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The survival benefits of re-irradiation and chemotherapy for patients with relapsed glioblastoma

Submission date
02/02/2021

Recruitment status
No longer recruiting

Registration date
25/02/2021

Overall study status
Ongoing

Last Edited
30/08/2024

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English Summary

Background and study aims
Glioblastoma (GBM) is the most common adult malignant brain tumour, with an incidence of 5 per 100,000 per year in England. The condition is incurable and, despite aggressive treatment at first presentation (surgery, radiotherapy and chemotherapy), after an average of 7 months, almost all tumours recur within the brain. At the time of recurrence, prognosis is measured in months, with median survival around 6.5 months. The aim of further treatment at the time of recurrence is to prolong survival and maintain health-related quality of life (HRQOL), which is of paramount importance to patients and carers, given the limited life expectancy. Chemotherapy is typically employed in the setting of recurrent GBM, often using nitrosourea-based regimens. Effectiveness is limited, with a median survival of around 5-9 months. Chemotherapy is delivered over a protracted period, lasting up to 6.5 months. There is growing evidence that re-irradiation is an alternative treatment for recurrent GBM, which is less commonly used in the UK. Evidence suggests that a 10-day outpatient course of external beam re-irradiation results in survival outcomes that are at least similar to patients treated with nitrosourea-based chemotherapy. The aim of this study is to assess the survival benefits of re-irradiation and chemotherapy and provide clinically meaningful HRQOL data for both treatments.

Who can participate?
Patients aged 18 and over with relapsed GBM who have previously completed their first round of chemoradiotherapy treatment more than 6 months ago

What does the study involve?
Patients will receive either radiotherapy (re-irradiation) treatment in 10 daily fractions over 2 weeks, or chemotherapy regimens delivered in six 6-week cycles. All patients will be followed up until 48 weeks after the start of treatment. Clinical visits and health-related quality of life will be performed every 6 weeks and MRI imaging will be performed every 3 months for up to 1 year. Interviews will take place in a small number of patients and carers, which will allow for a greater understanding of HRQOL.

What are the possible benefits and risks of participating?
By taking part in this study, the researchers hope to understand better how both chemotherapy and re-irradiation work in patients with GBM, what side effects these treatments cause and how they impact a patients quality of life. This will help hospitals in choosing the best treatment for future patients when their GBM recurs. Participants have a risk of side effects in both the chemotherapy and radiotherapy groups. Possible side effects of chemotherapy are tiredness, nausea, vomiting, taste changes, sore mouth or mouth ulcer, infections, bruising and bleeding, poor appetite, diarrhoea, constipation, abdominal pain, anaemia, skin changes and allergic reactions. Possible side effects from re-irradiation could include; tiredness, patchy hair loss, headaches, dizziness, swelling in the brain, nausea, vomiting, skin redness or irritation on the scalp, weakness, seizures and dry mouth or taste changes.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
May 2019 to May 2026

Who is funding the study?
The Jon Moulton Charity Trust (Guernsey)

Who is the main contact?
Dr Samantha Noutch
BRIOCHE@leeds.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-giving-radiotherapy-again-for-glioblastoma-brioche

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

2019-004053-91

IRAS number
1003313

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 46910, CO19/121741, IRAS 1003313

Study information

Scientific Title
Brain Re-Irradiation Or Chemotherapy: a Phase II randomised trial of re-irradiation and chemotherapy in patients with recurrent glioblastoma

Acronym
BRIOChe

Study hypothesis
To assess 9-month overall survival rates in patients with relapsed who have had at least a 6-month interval from completion of primary radiotherapy. The main aim will be to establish the efficacy and Health-Related Quality of Life (HRQoL) of re-irradiation for recurrent GBM, as well as gather HRQoL data for patients who receive chemotherapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/07/2020, Northern Ireland - Office for Research Ethics Committees Northern Ireland (ORECNI) (Business Services Organisation, Lissue Industrial Estate West, 5 Rathdown Walk, Moira Road, Lisburn, BT28 2RF, N. Ireland; +44 (0)28 9536 1407; reca@hscni.net), REC ref: 20/NI/0070

Study design
Randomized; Both; Design type: Treatment, Drug, Radiotherapy, Validation of investigation /therapeutic procedures

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
No participant information sheet available

Condition
Brain cancer, recurrent glioblastoma

Interventions
BRIOChe is a randomised phase II, multi-centre open-label study. The objectives of the trial are to assess 9-month overall survival rates in patients receiving re-irradiation or chemotherapy for recurrent GBM in conjunction with patients' health-related quality of life perception before, during (if randomised to chemotherapy) and after treatment. A total of 70 patients will be recruited from approximately 16 UK sites.
Patients who are eligible for the trial will be consented for trial participation and will be randomised (1:1) to enter either the chemotherapy arm or the re-irradiation arm.

