Cancer Chemother Pharmacol (2009) 64:665–672
DOI 10.1007/s00280-008-0914-4

ORIGINAL ARTICLE

Vandetanib with FOLFIRI in patients with advanced colorectal adenocarcinoma: results from an open-label, multicentre Phase I study

Mark P. Saunders · Richard Wilson · Marc Peeters · Robert Smith · Alex Godwood · Stuart Oliver · Eric Van Cutsem

Received: 6 October 2008 / Accepted: 19 December 2008 / Published online: 29 January 2009

Abstract
Purpose The safety and tolerability of vandetanib (ZACTIMA™; ZD6474) plus FOLFIRI was investigated in patients with advanced colorectal cancer (CRC).
Methods Patients eligible for first- or second-line chemotherapy received once-daily oral doses of vandetanib (100 or 300 mg) plus 14-day treatment cycles of FOLFIRI.
Results A total of 21 patients received vandetanib 100 mg ($n = 11$) or 300 mg ($n = 10$) + FOLFIRI. Combination therapy was well tolerated at both vandetanib dose levels. There were no DLTs in the vandetanib 100 mg cohort and one DLT of hypertension (CTCAE grade 3) in the 300 mg cohort. The most common adverse events were diarrhoea ($n = 20$), nausea ($n = 12$) and fatigue ($n = 10$). Two patients (one in each cohort) discontinued vandetanib due to adverse events (rash, 100 mg cohort; hypertension, 300 mg cohort). There was no apparent pharmacokinetic interaction between vandetanib and FOLFIRI. Preliminary efficacy results included two confirmed partial responses in the 100 mg cohort and 9 patients with stable disease ≥8 weeks (100 mg, $n = 7$; 300 mg, $n = 2$).
Conclusions Once-daily vandetanib (100 or 300 mg) in combination with a standard FOLFIRI regimen was generally well tolerated in patients with advanced CRC.

Keywords Vandetanib · FOLFIRI · Colorectal cancer

M. P. Saunders (✉)
Christie Hospital, Wilmslow Road,
Manchester M20 4BX, UK
e-mail: Mark.Saunders@christie.nhs.uk

R. Wilson
Belfast City Hospital, Belfast, UK

M. Peeters
University Hospital Ghent, Ghent, Belgium

R. Smith · S. Oliver
AstraZeneca, Macclesfield, UK

A. Godwood
AstraZeneca, Loughborough, UK

E. Van Cutsem
University Hospital Gasthuisberg, Leuven, Belgium

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in Europe and North America [1, 2]. Despite the introduction during the last decade of combination regimens incorporating fluorouracil (5-FU), irinotecan and oxaliplatin, median survival appears to plateau at less than 2 years for patients with metastatic disease receiving a chemotherapy-only treatment [3–5]. Therefore, there is a need for more effective treatment options in this disease setting.

Recent developments in CRC management have focussed on targeting growth factors that regulate tumour angiogenesis or tumour cell growth. Clinically validated therapeutic targets in CRC include vascular endothelial growth factor receptor (VEGFR)-dependent tumour angiogenesis and epidermal growth factor receptor (EGFR)-dependent tumour cell proliferation. The addition of bevacizumab, a humanized VEGF-A monoclonal antibody, to irinotecan, 5-FU and leucovorin chemotherapy improved response rate, progression-free survival and overall survival over chemotherapy alone in patients with first-line metastatic CRC [6]. In addition, cetuximab, a monoclonal antibody that targets EGFR, has demonstrated activity in metastatic CRC in combination with chemotherapy in both the first- and second-line setting [7, 8]. Data from the

CRYSTAL and OPUS studies suggested that the benefit from the addition of cetuximab to chemotherapy was higher in patients whose tumours contained the wild-type *k-ras* oncogene [9, 10]. Small molecule inhibitors of VEGFR or EGFR activity are also being investigated in patients with metastatic CRC, either alone or in combination with chemotherapy [11–13].

Combining strategies that target the VEGFR and EGFR signalling pathways may provide additive, or even synergistic, benefits for the management of patients with metastatic CRC. EGFR is overexpressed in 60–80% of colon cancers [14] and preclinical evidence shows that aberrant EGFR activity stimulates the secretion of proangiogenic factors, including VEGF [15, 16]. The rationale for targeting both pathways is also supported by the encouraging efficacy and safety findings from the BOND-2 study (bevacizumab added to cetuximab or to cetuximab plus irinotecan) in patients with irinotecan-refractory CRC, which suggest that dual inhibition of VEGFR and EGFR signalling may have greater antitumour efficacy than inhibitors of either pathway alone [17]. However, emerging negative data from the CAIRO2 and PACCE studies in first-line CRC patients (presented at the 2008 American Society of Clinical Oncology [ASCO] Annual Meeting [18] and Gastrointestinal Cancers Symposium [19]) have sounded a cautionary note about the relative safety and efficacy of combined anti-VEGF and anti-EGFR antibody regimens in CRC.

