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Olaparib and radiotherapy or olaparib and radiotherapy plus temozolomide in newly-diagnosed glioblastoma stratified by MGMT status

Submission date 31/05/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 06/06/2016	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 14/11/2024	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-olaparib-with-radiotherapy-and-chemotherapy-for-glioblastoma-paradigm-2

Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2016-000865-22

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
PARADIGM2-2016

Study information

Scientific Title
PARADIGM-2: OlaPArib and RADIotherapy or olaparib and radiotherapy plus temozolomide in newly-diagnosed Glioblastoma stratified by MGMT status: two parallel Phase I studies

Acronym
PARADIGM-2

Study objectives
The trial hypothesis is that combining olaparib with radiotherapy +/- temozolomide will improve outcomes for patients with newly diagnosed glioblastoma, without exacerbating toxicity.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West of Scotland REC1, 15/06/2016, ref: 16/WS/0089

Study design
Two parallel multi-centre open-label non-randomized dose-escalation Phase I studies within one clinical trial protocol

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

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

Interventions
Parallel 1 (Methylation of MGMT promoter region) – Patients will receive partial brain radiotherapy, consisting of 60 Gray in 30 fractions over 6 weeks (Monday to Friday), planned and delivered using Intensity Modulated Radiotherapy (IMRT) with fixed fields or arcs. Patients will receive oral temozolomide chemotherapy (75mg/m2) daily throughout radiotherapy, with concomitant, intermittent once daily olaparib starting on day 1 of radiotherapy and for 4 weeks immediaitely following completion of radiotherapy (total 70 +/- 2 days). Olaparib treatment will be on an intermittent schedule as defined by dose cohort. Patients will then receive 6 cycles of adjuvant temozolomide chemotherapy at standard dose and schedule.

Parallel 2 (Unmethylated MGMT promoter region) – Patients will receive partial brain radiotherapy, consisting of 60 Gray in 30 fractions over 6 weeks (Monday to Friday), planned and delivered using Intensity Modulated Radiotherapy (IMRT) with fixed fields or arcs. Patients will receive oral olaparib delivered daily in combination with radiotherapy, commencing 3 days prior to radiotherapy and for 4 weeks immediately afterwards (total 73 +/- 2 days). Olaparib treatment will be continuous during this period.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Olaparib

Primary outcome measure
The maximum tolerated dose and schedule of olaparib in combination with radiotherapy and temozolomide (parallel 1) and in combination with radiotherapy alone (parallel 2).

This will be measured by clinical and laboratory toxicity, NCI-CTC version 4.03.

Secondary outcome measures
1. Toxicity, including acute and subacute neurotoxicity – measured by clinical and laboratory toxicity, NCI-CTC version 4.03
2. Progression free survival – measured by MRI scan, reported using RANO criteria
3. Overall survival – measured by date of death/date patient last assessed

Overall study start date
01/08/2015

Completion date
30/08/2026

Eligibility

Key inclusion criteria
1. Age <70 years
2. Histologically confirmed diagnosis of glioblastoma (WHO grade 4, including variants)
3. WHO performance status 0 or 1
4. Sufficient tumour material for MGMT promoter methylation assay
5. Life expectancy greater than 12 weeks
6. No previous radiotherapy for primary or secondary CNS malignancy
7. Ability to provide informed consent prior to participating in the trial and any trial-related procedures being performed
8. Adequate haematological, hepatic and renal function defined as below:
8.1. Haemoglobin > 100g/L (no red blood cell transfusions in the 28 days prior to trial entry)
8.2. Absolute neutrophil count >1.5 x 109/L
8.3. White Blood Cells >3 x 109/L
8.4. Platelet count > 100 x 109/L
8.5. Bilirubin < 1.5 x upper limit of normal (ULN)
8.6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 2.5 x ULN
8.7. Adequate renal function with creatinine clearance / glomerular filtration rate > 50 ml/min calculated by Cockcroft-Gault/Wright formula
9. Able to commence radiotherapy treatment within 6 weeks (+ 1 week if necessary) of surgery
10. Willingness to comply with scheduled visits, treatment plans, laboratory tests and any other trial procedures
11. Ability to swallow oral tablets or capsules
12. Evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 7 days of trial entry
Postmenopausal is defined as:
12.1. Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments
12.2. LH and FSH levels within the postmenopausal range for women under 50
12.3. Surgical sterilisation (bilateral oophrectomy or hysterectomy)