Sample size
Thirty-three patients are required in the re-irradiation arm, 35 allowing for 5% drop out. For 1:1 randomisation against chemotherapy, 70 patients are required in total. This study is powered to demonstrate that the treatment strategy of re-irradiation demonstrates sufficient efficacy to warrant further large scale evaluation, including in combination with novel agents, based on 9 month OS with 80% power and 5% significance (one-sided)

Trial design details
A Sargent's three-outcome, phase II, single-stage, single-arm design will be used to determine whether re-irradiation demonstrates sufficient efficacy to warrant further larger-scale evaluation. The trial is designed to test the null hypothesis H0 that the proportion of participants alive at 9 months is <25% where re-irradiation would not be deemed worthy of further investigation against an alternative hypothesis H1 of >45% where re-irradiation would be deemed worthy of further investigation. If the proportion of participants alive at 9 months is ≥25% and ≤45%, this would be an inconclusive region where neither the null or alternative hypothesis would be rejected and the decision regarding further investigation would be based on other factors. Based on the 3 outcome design, the cut-off values and conclusions for the statistical test are defined as follows.
Green: If ≥13/33 patients were alive re-irradiation would demonstrate sufficient efficacy to warrant larger-scale evaluation. This is based on a 9-month OS >45% (i.e. competitive with the 'best' outcomes from prospective studies using nitrosourea-based chemotherapy)
Amber: If 11-12/33 patients were alive the decision to take re-irradiation forward will be uncertain and will be based on HRQOL and toxicity at 3 months, (this is based on 9-month OS 25%-45%; i.e. similar to outcomes from other prospective nitrosourea-based trials).
Red: If ≤10 patients were alive re-irradiation would be not considered worthy of further investigation, based on 9-month OS <25%.
The chemotherapy arm is included for calibration and will be used for validation ("benchmarking") of outcomes in the re-irradiation group with respect to previous series, and validation of the assumptions used to inform the statistical cut-offs

HRQOL
HRQOL is a key secondary outcome. Based on the sample size above, the power to detect changes in HRQOL score is as follows: with 28 patients in each arm (which is assuming 80% of patients are alive at 3 months) this would provide >80% power to detect a ≥16 point difference

in 3-month global health score (GHS) between re-irradiation and chemotherapy (2-sided, 10% significance), assuming a mean GHS of 67.0 (SD:22.9). For a ≥10 point difference there would be 48% power.

Broad timetable of the study

Prior to trial entry
Participants will be approached for possible recruitment by their clinical oncologist, following confirmation from the multidisciplinary team (MDT) that the changes on imaging represent recurrent glioblastoma and following the decision to treat with either chemotherapy or re-irradiation.

Suitability for inclusion into BRIOChe will be assessed according to the eligibility criteria. A verbal explanation of the trial, Patient Information Sheet (PIS) and Key Fact sheet will be provided to the patient by the attending medical staff (and/or the trial Clinical Research Nurse). For female patients of child bearing potential, they will be asked to confirm a negative pregnancy test prior to main consent. Female patients will be asked to consent to this test prior to consenting to the main trial.

The information provided will include a detailed description about the rationale, design and personal implication of the trial. Patients will have as long as they need to consider participation, normally a minimum of 24 hours, and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they are willing to take part.