Vandetanib (ZACTIMA™; ZD6474) is a once-daily, orally available anticancer agent that inhibits VEGFR- and EGFR-dependent signalling [20] as well as the RET (REarranged during Transfection) receptor tyrosine kinase, an important growth driver in certain types of thyroid cancer [21]. Phase I evaluation in patients with solid tumours showed that once-daily doses of vandetanib (up to and including 300 mg) were generally well tolerated [22, 23]. Furthermore, vandetanib was shown to have a long terminal half-life of approximately 5 days and a pharmacokinetic profile that supported a once-daily oral dosing regimen. In Phase II studies in patients with advanced non-small-cell lung cancer (NSCLC), vandetanib had significant antitumour activity, both as monotherapy [24] and in combination with docetaxel or paclitaxel plus carboplatin [25, 26]. This Phase I study was conducted to evaluate the safety and tolerability of vandetanib when administered in combination with FOLFIRI in patients with advanced CRC.

Patients and methods

Patients

Patient eligibility included histologically confirmed metastatic colorectal adenocarcinoma (stage IV); suitability for first- or second-line chemotherapy; age ≥18 years; a WHO performance status of 0 or 1; and adequate cardiac, haematopoietic, hepatic and renal function. Patients with brain metastases were eligible if treated at least 4 weeks before the start of study treatment and if clinically stable without steroid treatment for ≥1 week. Patients were ineligible if they had received chemotherapy and/or radiotherapy less than 4 weeks before the start of study therapy; or had received any second-line or subsequent chemotherapy. All patients provided written informed consent. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, applicable guidelines on good clinical practice, local Institutional Review Board approval, and the AstraZeneca policy on Bioethics.

Study design and treatments

This was a multicentre, open-label, ascending dose, Phase I study of the safety, tolerability and pharmacokinetics of vandetanib in combination with FOLFIRI in patients with advanced CRC. Patients received once-daily oral doses of vandetanib in combination with standard 14-day treatment cycles of FOLFIRI (irinotecan 180 mg/m^2 1.5-h and leucovorin 400 mg/m^2 2-h simultaneous i.v. infusions on day 1, immediately followed by 5-FU 400 mg/m^2 i.v. bolus then 5-FU 2,400 mg/m^2 46–48-h i.v. infusion). To obtain pharmacokinetic data for FOLFIRI in the absence of vandetanib, dosing with vandetanib was delayed until day 3 of the first cycle.

An initial cohort of 10 patients (planned) received vandetanib 100 mg in combination with FOLFIRI for ≥6 weeks or until toxicity or progressive disease occurred. If <2 of 6 evaluable patients (i.e., having completed 6 weeks of treatment) experienced a dose-limiting toxicity (DLT) considered to be possibly related to vandetanib, dose escalation occurred and a second cohort of up to 10 patients was then enrolled and received daily oral doses of vandetanib 300 mg in combination with FOLFIRI. No intra-patient dose escalation of vandetanib was allowed in this study. Vandetanib 100 and 300 mg/day were selected for investigation based on previous Phase I studies that showed these doses to be tolerable and to achieve steady-state plasma concentrations that are several-fold greater than the IC_{50} values for inhibition of VEGF- or EGF-stimulated HUVEC proliferation [22, 23, 27].

Safety and tolerability

Adverse events were assessed at each scheduled visit and were recorded (along with investigator's assessment of causality) and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3. Clinical chemistry, 12-lead

electrocardiogram parameters, vital signs, haematology and urinalysis assessments were also conducted throughout the study.

A DLT was defined as the occurrence of any of the following: CTCAE grade 4 neutropenia or thrombocytopenia lasting more than 5 days and considered to be possibly related to vandetanib; febrile neutropenia (temperature >38.5°C on at least two occasions in 24 h, in association with grade 3 or 4 neutropenia); any other non-manageable drug-related CTCAE grade 3 or 4 non-haematological toxicity considered to be possibly treatment-related; and QTc prolongation (a single QTc measurement ≥550 ms; two consecutive QTc measurements ≥500 but <550 ms; an increase of ≥100 ms from baseline; or an increase of ≥60 ms, but <100 ms from baseline QTc to a QTc value ≥460 ms).

