The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article: “Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma”
Tracy T Batchelor, et al.

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A Phase III, Randomized, Parallel Group, Multi-Centre Study in Recurrent Glioblastoma Patients to Compare the Efficacy of Cediranib [RECENTIN™, AZD2171] Monotherapy and the Combination of Cediranib with Lomustine to the Efficacy of Lomustine Alone

CONTENTS

Source material

Taken from Clinical Study Protocol (study code D8480C00055), dated 27 September 2010.

1. SELECTION OF STUDY POPULATION

1.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but were never enrolled eg, patient screening log. This information is necessary to establish that the patient population was selected without bias.

1.2 Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:

1. Provision of written informed consent
2. Aged 18 years or over
3. Life expectancy ≥12 weeks
4. Histological or cytological confirmation of glioblastoma
5. Patients with measurable disease (contrast-enhancing tumour ≥10 mm by shortest diameter on 2 axial slices) by MRI imaging within 4 weeks prior to enrolment (Visit 1). Or patients who have undergone a resection without measurable disease prior to enrolment.
6. Patients must have been on no steroids or a stable dose of steroids for at least 5 days before the baseline MRI (Visit 2)
7. Patients must have failed standard frontline treatment for glioblastoma including surgery (with exception, if patient does not receive surgery as part of frontline treatment due to anatomical location, based on neurosurgeon's assessment), cranial radiotherapy and chemotherapy with temozolomide. The last dose of temozolomide must be more than 28 days from randomization**.** Gliadel® wafers are permitted, as it is part of local treatment.
8. Patients must have a Karnofsky Performance Score of 70 or above
9. Patients must have a mini-mental status examination score of 15 or greater
10. Patients who require either oral anticoagulants (coumadin, warfarin) or low molecular weight heparin are eligible provided there is increased vigilance with respect to monitoring INR.

1.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Patients on enzyme-inducing anti-epileptic drugs within 2 weeks prior to randomization

- Note: Patients are eligible if they switched to non-enzyme inducing agents and discontinued enzyme-inducing agents for more than or equal to 2 weeks prior to randomization

2. Inadequate bone marrow reserve as demonstrated by an absolute neutrophil count ≤1.5 x 10^9 /L or platelet count ≤100 x 10^9 /L or requiring regular blood transfusions to maintain haemoglobin >9g/dL
3. Serum bilirubin ≥ 1.5 x ULRR (except for patients with known documented cases of Gilbert's Syndrome)
4. ALT or AST ≥2.5 x ULRR
5. Serum creatinine >1.5 x ULRR or a creatinine clearance of ≤50mL/min calculated by Cockcroft-Gault
6. Greater than +1 proteinuria on two consecutive dipsticks taken no less than 1 week apart unless urinary protein < 1.5g in a 24 hr period or UPC ratio <1.5
7. History of significant gastrointestinal impairment, as judged by the Investigator, that would significantly affect the absorption of cediranib, including the ability to swallow the tablet whole
8. Patient with a history of poorly controlled hypertension with resting blood pressure >150/100mmHg in the presence or absence of a stable regimen of anti-hypertensive therapy, or patients who are requiring maximal doses of calcium channel blockers to stabilise blood pressure
9. Any evidence of severe or uncontrolled diseases (eg, unstable or uncompensated respiratory, cardiac, hepatic or renal disease)
10. Unresolved toxicity >CTCAE grade 1 from previous anti-cancer therapy (including radiotherapy) except alopecia (if applicable)
11. Mean QT_c with Bazetts correction >470msec in screening ECG or history of familial, long QT syndrome
12. Significant haemorrhage (>30mL bleeding/episode in previous 3 months) or haemoptysis (>5mL fresh blood in previous 4 weeks)
13. Recent (<14 days) major thoracic or abdominal surgery or brain biopsy. Recent craniotomy (<28 days) prior to first dose, or a surgical incision that is not fully healed
14. Pregnant or breast-feeding women or women of childbearing potential with a positive pregnancy test prior to receiving study medication
15. Known hypersensitivity to cediranib or any of its excipients

16. History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ) within 5 years, unless the patient has been disease free for 2 years and they have tissue diagnosis of the target lesion
17. Known infection with hepatitis B or C or HIV
18. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)
19. Previous enrolment or randomization of treatment in the present study
20. Treatment with an investigational drug within 30 days prior to the first dose of cediranib
21. Other concomitant anti-cancer therapy except steroids
22. Previous anti-angiogenesis (eg bevacizumab, sorafenib, sunitinib) therapy
23. Patients with evidence of any intratumoral or peritumoral haemorrhage deemed significant by the treating physician
24. Patients who have received any form of cranial radiation within 3 months prior to study entry
25. Known hypersensitivity to lomustine or any of its excipients
26. Patients with a baseline below 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLCO). However, patients with values less than these for either FVC or DLCO may still be eligible for enrolment provided that lung pathology has been excluded after a full consultation by a pulmonologist including additional tests, for example: a high resolution CT scan
27. Patients who have progressed within 3 months of completion of standard cranial radiation
28. Patients that have received radiosurgery or brachytherapy
29. Patients with Celiac Disease

2. SCHEMA AND TREATMENT PLAN

2.1 Overall study design

This is a phase III, randomized, parallel group, multi-centre study in recurrent glioblastoma.

Approximately 300 patients with first recurrence of glioblastoma who have failed standard frontline treatment for glioblastoma including surgery, cranial radiotherapy and chemotherapy with temozolomide will be included in the trial. Patients must not have received previous anti-Vascular Endothelial Growth Factor (VEGF) therapy. One hundred and twenty patients will be randomized to receive 30 mg of cediranib in an open-label monotherapy arm, 120 patients will be randomized to receive 20 mg of cediranib in combination with lomustine in a double-blind combination arm, and 60 patients will be randomized to receive lomustine in combination with cediranib matched placebo in a double-blind combination arm.

