AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | Vandetanib (ZD6474) |
| Study Code | D4200C00047 |
| Date | 03 October 2008 |

# A Phase II, double-blind, placebo-controlled, randomised study to assess the efficacy and safety of 2 doses of ZACTIMA (ZD6474) in combination with FOLFOX vs FOLFOX alone for the treatment of colorectal cancer in patients who have failed therapy with an irinotecan and fluoropyrimidine containing regimen

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| **Study dates:** | First patient randomised: 19 March 2007<br>Last patient randomised: 11 Nov 2007<br>Data cut-off date: 8 March 2008 |
| **Phase of development:** | Therapeutic Exploratory (Phase II) |

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

**A Phase II, double-blind, placebo-controlled, randomised study to assess the efficacy and safety of 2 doses of ZACTIMA (ZD6474) in combination with FOLFOX vs FOLFOX alone for the treatment of colorectal cancer in patients who have failed therapy with an irinotecan and fluoropyrimidine containing regimen**

## Clinical Study Report Synopsis

This Clinical Study Report is presented as a Synopsis report as the data from this study indicated that there was no benefit of giving vandetanib (ZACTIMA™, ZD6474) in combination with FOLFOX (oxaliplatin, leucovorin, fluorouracil combination regimen) versus FOLFOX alone for the treatment of colorectal cancer in patients who have failed therapy with an irinotecan and fluoropyrimidine containing regimen. Full study data are provided in Appendices A-D.

## Primary objective

The primary objective of this study was to assess the efficacy of vandetanib (100 mg and 300 mg) in combination with the modified FOLFOX6 regimen (mFOLFOX6) versus mFOLFOX6 alone for the treatment of patients with colorectal cancer that have failed prior treatment with irinotecan and a fluoropyrimidine by assessment of disease progression.

## Secondary objectives

The secondary objectives of the study were to assess the safety and tolerability of vandetanib (100 mg and 300 mg) in combination with mFOLFOX6 in the treatment of colorectal cancer by review of adverse events (AEs) and laboratory parameters.

## Patients

A minimum of 96 patients (from around 16 centres in approximately 5 countries) were to be randomised to receive either vandetanib 100 mg and mFOLFOX6, or vandetanib 300 mg and mFOLFOX6, or placebo and mFOLFOX6.

## Design

This was a double-blind, placebo controlled, parallel group study. Following baseline assessments, patients were to be randomised in a 1:1:1 ratio to receive either vandetanib 100 mg and mFOLFOX6 or vandetanib 300 mg and mFOLFOX6 or placebo and mFOLFOX6. Patients were to be followed up every week for 4 weeks then every two weeks whilst on study treatment until data cut-off (approximately 5 months following the recruitment of the last patient). Weekly blood tests were recommended whilst the patient was receiving FOLFOX and were required for the first 8 weeks whilst on vandetanib or placebo. After the data cut-off, patients remaining on study treatment were to be followed up at 3 monthly intervals for serious adverse events (SAEs). Additionally, for patients continuing on vandetanib or placebo after data cut-off, electrocardiograms (ECGs) were to be checked every 3 months and electrolytes monitored as clinically indicated. Once study treatment (FOLFOX and vandetanib [100 mg or 300 mg] or FOLFOX and placebo) was stopped there was to be a follow-up visit at 30 days and for those patients stopping vandetanib or placebo an additional 60 day follow-up. Patients could discontinue one or more treatments, but were to remain in

the study unless consent was withdrawn or the patient had progressed. The data cut-off date for the study was 8 March 2008. There was a 7-day window up to data cut-off during which patients could attend for a mandatory tumour assessment visit (MTAV, 5 March 2008 ± 3 days).

**Study treatments**

Vandetanib 100 mg or 300 mg or placebo tablets were to be dispensed every 4 weeks and taken once daily continuously from the first day of the study.

FOLFOX was to be administered with appropriate premedication according to the following regimen every 14 days:

- Oxaliplatin 85 mg/m$^2$ intravenous infusion given over 120 minutes
- Leucovorin 400 mg/m$^2$ intravenous infusion over 120 minutes given concurrently with oxaliplatin
- 5-fluorouracil (5-FU) 400 mg/m$^2$ intravenous bolus over 2-4 minutes immediately after leucovorin followed by 2400 mg/m$^2$ intravenous infusion given over the following 46 hours.