Patients who do decide to enter the trial will then be formally assessed for eligibility and invited to provide informed written consent. The formal assessment of eligibility and informed consent may only be obtained but the Principal Investigator (PI) or an appropriate medically qualified healthcare professional. The following procedures are part of the standard assessment for glioblastoma (GBM). These assessments are usually already obtained as apart of standard care, and will be used to establish eligibility. Clinical assessment including medical history, concomitant medication including dexamethasone and anti-epileptic use, physical examination, including neurological examination, Karnofsky performance score, blood test including full blood count, urea and electrolytes, liver function test, creatinine, bilirubin, pregnancy screening (performed within 7 days prior to randomisation) and MRI scan using RANO criteria.

Randomisation
Patients will then be randomised to either the chemotherapy arm or the re-irradiation arm (1:1). A computer-generated minimisation
1. Less than 50 or more than or equal to 50 years old
2. Site number
3. Time to randomisation from completion of previous radiotherapy less than or equal to 12 months or more than 12 months
4. Methylation (MGMT) status

For the chemotherapy arm
Prior to patient consent, pregnancy test
Clinical assessment, Karnofsky performance score, bloods, MRI (using Response assessment in neuro-oncology
(RANO) criteria)

Baseline (prior to randomisation)
Informed consent will be taken.

Baseline (prior to randomisation but after consent)
Baseline CTCAE scores will be taken and the participant will complete the HRQOL.

Clinical assessment, Karnofsky performance score and bloods will need to be performed within 7 days of cycle 1 chemotherapy and within 3 days of all subsequent cycles. Chemotherapy doses may be modified based on patient tolerance or blood results throughout.

Week 0, Cycle 1
Clinical assessment, Karnofsky performance score, bloods, pregnancy test if the previous test is equal to or over 7 days from the previous test, chemotherapy treatment (options based on institutional/ clinician usual practice: i) lomustine alone, ii) procarbazine, lomustine and vincristine (PCV), iii) lomustine and procarbazine (PC), iv) lomustine and vincristine (CV) (doses: lomustine 100-130 mg/m², with dose capping as per the institution's usual practice, day 1, taken by mouth (PO), on a 42-day cycle for up to 6 cycles. procarbazine 50-100 mg/m², with dose capping as per the institution's usual practice, once daily on days 1-10 or days 2-11, PO, on a 42-day cycle for up to 6 cycles. Vincristine 1.4-1.5 mg/m² (or a flat dose of 2 mg), with dose capping as per the institution's usual practice, injection into the vein - intravenous injection (IV), day 1, on a 42-day cycle for up to 6 cycles), toxicity Common Terminology Criteria for Adverse Event (CTCAE) scoring.

6 week, Cycle 2
Clinical assessment, Karnofsky performance score, bloods, pregnancy screening, treatment (options based on institutional/clinician usual practice: i) lomustine alone, ii) procarbazine, lomustine and vincristine (PCV), iii) lomustine and procarbazine (PC), iv) lomustine and vincristine (CV) (doses: lomustine 100-130 mg/m², with dose capping as per the institution's usual practice, day 1, taken by mouth (PO), on a 42-day cycle for up to 6 cycles. Procarbazine 50-100 mg/m², with dose capping as per the institution's usual practice, once daily on days 1-10 or days 2-11, PO, on a 42-day cycle for up to 6 cycles. Vincristine 1.4-1.5mg/m2 (or a flat dose of 2mg), with dose capping as per the institution's usual practice, injection into the vein - intravenous injection (IV), day 1, on a 42-day cycle for up to 6 cycles), toxicity CTCAE scoring and HRQOL.

12 week, Cycle 3
Clinical assessment, Karnofsky performance score, bloods, pregnancy screening, treatment (options based on institutional/clinician usual practice: i) lomustine alone, ii) procarbazine, lomustine and vincristine (PCV), iii) lomustine and procarbazine (PC), iv) lomustine and vincristine (CV) (Doses: lomustine 100-130 mg/m², with dose capping as per the institution's usual practice, day 1, taken by mouth (PO), on a 42-day cycle for up to 6 cycles. Procarbazine 50-100 mg/m², with dose capping as per the institution's usual practice, once daily on days 1-10 or days 2-11, PO, on a 42-day cycle for up to 6 cycles. Vincristine 1.4-1.5 mg/m² (or a flat dose of 2mg), with dose capping as per the institution's usual practice, injection into the vein - intravenous injection (IV), day 1, on a 42-day cycle for up to 6 cycles), MRI scan (RANO criteria)toxicity CTCAE scoring and HRQOL.