It is vital that patients are assessed at the scheduled visits and that patients should be followed for progression and survival regardless of whether they discontinue all or part of their randomized therapy or start to receive other anti-cancer therapy.

2.2 Patient population and recruitment

This study will be conducted in approximately 300 patients recruited in the USA, Australia and Europe from approximately 70 centres.

Patients will be randomized to either cediranib 30 mg alone or cediranib 20 mg in combination with oral lomustine or oral lomustine with cediranib matched placebo in a 2:2:1 manner. Randomization, double-blind (for the two lomustine containing arms) and placebo together with an independent radiographic, central review are used to reduce assignment/assessment biases and placebo effect biases. Therefore, this design will provide unbiased assessment of efficacy in this patient population.

2.3 Study treatment

Cediranib

Patients randomized to the monotherapy arm will take 1 x 30 mg tablet orally, once daily. Patients randomized to the lomustine containing arms will take 1 x 20 mg cediranib, or matched cediranib placebo, tablet orally, once daily in combination with lomustine.

Cediranib, or matching cediranib placebo, should be taken no less than 1 hour prior to the consumption of a meal or more than 2 hours after a meal has been ingested. Patients will be instructed to take cediranib, or matching cediranib placebo, at approximately the same time each day (preferably in the morning).

If a patient forgets to take a tablet, and it is within 6 hours of the scheduled time, then the patient should be advised to take the tablet as soon as possible. If it is more than 6 hours after the scheduled time, then study medication should not be taken for that day. Study medication should continue as previously scheduled on the subsequent day. A patient should not take more than a single day's dose of tablets within a day.

In the event that the patient cannot hold the tablet(s) down (if the patient vomits) within 30 minutes from taking the tablet(s) or if can identify the tablet(s) in the vomit content, the patient can re-take a new tablet(s) from the bottle.

Lomustine

Lomustine will be administered orally every 6 weeks at a dose of 110 mg/m^2. Patients should be instructed to wear gloves when handling lomustine. Doses of lomustine should be rounded down to the nearest 10 mg.

Patient management procedures following final planned analyses of the study

The following sections describe the treatment provisions, following un-blinding.

Patients randomized to placebo

Patients who are receiving placebo, in the absence of lomustine, will be discontinued from the study by the next scheduled visit.

Patients randomized to cediranib

Where the investigator believes patients are gaining clinical benefit, patients may continue to receive cediranib treatment until a criterion for discontinuation has been met.

Patients who have not progressed and remain on lomustine

For those patients where lomustine is being supplied by AstraZeneca, this can continue to be supplied for an individual patient on request from the investigator, until the investigator deems that the patient has progressed. This applies for patients on lomustine alone, or in combination with cediranib. Lomustine will not be supplied by AstraZeneca following progression.

2.4 Treatment regimens

Patients will be randomized to either the cediranib monotherapy arm or one of the lomustine containing arms.

Patients randomized to the cediranib monotherapy arm will receive cediranib 30 mg orally daily.

Patients randomized to the lomustine and placebo arm will receive lomustine and placebo to match cediranib according to the following schedule:

- Baseline, and every 6 weeks thereafter: Lomustine 110 mg/m^2 orally
- Daily: Placebo to match cediranib 20 mg orally

Patients randomized to the lomustine and cediranib arm will receive lomustine and cediranib according to the following schedule:

- Baseline, and every 6 weeks thereafter: Lomustine 110 mg/m^2 orally
- Daily: Cediranib 20 mg orally

Lomustine is given at 110 mg/m^2 orally as starting dose, but should be capped at a maximum total dose of 240 mg.