Patients were to continue to receive study treatment until objective and/or clinical disease progression provided there was no unacceptable toxicity and the patient was willing to continue.

Objective disease progression was defined as at least 20% increase in the sum of longest diameters of measurable lesions, presence of new lesions, or unequivocal progression on non-measurable lesions; lesions in previously irradiated areas were considered evaluable for progression. Clinical disease progression was defined as a global deterioration of health status requiring discontinuation of treatment as a result of the underlying disease and not due to intercurrent illness or adverse effects from therapy.

If a patient experienced toxicities, the daily dose of vandetanib (or placebo) could be reduced or withheld; to enable dose reduction, the patient's treatment was unblinded and 300 mg daily was reduced to 200 mg daily, and 100 mg daily was reduced to 100 mg on alternate days. Management of toxicity with oxaliplatin, 5-FU, or leucovorin was to follow guidelines in the relevant product characteristics (see Study Protocol, Appendix E).

If treatment with FOLFOX was stopped for any reason, patients could continue vandetanib (or placebo) providing they were receiving clinical benefit, ie, absence of both progressive disease and unacceptable toxicity. Likewise FOLFOX could be continued if vandetanib (or placebo) was discontinued.

Following data cut-off, patients could continue to receive blinded study treatment provided they were continuing to derive clinical benefit and the patient and investigator believed

continued treatment was in the best interest of the patient. Following unblinding of treatment those patients receiving vandetanib could continue to receive it, through open label supplies.

**Methods of statistical analysis**

The primary outcome variable in this study was the number of patients with a progression event occurring on or before the MTAV. A progression event was defined as the earliest of objective and/or clinical disease progression or death from any cause.

Tumour assessments were to be performed at screening, then per site clinical practice (expected to be at least every 3-4 months) with a mandatory tumour assessment at data cut-off unless the patient had previously progressed. The mandatory tumour assessment for each patient was to be approximately 5 months after the last patient was randomised, an estimated timing based on when the required number of progression events would be expected to have occurred. All patients (including those previously withdrawn from treatment) needed an assessment at this time point if they had not already had confirmed disease progression.

The number of patients with a progression event occurring on or before the data cut-off was to be compared between each dose of vandetanib and the placebo comparator arm using a logistic regression model with a complementary log-log function and including a factor for treatment group. The results were to be approximated as a hazard ratio (HR). The estimated HR of a progression event was to be reported, together with the corresponding confidence interval(s) (CIs) and p-value. The analysis was to be performed on an Intention-To-Treat (ITT) basis. Patients were to be analysed according to their randomised study medication.

The patients evaluable for safety and tolerability (ie, the Evaluable for Safety [EFS] analysis set) were all those who received at least 1 dose of study medication. No formal statistical analyses were to be performed for safety and tolerability. The treatment groups were to be compared descriptively using summary statistics and percentage counts. Patients were to be summarised according to the initial study medication actually received.

**Results**

**Summary of patients**

One-hundred and nine patients were recruited in total, from 19 centres in 6 countries (France, Hungary, Spain, Taiwan, Korea, Slovakia). Five patients did not meet the inclusion/exclusion criteria, and 104 patients were randomised to study treatment (ITT population).

Thirty-two patients were randomised to the FOLFOX plus vandetanib 100 mg group, 35 patients to the FOLFOX plus vandetanib 300 mg group, and 37 patients to the FOLFOX plus placebo group. All randomised patients received study treatment and were included in the EFS analysis set. The time from the first patient enrolled until last patient randomised was approximately 8 months. The time from last patient randomised to MTAV at data cut-off was approximately 4 months.

The randomised patients were considered to be representative of the broad population of patients with colorectal cancer, and generally were well balanced between the 3 treatment

groups for factors such as age and race, but with a small imbalance for gender and for prior treatment with bevacizumab (Avastin). Table 1 summarises key patient baseline characteristics and prior treatment for colorectal cancer. See Table 11.1.1.1 for patient disposition and Table 11.1.2 for analysis sets, Appendix B. See Tables 11.1.3 to 11.1.5 for patient demographic and baseline characteristics, Appendix B.

