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5G: A next generation agile genomically guided glioma modular platform for proof-of-concept molecular hypothesis testing in patients with malignant brain tumours

Submission date
03/08/2023

Recruitment status
Recruiting

Registration date
24/02/2026

Overall study status
Ongoing

Last Edited
17/03/2026

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
The 5G-PEARL is a clinical study looking at a new drug called paxalisib. This drug blocks the PI3K signalling pathway which is a cell pathway in the body that helps cancer cell growth when it is overactive. Paxalisib is currently in clinical studies for lung cancer and ovarian cancer, and being evaluated for the treatment of molecularly unselected newly diagnosed GBM patients in an experimental study (NCT03970447) as well in other experimental studies of patients with brain metastases and paediatric cancers.

The main aim of this part (Phase 1b/2) of the clinical study is to document any clinical safety and efficacy of paxalisib combined with TMZ, by measuring tumour responses and clinical benefit.

Who can participate?
In 5G-PEARL, we hope to select patients whose tumours are highly dependent on the overactive PI3K signalling pathway. Those patients would be most likely to respond to paxalisib treatment.

What does the study involve?
Paxalisib will be given in combination with temozolomide (TMZ). TMZ works by stopping cancer cells from making DNA. DNA stands for Deoxyribonucleic Acid and it is the genetic material of a cell. If the cancer cells cannot make DNA, they cannot split into two new cells, so the cancer cannot grow.

What are the possible benefits and risks of participating?
The potential benefits of the IMPs are under investigation therefore patients may not derive any clinical benefit from participating in the research. This issue will be discussed fully with the patient during the informed consent process. As with many other treatments for cancer, the side effects may be serious or life-threatening and there may be risks involved in taking this medication that are not yet known. There is always a risk involved when taking a new medication but every precaution will be taken to protect patient safety. These risks will be fully discussed

with patients during the process of informed consent and careful monitoring of the patient will be conducted throughout the study by regular assessment of their vital signs, blood tests and physical examinations by the study doctor and research nurses.
The study drug may have other side effects that are not known at this time. The patients will be told about any new side effects in a timely manner and are free to withdraw from the study at any time.
Participation in this study will require patients to have an increased number of CT, MRI and possibly bone scans outside of their normal care. These scans involve exposure to ionising radiation that may lead to cancer later in life after a delay called the latency period – this period being from 2 years for leukaemia, and up to several decades for solid tumours. The risk to the cohort of patients participating in this study with a pre-existing clinical condition may therefore be considered to be very small.
Before a CT scan, a contrast dye may be injected into the vein. Some people may develop hives and itching or other allergic symptoms from injection of this dye. In addition, this dye can temporarily decrease kidney function, especially if the kidneys are already impaired. Kidney function will be checked before the scan to minimise this risk.
An MRI scan involves lying on a bed in a magnet which can be very noisy, and uncomfortable and some patients may feel slightly claustrophobic. The radiographer will work closely with the patient to ensure that they are lying in a comfortable position. As the MRI involves a strong magnetic field patients will be asked before the scan if they have a pacemaker (the magnetic field can cause the pacemaker to malfunction), hearing aid or a metal prosthesis (implant) in their body.
The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used,
such as oral contraceptives and condoms, intra-uterine devices (IUD) and condoms, or diaphragms with spermicidal gel and condoms.
Contraceptives should be used from the date of study consent or from four weeks prior to the first dose of the study drug, throughout the study and for 6 months after completing the study.
The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to six months after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until the conclusion of the pregnancy if the patient or the patient' s partner has consented to this.

Where is the study run from?
Institute of Cancer Research (UK)

When is the study starting and how long is it expected to run for?
July 2023 to August 2029

Who is funding the study?
1. Minderoo Foundation (UK)
2. Cancer Research UK

Who is the main contact?
5G-enquiries@icr.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-paxalisib-temozolomide-glioblastoma-5g-pearl

Contact information

Type(s)
Public

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None - 5G Team

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Additional identifiers

Integrated Research Application System (IRAS)
1007726

Central Portfolio Management System (CPMS)
55941

Protocol serial number
CCR5814

Study information

Scientific Title

5G-PEARL: Paxalisib in combination with temozolomide in patients with high grade malignant brain tumours within the 5G Platform

Acronym
5G-Master and 5G-PEARL

Study objectives
The main objective of the trial is to evaluate the safety and efficacy of paxalisib in combination with temozolomide for biomarker-selected malignant brain tumours.

Primary objectives:
Phase 1b:
1. To evaluate the safety and tolerability of the investigational agent in patients with malignant brain tumours;
2. To determine the preliminary antitumour activity of the investigational agent administered at the RP2D in patients with molecularly defined malignant brain tumours.

