A Phase III, Randomised, Parallel Group, Multi-Centre Study in Recurrent Glioblastoma Patients to Compare the Efficacy of Cediranib (AZD2171) Monotherapy and the Combination of Cediranib with Lomustine to the Efficacy of Lomustine Alone

Study dates: First patient enrolled: 8 October 2008
Last patient enrolled: 2 September 2009

Phase of development: Therapeutic confirmatory (III)

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

Study centres

71 centres across 10 countries (Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Netherlands, UK, and US) participated in this study.

Publications

Batchelor T et al. Ann Oncol 21 (suppl 8), page viii4. October 2010. Abstract LBA7.

Objectives

Table S1   Primary and secondary objectives and their associated variables

Objectives	Variables
Primary	
To determine the relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of PFS as assessed by independent radiographic review.	Progression-free survival (PFS)
Secondary	
To determine the relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of OS.	Overall survival (OS)
To determine the relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of radiographic response rate (RR).	RR [Note: for a patient to have a Visit response of PR, they were to have had no increase in their steroid dose for the previous 10 days].
To determine the relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of APF6 defined as 24 weeks after randomisation.	Proportion of patients alive and progression-free at 6 months (24 weeks after randomisation)
To determine the steroid sparing effects of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of average daily steroid dosage change from baseline until progression and average number of progression-/steroid-free days.	% change in average daily steroid dose from baseline, for patients on steroids at baseline; and number of days that a patient was known not to have used steroids prior to progression regardless of baseline steroid use.
To determine the time to deterioration of the neurological status of patients receiving cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone.	Neurological status: 'stable', 'improving' and 'worsening'.
To determine in patients with neurological symptoms at baseline, an improvement in neurological symptoms (visual disorder, motor dysfunction, communication deficit, and drowsiness) concurrent with stable or decreasing steroid use for patients receiving cediranib monotherapy or in combination with oral lomustine compared to patients receiving oral lomustine alone as measured by the EORTC brain cancer module BN-20 by patient-reported outcome.	Raw domain scores for visual disorder, motor dysfunction, communication deficits, and drowsiness. (EORTC: European Organisation for Research and Treatment of Cancer QoL questionnaire)
To determine the safety and tolerability of cediranib (either in monotherapy or in combination with oral lomustine).	AEs, clinical chemistry, haematology, urinalysis, vital signs, ECG.

Study design

Randomised, controlled, parallel-group study in patients with recurrent glioblastoma, randomised 2:2:1 to cediranib 30 mg monotherapy; cediranib 20 mg + lomustine; or placebo

to cediranib 20 mg + lomustine. Study treatment was double-blinded in the 2 lomustine-containing arms, but the cediranib monotherapy arm was open-label, as placebo to lomustine was not available.

PFS, RR, and APF6 were derived from contrast-enhanced MRI scans of the brain. Primary assessment based on T1-weighted MRI from central (independent) radiographic review. Supportive assessments based on T1-weighted MRI from investigator (site) review, and T1 and T2/FLAIR MRI from central review.

Target patient population and sample size

Males and females aged ≥18 years, with first recurrence of glioblastoma following standard frontline treatment for glioblastoma, including surgery, cranial radiotherapy, and chemotherapy with temozolomide. Patients were not to have received previous treatment with a VEGF signalling inhibitor. Approximately 300 patients in total were planned to be randomised to the 3 arms.

Investigational product and comparators: dosage, and mode of administration

Cediranib or matching placebo tablets were taken orally, once-daily, not less than 1 h prior to a meal or >2 h after a meal. Cediranib 30 mg taken as 1 x 30 mg tablet, cediranib 20 mg or placebo taken as 1 x 20 mg cediranib tablet, or matched placebo (batch numbers are provided in the main study report). Lomustine capsules were administered orally every 6 weeks, with a start dose of 110 mg/m^2. The lomustine dose was capped at a total maximum of 240 mg.

Duration of treatment

Study treatment was to continue until a discontinuation criterion was met, and patients were to be assessed and followed for progression and survival regardless of whether they had discontinued all or part of their randomised treatment, or had started other anticancer therapy.

Statistical methods

2 comparisons of interest: cediranib monotherapy vs placebo + lomustine, and cediranib + lomustine vs placebo + lomustine. To maintain an overall Type 1 error rate of 5% for each endpoint, a Dunnett and Tamhane step-up procedure was used; this allows for the correlation of 0.67 between the standard normal deviate for each comparison. Statistical significance was to be declared if both comparisons were significant at the 2-sided 5% level, or if either comparison was statistically significant at the 2-sided 2.77% level.