**Table 1 Patient demographic and baseline characteristics**

| Patient characteristic | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| | vandetanib 100 mg + FOLFOX (n = 32) | | vandetanib 300 mg + FOLFOX (n = 35) | | placebo + FOLFOX (n = 37) | |
| | n | % | n | % | n | % |
| Age (years) | | | | | | |
| Mean: min-max | 57.1: 34-75 | | 57.9: 37-71 | | 58.8: 32-81 | |
| Gender: | | | | | | |
| Male | 16 | (50%) | 24 | (69%) | 24 | (65%) |
| Female | 16 | (50%) | 11 | (31%) | 13 | (35%) |
| Race: | | | | | | |
| Caucasian | 20 | (63%) | 21 | (60%) | 23 | (62%) |
| Oriental | 12 | (38%) | 14 | (40%) | 14 | (38%) |
| 1 metastatic site | 12 | (38%) | 13 | (37%) | 13 | (35%) |
| >1 metastatic site | 20 | (63%) | 22 | (63%) | 23 | (62%) |
| Unknown number of metastatic sites | 0 | (0%) | 0 | (0%) | 1 | (3%) |
| Radiotherapy to primary tumour | 4 | (13%) | 4 | (11%) | 7 | (19%) |
| Initial surgery with curative intent | 26 | (81%) | 27 | (77%) | 28 | (76%) |
| Metastasectomy | 8 | (25%) | 11 | (31%) | 8 | (22%) |
| Surgery for intercurrent complications | 7 | (22%) | 4 | (11%) | 6 | (16%) |
| Adjuvant irinotecan | 1 | (3%) | 3 | (9%) | 3 | (8%) |
| Adjuvant oxaliplatin | 1 | (3%) | 1 | (3%) | 2 | (5%) |
| Prior bevacizumab | 8 | (25%) | 15 | (43%) | 10 | (27%) |
| Prior cetuximab | 0 | (0%) | 1 | (3%) | 0 | (0%) |

Data derived from Tables 11.1.3 to 11.1.5, Appendix B.

### Exposure to study treatment, dose interruptions, and dose reductions

The mean total duration of exposure to vandetanib (ie, time from first dose to last dose including periods of dose interruption or dose reduction and planned rest periods) for the vandetanib 100 mg group, vandetanib 300 mg group, and the placebo group was 149.8, 140.0

and 145.6 days, respectively. The mean total duration of exposure on FOLFOX (ie, time from first dose of any component of FOLFOX to last dose of any component of FOLFOX including periods of dose interruption or dose reduction and planned rest periods) for the vandetanib 100 mg group, 300 mg group, and placebo group was 138.9, 129.1 and 134.1 days, respectively.

Those patients who had dose interruption or dose reduction because of unacceptable toxicity or coincidental AEs are shown in Table 2.

**Table 2 Number (%) of patients who had dose interruption or dose reduction because of unacceptable toxicity or coincidental AEs.**

| | N (%) of patients | | |
|---|---|---|---|
| | **Vandetanib 100 mg + FOLFOX (n = 32)** | **Vandetanib 300 mg + FOLFOX (n = 35)** | **Placebo + FOLFOX (n = 37)** |
| Vandetanib or placebo: | | | |
| Dose interruption | 8 (25%) | 15 (43%) | 4 (11%) |
| Dose reduced | 5 (16%) | 10 (29%) | 4 (11%)[a] |
| 5-FU: | | | |
| Dose reduced | 15 (47%) | 13 (37%) | 11 (30%) |
| Leucovorin: | | | |
| Dose reduced | 4 (13%) | 4 (11%) | 5 (14%) |
| Oxaliplatin: | | | |
| Dose reduced | 16 (50%) | 13 (37%) | 13 (35%) |

[a] Patients were unblinded with view to dose reduction
n = Number of randomised patients
Data derived from Tables 11.3.1.1 to 11.3.1.4, Appendix B.

Three (9%), 6 (17%) and 4 (11%) patients in the vandetanib 100 mg, vandetanib 300 mg, and placebo groups, respectively, permanently discontinued vandetanib (or placebo) treatment due to AEs and/or death due to AEs. The 4 (11%) patients in the placebo group who permanently discontinued treatment were the patients referred to above (Table 2) who were unblinded with view to dose reduction (see Table 4).

Twenty-five (78%) patients in the vandetanib 100 mg group, 31 (89%) patients in the vandetanib 300 mg group, and 27 (73%) patients in the placebo group had permanently discontinued vandetanib (or placebo) by data cut-off, leaving 7 (22%), 4 (11%) and 10 (27%) patients, respectively, continuing treatment.