Phase 2: To determine the antitumour activity of the investigational agent administered at the RP2D in patients with molecularly defined malignant brain tumours

Secondary objectives:
Phase 1b:
1. To identify molecular determinants of response and antitumour activity of the investigational agent in patients with molecularly selected brain tumours

Phase 2:
1. To identify molecular determinants of response and antitumour activity of the investigational agent in patients with molecularly selected brain tumours
2. To assess changes in quality of life over time

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/11/2023, London - Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; -; londoncentral.rec@hra.nhs.uk), ref: 23/LO/0720

Primary study design
Interventional

Study design
-

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Glioblastoma

Interventions

The clinical trial will be divided into two parts: Phase 1b (proof of concept of hypothesis-driven biomarker-guided therapies) and Phase 2 (preliminary efficacy testing).
This is a study within 5G: A Next Generation AGile Genomically Guided Glioma Modular Platform for proof-of-concept molecular hypothesis testing in patients with high grade malignant brain tumours.
5G-PEARL is a Bayesian multi-centre, multi-arm, open-label, adaptive, seamless Phase 1/2 trial of paxalisib in combination with temozolomide, for patients with malignant brain tumours.

5G-PEARL will recruit patients with glioblastoma (GBM) into two molecularly-defined biomarker arms of patients who have tumours that harbour:
-Hyperactivating PI3K pathogenic mutations in either PIK3CA (p100) or PIK3R1 (p85) as defined by COSMIC.
-PTEN loss as defined by 'two hits' (including either biallelic loss of PTEN, or PTEN LOH + loss of function mutation) NB: Patients with both co-occurring pathogenic PI3K mutation and PTEN loss will be defaulted to the PTEN arm.

Each biomarker arm, within Phase 1, will have robust GO/ADAPT decision points, reviewed by the Safety Review Committee (SRC) to allow for both agility and clear direction for next steps. A 2-stage Bayesian adaptive design will be performed to assess preliminary efficacy.

In the Phase 1b of this study parallel biomarker defined arms will be opened, initially in the front-line unmethylated MGMT setting, enrolling 10 patients onto each arm. These patients will be treated with paxalisib in combination with temozolomide. The starting dose of paxalisib will be 45mg once a day (OD) with the option of increasing to 60 mg (30 mg BD) in Cycle 2. TMZ will be administered once daily by mouth on days 1 to 5 in a 28-day cycle, with a starting dose of 150mg /m2 during cycles 1 and 2, and subsequent dose escalation to 200mg/m2 at the start of cycle 3 if cycles 1 and 2 have been well tolerated with no significant toxicity.
Assuming all ‘GO’ decisions are met, each biomarker arm will recruit a maximum of 32 patients across Phase 1b/2.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Paxalisib, temozolomide

Primary outcome(s)
1. Phase 1b - Incidence, nature and severity of adverse events measured using NCI CTCAE v5.0 at baseline and 12 months

2. Phase 1b - Progressionfree survival measured using investigatorassessed disease status according to RANO at 12 months

3. Phase 2 - Progressionfree survival measured using investigatorassessed disease status according to RANO at 24 months

4. Phase 2 - Overall survival measured using survival status from study records at baseline and 24 months

Key secondary outcome(s)
1. Phase 1b - Cooccurring genetic biomarkers of response measured using genetic profiling assays at over 12 months

2. Phase 2 - Cooccurring genetic biomarkers of response measured using genetic profiling assays at over 24 months

3. Phase 2 - OS12 measured using survival status from study records at baseline and 12 months

4. Phase 2 - PFS6 measured using investigatorassessed disease status according to RANO at baseline and 6 months

5. Phase 2 - Incidence, nature and severity of treatmentemergent adverse events during combination with TMZ measured using NCI CTCAE v5.0 at over 24 months

6. Phase 2 - Global healthrelated quality of life measured using EORTC QLQC30 at baseline, end of Cycle 1 and Cycle 3 Day 1

7. Phase 2 - Global healthrelated quality of life measured using EORTC QLQBN20 at baseline, end of Cycle 1 and Cycle 3 Day 1

Completion date
13/08/2029

Eligibility

Key inclusion criteria
Phase 1b:
1. Patients with:
1.1. Glioblastoma, IDH-wildtype Grade 4
2. Patients for Phase 1b will need to have consented to the Minderoo Precision Brain Tumour Programme and have available whole genome and transcriptome data available.
3. Patients for the front-line minimal residual disease (MRD) cohort will be eligible following completion of optimal surgery and Stupp-based adjuvant chemoradiotherapy as long as they meet all other inclusion/exclusion criteria.
4. Aged 16 years or over.
5. Life expectancy of at least 12 weeks.
6. World Health Organisation (WHO) performance status of 0–1.
7. Neurologically stable (eg without a progression of neurological symptoms or requiring escalating doses of systemic steroid therapy within the last week prior to informed consent).
8. Written (signed or dated) informed consent and be capable of co-operating with treatment and follow-up.
9. Haematological and biochemical indices within the ranges shown below. These measurements must be performed within one week prior to the first dose of either IMP.
9.1. Haemoglobin (Hb): ≥ 9.0 g/dL
9.2. Absolute neutrophil count: ≥1.5 x 10^9/L
9.3. Platelet count: ≥100 x 10^9/L
9.4. Coagulation: INR < 1.5 and APTT <1.5x if not anticoagulated
9.5. INR stable > 7 days within intended therapeutic range if anticoagulated
9.6. Bilirubin: Within institution normal ranges
9.7. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST): <3 x ULN

9.8. Albumin: ≥28 g/dL
9.9. Creatinine: <1.5 x ULN
9.10. Sodium: ≥130 mmol/L
9.11. Potassium, Calcium, Magnesium, phosphate: Within institution normal ranges (replacement is permitted)
9.12. HbA1C (%): <8.0
9.13. Urinary protein: <1+ on dipstick
10. Female patients with reproductive potential must have a negative serum pregnancy test within 14 days prior to the start of the trial.
11. Men and women of childbearing potential must agree to comply with the use of a highly effective method of contraception so as to avoid impregnating a partner or becoming pregnant, respectively, during the study and for at least 150 days after the last dose of either investigational drug.