Pharmacokinetic assessments

At prespecified time points, plasma samples were collected to measure the plasma concentrations of vandetanib, irinotecan, SN-38 (the active metabolite of irinotecan) and 5-FU as follows; for vandetanib: days 3 and 8 (cycle 1), days 1 and 8 (cycle 2), days 1, 8 and 14 (cycle 3), and days 1 and 2 (cycle 4); for irinotecan (and SN-38): prior to irinotecan infusion, following completion of irinotecan infusion, 5, 15, 30 min, 1, 2, 4, 6, 10, 22 and 28 h post-infusion (cycles 1 and 4); for 5-FU: 2 h following iv bolus (prior to infusion), 3.5, 9.5, 21.5 and 48 h during infusion, 15, 30 and 90 mins post-infusion (cycles 1 and 4). The PK samples collected during cycle 1 on days 1 and 2 for irinotecan and on days 1 and 3 for 5-FU provided exposure data for irinotecan and 5-FU in the absence of vandetanib. Results from previous studies indicate that steady-state concentrations of vandetanib are reached from approximately 4 weeks onwards. Plasma samples were therefore collected in this study on day 14 of cycle 3 (study day 42) to determine the steady-state exposure to vandetanib alone. Repeat sampling of irinotecan, 5-FU and vandetanib at the start of cycle 4 allowed the exposures to each to be determined when administered in combination.

Plasma concentrations of vandetanib and 5-FU were determined by reverse-phase high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS-MS). The calibration range was 5.0–1,000 ng/ml and 5.0–5,000 ng/ml for vandetanib and 5-FU, respectively. Concentrations of irinotecan and SN-38 were determined by HPLC with fluorescence detection. The calibration range of this method was 10.0–2,500 ng/ml for irinotecan and 1.0–100 ng/ml for SN-38.

All plasma concentration–time data were analyzed using standard non-compartment methodology and WinNonlin version 4.1 Enterprise.

Efficacy measurements

Objective tumour assessments were evaluated by site investigators using RECIST (Response Evaluation Criteria in Solid Tumours) at baseline and every 8 weeks thereafter. Responders (complete or partial response) were confirmed by repeat imaging at not less than 3 weeks following the date of response.

Results

Patients

A total of 21 patients received study medication. The initial cohort comprised 11 patients who received vandetanib 100 mg plus FOLFIRI. As fewer than two patients in this cohort experienced a vandetanib-related DLT, protocol-defined dose escalation occurred and a second cohort of 10 patients was enrolled and received vandetanib 300 mg plus FOLFIRI. Patient characteristics and baseline demographics are summarized in Table 1. The patients who participated in this study were considered to be representative of the advanced CRC population. All patients were Caucasian. There was a slight difference in the male/female distribution between the two cohorts, but this was not anticipated to affect the safety and tolerability results of the study. In addition, the vandetanib 300 mg cohort included a greater proportion of second-line patients than the vandetanib 100 mg cohort.

Treatment administration

At the time of data cut-off (5 May 2006), 9 patients were ongoing in the 100 mg cohort [six receiving combination treatment, three ongoing for follow-up (with one of these patients ongoing on FOLFIRI alone)] and 10 patients were ongoing in the 300 mg cohort [eight receiving combination treatment, two ongoing for follow-up (with one of these patients ongoing on FOLFIRI alone)]. Since the 100 mg cohort commenced therapy before the 300 mg cohort, there was a longer duration of treatment of vandetanib in the 100 mg cohort (mean vandetanib exposure = 148.4 days) compared with the 300 mg cohort (mean vandetanib exposure = 65.5 days). In addition, there was a higher exposure to FOLFIRI in the 100 mg cohort (9 patients receiving ≥6 cycles of FOLFIRI) compared to the 300 mg cohort (2 patients receiving ≥6 cycles of FOLFIRI). Consequently, cross-cohort comparisons of safety, tolerability and efficacy are unreliable due to the differing exposures to vandetanib and FOLFIRI and these data are therefore reported separately for each cohort.

