PARADIGM- 2 (BR36)

Ola**PA**rib and **RADI**otherapy or olaparib and radiotherapy plus temozolomide in newly-diagnosed **G**lioblastoma stratified by **M**GMT status: **2** parallel phase I studies

INITIATION SLIDES
VERSION 2, 16 Nov 2016

TRIAL DETAILS

- The trial is being co-ordinated by CRUK via the Cancer Research UK Clinical Trials Unit, Glasgow (CRUK CTU)
- Co-sponsors of the trial are Greater Glasgow & Clyde Health Board (GG&CHB) and University of Glasgow (GU)
- Chief Investigator is Professor Anthony Chalmers
- The trial has been endorsed by Cancer Research UK and will be funded by AstraZeneca under the terms of their collaboration with the National Cancer Research Network.

Please note this presentation has been prepared as part of your site initiation. These slides are a complement to the protocol. All site staff must have read and understood the protocol and the trial requirements prior to signing off the initiation acknowledgment sheet.

- The trial will be conducted according to ICH GCP guidelines
- The trial will be conducted in accordance with the EU Directive 2001/20/EC
- The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington (2002), Tokyo (2004), Seoul (2008) amendments

TRIAL TEAM

- Chief Investigator : Professor Anthony Chalmers
- Trial Statisticians: Caroline Kelly and Jamie Stobo
- Project Manager: Anna Morris
- Sponsor Pharmacist: Paula Morrison
- Pharmacovigilance Manager: Lindsey Connery
- Clinical Trial Coordinator: Susan Dillon
- Trial Monitor: Barbara Ross
- Co-Sponsor Representative: Joanne McGarry

TRIAL DESIGN AND OBJECTIVES

- 2 parallel, multi-centre, open-label, non-randomised, dose-escalation phase I studies within one clinical trial protocol.
- There will be 2 parallel groups, each of which will follow the principles of a 3+3 cohort design but also take into account other analyses of current and all previous cohort data within each parallel study and information from external sources.
- Approximately 44-68 patients across both parallels of the trial will be recruited .

Primary objectives :

- Parallel 1 (methylation of the MGMT promoter region)– to establish the safety, toxicity and maximum tolerated dose of olaparib in combination with radiotherapy and temozolomide.
- Parallel 2 (unmethylated MGMT promoter regions)– to establish the safety, toxicity and maximum tolerated dose of olaparib in combination with radiotherapy.

ELIGIBILITY CRITERIA

- The trial includes a population of patients with newly diagnosed glioblastoma who meet the NICE TA23 eligibility criteria for treatment with radical radiotherapy and concomitant temozolomide.

- All patients will be under the age of 70 years and WHO performance status 0 or 1.

- Eligibility to enter the trial will be assessed by histological diagnosis and suitability for radical radio-chemotherapy, as defined by the inclusion criteria.

- Performance status will be assessed at the first oncology appointment (post-biopsy or resection) by the oncologist responsible for the patient's non-surgical management.

Please refer to section 3.1 of the study protocol for full details of the eligibility criteria for the study.

There will be no exceptions to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed prior to calling for registration. Patients are eligible for the trial if all the inclusion are met and none of the exclusion criteria applies.

SLOT REQUESTS AND SLOT ALLOCATION

Each cohort has an initial 3 places which should be filled using the slot request system. Ethically we cannot refuse treatment to an eligible patient that has consented to a trial so **each site must ensure that they have a slot on the cohort before the patient has been approached with the patient information.**

SLOT ALLOCATION

- CRUK CTU will provide a slot request form for the site that should be completed and returned to the CRUK CTU in order for a slot to be allocated.
- Upon receipt of the slot request form CRUK CTU will process the form and allocate the slot if there is one available.
- Upon confirmation of the slot allocation the site can approach the patient with the patient information, consent (if patient agrees) and begin the screening process.
- For patients that decline participation or fail to meet the eligibility criteria please contact the CRUK CTU asap in-order to re-allocate the slot.