Phase 2: Patients with any other CNS tumours will only be eligible for defined Phase 2 biomarker arms once a Phase 1b GO decision has been met. Specific eligibility criteria for these tumours will be defined following an amendment.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 Years

Upper age limit
99 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Phase 1b:
1. Receipt of treatment before the first dose of the study drug (Cycle 1 Day 1) within an interval shorter than the following, as applicable:
1.1. Cytotoxic chemotherapy during the prior 2 weeks or 6 weeks for nitrosoureas
1.2. Bevacizumab during the prior 6 weeks
1.3. Five half-lives of any small molecule investigational or licensed medicinal product.
2. Prior immune checkpoint inhibitor therapy or vaccine therapy is not permitted. Prior use of any other immune-modulatory investigational agent must be discussed with sponsor team and CI.
3. Ongoing Grade 2 or greater toxicities from pre-existing conditions or from previous treatments.

4. Patients with carcinomatous meningitis, leptomeningeal spread of tumour, spread of tumour to the brain stem or spinal cord.
5. Has evidence of recent intratumoural or peritumoural haemorrhage on baseline MRI. Patients with radiological findings that are stable on at least 2 consecutive MRI scans at least 3 weeks apart will be eligible.
6. History of clinical relevant bleeding disorders, including significant GI bleeding within the last 6 months.
7. History of arterial thromboembolism.
8. Recent (within 3 months) deep vein thrombosis or pulmonary embolism or other significant thromboembolism. Venous port of catheter thrombosis or superficial thrombosis are not considered significant. Patients with prior thrombosis (> 3 months ago) on stable anticoagulation are permitted to be enrolled.
9. History of clinically significant cardiac disorders:
9.1. Myocardial infarction, or New York Heart Association Class II to IV congestive heart failure, within 6 months of the first dose of the study drug.
9.2. Concurrent and clinically significant abnormalities on ECG at Screening, including a corrected QT interval (QTcF >480ms).
10. History of malabsorption syndrome or other conditions that may interfere with enteral absorption. Patients with a history of or active inflammatory bowel disease (eg Crohn's disease or ulcerative colitis). History of gastrointestinal perforation or fistulae.
11. History of uncontrolled diabetes. Patients with controlled diabetes on therapy with HbA1C <8% will be eligible.
12. Has urine protein > 1g/24 hours. Participants with >1+ on urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria.
13. Has significant lung disease including pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, active tuberculosis, or history of opportunistic infections (including PCP or CMV pneumonia).
14. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
15. Steroid requirement for neurological symptom control of >3mg Dexamethasone per day (patients will be allowed to enrol if they have been on a stable dose of steroids of equivalent or less than 3mg Dexamethasone for at least 5 days prior to Day 1 of Cycle 1).
16. Has received a live vaccine within 30 days of the planned start of study therapy. Note: inactive vaccines including COVID vaccines are allowed prior to 1 week of Day 1 of Cycle 1).
17. Current active concurrent malignancy. Cancer survivors who have undergone potentially curative therapy for a prior malignancy, have no evidence of that disease recurrence for three years or more and are deemed at negligible risk of recurrence will be eligible.
18. Is a participant or plans to participate on another interventional clinical trial while taking part in this Phase 1 study. Participation in an observational trial would be acceptable.
19. Any other condition which in the investigator's opinion would not make the patient a good candidate for the clinical trial.
20. Exposure to medications (with or without prescriptions), supplements, herbal remedies, or foods with potential for drug-drug interactions with study interventions within 14 days prior to the first dose of study intervention and during the course of therapy, including strong CYP3A4 inhibitors or inducers, due to potential drug-drug interactions with both paxalisib and temozolomide.
21. Major surgery within 4 weeks (excluding placement of vascular access), minor surgery within 2 weeks.
22. Live and attenuated vaccines are not permitted during or within 4 weeks prior to initiation of study treatment.

Date of first enrolment

13/02/2026

Date of final enrolment
13/02/2029

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
The Royal Marsden Hospital – Drug Development Unit
Downs Road
Sutton
England
SM2 5PT

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
England
SO16 6YD

Study participating centre
Edinburgh Cancer Centre, Western General Hospital
Crewe Road South
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Scotland
EH4 2XU

Sponsor information

Organisation
Institute of Cancer Research

ROR
https://ror.org/043jzw605

Funder(s)

Funder type
Charity

Funder Name
Minderoo Foundation

Alternative Name(s)
The Minderoo Foundation Pty Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Australia

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