Table 1 Patient characteristics

	Vandetanib 100 mg/day + FOLFIRI ($n = 11$)	Vandetanib 300 mg/day + FOLFIRI ($n = 10$)	Total ($n = 21$)
Mean age, years (range)	52 (33–72)	54 (37–71)	53 (33–72)
Male (n)	5	7	12
Female (n)	6	3	9
Race (n)			
Caucasian	11	10	21
First-line patients (n)	4	1	5
Second-line patients (n)	7	9	16
Previous chemotherapy (n)			
5-FU	4	4	8
5-FU/capecitabine	1	–	1
Oxaliplatin	–	1	1
Oxaliplatin/5-FU	1	–	1
Oxaliplatin/capecitabine/cetuximab	–	1	1
Oxaliplatin/5-FU/capecitabine	–	1	1
FOLFOX	1	1	2
FOLFOX/capecitabine	–	1	1

5-FU, 5-fluorouracil; FOLFOX, oxaliplatin, leucovorin and 5-FU i.v. bolus/infusion

Vandetanib 100 mg cohort

Safety and tolerability

No patients in this cohort experienced a DLT and the protocol definition of a tolerable dose of vandetanib was met. The most frequently reported adverse events, irrespective of causality, were diarrhoea ($n = 11$), nausea ($n = 8$), fatigue ($n = 6$) and alopecia ($n = 7$) (Table 2). Eight patients experienced CTCAE grade 3 or 4 adverse events (Table 3), all but one of which occurred as single incidences, with the exception of pulmonary embolism ($n = 2$, both grade 4). One of these events was considered by the investigator to be causally related to vandetanib but it resolved with standard treatment. This patient subsequently developed a urinary tract infection that was treated with cefalexin and then a photosensitive erythematous rash (on the arms, eyelids and face) that required hospitalization and led to the permanent discontinuation of vandetanib (this was the only discontinuation due to an adverse event in this cohort). The photosensitive rash, which developed 137 days after the start of vandetanib treatment, was considered to be related to both vandetanib and cefalexin. The grade 3 events of hypertension and neutropenia in this cohort were considered to be related to vandetanib and FOLFIRI, respectively. The hypertension event resolved with treatment and the neutropenia resolved following a delay in FOLFIRI treatment. One patient experienced a fatal adverse event of haematemesis, which was related to disease progression and developed approximately 4 weeks after stopping vandetanib and FOLFIRI. There were no vandetanib dose reductions due to adverse events in this cohort.

Pharmacokinetics

At the 100 mg dose level, all 11 patients were evaluable for pharmacokinetic analysis of at least one analyte. The steady-state exposure to vandetanib in the presence of FOLFIRI (gmean AUC_{ss} = 6,039 ng·h/ml, $n = 11$) was similar to that when given alone (gmean AUC_{ss} = 6,307 ng·h/ml, $n = 11$). There appeared to be a trend towards an increase in exposure to irinotecan [AUC = 9374 ng·h/ml ($n = 9$) compared to 10,840 ng·h/ml ($n = 10$)] and SN-38 [$AUC_{(0-t)}$ = 222 ng·h/ml ($n = 11$) compared to 245 ng·h/ml (n = 11)] but these increases were not large and were within the residual variability of irinotecan and SN-38 exposure determined in a previous population pharmacokinetic analysis [28]. In addition, there was no requirement for any dose reductions in FOLFIRI during this study and so, overall, these increases are not likely to be clinically relevant. Similarly, coadministration of vandetanib had no clinically relevant effect on the exposure to 5-FU [CL = 262 l/h (alone, $n = 8$) compared to 224 l/h (plus vandetanib, $n = 8$)]. Plasma drug versus time profiles for vandetanib and the chemotherapy agents are shown in Fig. 1.

Efficacy

Preliminary evaluation of the efficacy of vandetanib 100 mg and FOLFIRI when given in combination showed two confirmed partial responses (in one male and one

Table 2 Adverse events, irrespective of causality, reported in ≥ 5 patients

MedDRA-preferred term (%)	Vandetanib 100 mg/day + FOLFIRI (n = 11)	Vandetanib 300 mg/day + FOLFIRI (n = 10)	Total (n = 21)
Diarrhoea	11 (100)	9 (90)	20 (95)
Nausea	8 (72)	4 (40)	12 (57)
Fatigue	6 (55)	4 (40)	10 (48)
Alopecia	7 (64)	2 (20)	9 (43)
Abdominal pain	5 (45)	3 (30)	8 (38)
Headache	5 (45)	3 (30)	8 (38)
Vomiting	5 (45)	3 (30)	8 (38)
Dyspepsia	5 (45)	2 (20)	7 (33)
Erythema	5 (45)	2 (20)	7 (33)
Lethargy	4 (36)	3 (30)	7 (33)
Neutropenia	3 (27)	4 (40)	7 (33)
Rash	6 (55)	1 (10)	7 (33)
Constipation	5 (45)	1 (10)	6 (29)
Insomnia	5 (45)	1 (10)	6 (29)
Nasopharyngitis	5 (45)	0	5 (24)
Pruritis	4 (36)	1 (10)	5 (24)
Stomatitis	4 (36)	1 (10)	5 (24)