2.5 Study visits

Study flow chart

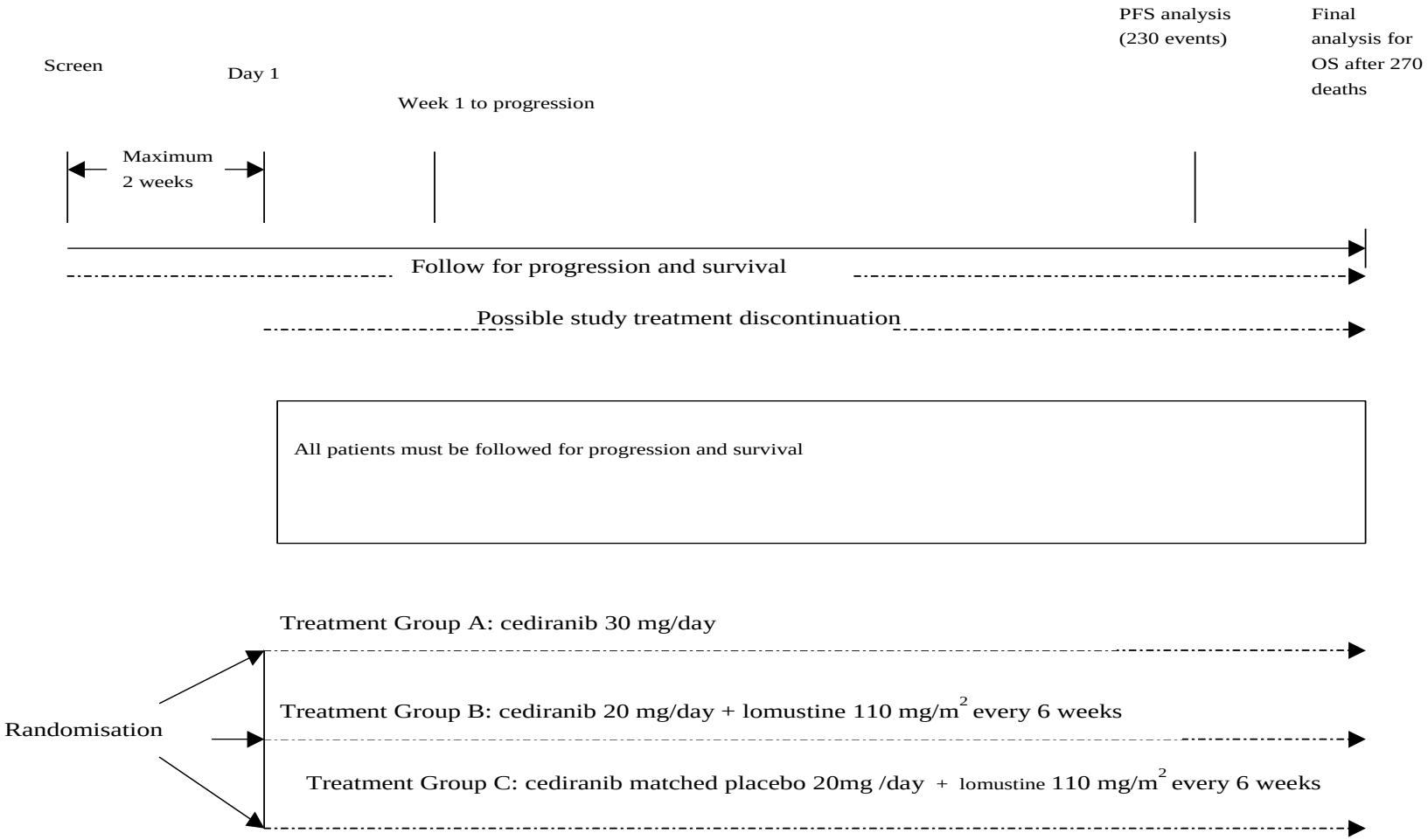

Table 1. Study plan

Table 1 **Study Plan**

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Onward**	**D**
Visit Description	Screening[n] (enrolment)	Start Treatment (baseline)	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment[o]	Discontinuation
Visit Window (No. Weeks ± No. Days)	-2 weeks	Day 1	1 week from baseline (± 3days)	2 weeks from baseline (± 3days)	3 weeks from baseline (± 3 days)	4 weeks from baseline (± 3days)	5 weeks from baseline (± 3days)	6 weeks from baseline (± 3 days)	Every 3 weeks from previous visit until discontinuation (± 3 days)	Every 6 weeks from previous visit until discontinuation (± 3 days)	Any time a patient discontinues study treatment due to progression or toxicity
Informed consents	X										
Demographic details	X										
Medical history/ Surgical history (including histological sub type of tumour)	X										
Inclusion/ Exclusion criteria	X										
Physical examination	X	X			X			X		X	X
Neurological examination	X	X			X			X		X	X
Pulmonary Function Test[a]	X										X
Vital signs/BP/weight[b]	X	X	X	X	X	X	X	X	X	X	X
ECG[c]	X	X			X						X
Clinical chemistry/ Haematology[c]	X	X			X			X		X	X
CBC[d]	X	X	X	X	X	X	X	X	X	X	X
Randomization		X									

Table 1 **Study Plan**

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Onward**	**D**
Visit Description	Screening[n] (enrolment)	Start Treatment (baseline)	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment[o]	Discontinuation
Visit Window (No. Weeks ± No. Days)	-2 weeks	Day 1	1 week from baseline (± 3days)	2 weeks from baseline (± 3days)	3 weeks from baseline (± 3 days)	4 weeks from baseline (± 3days)	5 weeks from baseline (± 3days)	6 weeks from baseline (± 3 days)	Every 3 weeks from previous visit until discontinuation (± 3 days)	Every 6 weeks from previous visit until discontinuation (± 3 days)	Any time a patient discontinues study treatment due to progression or toxicity
TSH, T3 and T4[c, e]	X	X			X			X		X	X
Urinalysis[f]	X	X			X			X		X	X
Creatinine Clearance (cockcroft-gault equation)	X	X			X			X		X	X
EORTC QLQ-C30 plus BN-20[g]		X			X			X		X	X
EQ-5D[g]		X			X			X		X	X
Pregnancy tests (females)[h]	X										
MRI[m]	X [m]	X						X		X	X
Karnofsky Performance Status	X	X			X			X		X	X
Dispense lomustine		X						X		X	
Dispense cediranib		X			X			X		X	
Adverse Events[i]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X			X			X		X	X
Overall Survival[j]											X
Biomarker sample[k]		X						X		X	X

Table 1 **Study Plan**

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 Onward**	**D**
Visit Description	Screening[n] (enrolment)	Start Treatment (baseline)	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment[o]	Discontinuation
Visit Window (No. Weeks ± No. Days)	-2 weeks	Day 1	1 week from baseline (± 3days)	2 weeks from baseline (± 3days)	3 weeks from baseline (± 3 days)	4 weeks from baseline (± 3days)	5 weeks from baseline (± 3days)	6 weeks from baseline (± 3 days)	Every 3 weeks from previous visit until discontinuation (± 3 days)	Every 6 weeks from previous visit until discontinuation (± 3 days)	Any time a patient discontinues study treatment due to progression or toxicity
Optional Tumour sample for biomarker and pharmacogenetic analysis		X									
Pharmacogenetic blood sample (if separate consent given) [l]		X									

Assessments are to be performed prior to dosing, unless otherwise stated.

[a] Pulmonary function test will be performed as scheduled or when clinically indicated. However, if patients are on cediranib monotherapy arm, no pulmonary function test is required at discontinuation, as there is no evidence that cediranib has any effect on lung function, based on experience across the cediranib clinical trial program.