For slot allocations and requests contact: Susan Dillon

Tel: 0141 301 7232

Fax: 0141 301 7946

Email: susan.dillon@glasgow.ac.uk

ReoGlio: This study recruits from the same patient population, and is predicted to open December 2016. Weekly updates on available slots for both studies will be issued to all participating sites to allow oversight and tracking of recruitment.

REGISTRATION PROCEDURE

Patients cannot be screened or registered to the trial until the site has been activated to begin recruitment.

There is a three-step process for trial registration:

1. Request screening number using the Screening Registration Form

2. Record result of MGMT central testing using the Result of MGMT Testing Form

3. Register patient for trial treatment using the Registration Form

1. SCREENING REGISTRATION

- The site should contact the CRUK Clinical Trials Unit (CTU), Glasgow to request a patient identifier for the patient. This should be done by completing the Screening Form for MGMT Testing.

- Each patient will be allocated a unique sequential patient ID number (6 digit number) for the trial.

- The site should immediately complete the Neuropathology Referral Form and send with the sample to Bristol Genetics Laboratory.

- The MGMT testing should take no more than 7 days from the receipt of the sample.

- Once the MGMT status is known, the patient can be registered to the trial.

2. CENTRALISED MGMT TESTING

- The Bristol Genetics Laboratory will notify both the CTU and the site study team of the outcome of the MGMT testing.

- Once this has been received, the site should complete the Result of MGMT Testing Form and submit to CRUK CTU Glasgow.

- At this point, it will be determined whether the patient will proceed to registration to the trial.

3. REGISTRATION FOR TRIAL TREATMENT

Prior to commencing any trial related procedures, all participants will be fully informed about the risks, benefits and procedures involved in trial participation, and will sign a consent form confirming this process. All patients will then undergo a period of screening during the 28 days prior to initiation of trial treatment. All patients must be registered onto the trial prior to commencement of any treatment.

Screening evaluations (within 28 days of registration) will consist of:

- Demographic details
- Medical history
- MGMT testing
- MRI of the brain - *Must be reported as per protocol. This involves using RANO Criteria.*

Screening evaluations (within 7 days of registration) will consist of:

- Physical examination
- WHO performance status
- Review of medications including steroid use
- Vital signs
- Pregnancy test
- Full neurological examination
- Full blood count
- Serum biochemistry

→ Check that patient fulfils eligibility criteria as per trial protocol section 3.1 and 3.2 - *There will be no exceptions to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed prior to calling for registration. Patients are eligible for the trial if all the inclusion are met and none of the exclusion criteria applies.*
→ Check that patient has given written informed consent as per the informed consent process.
→ Complete Registration Form.

Site staff must contact the CRUK CTU to register the patient for trial treatment, this can be done by either telephone or fax on the following numbers:

Tel no: 0141 301 7232
Fax no: 0141 301 7946*
08.30-17.00 Mon-Thurs and 08.30-16.30 Friday, except public holidays
* **Faxes received outside of office hours will be processed the next working day**

✓ Dose level of trial drug will be provided dependent on the dose cohort the patient is being registered onto.

DOSE ESCALATION COHORTS

- Patients will be recruited into the dose escalation component in cohorts of 3-6 patients. Each cohort will consist of a minimum of 3 patients.
- The starting dose of olaparib will be 100 mg once daily on one day per week and if tolerated will be increased for subsequent cohorts.
- There will be no dose reduction permitted if the starting dose (Cohort 1) is not tolerated. If the patient is already on the lowest dose of olaparib, no further dose reductions are allowed and the patient should come off study.