Table 3 Number of patients with adverse events of CTCAE grade 3 or 4

MedDRA-preferred term	Vandetanib 100 mg/day + FOLFIRI (n = 11)	Vandetanib 300 mg/day + FOLFIRI (n = 10)	Total (n = 21)
Neutropenia (%)	1 (9)	3 (30)	4 (19)
CTCAE grade 3/4	1/0	3/0	4/0
Hypertension (%)	1 (9)	2 (20)	3 (14)
CTCAE grade 3/4	1/0	2/0	3/0
Catheter-related complication (%)	0	2 (20)	2 (10)
CTCAE grade 3/4	0/0	2/0	2/0
Pulmonary embolism (%)	2 (18)	0	2 (10)
CTCAE grade 3/4	0/2	0/0	0/2
Back pain (%)	1 (9)	0	1 (5)
CTCAE grade 3/4	1/0	0/0	1/0
Constipation (%)	1 (9)	0	1 (5)
CTCAE grade 3/4	1/0	0/0	1/0
Spinal osteoarthritis (%)	1 (9)	0	1 (5)
CTCAE grade 3/4	1/0	0/0	1/0
Stomatitis (%)	1 (9)	0	1 (5)
CTCAE grade 3/4	1/0	0/0	1/0

female patient) and seven patients with stable disease ≥8 weeks. Progressive disease was the best response in two patients.

Vandetanib 300 mg cohort

Safety and tolerability

The protocol definition of a tolerable dose of vandetanib was achieved in this cohort, with one patient experiencing a DLT. This 48-year-old female patient with a previous history of controlled hypertension developed grade 2 hypertension 5 days prior to starting vandetanib treatment (and 2 days prior to FOLFIRI treatment). The hypertension increased to grade 3 at the end of the first cycle of treatment and was associated with bradycardia and a transient prolongation of QTc interval (maximum: 529 ms), which did not meet the protocol definition of QTc prolongation. This hypertension event led to the discontinuation of vandetanib treatment (the only discontinuation due to an adverse event in this cohort) and the hypertension subsequently resolved slowly with treatment. The most frequently reported adverse events were diarrhoea (n = 9), nausea, fatigue and neutropenia (all n = 4; Table 2). Seven patients experienced CTCAE grade 3 or 4 adverse events (Table 3). Both grade 3 hypertension events, which includes the DLT described above, were considered to be related to vandetanib. Three adverse events of grade 3 neutropenia were observed in this cohort and these were all considered by the investigator to be related to FOLFIRI. In addition, one patient developed a grade 3 catheter-related complication (venous thrombi in association with an indwelling catheter). Such events are common in patients with advanced cancer but an association with vandetanib could not be fully excluded in this case. As with the 100 mg cohort, there were no vandetanib dose reductions due to adverse events in this cohort.

Pharmacokinetics

Six patients in this cohort were evaluable for pharmacokinetic analysis of at least one analyte. The steady-state exposure to vandetanib in the presence of FOLFIRI (gmean AUC_{ss} = 15,760 ng·h/ml, n = 6) was similar to that when given alone (gmean AUC_{ss} = 16,040 ng·h/ml, n = 6) (Plasma drug versus time profile for vandetanib 300 mg shown in Fig. 1a). As observed in the 100 mg cohort, the presence of vandetanib appeared to have no clinically relevant effect on the exposure to co-administered irinotecan [AUC = 8,809 ng.h/ml (alone, n = 4) compared with 10,100 ng.h/ml (plus vandetanib, n = 5)], SN-38 [$AUC_{(0\text{-}t)}$ = 135 ng.h/ml (alone, n = 5) compared with 169 ng.h/ml (plus vandetanib, n = 5)] and 5-FU [CL = 223 l/h (alone, n = 5) compared to 198 l/h (plus vandetanib, n = 5)].