[b] Patient's BP needs to be monitored weekly for the first 6 weeks of treatment of cedrianib. If a patient has BP ≥150/100 mmHg at Screening, a further reading should be taken at least 24 hours later to assess eligibility. In event of hypertension, refer to hypertension management plan for BP monitoring frequency. BP should be taken by a health care professional.

[c] Lab, TSH and ECG measurements should be retested at visit 2 **only** if the screening period is greater than 7 days. Labs and ECGs must be evaluated within 7 days prior to randomization to confirm eligibility.

[d] CBC will be performed weekly for 6 weeks after the first dose of lomustine, then every 3 weeks after each subsequent dose. Patients enrolled in the monotherapy arm do not need weekly CBC.

[e] Monitoring of thyroid function should be carried out at the specified time points and when clinically indicated.

[f] Urinalysis- if a patient has two consecutive one plus (+) urine protenuria dipsticks measurements at baseline, please measure urine protein/creatinine ratio (UPC) or collect 24 hours urine for total protein. If the patient has a change of two plus (++) or greater from baseline on two consecutive proteinuria dipsticks, please measure urine protein/creatinine ratio or collect 24 hours urine for total protein. If 24 hours protein or UPC Ratio is classified as CTCAE grade 3 please refer to guidance in Management of proteinuria.

[g] EORTC QLQ-C30, BN-20 and EQ-5D questionnaires should be completed before the patient received any treatment and before given the results of their tumour assessments.

[h] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test in the 7 days prior to Day 1 of treatment, In the event of suspected pregnancy during the study, the test should be repeated.

[i] Adverse events will be collected from the time informed consent is given, throughout the treatment period and up to and including the 30 days after last dose of study medication. Any ongoing study-related toxicity or SAE at discontinuation must be monitored until resolution, unless in the Investigator's opinion the condition is unlikely to resolve due to the patient's underlying disease. After discontinuation from treatment, patients must be followed up for all existing and new AEs for 30 calendar days after the last dose of study drug (if SAEs, they must be reported to AstraZeneca within 24 hours) and followed until resolution where possible.

[j] If a patient discontinues due to toxicity, the patient will be followed-up every 6 weeks for progression and 12 weeks for survival. Patients that have discontinued due to progression will be followed every 12 weeks for survival, no scans will be performed.

[k] Biomarker blood samples should be drawn prior to administration of study medications at baseline, week 6, week 12, week 18, week 24 and at discontinuation.

[l] Sample must only be taken after provision of separate consent for genetics sample and ideally prior to administration of investigational product. If not possible to take sample before Day 1 it may be taken at any visit.

[m] Screening contrast enhanced MRI is not required if results available from contrast enhanced MRI performed within 4 weeks prior to screening visit. Baseline contrast enhanced MRI must be completed within 7 days prior to date of randomization according to acquisition guidelines (exception: if screening MRI is performed within 7 days of randomization and according to the acquisition guidelines, then the baseline MRI is not required). Follow-up scans should be performed at scheduled time points ± 10 days according to the acquisition guidelines. Patients must be on a stable dose of steroids for at least 5 days prior to baseline scan and at least 10 days prior to all follow-up scans.

[n] Screening for all patients begins once the first screening procedure is completed. If none of the screening procedures can be performed on the same day that the Informed Consent Form (ICF) is signed by the patient or legal representative, the 14-day timeframe for screening starts at the time of first screening procedure is performed. All screening procedures must be completed within two weeks prior to randomization. For patients switching from enzyme inducing anti-epileptic drugs to non-enzyme inducing anti-epileptic drugs, only; their two week screening period could be extended to a maximum of 3-weeks. However, all screening procedures for such patients must be completed within two weeks prior to randomization.

[O] Cycle start is defined by the start of lomustine dose. Therefore if lomustine dose is delayed all assessments should be performed according to the lomustine dosing cycle, with the exception of MRI assessments which must remain on the original scheduled time points ± 10 days according to the acquisition guidelines.

3. DOSE MODIFICATION

3.1 Management of toxicity

With the exception of hypertension and diarrhoea, the following management plan should be followed for management of toxicities and dose de-escalation:

1. All dose changes should be documented with clear reasoning and documentation of the approach taken.

2. Treat each of the toxicities with maximum supportive care (including holding the experimental therapy where required).

3. If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of study medications along with appropriate continuing supportive care providing continued treatment with study therapy is considered medically appropriate and, in the opinion of the investigator, the patient is considered to be receiving benefit. If medically appropriate, dose reductions are permitted for study medications (Table 2).

Management of lomustine toxicity

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose. Doses subsequent to the initial dose should be adjusted according to the haematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

Table 2. Lomustine dose modifications for haematological toxicity

Nadir After Prior Dose		**Percentage of Prior Dose to be Given**
Leukocytes	**Platelets**	
> 4000	> 100,000	100%
3000–3999	75,000–99,999	100%
2000–2999	25,000–74,999	70%
< 2000	< 25,000	50%

A repeat course of lomustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm^3; leukocytes above 4000/ mm^3 or absolute neutrophil count 1500/mm^3). This usually occurs within 6 weeks. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the haematologic toxicity is delayed and cumulative. Growth factor support is permitted.

Lomustine may be dose reduced a maximum of 2 times.

For gastrointestinal toxicities
Administration of antiemetics is recommended to treat and prevent nausea and vomiting according to standard of care. Additionally, the dose of lomustine may be split over 3 days if necessary.

For pulmonary toxicities
Patients will be assessed with pulmonary function tests at screening, discontinuation and as clinically indicated during the course of therapy.

Management of toxicity attributable to cediranib
Dose interruptions should be used as the first approach to managing toxicity and dose reduction may be considered.