PARALLEL 1

Dose level	Olaparib dose (starting day 1 of radio-chemotherapy and continuing until 4 weeks after end of radio-chemotherapy)	Temozolomide dose (starting day 1 and continuing daily throughout radio-chemotherapy)
-1	50 mg once daily Day 1 of each week	75 mg/m^2 once daily
1	100 mg once daily Day 1 of each week	75 mg/m^2 once daily
2	100 mg once daily Days 1 and 2 of each week	75 mg/m^2 once daily
3	100 mg once daily Days 1 – 3 of each week	75 mg/m^2 once daily
4	150 mg once daily Days 1 – 3 of each week	75 mg/m^2 once daily
5	150 mg once daily Days 1 – 4 of each week	75 mg/m^2 once daily
6	150 mg once daily Days 1 – 5 of each week	75 mg/m^2 once daily

DOSE ESCALATION COHORTS

PARALLEL 2

Dose level	Olaparib dose (starting three days prior to radiotherapy and continuing until 4 weeks afterwards)
1	50 mg once daily, continuous
2	100 mg once daily, continuous
3	100 mg twice daily, continuous
4	200 mg twice daily, continuous

- Treatment within a new cohort may commence once the 3rd patient from the previous cohort becomes evaluable and there have been no new DLTs in that cohort.
- If one patient from the first 3 in a cohort experiences a DLT, that cohort will be expanded to include a further 3 evaluable patients. If no further patients in that cohort experience a DLT, then treatment within the next cohort may commence.
- If two or more patients among the first 3-6 patients in a cohort experience DLTs, then that dose cohort will be considered non-tolerable. Enrolment into that cohort will cease and the dose used in the previous cohort will be taken forward as the Maximum Tolerated Dose (MTD).

DOSE LIMITING TOXICITIES (DLTs)

Dose Limiting Toxicities will be defined as:

- Failure to complete radiotherapy because of toxicity, as considered by the investigator in consultation with the safety review committee (SRC) (i.e. with no evidence of tumour progression).
- In parallel 1 (MGMT methylated), failure to complete concomitant temozolomide chemotherapy because of toxicity, as considered by the investigator in consultation with the SRC (i.e. with no evidence of tumour progression).
- Any grade ≥3 non-haematological toxicity (see appendix CTCAE 4.03) that was not present prior to commencing olaparib and which, in the opinion of the investigator in consultation with the SRC, is due to olaparib or the combination of olaparib and radiotherapy (+/- temozolomide). Such toxicities will be classed as a DLT from start of olaparib treatment until the end of olaparib treatment (ie. 4 weeks after the end of radiotherapy treatment).
- In parallel 1 only, any toxicities grade ≥3 occurring during adjuvant temozolomide will not be considered a DLT. However any toxicity grade ≥3 deemed due to interaction between temozolomide and olaparib will be considered a DLT.
- Neutropenia grade 4 that persists for ≥5 days and occurs during the olaparib treatment period.
- Febrile neutropenia grade ≥3 (absolute neutrophil count $<1.0 \times 10^9$/L and fever ≥38.5^{o}C) that occurs during the olaparib treatment period.
- Thrombocytopenia grade 4 which persists for ≥5 days or is associated with active bleeding or requiring platelet transfusion and occurs during the olaparib treatment period.

EVALUABLE PATIENTS

All patients receiving at least one fraction of radiotherapy with concomitant olaparib will be evaluable for safety decisions.

The following patients will not be evaluable (unless they experience a DLT):

- Patients who have missed five or more fractions of radiotherapy, five or more days of olaparib during the radiotherapy treatment, or seven or more days of olaparib during the post-radiotherapy period for reasons other than a DLT (or dose interruption due to toxicity) will not be evaluable for dose escalation decisions and will be replaced.

- Any patient who has dose modifications not permitted by the trial protocol.

Non-evaluable patients will be replaced unless 2 or more DLTs have already been observed in that cohort.

DOSE ESCALATION DECISION

The decision to escalate to the next dose cohort will be made by a safety review committee with clinical representation from each of the participating phase I sites.

When the criteria to stop dose escalation are met, the information will be communicated to all participating sites by email correspondence from the trial team at the CRUK CTU to the trial CI, all PIs and main contacts for each phase I site so that no patients are further exposed to dosages above the maximum tolerated dose (MTD).