Efficacy

Preliminary evaluation of the efficacy of vandetanib 300 mg and FOLFIRI when given in combination showed

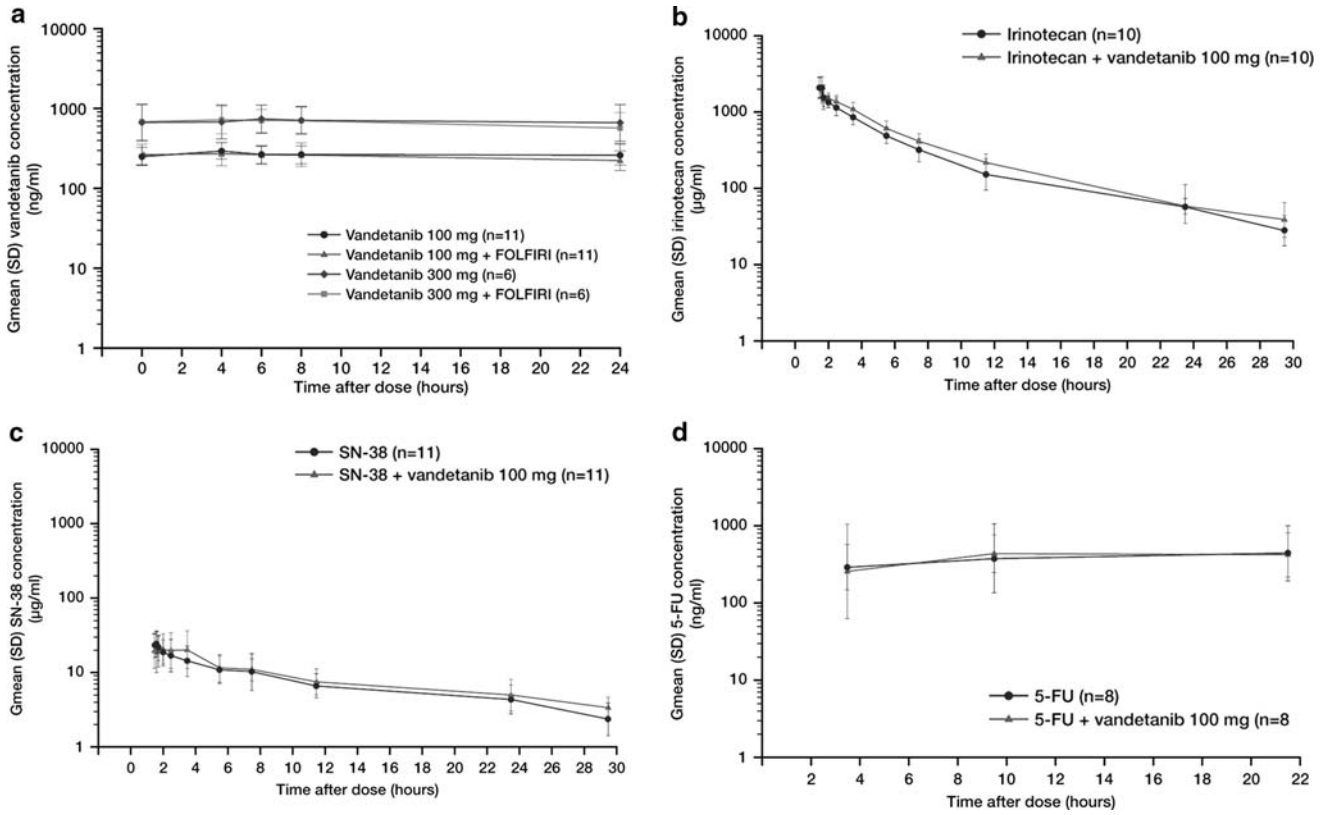

Fig. 1 Plasma drug concentration (geometric mean ± SD) versus time profiles for **a** vandetanib, **b** irinotecan, **c** SN-38 and **d** 5-FU. For b, c and d, data for the vandetanib 300 mg cohort were similar and are not shown

two patients with stable disease ≥8 weeks. Progressive disease was the best response in one patient. Seven patients in this cohort were not evaluable for RECIST; six of these patients were ongoing on study treatment at data cut-off but had not yet had a RECIST assessment 8 weeks after starting study treatment, and the other patient withdrew due to an adverse event prior to having a post-baseline RECIST assessment.