Primary analysis of PFS was based on central radiographic review of T1 MRI data; the statistical analysis was to be performed after 230 progression events had occurred. PFS was analysed using a log-rank test stratified by surgical resection (yes/no prior to enrolment) and age (≤65 vs >65 years). Supportive analyses were based on PFS data from investigator review only; based on PFS data from central review on T1 and T2/FLAIR MRI data; and using a grouped survival approach. A sensitivity analysis using the earlier of the site and central assessments of progression was undertaken, as well as subgroup analyses for surgical

resection, age, baseline KPS, baseline VEGF, baseline LDH, sex, duration of prior temozolomide treatment, and time from completion of radiotherapy to randomisation.

OS was planned to be analysed twice: firstly at the same time as the PFS analysis and finally when 270 deaths had occurred, using a log-rank test stratified by surgical resection (yes/no prior to enrolment) and age (age ≤65 vs >65 years). In order to maintain an overall Type I error rate of 5%, the significance level was pre-specified at 0.00785 at interim for both comparisons, and at 0.00417 at interim for either comparison. Therefore, treatment comparisons on OS would be declared statistically significant if either p<0.00417 for either comparison, or p<0.00785 for both comparisons (p-values were 2-sided).

As many of the secondary variables relate to distinct families that address different questions or aspects of the patient experience, Type-1 error was controlled within each of these families, but not between them, by testing variables using a closed hierarchical testing procedure.

Patient population

423 patients enrolled, 325 randomised, and 315 of those randomised received ≥1 dose of study treatment. Median age was 54 years (range: 18 to 84 years), 211 (64.9%) were male; 313 (96.3%) were White. Patients were representative of the intended population. The treatment arms were generally well balanced with respect to demographic and baseline characteristics, though in the placebo + lomustine arm there was a lower proportion of patients with KPS ≤80 and a lower proportion on steroids at baseline.

Summary of efficacy results

251 progression events were included in the primary analysis (data cut-off: 25 April 2010). There was no statistically significant difference in PFS between arms for either comparison. For cediranib 30 mg vs placebo + lomustine, HR=1.05, 95% CI (0.74, 1.50), p=0.8992. For cediranib + lomustine vs placebo + lomustine, HR=0.76, 95% CI (0.53, 1.08), p=0.1624. Median PFS was numerically longest on the cediranib 20 mg + lomustine arm (125 days), compared with 92 days on cediranib 30 mg, and 82 days on lomustine + placebo. Conclusions for the supportive and sensitivity analyses of PFS were consistent with the primary analysis.

Survival data at the time of data cut-off were at a high level of maturity (197 death events); the current OS analysis was conducted at approximately 73% of the events pre-specified for the final analysis. For both OS comparisons, the HR was numerically in favour of placebo + lomustine, but the differences were not statistically significant. Cediranib 30 mg vs lomustine HR=1.43, 95% CI (0.96, 2.13), p=0.1002. Cediranib + lomustine vs placebo + lomustine HR=1.15, 95% CI (0.77, 1.72), p=0.4985. Median OS was numerically shorter on cediranib 30 mg (8.0 months) compared with cediranib + lomustine (9.4 months) and placebo + lomustine (9.8 months).

No subgroup had a better or worse outcome for PFS and OS.

An exploratory analysis adjusting for the imbalance noted above on KPS and steroid usage did not change the conclusions for the PFS or OS outcomes.

RR was 15.3% on cediranib 30 mg, 17.2% on cediranib + lomustine, and 8.9% on placebo + lomustine. The treatment differences were not statistically significant. Change in contrast-enhancing area from baseline to first scan and best change from baseline were numerically greater for both cediranib arms than for placebo + lomustine, and most marked on cediranib monotherapy (median best change from baseline was -35.70%). Percentage of patients with a decrease in contrast-enhancing area was 79.8% on cediranib 30 mg, 73.8% on cediranib + lomustine, and 34.6% on placebo + lomustine.

APF6 was numerically higher for the cediranib + lomustine arm (34.5%) compared with the other 2 arms, but there was no statistically significant difference for either comparison.

There was a reduction in steroid use from baseline in both the cediranib monotherapy and combination therapy arms, and an increase from baseline on the placebo + lomustine arm. Change from baseline in mean steroid dose achieved a nominal significant p-value in both comparisons. On average, patients who were on steroids at baseline tended to remain on steroids during study treatment, while patients who were not on steroids at baseline tended not to start taking steroids during the study. Analysis of the number of steroid-free days to progression adjusted for baseline steroid use showed no significant differences between arms: cediranib 30 mg vs placebo + lomustine, p=0.713; cediranib 20 mg + lomustine vs placebo + lomustine, p=0.217.

For time to deterioration in neurological symptoms, based on a nominal p-value there was a significant difference in favour of cediranib 20 mg + lomustine compared with placebo + lomustine (HR=0.63; 95% CI 0.42, 0.95; p=0.0091); however, there was no significant difference between cediranib 30 mg and placebo + lomustine.

