AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00041 (OS)
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A Phase II, Double-blind, Randomised Study to Compare the Efficacy of AZD2171 in Combination with 5-fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX) and the Efficacy of Bevacizumab in Combination with FOLFOX in the Second-line Treatment of Patients with Metastatic Colorectal Cancer (Overall Survival Analysis)

Study dates: First subject enrolled: 4 January 2006
Last subject enrolled: 12 June 2007

Phase of development: Therapeutic exploratory (II)

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

The results of the overall survival (OS) analysis and safety results up to the date of cut-off for the OS analysis (30 January 2009) are reported in this Clinical Study Report (CSR).

Study centres

42 centres in 10 countries (Austria, Belgium, Czech Republic, France, Germany, Italy, Slovakia, Spain, United Kingdom and Canada).

Publications

Cunningham D, et al on behalf of the HORIZON I study group. A phase II, double-blind, randomized multicenter study of cediranib with FOLFOX versus bevacizumab with FOLFOX in patients with previously treated metastatic colorectal cancer (mCRC): Final PFS results. J Clin Oncol 2008 (2008 ASCO Annual Meeting Proceedings); 26 (15S) (May 20 Supplement): 4028.

Objectives and criteria for evaluation

The purpose of this synopsis is to report the result of the OS analysis and safety data up to the date of cut-off for the OS analysis (30 January 2009). For details of all other objectives and variables of this study, see the primary analysis synopsis (data cut-off November 2007).

The following objectives and variables are reported in the current synopsis:

- Secondary efficacy objective: the efficacy of cediranib in combination with oxaliplatin, leucovorin and 5-fluorouracil (5-FU) (FOLFOX) compared to the efficacy of bevacizumab in combination with FOLFOX (by assessment of the variable OS, defined as the time from randomisation to the date of death from any cause).

- Safety objectives: the safety and tolerability of randomised study therapies in combination with FOLFOX (variables include adverse events [AEs], laboratory findings [clinical chemistry, haematology, urinalysis], blood pressure [BP], electrocardiogram [ECG] and physical examination).

- Exploratory efficacy objective: to obtain archival tumour samples for biomarkers and DNA extraction and retrospective mutation analysis of genes as potential markers of the activity of cediranib, bevacizumab and FOLFOX (variables include progression-free survival [PFS] and OS according to K-Ras mutation status).

Study design

Randomised, double-blind study to compare the efficacy of cediranib (RECENTIN™, AZD2171) in combination with FOLFOX to the efficacy of bevacizumab (Avastin®) in combination with FOLFOX, in the second-line treatment of patients with metastatic colorectal cancer (CRC). All patients received FOLFOX and were randomised in a 1:1:1 ratio to receive cediranib 20 mg daily, cediranib 30 mg daily or bevacizumab every 2 weeks.

Target subject population and sample size

Key inclusion criteria: Male and female patients aged ≥18 years with histologically- or cytologically-confirmed metastatic CRC who had received 1 prior systemic therapy for

metastatic CRC and had documented progression during or following this therapy. World Health Organisation (WHO) performance status of ≤2 and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines.
Key exclusion criteria: Patients must not have received previous treatment with FOLFOX or other oxaliplatin-containing regimens unless given as adjuvant therapy more than 12 months before entry into the study. Patients must not have received a vascular endothelial growth factor (VEGF) inhibitor in the first-line setting.

The sample size (approximately 200 patients) was planned based on the primary analysis of PFS. The analysis of OS was planned for when approximately 150 deaths had occurred.

Investigational product and comparators: dosage, mode of administration and batch numbers

Cediranib 20 mg or 30 mg or matching placebo, bevacizumab or placebo (physiological saline), and the FOLFOX regimen used in the study was administered as reported in the primary analysis synopsis (data cut-off November 2007). Batch numbers of cediranib are provided in the study report.

Statistical methods

As for the primary analysis of PFS, OS was analysed using a log-rank test stratified by WHO performance status (0 or 1/2), baseline albumin (<4 and ≥4 g/dL) and baseline alkaline phosphatase (≤160 and >160 U/L). The effect of treatment was estimated by the adjusted hazard ratio (HR) together with its 95% confidence interval (CI) estimated from a Cox proportional hazards model including the same factors fitted in an identical manner as for the log-rank test.

