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Combination nivolumab and decitabine for treatment of primary glioblastoma

Submission date 16/11/2023	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 19/01/2024	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 05/03/2026	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Glioblastoma is the most common brain cancer in adults and unfortunately is life-limiting. It is most common in older patients with an average age of 55 at diagnosis. However, it can still affect young adults and even children. Currently, there is no cure for this type of brain tumour. The current gold standard treatment consists of having surgery to remove all of the visible tumour followed by chemotherapy and radiotherapy. Survival rates are better for younger patients (aged under 40) but remain generally poor, with 50% of patients only surviving 2 years from diagnosis.

There is a new set of drugs, termed immunotherapies, that aim to boost the body's own immune system to fight cancer. Immunotherapies have been shown to increase survival from certain cancers such as skin cancer and lung cancer. However, these drugs, on their own, do not have much effect on glioblastoma. Our research in Oxford has shown that the addition of an additional drug (enhancer drug) to the immunotherapy drug can potentially boost the effect of immunotherapy.

Who can participate?

Patients aged 18 years or older with newly suspected glioblastoma

What does the study involve?

We want to run a phase I safety study to look at the safety of giving a combination of nivolumab (immunotherapy drug) and decitabine (enhancer drug). Phase I studies aim to find the best dose of a new drug with the fewest side effects. Doctors start by giving very low doses of the drug to a few patients. This dose is gradually increased a little bit at a time in different groups of patients to help find the best dose with the least side effects. This will be a small trial to establish whether this combination is safe and to look for the best possible dose. Nivolumab has been given to patients in the past with glioblastoma and decitabine has been given to patients with leukaemia. This combination has not been tried together before in patients with glioblastoma, so it is important that we conduct this small trial first.

What are the possible benefits and risks of participating?

Risks from IMP:

The combination of decitabine and nivolumab has not been given together for patients with

glioblastoma, so there's a small chance of an unknown side effect or an increase in any of the known side effects.
However, both drugs have been given separately and have been shown to have different side effect profiles (mainly blood disorders for the enhancer drug decitabine and gut and skin problems for nivolumab), so we do not anticipate a large overlap of side effects. As we are giving this combination before surgery, there is a small chance that surgery may have to be delayed for the side effects to settle, this is likely to be 1-2 weeks if surgery must be delayed.

To try and prevent this, patients will be screened, and the trial only offered to those that are not deemed to be at higher risk of side effects as determined by the inclusion/exclusion criteria. The decitabine will be starting initially at a very low dose in the first participant and will increase the dose per participant slowly as more safety data is gathered during the trial. Participants will come into hospital weekly for a clinical review.

Extra visits and tests:
Participants will attend the hospital more frequently than the standard of care. They will have extra visits for baseline, for the administration of the decitabine, for the check-up and administration of nivolumab and for 2 further visits to monitor their response to the trial drugs. At each of these visits, participants will have additional checks and blood samples taken for safety monitoring and translational research. They will also have monthly follow up reviews until 4 months after their standard of care surgery to resect their tumour, these will also involve additional checks and blood tests taken for safety monitoring and translational research.

For the participants who choose to have the optional research biopsy, they will also have a pre-biopsy MRI for surgical planning purposes and may be admitted the night before their biopsy and remain an inpatient for a night post-biopsy, depending on local protocols. They will also have a CT scan prior to discharge to assess any complications from the biopsy surgery.

Extra samples:
Alongside the optional research biopsy of the tumour, participants will have blood taken at most visits for translational research purposes. Where possible these will be taken alongside standard of care blood tests to minimise discomfort and inconvenience to participants.

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

When is the study starting and how long is it expected to run for?
April 2026 to March 2029

Who is funding the study?
Cancer Research UK

Who is the main contact?
combatgb@nds.ox.ac.uk

Plain English summary under review with external organisation

Contact information

Type(s)
Scientific, Principal investigator

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Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1007984

Protocol serial number
17190

Central Portfolio Management System (CPMS)
56996

Study information

Scientific Title
COMBinATion nivolumab and decitabine for treatment of primary GlioBlastoma (COMBAT-GB)

Acronym
COMBAT-GB

Study objectives

Primary objective:
To determine the safety and maximum tolerated dose with the least harmful side effects of a combination of ASTX727 and Nivolumab in patients with a primary brain tumour (glioblastoma)