The events for which de-escalation of the cediranib dose is recommended include, with the EXCEPTION of hypertension:

- CTCAE grade 3 or higher toxicities of duration >3 days that are considered to be related to study treatment that are not responding to maximal supportive care within 48 hours, at the discretion of the investigator.

With the exception of hypertension, diarrhoea, proteuinuria, hypothyroidism and RPLS the following management plan should be followed for management of toxicity attributable to cediranib:
Dose interruptions should be used as the first approach to managing toxicity. For CTC Grade 3 or more, dosing with cediranib should be interrupted**.** Cediranib dosing

may be withheld for up to 14 days for management of toxicity. If a longer interruption is required due to unresolved toxicity, cediranib should be discontinued.

- If the symptoms promptly resolve to grade 1 or below with supportive care, consideration should be given to continuing the same dose of cediranib along with appropriate continuing supportive care
- If the symptoms of the toxicity are considered related to cediranib and do not resolve to grade 1 or below with maximum supportive care and following a dose interruption of up to 14 days, the next dose level of cediranib below that being dosed should be instituted
- If symptoms do not resolve, and it is considered medically appropriate, investigators may choose to permanently discontinue cediranib

For patients who have multiple low grade adverse events (for example, diarrhoea, weight loss, dehydration and fatigue) short dose interruptions (ie, 2–5 days) of the blinded cediranib tablets may help. Treatment can be restarted on resolution at the same dose.

Two dose reductions for the cediranib monotherapy arm and one dose reduction for the combination arms will be permitted during the study. No re-escalation of dose is permitted.

Details of the dose steps and corresponding tablet combinations that will ensure the blind is maintained in the event of dose reduction are presented in Table 3.

Table 3 Cediranib /placebo dose reduction information for treatment groups

Dose step	**Treatment group**	
	Cediranib monotherapy	**Cediranib /Placebo+lomustine**
Starting dose	30 mg	20 mg
First reduction	20 mg	15 mg
Second reduction	15 mg	

A maximum of a 14-day delay in dosing for cediranib is permitted. If a longer interruption is required due to unresolved toxicity, cediranib should be discontinued. In addition, there are certain circumstances in which study medication should be permanently discontinued.

4. MEASUREMENT OF TREATMENT EFFECT AND METHODS OF MEASUREMENT

4.1 Primary variable

The primary outcome variable is progression free survival and is based on independent radiographic central review.

4.2 Screening and demographic measurements

The data listed below will be collected on the appropriate electronic case report form (eCRF):

- Demographic details (date of birth, sex, race and ethnicity)
- Past and current medical and surgical history, previous hypertension and smoking history
- Physical examination including neurological examination to assess all conditions that are current and ongoing
- Height, weight and vital signs: pulse, resting systolic blood pressure and diastolic blood pressure
- Recording of adverse events
- Recording of concomitant medications and previous treatments
- Recording of steroid usage including type (eg dexamethasone, prednisone, etc) and dose per day
- Karnofsky performance score
- Haematology, clinical chemistry including TFT and creatinine clearance and urinalysis
- Pulmonary function test results including DLCO and FVC
- Pregnancy testing for female patients within 7 days prior to first dose of study medication. A test is unnecessary if there were no menses in the previous year and/or plasma LH and FSH is within the postmenopausal range.
- 12 lead electrocardiogram (ECG) recording
- Tumour assessment by contrast-enhanced MRI

4.3 Efficacy and pharmacodynamic measurement and variables

Following initial randomized study treatment on Day 1, subsequent visits and assessments should occur ±3 days of the protocol-specified visit times except for

tumour assessments. For tumour assessments, screening contrast enhanced MRI should be performed no more than 4 weeks before the date of randomization.

The baseline contrast enhanced MRI assessment must be performed within 7 days prior to the date of randomization and follow–up contrast enhanced MRI assessments will be performed every 6 weeks until progression within a visit window of ±10 days of the specified visit date. Steroid dose must be UNCHANGED within 10 days prior to all follow-up contrast enhanced MRI scans.

Following the baseline assessment, efficacy for all patients will be determined by objective tumour response assessment on contrast enhanced MRI by independent radiographic review every 6 weeks.

For patients on treatment it is vital to follow the assessment schedule as closely as possible because biases in analysis can occur if 1 treatment group is examined more often or sooner than the other. If an unscheduled tumour assessment is performed and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time (as detailed in the study plan, Table 1). For patients that discontinue study treatment for reasons other than disease progression every effort will be made to obtain follow-up scans.

Tumour assessments will be performed in accordance with the protocol schedule until a progression event occurs regardless of whether they discontinue all or part of their randomized therapy or start to receive other anti-cancer therapy including surgery and radiotherapy.

Progression-free survival

Methods of assessment

Standard imaging will consist of contrast enhanced MRI of the brain (T1 weighted without contrast, T1 weighted with contrast and T2 weighted MRI) according to the study plan.

All tumour measurements will be made on the T1 weighted contrast enhanced MRI and the other scans may be used to aid interpretation of tumour versus non tumour for tumour measurements on the T1 weighted contrast enhanced MRI.

For patients with measurable contrast enhancing lesions (≥10 mm in the shortest diameter on 2 axial slices) at baseline, the sum of the products of the largest perpendicular diameters for the tumour in the transaxial plane will be measured and recorded for all measurable separate tumours.

In addition, new enhancing lesions (≥10 mm shortest diameter) at follow-up, not within the original tumour volume defined will be recorded as new lesions.