Discussion

In this Phase I study, the combination of once-daily vandetanib (100 or 300 mg) with a standard FOLFIRI regimen was generally well tolerated in patients with advanced CRC. In general, the adverse events that were considered to be related to study treatment were managed adequately by concomitant medication or dose reduction and there were no unexpected adverse events reported for the combination of vandetanib and FOLFIRI in this study. Two patients in the study discontinued vandetanib treatment because of an adverse event; only one of these patients (the DLT of hypertension in the 300 mg cohort) stopped vandetanib within the first 6 weeks of treatment. Assessment of dose-dependent differences in the number of adverse events between cohorts was limited because of the differing mean durations of exposure to vandetanib, as well as by the small numbers of patients in this study. However, the protocol definition of a tolerable dose was achieved in both cohorts.

Overall, the most common adverse events were diarrhoea (95%), nausea (57%) and fatigue (48%). Diarrhoea was experienced by all but one patient, but all of these events were reported as CTCAE grade 1 or 2 and were manageable using standard approaches. This contrasts with two previous Phase I studies of the EGFR tyrosine kinase inhibitors gefitinib and erlotinib in combination with FOLFIRI in advanced CRC [29, 30]. Grade 3 diarrhoea was a commonly reported adverse event in both studies (31%, gefitinib + FOLFIRI; 67%, erlotinib + FOLFIRI) and contributed to the early termination of the erlotinib study [29]. Rash is another adverse event commonly reported with agents that target EGFR signalling. In the present study, one patient in the 100 mg cohort experienced rash in three body areas concurrently and this led to the discontinuation of vandetanib but rash/erythema events were otherwise all mild or moderate. The most commonly reported grade 3 or 4 adverse events in this study were neutropenia ($n = 4$, all grade 3) and hypertension ($n = 3$, all grade 3). Neutropenia is a recognised complication of FOLFIRI treatment, and the incidence and severity of neutropenia in this study was no

greater than would be expected from FOLFIRI treatment alone [31]. Hypertension has been previously reported in single-agent studies of vandetanib [22, 23], as well as with other VEGF pathway inhibitors [6, 32–34]. All three grade 3 hypertension adverse events in this study were considered to be related to vandetanib, including the only DLT in the study. It was noted that the hypertension events in this study were all experienced by patients with a history of hypertension or who were borderline hypertensive at study entry.

The pharmacokinetic characteristics of vandetanib in this study did not differ from those obtained during Phase I evaluation [22, 23] and no pharmacokinetic interaction was observed between vandetanib, irinotecan, SN-38 and 5-FU when given in combination.

Preliminary evaluation of the efficacy of vandetanib and FOLFIRI when given in combination, based on RECIST assessments of objective response, revealed two patients with a partial response and seven patients with stable disease $\geq$8 weeks in the 100 mg cohort, and two of three evaluable patients in the 300 mg cohort had stable disease $\geq$8 weeks. The small number of patients together with the differing exposures to vandetanib in each dose cohort did not allow any conclusions or comparisons between cohorts to be made regarding efficacy.

In summary, the primary objective of this Phase I study was achieved; it was demonstrated that vandetanib (100 or 300 mg) can be safely combined with FOLFIRI as treatment of advanced CRC. These encouraging results have led to an ongoing Phase II, double-blind, placebo-controlled, randomized study of vandetanib 100 or 300 mg in combination with FOLFIRI as second-line therapy in patients with CRC (6474IL0048). Clinical investigation of vandetanib continues in other tumour types, including Phase III development in NSCLC and medullary thyroid cancer.

Acknowledgments This study, including editorial assistance provided by Chris Watson of Mudskipper Bioscience, was supported financially by AstraZeneca. ZACTIMA is a trademark of the AstraZeneca group of companies.