There were no statistically significant differences between treatments for improvement in communication deficit, visual disorder, motor dysfunction, or drowsiness subscales.

Summary of safety results

Dose intensity of cediranib was generally well maintained; and over the first 3 months, mean dose intensity was >81% on both cediranib arms. Patients in the cediranib-containing arms were predominantly treated to progression with cediranib. Mean daily dose of cediranib/ placebo was 27.6 mg on the 30 mg arm, 18.5 mg on the cediranib 20 mg + lomustine arm, and 19.8 mg on the placebo + lomustine arm.

In general, duration of lomustine treatment was longer on the combination arm, reflecting the tail of the Kaplan-Meier curve. Notably, 13 (20.3%) patients received prolonged lomustine treatment (ie, ≥4 cycles) in the placebo + lomustine arm; however, the numbers were small. Of the patients who had >1 dose of lomustine, the incidence of lomustine dose reductions was higher on cediranib + lomustine (70%) than on placebo + lomustine (50%).

Table S2   Overview of adverse events (Safety set)

Category of adverse event	Number (%) of patients [a]		
	Cediranib 30 mg (N=128)	Cediranib 20 mg + lomustine (N=123)	Placebo + lomustine (N=64)
Any adverse event	127 (99.2)	121 (98.4)	63 (98.4)
Any adverse event of CTCAE grade 3 or higher	78 (60.9)	98 (79.7)	39 (60.9)
Any SAE (including events where outcome of death)	55 (43.0)	45 (36.6)	26 (40.6)
Any adverse event with outcome of death	1 (0.8)	2 (1.6)	1 (1.6)
Any SAE (with outcome other than death) [b]	55 (43.0)	44 (35.8)	26 (40.6)
Any AE leading to discontinuation of cediranib/placebo	19 (14.8)	22 (17.9)	10 (15.6)
Any AE leading to discontinuation of lomustine	1 (0.8) [c]	24 (19.5)	11 (17.2)

a   Patients with multiple AEs in the same category counted once in that category. Patients with events in >1 category are
      counted once in each of those categories.
b   All patients who had an SAE with non-fatal outcome (regardless of whether they later had a fatal SAE).
c   Patient randomised to cediranib 30 mg monotherapy, but received 3 doses of lomustine in error.

Most common AEs on cediranib 30 mg: diarrhoea, fatigue, and hypertension (71.1%, 51.6%, and 51.6% of patients, respectively); on cediranib 20 mg + lomustine: diarrhoea, fatigue, and thrombocytopenia (70.7%, 59.3%, and 58.5% of patients, respectively); on placebo + lomustine: fatigue, thrombocytopenia, and headache (46.9%, 46.9%, and 37.5% of patients, respectively).

Incidences of AEs related to haematological toxicity (eg, neutropenia, leukopenia, thrombocytopenia) were notably higher on both lomustine-containing arms than on cediranib monotherapy; the highest incidence was on cediranib + lomustine. AEs in the SOC 'Infections and infestations' were reported with higher frequency on the cediranib arms than on placebo + lomustine: 40.6% on cediranib monotherapy; 39.0% on cediranib + lomustine, and 26.6% on placebo + lomustine. Within this SOC, a range of preferred terms was reported; the majority were grade 1 or 2.

AEs ≥grade 3 associated with haematological toxicities (eg, thrombocytopenia, neutropenia, leukopenia, platelet count decreased, white blood cell count decreased) were reported with highest frequency in the cediranib 20 mg + lomustine arm. AEs of hypertension ≥grade 3 were reported on the 2 cediranib arms, but not on placebo + lomustine. Diarrhoea ≥grade 3 was more frequently reported on the cediranib arms than on placebo + lomustine.

Incidence of death was higher on cediranib 30 mg (85 patients [66.4%]), than on cediranib + lomustine (73 patients [59.3%]), and placebo + lomustine (33 patients [51.6%]). Most of the deaths were reported as a result of disease progression/worsening.

Most common SAEs were: convulsion (8.6%), pulmonary embolism (3.1%), and pneumonia (3.1%) on cediranib 30 mg; thrombocytopenia (6.5%), pulmonary embolism (4.9%), and

neutropenia (4.1%) on cediranib 20 mg + lomustine; pulmonary embolism (4.7%) and thrombocytopenia (3.1%) on placebo + lomustine.

The AE profile for cediranib 30 mg was generally consistent with previous cediranib monotherapy studies, except for convulsion. The incidence and severity of the haematological AEs associated with lomustine appeared to be exacerbated by combination with cediranib, but the haematological effects were manageable, and were not associated with clinical consequences such as febrile neutropenia. The haematology, clinical chemistry, urinalysis, and vital signs results were consistent with the known toxicity profiles of cediranib and lomustine. There were no safety concerns that warranted discontinuation of cediranib in patients who were still ongoing in this study at the time the data had been interpreted.