DOSE EXPANSION PHASE

There will be a dose expansion phase for each parallel group.

A total of 10 patients (including the estimated 3-6 patients in the MTD cohort) will be recruited into each expansion phase.

- **Parallel 1**: Patients will receive the recommended dose and schedule of olaparib in combination with radiotherapy and temozolomide. Patients will go on to receive adjuvant temozolomide as standard.

- **Parallel 2**: Patients will receive the recommended dose of olaparib in combination with radiotherapy.

TREATMENT AND DURATION (PARALLEL 1 AND 2)

- Hypofractionated, short-course radiotherapy (60 Gray in 30 fractions) over 30 – 35 days

- Olaparib will be commenced day 1 of radiation (Parallel 1) or 3 days prior to radiation (Parallel 2) and will continue throughout radiotherapy treatment and for a further four weeks for a total of 70 - 73 days.

- If there are delays in radiotherapy, olaparib dosing should continue on those days which may result in a total number of treatment days of >73 days.

- The dose of olaparib will be according to the current dose cohort that they are taking part in.

Patients in **PARALLEL 1** will also receive:

- Oral temozolomide chemotherapy (75mg/m^2) daily throughout radiotherapy.

- Patients will then receive 6 cycles of adjuvant Temozolomide 150mg/m^2 days 1-5 of each 28 day cycle, with the dose increased to 200mg/m^2 for cycles 2-6 if cycle 1 is tolerated with acceptable toxicity. Adjuvant temozolomide should start no earlier than 4 weeks after completion of radiotherapy (i.e. after completion of olaparib) and ideally within 8 weeks after completion of radiotherapy.

DOSE MODIFICATIONS FOR TOXICITY

- Delays of up to 7 days in radiotherapy are permitted once the patient has started radiotherapy.

- Patients should continue taking olaparib until radiotherapy is completed and for 4 weeks after completion of radiotherapy, unless the cause of the delay is thought to be related to olaparib or the olaparib/radiotherapy combination.

- Patients in parallel 1 (MGMT methylated) should also continue taking temozolomide until radiotherapy is completed, unless the cause of the delay is thought to be related to temozolomide or the olaparib/temozolomide/radiotherapy combination.

Please refer to the study protocol for full details of treatment modifications/ dose reductions/ delays

DOSE MODIFICATIONS FOR OLAPARIB

- The dose and/or schedule should be reduced to that of the previous (lower dose intensity) cohort. No more than two dose reductions per patient are allowed.
- If the patient is already on the lowest dose of olaparib, no further dose reductions are allowed and the patient should come off study.
- If a patient has had a dose reduction, no re-escalation of the dose is permitted.

DOSE DELAYS FOR OLAPARIB

- If patients experience dose limiting toxicities while taking olaparib, the drug should be discontinued during concomitant chemoradiation but can be recommenced at or during the adjuvant 4 week period if dose limiting toxicities have resolved and no grade ≥3 toxicities persist (excluding lymphopenia).
- For haematological toxicities (non-dose limiting), if platelet count falls below 100 x 109/L during concomitant chemoradiation, olaparib should be withheld but can be restarted at a reduced dose if platelet count recovers to ≥100. If neutrophil count drops below 1.0 x 109/L during concomitant chemoradiation, olaparib should be withheld but can be restarted at a reduced dose if neutrophil count recovers to ≥1.0.

DOSE MODIFICATIONS FOR TEMOZOLOMIDE

- If patients experience dose limiting toxicities whilst taking temozolomide, the drug should be discontinued.
- If interruptions in temozolomide dosing are required and criteria for re-starting it are met, the dose should be reduced to 50 mg/m^2.
- No further dose reductions are allowed. No re-escalation of the dose is allowed.
- Administration of adjuvant temozolomide should follow local clinical protocols.