Secondary objective:
To determine the rate of delayed surgery due to drug side effects for patients receiving combination ASTX727/Nivolumab therapy. Also to assess how effective the combination of ASTX727/Nivolumab is at treating the brain tumour.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 08/01/2024, Tyne and Wear South REC (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle-upon-Tyne, NE2 4NQ, United Kingdom; +44 2071048282; tyneandwearsouth.rec@hra.nhs.uk), ref: 23/NE/0226

Study design
Interventional non randomized

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Newly-diagnosed primary glioblastoma

Interventions
COMBAT- GB is a phase 1, non-randomised, dose escalation trial. It is looking for an effect of the "enhancer" drug ASTX727, given before immunotherapy (nivolumab), on patient outcomes and tumour responses to the immunotherapy. The trial aims to establish safety and efficacy of this novel drug combination and establish the best possible dose. Nivolumab has been given to patients in the past with glioblastoma, and ASTX727 has been given to patients with leukaemia.

Each participant will receive 1 dose of ASTX727 for 5 consecutive days. The doses will vary as the safety profile of the drug is established throughout the trial. The initial dose will be the lowest dose, and the first patient must complete the safety window prior to further recruitment. All participants will receive a single IV dose of Nivolumab immunotherapy on Day 8.

After receiving the trial medication, all participants receive normal standard of care treatment: surgical resection of their tumour, followed by post-operative radio/chemotherapy regimen, as determined by their normal clinical care team.

All participants will be actively followed up for 4 months. Beyond this, disease progression and survival data will be collected by the research team at sites from the participant's medical notes at 6 months and then 6-monthly until 6 months after the last participant is recruited.

All participants will undergo a brain MRI scan before and after their surgical tumour resection, as per normal standard of care treatment. In addition, participants will also be offered an optional

research tumour biopsy at baseline, before they take the trial medications. Participants who consent to this will have a brain CT scan after the biopsy, in addition to their standard of care MRI scans.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
ASTX727 (standard dose (SD) tablet) [cedazuridine, Decitabine], nivolumab, ASTX727 (low dose (LD) tablet) [cedazuridine, Decitabine], Decitabine

Primary outcome(s)
1. Safety profile of ASTX727/Nivolumab combination therapy measured at baseline, after neoadjuvant cycle of ASTX727/nivolumab (up to 4 weeks after first dose of ASTX727), then monthly up to 4 months following ASTX727/nivolumab
2. To determine the maximum tolerated dose (MTD) of ASTX727 when combined with nivolumab for the neoadjuvant treatment of participants with primary glioblastoma (the dose associated with no more than 25% DLT rate) measured from first dose of ASTX727 to 28 days following first dose ASTX727 or surgery, whichever is shortest

Key secondary outcome(s))
1. Clinical efficacy of combination ASTX727/nivolumab. Measured using progression free survival after surgery, 1 year survival rate, Overall Survival Time from diagnosis to death. Patients with no death recorded will be censored at last known alive time
2. Rate of delayed surgery due to drug toxicity for patients receiving combination ASTX727 /Nivolumab therapy measured form time to surgery from first dose of ASTX727

Tertiary:
1. Paired whole exome sequencing, RNAseq and Methylation array.
2. Immunohistochemistry, focusing on the amount of T cell infiltration and location of T cells. Single cell phenotyping and TCR sequencing of tumour infiltrating lymphocytes. Testing for tumour specific T cells.
3. Phenotyping of peripheral blood mononuclear cells

Completion date
31/03/2029

Eligibility

Key inclusion criteria
Current inclusion criteria as of 05/03/2026:

1. Aged 18 years and over on day of signed informed consent
2. Ability to provide written informed consent.
3. Willing and able to comply with the protocol scheduled follow-up visits and examinations for the duration of the trial.
4. WHO Performance status 0-1
5. Newly suspected glioblastoma on Gadolinium-enhanced MRI scan and reviewed in the local

Neuro-oncology multidisciplinary meeting, which is amenable for maximal resection.
6. Patients with tumours that do not exert significant mass effect and/or have significant oedema and where a delay to surgery is thought will lead to undue harm as determined by the MDT.
7. Male and female participants of reproductive potential must agree to avoid becoming pregnant or impregnating a partner and adhere to highly effective contraception requirements whilst receiving decitabine/nivolumab and for 6 months after their last dose of decitabine for female participants and for 3 months after their last dose of decitabine for male participants.