See Table 11.1.1.1, Appendix B, for patient disposition; and Tables 11.3.1.1 to 11.3.1.4, Appendix B, for exposure, dose interruption and dose reduction data.

## Efficacy

A greater percentage of patients had a disease progression event in the ITT analysis set in the vandetanib 100 mg group compared to the placebo group (72% versus 65%), and in the vandetanib 300 mg group compared to the placebo group (77% versus 65%). No statistically significant group differences were seen. The results of the disease progression event analysis are summarised in Table 3.

**Table 3 Number of patients with at least one disease progression event**

| Treatment group | Number of patients with event/N (%) | HR[a] | 2-sided 80% CI | 2-sided 95% CI | 2-sided p-value |
|---|---|---|---|---|---|
| Vandetanib 100 mg | 23/32 (72%) | 1.21 | 0.82, 1.80 | 0.66, 2.22 | 0.53 |
| Vandetanib 300 mg | 27/35 (77%) | 1.41 | 0.96, 2.07 | 0.78, 2.54 | 0.25 |
| Placebo | 24/37 (65%) | | | | |

[a] Comparison to placebo
CI confidence interval
HR hazard ratio
N Number of patients
Data derived from Table 11.2.1, Appendix B.

Seven patients failed to attend for tumour assessment at the MTAV (1 in the vandetanib 100 mg group; 3 in the vandetanib 300 mg group; and 3 in the placebo group) and were considered not to have had a progression event in the disease progression event ITT analysis set.

Death from any cause was the first event (ie, earlier than objective and/or clinical disease progression) for only 1 (3%) patient; this patient was in the vandetanib 300 mg group.

The data for time to progression event and overall best response using RECIST criteria were evaluated although should be treated with caution, because: (i) measurable disease was not required at baseline in this study; (ii) there was no fixed schedule for tumour assessment. This means that the time to progression could have been overestimated and the best response may have been missed. Analysis of the time to progression event was a further sensitivity analysis and gave a pattern of results that supported the disease progression event count. The estimated median times to a progression event was 173 days for the vandetanib 100 mg group, 161 days for the vandetanib 300 mg group, and 194 days for the placebo group, giving an HR of 1.26 for comparison between the vandetanib 100 mg group and the placebo group (2-sided 80% CI: 0.86, 1.84; 2-sided 95% CI: 0.71, 2.25; 2-sided p-value: 0.43) and a HR of 1.36 for comparison between the vandetanib 300 mg group and the placebo group (2-sided 80% CI: 0.95, 1.96; 2-sided 95% CI: 0.78, 2.37; 2-sided p-value: 0.27).

In terms of the investigators' opinion of overall best response using RECIST criteria, in the ITT analysis set no patients showed a complete response. In the vandetanib 100 mg group, vandetanib 300 mg group, and the placebo group, 7 (22%), 10 (29%) and 8 (22%) patients, respectively, showed a partial response; 18 (56%), 16 (46%) and 20 (54%) patients, respectively, showed stable disease; and 7 (22%), 7 (20%) and 8 (22%) patients, respectively, showed progressive disease; and 0 (0%), 2 (6%) and 1 (3%) patients, respectively, were not evaluable.

See Tables 11.2.1 to 11.2.7 for efficacy data, Appendix B.

**Safety**

All except one patient in each group in the EFS analysis set (ie, approximately 97% in each group) experienced an AE. The proportion of patients experiencing an SAE was greater in the vandetanib 300 mg group than the other two groups. Compared to the other 2 groups more patients in the vandetanib 300 mg group experienced AEs or SAEs that were considered by the investigator to have a possible causal relationship with vandetanib (or placebo); or that were considered to have a possible causal relationship and led to permanent discontinuation; or that were of CTCAE Grade 3-4 severity. Table 4 provides a summary of the numbers of AEs in each category.