18 week, Cycle 4
Clinical assessment, Karnofsky performance score, bloods, pregnancy screening, treatment (options based on institutional/clinician usual practice: i) lomustine alone, ii) procarbazine, lomustine and vincristine (PCV), iii) lomustine and procarbazine (PC), iv) lomustine and vincristine (CV) (Doses: Lomustine 100-130 mg/m², with dose capping as per the institution's usual practice, day 1, taken by mouth (PO), on a 42-day cycle for up to 6 cycles. Procarbazine 50-100 mg/m², with dose capping as per the institution's usual practice, once daily on days 1-10 or days 2-11, PO, on a 42-day cycle for up to 6 cycles. Vincristine 1.4-1.5 mg/m² (or a flat dose of 2 mg), with

dose capping as per the institution's usual practice, injection into the vein - intravenous injection (IV), day 1, on a 42-day cycle for up to 6 cycles), toxicity CTCAE scoring and HRQOL.

24 week, Cycle 5
Clinical assessment, Karnofsky performance score, bloods, pregnancy screening, treatment (options based on institutional/clinician usual practice: i) lomustine alone, ii) procarbazine, lomustine and vincristine (PCV), iii) lomustine and procarbazine (PC), iv) lomustine and vincristine (CV) (Doses: lomustine 100-130 mg/m², with dose capping as per the institution's usual practice, day 1, taken by mouth (PO), on a 42-day cycle for up to 6 cycles. procarbazine 50-100 mg/m², with dose capping as per the institution's usual practice, once daily on days 1-10 or days 2-11, PO, on a 42-day cycle for up to 6 cycles. Vincristine 1.4-1.5 mg/m² (or a flat dose of 2 mg), with dose capping as per the institution's usual practice, injection into the vein - intravenous injection (IV), day 1, on a 42-day cycle for up to 6 cycles), MRI scan (RANO criteria), toxicity CTCAE scoring and HRQOL.

30 week, Cycle 6
Clinical assessment, Karnofsky performance score, bloods, pregnancy screening, treatment (options based on institutional/clinician usual practice: i) lomustine alone, ii) procarbazine, lomustine and vincristine (PCV), iii) lomustine and procarbazine (PC), iv) lomustine and vincristine (CV) (Doses: Lomustine 100-130 mg/m², with dose capping as per the institution's usual practice, day 1, taken by mouth (PO), on a 42-day cycle for up to 6 cycles. Procarbazine 50-100 mg/m², with dose capping as per the institution's usual practice, once daily on days 1-10 or days 2-11, PO, on a 42-day cycle for up to 6 cycles. Vincristine 1.4-1.5 mg/m² (or a flat dose of 2 mg), with dose capping as per the institution's usual practice, injection into the vein - intravenous injection (IV), day 1, on a 42-day cycle for up to 6 cycles), toxicity CTCAE scoring and HRQOL.

36 week
Clinical assessment, Karnofsky performance score, MRI scan (RANO criteria), toxicity CTCAE scoring and HRQOL

42 week
Clinical assessment, Karnofsky performance score, toxicity CTCAE scoring and HRQOL

48 week
Clinical assessment, Karnofsky performance score, MRI scan (RANO criteria) toxicity CTCAE scoring and HRQOL.

For Re-irradiation Arm
Prior to patient consent
Pregnancy test, Clinical assessment, Karnofsky performance score, bloods, MRI (RANO criteria)

Baseline (prior to randomisation)
Informed consent will be taken.

Baseline (prior to randomisation but after consent)
Baseline CTCAE scores will be taken and the participant will complete the HRQOL

Baseline (after randomisation)
Radiotherapy planning (including pregnancy screening within 7 days prior to CT simulation)

Pre-treatment (less than or equal to 14 days prior to treatment): clinical assessment and Karnofsky performance score and CTCAE scores. Pregnancy screening is performed within 7 days prior to starting re-irradiation.

Week 0
Clinical assessment, Karnofsky performance score, radiotherapy treatment (Mon-Friday 35 Gy in 10 daily fractions delivered over 2 weeks), toxicity CTCAE scoring.