Participant type(s)
Patient

Age group
Adult

Upper age limit
70 Years

Sex
Both

Target number of participants
Approximately 50

Key exclusion criteria

1. Age ≥70 years
2. WHO performance status >2
3. Life expectancy less than 12 weeks
4. Active concurrent malignancy (except non-melanoma skin cancer or in-situ carcinoma of the cervix). If history of prior malignancy, must be disease-free for >5 years
5. Prior treatment for primary or secondary CNS malignancies
6. Confusion or altered mental state that would prohibit patient understanding and giving of informed consent
7. Concomitant treatment with medicines detailed in section 5.8 of the PARADIGM-2 protocol
8. Female patients who are able to become pregnant (or are already pregnant or lactating). Lactating patients should not breastfeed during treatment or for 1 month after the last dose of olaparib. However, those female patients who have a negative serum or urine pregnancy test before enrolment and are not lactating and agree to the use of two highly effective forms of contraception (as detailed in section 7.1.7) effective at the first administration of IMP, throughout the trial and for at least one month afterwards are considered eligible
9. Male partners of child-bearing potential (unless they agree to take measures not to father children by using one form of highly effective contraception, as detailed in section 7.1.7, effective at the time of administration of IMP, throughout the trial and for six months afterwards). Men with pregnant or lactating partners should be advised to use barrier method contraception to prevent exposure to the foetus or neonate
10. Administration of any investigational drug within 28 days prior to receiving the first dose of trial treatment
11. Any previous treatment with a PARP inhibitor, including olaparib
12. Any red blood cell transfusions within 28 days prior to trial entry (platelet and clotting factor transfusions are allowed)
13. Patients with myelodysplastic syndrome/acute myeloid leukaemia
14. Major surgery within 14 days of starting trial treatment; patients must have recovered from any effects of major surgery
15. Patients with a known hypersensitivity to any of the excipients of olaparib, temozolomide or dacarbazine (DTIC)
16. Patients with uncontrolled seizures
17. Patients who are known to be HIV positive, or who are known to have positive Hepatitis B or C serology

Date of first enrolment
01/08/2016

Date of final enrolment
01/04/2025

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Beatson West of Scotland Cancer Centre
Glasgow
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Study participating centre
The Christie NHS Foundation Trust
Manchester
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M20 4BX

Study participating centre
St James University Hospital
Leeds
United Kingdom
LS9 7TF

Study participating centre
Addenbrookes Hospital
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Bristol Haematology and Oncology Centre
Bristol
United Kingdom
BS2 8ED

Study participating centre
Velindre Cancer Centre
Cardiff
United Kingdom
CF14 2TL

Sponsor information

Organisation
NHS Greater Glasgow & Clyde and University of Glasgow

Sponsor details
Research and Development Office
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
Scotland
United Kingdom
G3 8SW

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Funder Name
The Brain Tumour Charity

Funder Name
Astra Zeneca

Results and Publications

Publication and dissemination plan
The PARADIGM-2 TMG is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from the trialand for assuring the confidentiality and integrity of the trial. It will provide collaborators with the International Committee of Medical Journal Editors (ICMJE) criteria which will be used to ensure all those who have contributed to the study are appropriately acknowledged.

No site or individual will publish data without prior approval of the TMG.

The data arising from PARADIGM-2 will belong to the trial Co-Sponsors NHS Greater Glasgow & Clyde and The University of Glasgow. The TMG shall act as custodian of this data.

Intention to publish date
30/11/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Anna Morris, Project Manager, anna.morris@glasgow.ac.uk

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