The investigator will record an overall visit assessment for patients with measurable lesions at baseline using the following criteria:

- Complete response: Disappearance of all contrast enhancing lesions on MRI compared to baseline.
- Partial response: ≥50% reduction sum of the products of the largest perpendicular diameters and no new lesions compared to baseline.
- Progression: See '*Derivation or calculation of outcome variable'*
- Stable Disease: A patient whose MRI scan does not meet the criteria for *Complete Response, Partial Response, or Progressive Disease*

For patients with no measurable contrast enhancing lesions at baseline, new enhancing lesions (≥10 mm shortest diameter) at follow-up will be recorded as new lesions. For small contrast enhancing lesions at base-line (<10 mm shortest diameter), progression will be recorded if there is significant size increase and the shortest diameter is ≥15 mm.

Patients who have interventional therapy other than study drug (eg resection) will only be assessed for progression.

If steroid dose has been changed within 10 days of the contrast enhanced MRI scan then the scan must be repeated after steroids have been stabilised for at least 10 days.

If the investigator is in doubt as to whether the progression has occurred the patient can continue to receive study treatment and the MRI scan repeated before or at the next scheduled imaging visit.

It is important that the patient return to the protocol schedule of assessments after a repeat scan. Tumour assessments will be recorded on the eCRF.

All contrast enhanced MRI scans should be performed according to standardized guidelines provided by an AstraZeneca appointed CRO prior to the start of the study, and sent to this CRO for independent radiographic central review. Results of this independent radiographic review will not routinely be communicated to investigators, and the management of patients will be based solely upon the results of the radiographic assessment conducted by the investigator.

Derivation or calculation of outcome variable

Assessment of PFS will be made on the basis of contrast enhanced MRI by independent radiographic central review.

For patients with measurable disease at entry (at least one lesion that has a shortest diameter ≥ 10 mm at baseline on 2 axial slices), progression will be defined as the earliest time that:

- The sum of the products of the largest perpendicular diameters of contrast enhancement for all lesions has increased by 25% in comparison to the nadir scan as long as the shortest diameter is ≥15 mm. If the dose of steroids has been reduced in the 10 days prior to the scan being conducted, progression will be based on a follow-up scan performed after the dose of steroids has been stabilised for 10 days.
- The patient has died from any cause
- A new lesion is detected that is outside the original tumour volume and has a shortest diameter ≥10 mm

For patients without measurable disease at entry (no lesions with a shortest diameter ≥10 mm at baseline on 2 axial slices), progression will be defined as the earliest time that:

- The patient has died from any cause
- A new lesion is detected that is outside the original tumour volume and has a shortest diameter ≥10mm
- A small enhancing lesion at baseline (<10 mm shortest diameter) has a significant increase in size to shortest diameter ≥15 mm.

Overall survival

Methods of assessment

Overall survival will be assessed by recording the exact date that patient death occurs. Patients should be followed up for survival every 12 weeks. All patients should be followed regardless of whether they have stopped treatment or received other cancer treatment until 270 deaths occur.

Derivation or calculation of outcome variable

The OS will be calculated as the interval from the date of randomization to the date of patient death (any cause). Patients who have not died at the time of the analysis for OS, who are lost to follow-up or who withdraw consent will be censored at the last date the patient was known to be alive.

Radiographic Response Rate

Methods of assessment

Response will be based on the contrast enhanced MRI scans of brain by independent radiographic central review according to criteria described below.

Derivation or calculation of outcome variable

Response rate will be defined as the proportion of patients with measurable disease at entry who have a partial response (PR) or complete response (CR) recorded at 2 consecutive visits 6 weeks apart.

An individual visit response of PR is defined as a greater than 50% reduction in the sum of the products of the largest perpendicular diameters of contrast enhancement for all lesions compared to baseline as long as the steroid dose has not been increased in the previous 10 days and no new lesions are present.

An individual visit response of CR is defined as the complete disappearance of all tumour on MRI scan.

Alive and progression free at 6 months (APF6), defined as 24 weeks

Methods of assessment

Assessment of APF6 will be based on the contrast enhanced MRI scans of brain by independent radiographic central review according to criteria described below.

Derivation or calculation of outcome variable

A patient will be defined as having progressed by 6 months, defined as 24 weeks (±10 days), if he/she has a progression event within 6 months of randomization.

Change in average daily steroid dosage from baseline until progression and number of progression/steroid free days

Methods of assessment

The steroid use prior and during treatment will be recorded up to progression on the eCRF

Derivation or calculation of outcome variable

The mean steroid dosage prior to treatment will be considered as the patient's baseline. The change in average daily steroid dosage from baseline is calculated as the mean daily steroid dosage recorded from the first day of therapy to progression subtracted from baseline. If a patient does not progress, average daily steroid dosage is calculated as the mean of daily actual steroid dosage recorded prior to the data cut-off.

Number of progression/steroid free days is the number of days that a patient is known not to have used any steroids prior to progression.

Time to deterioration of neurological status

Methods of assessment

Neurological status based on investigator's neurological examination prior to and during treatment will be recorded on the eCRF.

Derivation or calculation of outcome variable

Patient's last predose assessment will be defined as baseline. Patients without a baseline assessment will be excluded from analysis.

Time to neurological status deterioration will be defined as the time from randomization to the neurological status worsening recorded at 2 consecutive visits 6 weeks apart.

Patients, who do not experience either worsening in the neurological status, or disease progression, or death, will be treated as censored observations at the time of the last neurological examination.

Biomarker measurement and variables

Blood samples (plasma and serum) will be collected and assessed for biomarkers of disease activity, effect of cediranib and angiogenesis. Biomarkers will be investigated for possible correlation with clinical outcomes and for the effects of the study medication.

The results of this exploratory biomarker research will not form part of the clinical study report for this study. The results may be pooled with biomarker data from other studies on cediranib to generate hypotheses to be tested in future studies.

