be related to ZD6474 treatment). As a result, ZD6474 was temporarily stopped for both patients.

Overall, the small number of patients, as well as the longer mean actual exposure at ZD6474 100 mg (148.4 days) compared to 300 mg (65.5 days) due to the fact that the 100-mg cohort was started earlier, together mean that it would not be reliable to assess any dose related difference in the number of AEs between cohorts.

Seven patients experienced AEs of neutropenia. One of these AEs in the 100-mg cohort and 3 in the 300-mg cohort were CTCAE grade 3 (the others were CTCAE grade 2). There were falls in mean neutrophil and platelet counts for both cohorts, considered to be related to FOLFIRI treatment. Neutropenia is a recognised complication of FOLFIRI treatment, and the incidence and severity of neutropenia seen in this study was no greater than would be expected from FOLFIRI treatment alone.

There were no changes of major concern in clinical chemistry parameters, although reductions in serum calcium, potassium or magnesium were seen in some patients in both cohorts, which in a number of cases necessitated treatment with calcium, potassium or magnesium supplements. In addition, serum creatinine levels increased by 10-20% from baseline in both cohorts, without any clear change in other renal markers. This is most likely to be due to inhibition of the renal transporter of creatinine by ZD6474.

A number of subjects in both cohorts showed increases in systolic and/or diastolic blood pressure over the treatment period. This was particularly evident in patients with a history of hypertension or borderline hypertension at study entry. These increases in blood pressure were considered to be related to ZD6474.

Mean QTc values indicate little effect on QTc interval in the 100-mg cohort, but a mean increase in QTc interval of 10-20 ms in the 300-mg cohort. One patient was noted to have

experienced transient prolonged QTc interval (529 ms), although this did not reach the protocol-defined criteria for QTc interval prolongation.

Summary of pharmacokinetic results

For both dose levels of ZD6474, the gmean AUC_{ss} of ZD6474 alone was similar to that when ZD6474 was given in the presence of FOLFIRI (6307 ng.h/mL compared to 6039 ng.h/mL for 100 mg, and 16040 ng.h/mL compared to 15760 ng.h/mL for 300 mg), with similar inter-patient variability (%CVs). The gmean ratios of AUC_{ss} for the 100-mg and 300-mg dose groups were both near to 1.0, at 0.957 and 0.982 for each group, respectively. Parallel results were observed for the gmean and the gmean ratios of $C_{ss, max}$.

For both dose levels of ZD6474, the gmean AUC of irinotecan alone was similar to that when irinotecan was given in the presence of ZD6474 (9374 ng/h/mL compared to10840 ng/h/mL for 100-mg and 8809 ngh/mL and 10100 ngh/mL for 300-mg), with similar inter-subject variability for 100-mg, although for 300-mg it was slightly greater when in the presence of ZD6474. The gmean ratios of AUC for the 100-mg and 300-mg dose groups were both near to 1.0, at 1.133 and 1.184 for each group, respectively. Parallel results were observed for the gmean and the gmean ratios of C_{max}.

For both dose levels of ZD6474, the gmean $AUC_{(0–t)}$ of SN-38 alone was similar to that when SN-38 was given in the presence of ZD6474 (222.4 ng/h/mL compared to 245.1 ng/h/mL for 100 mg and 135.2 ng/h/mL compared to 169.3 ng/h/mL for 300 mg), with similar inter-subject variability, although that for 300 mg alone was slightly greater. The gmean ratios of $AUC_{(0–t)}$ for the 100-mg and 300-mg dose groups were both near to 1.0, at 1.102 and 1.252 for each group, respectively. Parallel results were observed for the gmean and gmean ratios of C_{max}.

For both dose levels of ZD6474, the gmean CL of 5-FU in the presence of ZD6474 was similar to that when 5-FU was given alone (261.6 ng/h/mL compared to 224.1 ng/h/mL for 100 mg and 223.0 ng/h/mL compared to 198.2 ng/h/mL for 300 mg), with similar inter-subject variability. The gmean ratios of CL for both the 100-mg and 300-mg dose groups were both near to 1.0, at 0.856 and 0.889 for each group, respectively.

Summary of pharmacodynamic results

See efficacy results for CEA analysis.

Summary of efficacy results

A dose-response relationship for the efficacy of ZD6474 (100 mg and 300 mg) with FOLFIRI in combination could not be assessed, due to the limited number of patients with RECIST data.

In the 100-mg cohort, 2 (18%) confirmed partial responses (PRs) were observed (in 1 male patient and 1 female patient). Seven (64%) patients had stable disease (SD) ≥8 weeks. Disease control for ≥8 weeks was observed in 9 (82%) patients. There were 2 (18%) patients with a RECIST best objective response of progression. Overall, 4 patients had a RECIST progression, and there were no deaths in the absence of progression.

Of the 10 patients in the 300-mg cohort, 7 (70%) were not evaluable for RECIST. Of these 7, 6 were ongoing on study medication at the time of data cut-off but had not had a RECIST assessment 8 weeks after starting study medication, and the other patient withdrew due to an AE prior to having a post-baseline RECIST assessment. Two of the 3 patients assessed for RECIST, in the 300-mg cohort, had a best objective response of SD ≥8 weeks. The other patient had a best objective response of disease progression. There were no other disease progressions or deaths in the absence of progression in the 300-mg cohort.

CEA data was limited. However, the available data appears to show a correlation with the RECIST responses; patients with the greatest reduction in CEA showing the best RECIST response.