Subject population

230 patients with metastatic CRC were enrolled, of whom 215 were randomised, 214 received both randomised study treatments, and 210 were included in the ITT Population (71 patients FOLFOX + cediranib 20 mg; 73 patients FOLFOX + cediranib 30 mg; 66 patients FOLFOX + bevacizumab 10 mg/kg).

The treatment groups were balanced for demographic characteristics with the exception of age. With regard to baseline disease characteristics, imbalances were noted for WHO performance status, primary tumour location (type of cancer) and the time from initial diagnosis to randomisation. The OS statistical analysis adjusted for imbalance in performance status. Additional statistical analyses demonstrate that the efficacy conclusions for the endpoint of OS are unaltered by imbalances in age, primary tumour location and time from diagnosis.

Summary of OS efficacy results

As of the data cut-off for the OS analysis (30 January 2009), 148 (70.5%) patients had died (54, 49 and 45 patients in the FOLFOX + cediranib 20 mg, FOLFOX + cediranib 30 mg and

FOLFOX + bevacizumab groups, respectively). Five (2.3%) patients were free from progression and still receiving study treatment.

The difference in OS between the FOLFOX + cediranib 20 mg and FOLFOX + bevacizumab groups was numerically in favour of FOLFOX + bevacizumab, although the difference was not significant (HR=1.39 [95% CI 0.92, 2.09]; p=0.10). OS was similar for the FOLFOX + cediranib 30 mg and FOLFOX + bevacizumab groups (HR=1.00; [95% CI 0.66, 1.50]; p=0.88). Median survival was 14.3 months in the FOLFOX + cediranib 20 mg group, 16.8 months in the FOLFOX + cediranib 30 mg group and 19.6 months in the FOLFOX + bevacizumab group (note that these data, unlike the HRs, do not correct for the more favourable prognosis in the bevacizumab group).

There were no consistent patterns for a difference in effect, in terms of OS or PFS, between FOLFOX + cediranib 20 mg or 30 mg versus FOLFOX + bevacizumab according to whether patients had mutant or wild-type K-Ras genes.

Summary of efficacy results at PFS analysis

The results of the analyses of the following objectives are provided in the primary analysis synopsis (data cut-off date November 2007): primary efficacy variable (PFS), secondary efficacy variables (overall response rate, quality of life and disease-related symptoms), and the exploratory variable of analysis of tumour size.

Summary of safety results

Safety results up to the data cut-off for the OS analysis (30 January 2009) are included in the synopsis.

All patients included in the safety population experienced at least 1 AE during the course of the study. There were no major differences between the 3 treatment groups for the most commonly reported AEs (diarrhoea, fatigue, nausea and hypertension). Overall, more patients reported serious adverse events (SAEs) in the cediranib 30 mg group compared to the other 2 treatment groups, with 30 (42.9%), 39 (53.4%) and 29 (43.9%) patients in the cediranib 20 mg, 30 mg and bevacizumab groups, respectively.

The most frequently reported AEs leading to discontinuation of cediranib/cediranib placebo (>3%) were: fatigue (4.3%), thrombocytopenia (4.3%), and abdominal pain (4.3%) in the 20 mg cediranib group; fatigue (9.6%), hypertension (5.5%), and proteinuria (5.5%), in the 30 mg cediranib group; and pulmonary embolism (4.5%) in the bevacizumab group. For fatigue and hypertension a slightly higher number of patients discontinued in the cediranib 30 mg group compared to the other 2 groups. Thrombocytopenia, abdominal pain, anorexia and pyrexia leading to discontinuation were seen in both cediranib groups but not in the bevacizumab group.

There were no further patients with AEs with an outcome of death reported since the primary analysis synopsis (data cut-off date November 2007).

Overall, the haematology, clinical chemistry, BP and ECG findings were consistent with the known toxicity profiles of both drugs and for FOLFOX6-related abnormalities, together with the advanced disease under investigation and pre-existing medical conditions.