Week 1
Clinical assessment, Karnofsky performance score, radiotherapy treatment (Mon-Friday 35 Gy in 10 daily fractions delivered over 2 weeks), toxicity CTCAE scoring.

Week 6
Clinical assessment, Karnofsky performance score, toxicity CTCAE scoring and HRQOL.

Week 12
Clinical assessment, Karnofsky performance score, MRI (RANO criteria), toxicity CTCAE scoring and HRQOL.

Week 18
Clinical assessment, Karnofsky performance score, toxicity CTCAE scoring and HRQOL.

Week 24
Clinical assessment, Karnofsky performance score, MRI (RANO criteria), toxicity CTCAE scoring and HRQOL.

Week 30
Clinical assessment, Karnofsky performance score, toxicity CTCAE scoring and HRQOL.

Week 36
Clinical assessment, Karnofsky performance score, MRI (RANO criteria), toxicity CTCAE scoring and HRQOL.

Week 42
Clinical assessment, Karnofsky performance score, toxicity CTCAE scoring and HRQOL.

Week 48
Clinical assessment, Karnofsky performance score, MRI (RANO criteria), toxicity CTCAE scoring and HRQOL.

For both the chemotherapy arm and the re-irradiation arm 15 patients/caregivers will be asked during treatment/follow-up if they would like to take part in an interview to discuss the treatment. Caregivers will be approached by one of the researchers and asked if they would like to participate. If they choose to participate they will then be asked to complete a consent form and read the accompanying caregivers patient information sheet. The timing of the interview will vary from participant to participant.

Wherever possible, clinically suspected disease progression will be confirmed with an MRI scan, as above. If the patient is too unwell to undergo MRI, then a CT scan may be used in order to try to determine if there has been tumour progression.

Intervention Type

Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Lomustine, procarbazine, vincristine

Primary outcome measure
Overall survival rates, (i.e. the number and proportion of patients alive) in the re-irradiation arm at 9 months post-start of treatment. Overall survival is defined from randomisation to the date of death from any cause and survival data will be collected at all standard follow-up visits. Overall survival rates in the chemotherapy arm will also be assessed for calibration purposes only and not for direct statistical comparison.

Secondary outcome measures
1. Health-related quality of life (HRQoL) measured using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaires core 30 (QLQ-C30) and brain cancer module (BN20) completed independently by patients at clinic visits at baseline and at 6-weekly intervals post-start of treatment, up to 48 weeks post-start of treatment.
2. HRQoL evaluated through one-off semi-structured qualitative interviews in a patient/carer subset (n~15 or until data saturation). This will include HRQoL before/during treatment, experience of treatment and what matters most to patients/carers.
3. Dexamethasone use defined as the dose and frequency of dexamethasone received. Data on dexamethasone use, including dose, any change in dose including the date of change, will be collected at baseline and then on a 6-weekly basis post-start of treatment.
4. Anti-epileptic drug use defined as the type, dose and frequency of anti-epileptics received. Data on anti-epileptic drug use including the name of anti-epileptic drug(s), dose, any change in dose including the date of change will be collected at baseline and then on a 6-weekly basis post-start of treatment.
5. Radiological response to treatment assessed via MR imaging in accordance with RANO criteria at 12 weeks post-start of treatment and then at 12-weekly intervals up to 48 weeks post-start of treatment or until disease progression
6. Acute and late toxicities assessed at 6-weekly intervals post-start of treatment up to 48 weeks or until progression, whichever is sooner. They will be evaluated according to the current NCI-CTCAE criteria and include all Adverse Events (AEs). Acute toxicities will be defined as those occurring up to 12 weeks post-end of treatment. Late toxicities will be defined as those occurring after 12 weeks post-end of treatment. The period of collection of acute toxicity data will differ between arms due to different treatment lengths, but the overall period of data collection for toxicities will be the same for both treatment arms.
7. Progression-free survival (PFS) defined as the time from randomisation to the first documented evidence of disease progression or death (from any cause). PFS includes radiological progression assessed with RANO criteria and non-RANO evaluable progression where RANO assessment is not possible, (e.g. clinical progression in a patient who is too unwell for further imaging).