References

1. Ferlay J, Autier P, Boniol M et al (2007) Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 18:581–592
2. Jemal A, Siegel R, Ward E et al (2007) Cancer Statistics, 2007. CA Cancer J Clin 57:43–66
3. Saltz LB, Cox JV, Blanke C et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan study group. N Engl J Med 343:905–914
4. Giacchetti S, Perpoint B, Zidani R et al (2000) Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136–147
5. Kohne CH, Van Cutsem E, Wils J et al (2005) Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. J Clin Oncol 23:4856–4865
6. Hurwitz H, Fehrenbacher L, Novotny W et al (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335–2342
7. Tabernero J, Van Cutsem E, Diaz-Rubio E et al (2007) Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 25:5225–5232
8. Cunningham D, Humblet Y, Siena S et al (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351:337–345
9. Van Cutsem E, Lang I, D'Haens G et al (2008) KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. J Clin Oncol 26:2A
10. Bokemeyer C, Bondarenko I, Hartmann J et al (2008) KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: The OPUS experience. J Clin Oncol 26: Abst 4000
11. Townsley CA, Major P, Siu LL et al (2006) Phase II study of erlotinib (OSI-774) in patients with metastatic colorectal cancer. Br J Cancer 94:1136–1143
12. Hecht JR, Trarbach T, Jaeger E et al (2005) A randomized, double-blind, placebo-controlled, phase III study in patients (Pts) with metastatic adenocarcinoma of the colon or rectum receiving first-line chemotherapy with oxaliplatin/5-fluorouracil/leucovorin and PTK787/ZK 222584 or placebo (CONFIRM-1). Proc Am Soc Clin Oncol abst 3
13. Saltz LB, Rosen LS, Marshall JL et al (2007) Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. J Clin Oncol 25:4793–4799
14. Porebska I, Harlozinska A, Bojarowski T (2000) Expression of the tyrosine kinase activity growth factor receptors (EGFR, ERB B2, ERB B3) in colorectal adenocarcinomas and adenomas. Tumour Biol 21:105–115
15. Ciardiello F, Caputo R, Bianco R et al (2001) Inhibition of growth factor production and angiogenesis in human cancer cells by ZD1839 (Iressa), a selective epidermal growth factor receptor tyrosine kinase inhibitor. Clin Cancer Res 7:1459–1465
16. Riedel F, Gotte K, Li M et al (2002) EGFR antisense treatment of human HNSCC cell lines down-regulates VEGF expression and endothelial cell migration. Int J Oncol 21:11–16
17. Saltz LB, Lenz HJ, Kindler HL et al (2007) Randomized phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. J Clin Oncol 25:4557–4561
18. Punt CJ, Tol J, Rodenburg CJ et al (2008) Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). Proc Am Soc Clin Oncol 26
19. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, Shahin S, Griffin T (2008) An updated analysis of safety and efficacy of oxaliplatin (Ox)/bevacizumab (bev) +/− panitumumab (pmab) for first-line treatment (tx) of metastatic colorectal cancer (mCRC) from a randomized, controlled trial (PACCE)
20. Wedge SR, Ogilvie DJ, Dukes M et al (2002) ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 62:4645–4655

21. Ichihara M, Murakumo Y, Takahashi M (2004) RET and neuroendocrine tumors. Cancer Lett 204:197–211
22. Holden SN, Eckhardt SG, Basser R et al (2005) Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. Ann Oncol 16:1391–1397
23. Tamura T, Minami H, Yamada Y et al (2006) A Phase I dose-escalation study of ZD6474 in Japanese patients with solid, malignant tumors. J Thorac Oncol 1:1002–1009
24. Natale RB, Bodkin D, Govindan R et al (2009) Vandetanib versus gefitinib in patients with advanced NSCLC: results from a two-part, double-blind, randomized phase II study. J Clin Oncol (in press)
25. Heymach JV, Johnson BE, Prager D et al (2007) Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer. J Clin Oncol 25:4270–4277
26. Heymach JV, Paz-Ares L, De Braud F et al (2008) Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol 26:5407–5415
27. Herbst RS, Heymach JV, O'Reilly MS et al (2007) Vandetanib (ZD6474): an orally available receptor tyrosine kinase inhibitor that selectively targets pathways critical for tumor growth and angiogenesis. Expert Opin Investig Drugs 16:239–249
28. Klein CE, Gupta E, Reid JM et al (2002) Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. Clin Pharmacol Ther 72:638–647
29. Messersmith WA, Laheru DA, Senzer NN et al (2004) Phase I trial of irinotecan, infusional 5-fluorouracil, and leucovorin (FOLFIRI) with erlotinib (OSI-774): early termination due to increased toxicities. Clin Cancer Res 10:6522–6527
30. Wolpin BM, Clark JW, Meyerhardt JA et al (2006) Phase I study of gefitinib plus FOLFIRI in previously untreated patients with metastatic colorectal cancer. Clin Colorectal Cancer 6:208–213
31. Douillard JY, Cunningham D, Roth AD et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041–1047
32. Mross K, Drevs J, Muller M et al (2005) Phase I clinical and pharmacokinetic study of PTK/ZK, a multiple VEGF receptor inhibitor, in patients with liver metastases from solid tumours. Eur J Cancer 41:1291–1299
33. Faivre S, Delbaldo C, Vera K et al (2006) Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 24:25–35
34. Drevs J, Siegert P, Medinger M et al (2007) Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol 25:3045–3054