Methods of assessment

Plasma and serum samples will be prepared from urine and venous blood (10 ml, 4 ml and 7 ml respectively). A baseline sample for biomarker analysis should be taken prior to the first dose of cediranib. Following the baseline assessment, changes in biomarkers will be assessed at Week 6, Week 12, Week 18, and Week 24. Another sample should be obtained at discontinuation.

A central laboratory will be used to support centres with logistics surrounding sample collection, preparation, shipment and storage.

5. REASONS FOR EARLY CESSATION OF TREATMENT THERAPY

5.1 Discontinuation of patients from treatment or assessment

Patients may be discontinued from study treatment and assessments at any time.

Criteria for discontinuation

Specific reasons for discontinuing a patient from study treatment are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment. At the time of discontinuation, the investigator should establish if the patient is willing to be followed for disease progression
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrect enrolment (ie the patient does not meet the required inclusion/exclusion criteria) of the patient if there are safety reasons as judged by the investigator and/or AstraZeneca
- Patient lost to follow-up
- Disease progression (unless, in the investigator's opinion and in discussion with AstraZeneca, the patient is receiving benefit from treatment with cediranib)
- Pregnancy

Cediranib should be permanently discontinued in patients with the following conditions:

- Gastrointestinal perforation or wound dehiscence requiring medical intervention
- Serious haemorrhage (ie, requiring medical intervention)
- Severe hypertension
- Nephrotic syndrome
- Severe arterial thromboembolic event

Procedures for discontinuation from treatment

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up and the patient should return investigational products.

If study treatment is stopped during the study, the Principal Investigator/Sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate treatment and all possible measures for the safety of the patient. In addition, they will record on the electronic Case Report Form (eCRF) the date of withdrawal, the reasons, and treatment at the time of withdrawal. They will also immediately inform AstraZeneca of the withdrawal. Any serious adverse events should be communicated to AstraZeneca.

All patients who have any CTCAE grade 3 or 4 laboratory values at the time of withdrawal must have further tests performed and the results recorded on the appropriate eCRF until the lab values have returned to CTCAE grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

At withdrawal, all on-going study-related toxicities and SAEs must be followed until resolution, unless in the Investigator’s opinion, the condition is unlikely to resolve due the patient’s underlying disease.

All new AEs occurring for up to 14 days after the last dose of study medication must be recorded in the eCRF. All study-related toxicities and all SAEs occurring up to 14 days after the last dose of study medication must be followed until resolution.

Patients who are not receiving treatment, but are being followed up for tumour assessments should also be followed up for procedure related SAEs, these should be recorded in the appropriate eCRF. AE collection is not required for patients who have progressed and are being followed up for survival only.

For patients who are withdrawn from study treatment for reasons other than disease progression every effort will be made to obtain objective tumour assessments completed every 6 weeks.

When disease progression has been documented or the patient has withdrawn from study treatment, the long-term follow up information for survival should be collected at least every 12 weeks by telephone contact with the patient, patient's family, or by contact with the patient's physician.

6. OBJECTIVES AND STATISTICS

6.1 Primary objective

The primary objective of this study is to determine:

- The relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by radiographic assessment of PFS

6.2 Secondary objectives

The secondary objectives of this study are to determine:

1. The relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of overall survival
2. 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
3. The relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by assessment of alive and progression free rate at 6 months defined as 24 weeks (APF6), after randomization
4. 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 receiving oral lomustine alone as measured by neurological examination
5. 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
6. The safety and tolerability of cediranib (either in monotherapy or in combination with oral lomustine).

6.3 Exploratory endpoints

The exploratory endpoints of this study included:

1. Based on the Karnofsky Performance Status (KPS), investigation of the TDPS (time to deterioration in patient KPS) during the period of treatment with investigational therapy (pre and post progression)
2. Investigation of the relationship between the effects of cediranib on soluble angiogenesis biomarkers and clinical efficacy

6.4 Description of outcome variables in relation to objectives and hypotheses

The primary objective of the study is to determine the relative efficacy of cediranib (either in monotherapy or in combination with oral lomustine) compared to oral lomustine alone by radiographic assessment of PFS. This objective will be assessed by the primary variable of PFS. The study has been powered to show superiority.

The secondary efficacy variables of OS, RR and APF6 are used to provide supportive evidence that cediranib monotherapy or in combination with oral lomustine has superior efficacy compared to oral lomustine alone.

The secondary efficacy variables of average daily steroid dosage change from baseline until progression and average number of progression/steroid free days are used to provide superior steroid sparing effect compared with oral lomustine alone.

Another secondary objective of the study is to demonstrate a longer time to deterioration in neurological status for patients receiving cediranib monotherapy or in combination with oral lomustine compared to patients receiving oral lomustine alone as measured by neurological examination.

The safety and tolerability of either cediranib monotherapy or in combination with lomustine in this patient population will be assessed by adverse events, blood pressure, vital signs, physical exam, ECG parameters, clinical chemistry, haematology and urinalysis throughout the study.

6.5 Description of analysis sets

Two populations, intention-to-treat ITT and evaluable for safety (EFS) will be used for the analysis and are defined in the table below**:**

Table 4 Analysis populations

Population	Definition
Intention-to-treat (ITT)[a]	All randomized patients categorized by randomized treatment arms
Evaluable for safety (EFS)	This is a subset of the ITT population that includes all patients who received at least 1 dose of trial medication. Patient will be analysed according to the study medication actually received

[a]Sensitivity to incorrect randomizations may be investigated

6.6 Method of statistical analysis

The efficacy analysis will be performed on an in intention-to-treat (ITT) basis using the ITT full analysis set. There are two comparisons of interest, namely comparisons of cediranib monotherapy versus lomustine alone and cediranib in combination with lomustine versus lomustine alone. In order to maintain an overall type 1 error rate of 5%, a Dunnett and Tamhane step-up procedure will be used, which allows for the correlation of 0.67 between each comparison (**Error! Reference source not found.**). Applying the Dunnett and Tamhane approach, statistical significance will be declared if both comparisons are significant at the two-sided 5% level, or if either comparison is statistically significant at the two-sided 2.77% level.