Overall study start date
15/05/2019

Overall study end date
30/05/2026

Eligibility

Participant inclusion criteria

1. Histologically proven diagnosis of GBM with consistent molecular pathology, based on original pathology (repeat biopsy at recurrence is NOT required).
2. First recurrence of GBM, with contrast-enhancing disease, following primary treatment (or following surgery alone for first recurrence of GBM; i.e. no previous systemic therapy or re-irradiation for recurrence permitted).
3. The MRI scan that reveals recurrence must be reviewed by the local multi-disciplinary meeting, including agreement of a Consultant Neuro-Radiologist that imaging changes are in keeping with recurrence and not pseudoprogression.
4. Randomisation must be performed within 21 days of the MRI that confirms recurrence. Outside of 21 days, an updated MRI is required to confirm eligibility and serve as a contemporaneous baseline scan to assess response to further treatment. Please see section 4.1 Inclusion Criteria for further details for achieving this.
5. ≥6 months since completion of primary radiotherapy (where the interval since radiotherapy completion is 5 months and 2 weeks or greater, this may be rounded up to 6 months and the patient included in the trial).
6. Prior history of standard dose, conventionally fractionated CNS radiotherapy (i.e. 54-60Gy in 28-33 fractions).
7. As a minimum patients will have completed at least two weeks of temozolomide, concurrent with their original radiotherapy.
8. Up to and including three enhancing lesions:
8.1. In cases of a single recurrent enhancing lesion:
8.1.1. Predicted re-irradiation GTV<75cm3 (based on diagnostic MR imaging and on maximum diameters of enhancing disease in all 3 planes, calculated from 4/3π x ½ x diameter 8.1.1. 1 x ½ x diameter 2 x ½ x diameter 3: see Appendix D – Calculation of volume and explanation for volume limitations for study eligibility for explanation) and
8.1.2. Maximum diameter of enhancing disease must be ≤6 cm. In cases where there is circumferential enhancement around a cavity, such that the cavity and enhancing disease will be included in the GTV, then the maximum diameter of enhancing disease and cavity must be ≤6 cm.
8.2. In cases of multiple (i.e. two or three) discrete recurrent enhancing lesions:
8.2.1. The total (i.e. combined) predicted reirradiation GTV must be <50cm3 and lesions must be clustered in a similar brain region such that PTVs are anticipated to be adjacent or overlapping and
8.2.2. Maximum diameter of the combined enhancing disease, across all enhancing lesions (including any gaps between), must be ≤6 cm
9. Karnofsky Performance Status 70+
10. Adequate hematologic, renal, and hepatic function (absolute neutrophil count, ≥1.5 x 109/l; platelet count, ≥100 x 109/l; White cell count ≥3.0 x 109/l; haemoglobin ≥10 g/l (may be corrected by transfusion); serum creatinine clearance (measured or estimated) ≥30ml/min; total serum bilirubin level <1.5 times ULN; and ALT <5 times ULN) within 14 days prior to randomisation. (Dose modifications may still be required based on these parameters. See section 9.1 Chemotherapy Arm for further details). Lymphopaenia is not a contra-indication to trial entry.
11. Patients who have had surgery for first recurrence may also be included provided there is residual enhancing disease on the immediate post-operative MRI or if enhancing disease develops on subsequent follow-up imaging, provided no prior systemic therapy or reirradiation for recurrence has been given. As above, this MRI must be reviewed within the local multi-disciplinary meeting, with agreement of a Consultant NeuroRadiologist that the imaging

