

Assessment of the safety of a combined drug treatment of ASTX727 and Nivolumab, in patients with newly diagnosed brain tumours before tumour removal surgery.

Submission date 16/11/2023	Recruitment status Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 19/01/2024	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 07/03/2024	Condition category Cancer	<input type="checkbox"/> Individual participant data <input type="checkbox"/> 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. 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 ASTX727 ("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 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 ASTX727 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 ASTX727 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 ASTX727 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 ASTX727 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 initial dose of ASTX727, 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 for 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?

January 2023 to October 2026

Who is funding the study?

Cancer Research UK

Who is the main contact?

combatgb@nds.ox.ac.uk

Contact information

Type(s)

Scientific, Principal Investigator

Contact name

Prof Puneet Plaha

Contact details

Nuffield Dept. Surgical Sciences, University of Oxford, Level 3, West Wing, John Radcliffe Hospital
Oxford
United Kingdom
OX3 9DU
+44 1865 220041
puneet.plaha@nds.ox.ac.uk

Type(s)

Public

Contact name

Dr Study Team

Contact details

Nuffield Dept. Surgical Sciences, University of Oxford, Level 3, West Wing, John Radcliffe Hospital
Oxford
United Kingdom
OX3 9DU
-
combatgb@nds.ox.ac.uk

Additional identifiers

EudraCT/CTIS number

Nil known

IRAS number

1007984

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

17190, IRAS 1007984, CPMS 56996

Study information

Scientific Title

COMBinATion Nivolumab and ASTX727 (decitabine and cedazuridine) for treatment of primary Glioblastoma

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

Secondary study design

Non randomised study

Study setting(s)

Hospital

Study type(s)

Safety, Efficacy

Participant information sheet

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

Pharmaceutical study type(s)

Therapy

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 measure

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

Secondary outcome measures

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 from 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

Overall study start date

01/01/2023

Completion date

01/10/2026

Eligibility

Key inclusion criteria

Current 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

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

30

Key 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.
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.

Date of first enrolment

31/03/2024

Date of final enrolment

31/03/2026

Locations

Countries of recruitment

United Kingdom

Study participating centre

Churchill Hospital

Churchill Hospital

Old Road

Headington

Oxford

United Kingdom

OX3 7LE

Study participating centre

Bristol Haematology and Oncology Centre

22 Horfield Rd

Bristol

United Kingdom

BS2 8ED

Study participating centre

The Clatterbridge Cancer Centre NHS Foundation Trust

Clatterbridge Hospital

Clatterbridge Road

Bebington

Wirral

United Kingdom

CH63 4JY

Study participating centre

University Hospitals Birmingham NHS Foundation Trust

Queen Elizabeth Hospital

Mindelsohn Way

Edgbaston

Birmingham

United Kingdom

B15 2GW

Study participating centre

Velindre Cancer Centre

Velindre Road

Cardiff
United Kingdom
CF14 2TL

Sponsor information

Organisation

University of Oxford

Sponsor details

University of Oxford, Botnar Research Centre, Nuffield Orthopaedic Centre, Windmill Road
Oxford
England
United Kingdom
OX3 7LD

-

rgea.sponsor@admin.ox.ac.uk

Sponsor type

University/education

Website

<http://www.ox.ac.uk/>

ROR

<https://ror.org/052gg0110>

Funder(s)

Funder type

Charity

Funder Name

Cancer Research UK

Alternative Name(s)

CR_UK, Cancer Research UK - London, CRUK

Funding Body Type

Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location

United Kingdom

Results and Publications

Publication and dissemination plan

Peer reviewed scientific journals

Conference presentation

Publication on website

Other publication

Submission to regulatory authorities

Intention to publish date

30/09/2027

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary

Data sharing statement to be made available at a later date