Previous inclusion criteria as of 07/03/2024:

1. Aged 18 years and over on day of signed informed consent
2. Ability to provide written informed consent.
3. Willing and able to comply with the protocol scheduled follow-up visits and examinations for the duration of the trial.
4. WHO Performance status 0-1
5. Newly suspected glioblastoma on Gadolinium-enhanced MRI scan and reviewed in the local Neuro-oncology multidisciplinary meeting, which is amenable for maximal resection.
6. Patients with tumours that do not exert significant mass effect and/or have significant oedema and where a delay to surgery is thought will lead to undue harm as determined by the MDT.
7. Male and female participants of reproductive potential must agree to avoid becoming pregnant or impregnating a partner and adhere to highly effective contraception requirements whilst receiving ASTX727/Nivolumab and for 6 months after their last dose of ASTX727 for female participants and for 3 months after their last dose of ASTX727 for male participants.

Previous inclusion criteria:

1. Aged 16 years and over on day of signed informed consent
2. Ability to provide written informed consent.
3. Willing and able to comply with the protocol scheduled follow-up visits and examinations for the duration of the trial.
4. WHO Performance status 0-1
5. Newly suspected glioblastoma on Gadolinium-enhanced MRI scan and reviewed in the local Neuro-oncology multidisciplinary meeting, which is amenable for maximal resection.
6. Patients with tumours that do not exert significant mass effect and/or have significant oedema and where a delay to surgery is thought will lead to undue harm as determined by the MDT.
7. Male and female participants of reproductive potential must agree to avoid becoming pregnant or impregnating a partner and adhere to highly effective contraception requirements whilst receiving ASTX727/Nivolumab and for 6 months after their last dose of ASTX727 for female participants and for 3 months after their last dose of ASTX727 for male participants.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
120 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 05/03/2026:
1. Patients with suspected glioblastoma who have significant mass effect and need emergency surgery.
2. Any concern on initial MRI that the tumour may not be a primary glioblastoma.
3. Patients that have previously received immunotherapy or hypomethylating agents.
4. Impaired gastrointestinal function that may significantly alter absorption of decitabine.
5. Has a known diagnosis of immunodeficiency (human immunodeficiency virus [HIV] 1/2 antibodies) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment excluding steroids.
6. Another advanced malignancy or history of another early malignancy that the investigator considers is likely to impact life expectancy.
7. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease. Patients with vitiligo, resolved childhood asthma/atopy/psoriasis or hypothyroidism stable on hormone replacement would be an exception. Patients that require intermittent use of bronchodilators or local steroid injections are not excluded.
8. Has evidence of or a history of interstitial lung disease or (non-infectious) pneumonitis.
9. History of severe allergic reactions to any unknown allergens or any components of the trial drugs.
10. Is pregnant or breastfeeding or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of trial treatment for female participants, or is expecting to father children in that time through 3 months after the last dose of trial treatment for male participants.
11. Has known active hepatitis B or hepatitis C.
12. Concurrent or recent (<28 days) treatment in any other interventional clinical trial involving novel surgical technique or medication.
13. Any psychological, social or medical condition, physical examination finding or laboratory abnormality that in the judgement of the Investigator is likely to interfere with participation in the trial.
14. Any condition that, in the clinical judgment of the treating physician, is likely to interfere with evaluation of trial treatment, interpretation of subject safety or trial results, prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.

Previous exclusion criteria:
1. Patients with suspected glioblastoma who have significant mass effect and need emergency surgery.
2. Any concern on initial MRI that the tumour may not be a primary glioblastoma.
3. Patients that have previously received immunotherapy or hypomethylating agents.
4. Impaired gastrointestinal function that may significantly alter absorption of ASTX727.
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14. Any condition that, in the clinical judgment of the treating physician, is likely to interfere with evaluation of trial treatment, interpretation of subject safety or trial results, prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.

Date of first enrolment
01/04/2026

Date of final enrolment
31/03/2028

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington
Oxford
England
OX3 7LE

Study participating centre
Bristol Haematology and Oncology Centre
22 Horfield Rd
Bristol
England
BS2 8ED

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
Bebington
Wirral
England
CH63 4JY

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

Study participating centre
Velindre Cancer Centre
Velindre Road
Cardiff
Wales
CF14 2TL

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date