changes are in keeping with residual or new enhancing disease. Randomisation must be performed within 21 days of the MRI that confirms recurrence. Outside of 21 days, an updated MRI is
required to confirm eligibility and serve as a contemporaneous baseline scan to assess response to further treatment. Please see section 4.1 Eligibility for further details for achieving this.
12. Patients must have recovered from the prior effects of therapy:
12.1. There must be a gap of at least 28 days since completion of adjuvant temozolomide or any other systemic anti-cancer therapy and commencement of re-irradiation or nitrosourea-based chemotherapy (note randomisation may occur prior to this provided all other eligibility criteria are met and the gap is at least 28 days when the trial treatment commences).
12.2. Patients who receive resection for recurrence must have adequate wound healing and resolution of any significant meningocoele or any other cause of swelling in close proximity to the wound.
13. Medical history and physical examination, including CNS examination, must be performed within 14 days prior to randomisation.
14. Female participants of childbearing potential must agree to be pregnancy screened prior to entering the BRIOChe trial and before signing the main informed consent form. They should provide informed consent on the eligibility pregnancy screening PISICF to allow pregnancy screening. They should provide a negative pregnancy result and agree to continue to practice methods of contraception that are considered medically acceptable for the duration of the trial treatment and, if randomised to chemotherapy, for 6 months post-end of treatment. They must have a negative pregnancy test within 7 days prior to randomisation. Male participants must agree to practice methods of contraception that are considered medically acceptable for the duration of the trial treatment and, if randomised to chemotherapy, for 6 months post-end of treatment if sexually active with a female of child-bearing potential. See section 4.3 Birth control: contraception and pregnancy testing for further details.
15. Patients must be able to provide study-specific informed consent
16. Aged 18 years or over
17. Should be able to start treatment within 21 days of randomisation and must start within 28 days of randomisation
18. Patients must be able to swallow oral medication

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 70; UK Sample Size: 70

Participant exclusion criteria
1. Pregnant (positive pregnancy test) or lactating
2. Critical normal brain structures treated above usual tolerance during initial radiotherapy (i.e. based on 30 fractions initial treatment, >55 Gy delivered to 1% or 0.1 cm^3 of optic nerve or

chiasm or >55 Gy delivered to >1 cm^3 of brainstem or >57 Gy delivered to >0.1 cm^3 of brainstem or >50 Gy to 1% or 0.1 cm^3 of globes)
3. Recurrence with leptomeningeal disease or only leptomeningeal disease
4. Recurrence defined by non-enhancing disease only
5. More than three enhancing lesions present on MRI or multi-focal recurrence
6. IDH1/2 mutant tumours on original pathology (to avoid unbalance between arms)
7. GBM with known features of PXA, BRAF mutations or 1p19q co-deletion (on original pathology or updated pathology if available)
8. Prior invasive malignancy (except non-melanomatous skin cancer), unless disease-free for a minimum of 1 year
9. Severe active co-morbidity making patient unsuitable for chemotherapy or re-irradiation (e.g. uncontrolled diabetes, uncontrolled hypertension)
10. Prior allergic reaction to nitrosoureas
11. Coeliac disease
12. Any recognised genetic syndrome causing sensitivity to radiotherapy
13. Patient unwilling/unable to attend for follow up in the radiotherapy centre
14. Contraindication to MRI or gadolinium
15. Previous radiotherapy dose distribution unavailable
16. Previous systemic therapy or re-irradiation for recurrent GBM

Recruitment start date
01/04/2021

Recruitment end date
31/05/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Addenbrookes Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre

St Mary's Hospital
Imperial College Healthcare NHS Trust
Praed Street
London
United Kingdom
W2 1NY

Study participating centre
Queen Elizabeth Medical Centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
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Birmingham
United Kingdom
B15 2TH

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
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M20 4BX

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Road
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CH63 4JY

Study participating centre
Guy's Hospital
Guy's and St Thomas' NHS Foundation Trust
Trust Offices
Great Maze Pond
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United Kingdom
SE1 9RT

Study participating centre

St. James's University Hospital
Leeds Teaching Hospitals NHS Trust
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Study participating centre
Freeman Hospital
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Road
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Study participating centre
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Study participating centre
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Study participating centre
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The Royal London Hospital
Barts Health NHS Trust
Whitechapel
London
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E1 1BB

Study participating centre
Velindre NHS Trust
Unit 2
Charnwood Court
Heol Billingsley
Cardiff
United Kingdom
CF15 7QZ

Sponsor information

Organisation
University of Leeds

Sponsor details
Faculty of Medicine and Health
Worsley Building
Leeds

England
United Kingdom
LS2 9JT
+44 (0)113 343 7587
governance-ethics@leeds.ac.uk

Sponsor type
University/education

Website
https://medicinehealth.leeds.ac.uk/

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
The Jon Moulton Charity Trust (Guernsey)

Results and Publications

Publication and dissemination plan
1. The trial protocol will be published at a later date.
2. Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/08/2026

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all

applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree on suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol article		08/03/2024	11/03/2024	Yes	No