Analysis of Primary Endpoint

The statistical analysis for the primary endpoint will be performed after 230 progression events have occurred. This number of progression events is expected to have occurred approximately 19 months after the first patient has entered the study assuming a 12 month recruitment period. The analysis of PFS will be based on recordings made by an independent radiographic, central review panel who will provide AstraZeneca with the visit responses and individual tumour measurements. On the basis of these, AstraZeneca will derive PFS by incorporating steroid dosage change and the timing of scans. PFS will be analysed using a log-rank test stratified by resection (yes/no prior to enrolment) and age (Age ≤65 vs >65). The hazard ratio and associated 95% confidence

interval will be estimated from a Cox model using the stratification levels as covariates. The sensitivity analysis that uses the earlier of the investigator and independent radiographic assessments of progression will be performed using the same methodology.

Analysis of Secondary Endpoints

No further analysis of OS data will be performed.

Follow up for OS data will cease following approval of clinical protocol amendment 3. Patients being followed up for OS and who are not receiving study medication will be discontinued from the study.

To account for the interim analysis of the data, a spending function that approximates O'Brien/Fleming boundaries for unequally spaced intervals will be used (**Error! Reference source not found.**). These calculations will be performed once it is known what proportion of the final deaths had occurred at the interim, and consequently what significance level for the interim and final analysis should be.

RR will be analysed on patients who had measurable disease at baseline using logistic regression, adjusting for resection (yes/no prior to enrolment) and age (Age ≤65 vs >65). The effect of treatment will be estimated using the adjusted odds ratio and its 95% Confidence Interval together with the response rate in each treatment group.

Kaplan-Meier (KM) estimates of APF6 will be calculated and compared between treatment groups. The analysis will be stratified according to resection (yes/no prior to enrolment) and age (Age ≤65 vs >65). Within each stratum, the log hazard ratio will be calculated using the difference in log(-log) of the KM estimates of APF6. The variance of the stratum specific log hazard ratios will be calculated using the corresponding logged version of Greenwood's formula for the standard error of a survival estimate (**Error! Reference source not found.**). The overall log hazard ratio will be calculated from a weighted average of individual stratum specific estimates, weighting inversely proportional to their variance (**Error! Reference source not found.**). Results will be back transformed and presented as a hazard ratio together with its 95% confidence interval.

Average daily steroid dosage will be analysed by comparing mean changes from baseline to progression between treatment groups using analysis of covariance (ANCOVA) models adjusting for the fixed factors of treatment, and baseline. Number of progression/steroid free days will be analysed with the Wilcoxon rank-sum test.

The analysis of time to deterioration of neurological status will use the same methodology as described for PFS.

The safety analysis will be performed on study treatment actually received for all patients who received at least one dose of study medication. There will be no formal statistical analyses for safety and tolerability. The treatment groups will be compared descriptively using summary statistics and percentage counts.

The Medical Dictionary for Regulatory Activities (medDRA) will be used for the coding and classification of AEs and SAEs in the database. AEs will be summarised by system organ class and preferred term using medDRA.

The effect of cediranib on changes in biomarkers will be analysed with an ANCOVA model, adjusting for the fixed factor of treatment and for the covariate of baseline biomarker level.

6.7 Determination of sample size

This trial is powered for both PFS and OS.

Approximately 300 patients will be randomized into three groups at a 2:2:1 ratio (cediranib 30 mg to lomustine + cediranib 20 mg to lomustine + cediranib matched placebo) ratio. With 230 progression events, if the true hazard ratio is 0.55, this trial will have > 80% power to demonstrate a statistically significant difference in PFS at a 2-sided 2.5% level for both cediranib 30 mg versus lomustine + cediranib matched placebo and lomustine + cediranib 20 mg versus lomustine + cediranib matched placebo. Hazard ratios less than 0.55 have been reported in recently completed clinical studies with progression endpoints in other advanced setting, eg, sorafenib

(RCC) and sunitinib (RCC and gastro-intestinal stromal tumours [GIST]). In the recurrent glioblastoma setting, a HR of 0.55 would correspond to an increase of 80% in PFS, with an observed increase of 50% being statistically significant.

No further analysis of OS data will be performed.

Follow up for OS data will cease following approval of clinical protocol amendment 3. Patients being followed up for overall survival and who are not receiving study medication will be discontinued from the study.

6.8 Interim analyses

There are no planned interim efficacy analyses for this study; however, one interim safety review will be performed by IDMC. The safety review will occur approximately after 100 patients have been recruited into the study. The primary of objective is to confirm if the treatment arms are sufficiently tolerable to allow continuation of the study without modification.

6.9 Data Monitoring Board

The Independent Data Monitoring Committee (IDMC) is responsible for safeguarding the interests of study participants for this study. The IDMC also will provide AstraZeneca with recommendations for action with study conduct and the management of patients treated under the auspices of the study protocol. In particular, the IDMC will review safety and tolerability data for the initial 100 patients recruited into the study and provide AstraZeneca with a recommendation whether to continue this study with cediranib 20 mg + lomustine as the combination arm.

The IDMC will be composed of therapeutic area experts and statisticians who do not have significant conflicts of interests and therefore, will neither be study investigators or individuals employed by AstraZeneca. The safety review will be conducted by the IDMC who will not disclose results if the recommendation is to continue the study.

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