**Table 4 Number (%) of patients who had an adverse event in any category (EFS analysis set)**

| Category of adverse event | N (%) of patients who had an adverse event in each category [a] | | |
|---|---|---|---|
| | Vandetanib 100 mg + FOLFOX (n = 32) | Vandetanib 300 mg + FOLFOX (n = 35) | Placebo + FOLFOX (n = 37) |
| Any AEs | 31 (97%) | 34 (97%) | 36 (97%) |
| Any causally-related AE [b] | 24 (75%) | 29 (83%) | 28 (76%) |
| Any SAE | 4 (13%) | 9 (26%) | 4 (11%) |
| Any causally-related SAE [b] | 1 (3%) | 4 (11%) | 2 (5%) |
| Any AE leading to permanent discontinuation of vandetanib (or placebo) | 3 (9%) | 5 (14%) | 5 (14%)[c] |
| Any causally-related AE leading to permanent discontinuation of vandetanib (or placebo) [b] | 3 (9%) | 5 (14%) | 4 (11%)[c] |
| Any AE CTC Grade 3-4 | 20 (63%) | 28 (80%) | 20 (54%) |
| Any causally-related AE CTC Grade 3-4 [b] | 8 (25%) | 17 (49%) | 5 (14%) |

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Assessed by investigator as having a reasonable possibility that the AE may have been caused by vandetanib (or placebo).

[c] Includes 4 patients unblinded with view to dose reduction.
n = Number of patients in the EFS analysis set
Data derived from Table 11.3.2.1, Appendix B.

Table 5 shows the most frequently reported AEs (ie, those AEs that occurred in over 25% of patients in at least one of the three treatment groups). See Table 11.3.2.2 for patients with ≥1 AE, Appendix B.

**Table 5 Most frequently reported AEs (ie, in >25% of patients in at least one of the three treatment groups): number (%) of patients (EFS analysis set)**

| Adverse event | N (%) of patients | | |
|---|---|---|---|
| | Vandetanib 100 mg + FOLFOX (n = 32) | Vandetanib 300 mg + FOLFOX (n = 35) | Placebo + FOLFOX (n = 37) |
| Diarrhoea | 16 (50%) | 23 (66%) | 16 (43%) |
| Thrombocytopenia | 16 (50%) | 18 (51%) | 13 (35%) |
| Nausea | 13 (41%) | 15 (43%) | 24 (65%) |
| Hypertension | 14 (44%) | 13 (37%) | 5 (14%) |
| Peripheral sensory neuropathy | 16 (50%) | 12 (34%) | 18 (49%) |
| Anorexia | 10 (31%) | 12 (34%) | 9 (24%) |
| Neutropenia | 12 (38%) | 11 (31%) | 13 (35%) |
| Stomatitis | 8 (25%) | 11 (31%) | 10 (27%) |
| Fatigue | 8 (25%) | 10 (29%) | 15 (41%) |
| Vomiting | 9 (28%) | 5 (14%) | 14 (38%) |
| Abdominal pain | 2 (6%) | 3 (9%) | 10 (27%) |

n = Number of patients in the EFS analysis set
Data derived from Table 11.3.2.2, Appendix B.

Most CTCAE Grade 3, 4 and 5 events occurred in 1 to 2 patients. Table 6 shows the AEs of CTCAE Grade 3 and 4 that occurred in more than 2 patients in the entire study, or in more than one patient in either the vandetanib 100 mg, vandetanib 300 mg or placebo group; no Grade 5 CTCAE (ie, death) occurred in more than 2 patients in the entire study or in more than 1 patient in any group. The only Grade 4 CTCAE that occurred in more than 1 patient in any group was neutropenia that occurred in 2 (6%) patients in the vandetanib 100 mg group, 0 patients in the vandetanib 300 mg group, and 3 (8%) in the placebo group. See Table 11.3.2.5 for patients with ≥1 AE presented by maximum reported CTCAE grade, Appendix B.

**Table 6** **Most frequently reported CTCAE Grade 3 and Grade 4 events (ie, occurred in more than 2 patients in the entire study, or in more than one patient in any treatment group): number (%) of patients (EFS analysis set)**

| Adverse event | N (%) of patients | | |
|---|---|---|---|
| | Vandetanib 100 mg + FOLFOX (n = 32) | Vandetanib 300 mg + FOLFOX (n = 35) | Placebo + FOLFOX (n = 37) |
| Thrombocytopenia | 5 (16%) | 12 (34%) | 4 (11%) |
| Neutropenia | 9 (28%) | 8 (23%) | 8 (22%) |
| Diarrhoea | 5 (16%) | 8 (23%) | 0 (0%) |
| Hypertension | 5 (16%) | 3 (9%) | 1 (3%) |
| Drug hypersensitivity | 1 (3%) | 3 (9%) | 2 (5%) |
| Electrocardiogram QT prolonged | 0 (0%) | 3 (9%) | 1 (3%) |
| Asthenia | 0 (0%) | 2 (6%) | 0 (0%) |
| Anorexia | 2 (6%) | 1 (3%) | 0 (0%) |
| Leucopenia | 2 (6%) | 1 (3%) | 1 (3%) |
| Peripheral sensory neuropathy | 1 (3%) | 1 (3%) | 1 (3%) |
| Pneumonia | 0 (0%) | 2 (6%) | 0 (0%) |
| Vomiting | 0 (0%) | 0 (0%) | 3 (8%) |

n = Number of patients in the EFS analysis set
Data derived from Table 11.3.2.5, Appendix B.

Those AEs that were reported in more than 10% of patients in either the vandetanib 100 mg, vandetanib 300 mg or placebo group that were considered by the investigator to be possibly related to vandetanib (or placebo) are shown in Table 7. See Table 11.3.2.3 for patients with ≥1 causally related AE, and Table 11.3.2.4 for patients with most frequently reported AEs (>10% of patients), Appendix B.

**Table 7** **Most frequently reported AEs (ie, >10% of patients in any treatment group) that were considered by the investigator to be possibly related to vandetanib (or placebo): number (%) of patients (EFS analysis set)**

| Adverse event | N (%) of patients | | |
|---|---|---|---|
| | Vandetanib 100 mg + FOLFOX (n = 32) | Vandetanib 300 mg + FOLFOX (n = 35) | Placebo + FOLFOX (n = 37) |
| Diarrhoea | 6 (19%) | 14 (40%) | 8 (22%) |
| Hypertension | 11 (34%) | 11 (31%) | 3 (8%) |
| Nausea | 5 (16%) | 7 (20%) | 12 (32%) |
| Thrombocytopenia | 3 (9%) | 7 (20%) | 4 (11%) |
| Photosensitivity reaction | 3 (9%) | 7 (20%) | 1 (3%) |
| Rash | 6 (19%) | 7 (20%) | 1 (3%) |
| Stomatitis | 3 (9%) | 7 (20%) | 7 (19%) |
| Electrocardiogram QT prolonged | 1 (3%) | 6 (17%) | 1 (3%) |
| Anorexia | 4 (13%) | 6 (17%) | 6 (16%) |
| Fatigue | 5 (16%) | 6 (17%) | 8 (22%) |
| Dermatitis acneiform | 1 (3%) | 5 (14%) | 1 (3%) |
| Asthenia | 1 (3%) | 4 (11%) | 4 (11%) |
| Neutropenia | 4 (13%) | 4 (11%) | 2 (5%) |

n = Number of patients in the EFS analysis set
Data derived from Table 11.3.2.3, Appendix B.

In the vandetanib 100 mg, vandetanib 300 mg and placebo groups, respectively, the following SAEs occurred in >1 patient (>3%) in at least 1 of the treatment groups: pneumonia (1 [3%] vs 2 [6%] vs 0 patients), central line infection (2 [6%] vs 0 vs 0 patients). See Tables 11.3.4.1 to 11.3.4.2.2 for SAEs, Appendix B, and electronic narratives for these patients are in Table 11.3.3.3.1, Appendix D.

In the vandetanib 100 mg, vandetanib 300 mg and placebo groups 3 (9%), 5 (14%) and 5 (14%) patients, respectively, had AEs that led to discontinuation, but these were mainly isolated events, with only hypertension resulting in discontinuation of vandetanib in >1 patient in any group (ie, 2 patients in both the vandetanib 100 mg and the vandetanib 300 mg groups). See Tables 11.3.5.1 and 11.3.5.2 for AEs leading to discontinuation, Appendix B, and electronic narratives for these patients are in Table 11.3.5.3, Appendix D.

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One patient in the vandetanib 100 mg group died due to an AE (pneumonia) that was not considered by the investigator to be related to vandetanib (or placebo) or FOLFOX; and one death in the vandetanib 300 mg group was due to an AE (ileus) that was considered disease related by the investigator and not related to vandetanib (or placebo) or FOLFOX; see Appendix D for detailed patient narratives. There were 10 other deaths (1 [3%] patient in the vandetanib 100 mg group, 5 [14%] patients in the vandetanib 300 mg group, and 4 [11%] patients in the placebo group) and these were all related to disease progression and were not recorded as due to an AE. See Tables 11.3.3.1 to 11.3.3.4 for deaths, Appendix B, and electronic narratives for these patients are in Table 11.3.3.3.1, Appendix D.

Hypertension and QTc prolongation are recognised adverse effects of vandetanib. In this study, hypertension was reported in 14 (44%) patients in the vandetanib 100 mg group, 13 (37%) in the vandetanib 300 mg group, and 5 (14%) in the placebo group; whereas QTc prolongation was reported in only 1 (3%) patient in the vandetanib 100 mg group, 6 (17%) patients in the vandetanib 300 mg group, and 1 (3%) patient in the placebo group.

Review of the laboratory data revealed no appreciable difference in haematological profile or hepatic parameters between groups. Small increases in mean creatinine within the normal range were seen in both vandetanib groups, with more patients showing an increase of one CTCAE grade from baseline on vandetanib 300 mg (9 [26%] patients) than on vandetanib 100 mg (4 [13%] patients) or placebo (2 [5%] patients). More patients in the vandetanib 300 mg group (13 [37%] patients) than the vandetanib 100 mg group (7 [22%] patients) or the placebo group (3 [8%] patients) showed a fall from baseline of one or more CTCAE grades for potassium. There appeared to be a trend for a greater fall in mean calcium in the vandetanib 300 mg group with more patients in this group (19 [54%] patients) than the 100 mg group (7 [22%] patients) or the placebo (5 [14%] patients) having a fall of one or more CTC grades. When adjusted for albumin more patients had a fall in adjusted calcium of one or more CTC grades in both vandetanib groups compared with placebo: 14 [47%] patients in the vandetanib 100 mg group, 15 [47%] patients in the 300 mg group, and 7 [21%] patients in the placebo group. Other than these findings, the laboratory data were unremarkable. See Tables 11.3.7.1.1 to 11.3.7.1.22 for laboratory data, Appendix B.

**Discussion**

No efficacy benefit for the vandetanib (either 100 mg or 300 mg) plus FOLFOX combination was seen over FOLFOX plus placebo for the treatment of colorectal cancer in patients who have failed therapy with an irinotecan and fluoropyrimidine containing regimen. Greater percentages of patients with a progression event were observed in both the vandetanib 100 mg group (72%) and 300 mg group (77%) than the placebo group (65%).

A greater number of dose interruptions and dose reductions were seen in the vandetanib 100 mg group (8 [25%] and 5 [16%] patients, respectively) and the vandetanib 300 mg group (15 [43%] and 10 [29%] patients, respectively) than the placebo group (4 [11%] patients with dose interruptions and 4 (11%) patients who were unblinded with view to dose reduction). Similar numbers of patients discontinued treatment with vandetanib 100 mg (25 [78%] patients), vandetanib 300 mg (31 [89%] patients) or placebo (27 [73%] patients).

Adverse events were common (approximately 97%) in all three groups. The most common AE in the vandetanib 300 mg group was diarrhoea; the incidence of this AE (23 [66%] patients) was observed to be worse in this group than in either the vandetanib 100 mg group (16 [50%] patients) or the placebo group (16 [43%] patients). The incidence of Grade 3-4 AEs was numerically higher in the vandetanib 300 mg group (28 [80%] patients) than either the vandetanib 100 mg group (20 [63%] patients) or the placebo group (20 [54%] patients). AEs leading to permanent discontinuation of vandetanib (or placebo) were generally similar for both the vandetanib 100 mg group, the vandetanib 300 mg group and the placebo group (3 [9%], 5 [14%] and 5 [14%] patients, respectively). Out of the 5 (14%) patients in the placebo group who had AEs leading to permanent discontinuation, 4 were unblinded with view to dose reduction, but were discontinued because their dose (placebo) could not be reduced. SAEs were relatively uncommon with a greater number observed in the vandetanib 300 mg group (9 [26%] patients) than either the vandetanib 100 mg group (4 [13%] patients) or the placebo group (4 [11%] patients).

In the vandetanib 100 mg group, vandetanib 300 mg group and placebo group, 75%, 83% and 76% of AEs, respectively, and 3%, 11% and 5% of SAEs, respectively, were considered by the investigator to have a possible causal relationship with vandetanib (or placebo).

No new or unexpected AEs were seen, and the reduced tolerability of the vandetanib FOLFOX combination (most notably seen in terms of Grade 3-4 AEs in the vandetanib 300 mg group) was no worse than would be expected from the known safety profile of these agents.