DOSE DELAYS FOR TEMOZOLOMIDE

- If patients experience dose limiting toxicities whilst taking temozolomide, the drug should be discontinued.
- If platelet count falls below 100 x 10^9/L during concomitant chemoradiation, temozolomide should be withheld but can be restarted at a reduced dose if platelet count recovers to ≥100.
- If neutrophil count drops below 1.0 x 10^9/L during concomitant chemoradiation, temozolomide should be withheld but can be restarted at a reduced dose if neutrophil count recovers to ≥1.0.
- Administration of adjuvant temozolomide should follow local clinical protocols.

INFORMED CONSENT PROCESS

Informed consent process:

- Two original Consent Forms must be completed by a clinician (or deputy listed on delegation log)
- Two originals signed and completed by the patient
- Date must be prior to registration
- Make one photocopy
  - Original to be filed in Investigator File
  - Original to be given to patient (+PIS)
  - Photocopy to be filed in hospital notes
- Consent Form must not be sent to CRUK CTU Glasgow

FOR ERRORS NOTED AFTER CONSENT

- Add explanatory note/file note
- New version of Patient Information Sheet must be provided to patients consented with previous version. This must be given to all patients regardless of treatment stage, during next possible clinic visit.
- Patients who are still on active treatment will be required to repeat the consent process using the updated form. If it is not appropriate to re-consent patient (i.e. patient terminally ill) please make a note regarding this in the patients case notes and on re- consent log which is filed in your study site file.

CONSENT WITHDRAWAL

When the patient specifically asks to withdraw their consent at any point in the trial. If this occurs:

- Document clearly in the patient notes that the patient has withdrawn consent, the level of consent withdrawal and the reason (if the patient has given any)
- Contact CRUK CTU Glasgow for further guidance.
- If requested, send the consent withdrawal notification form to the CRUK CTU
- No further follow-up should be collected on the patient from that point onwards.

PROCESS FOR NOTIFICATION OF PROTOCOL DEVIATIONS BY SITES

- All participating sites must notify the Sponsor via CRUK CTU Glasgow of all protocol deviations from the protocol or GCP immediately.

- The Sponsor requires a report on the incident and a protocol deviation form will be provided during site initiation which should be used for informing of protocol deviations.

- If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the CRUK CTU trial team and Sponsor can be contacted immediately to discuss. The Sponsor will assess all incidents with respect to the criteria of a “serious breach”.

MANAGEMENT OF SERIOUS BREACHES

- The PI and site staff will be notified of any potential issues that have been identified which are considered to require escalation to the Sponsor.

- CRUK CTU will act as the liaison between the PI and Sponsor to clarify any details or request any further information in relation to the issues.

- Once agreed by the Sponsor that the issues are a potential serious breach or are a serious breach they will prepare the report to the MHRA.

- It is important that sites respond to requests for further information in a timely manner as serious breaches are required to be reported within 7 days of the Sponsor becoming aware of the issue.

- Sponsor will onwardly report as required.

- The MHRA respond to Sponsor and further investigation is carried out as appropriate with same staff as outlined above.

MONITORING (1)

CENTRAL MONITORING

Trial sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. Trial staff will be in regular contact with site personnel (by phone/ email) to check on progress and deal with any queries that they may have.

TELEPHONE AND REMOTE MONITORING

The 1st visit will take the form of a remote telephone monitoring visit:

- The time & date will be agreed with a member of the Site Trial Team & a separate time & date agreed with a member of the Clinical Trials Pharmacy Department
- A pro forma covering the questions which will be covered during the telephone monitoring visit will be sent with confirmation of the confirmation of the agreed date
- Please set aside 50 to 70 minutes for this call.

MONITORING (2)

ON SITE MONITORING

The 2nd visit will take the form of an on- site monitoring visit:

- Investigators and site staff will be notified in advance about forthcoming pre arranged monitoring visits
- All patient source documentation should be made available to enable Source Document Verification by the Clinical Trial Monitor
- A full working day is required for on-site visits & arrangements should be in place to facilitate the monitor access on the agreed date
- If sites are able to provide printed results/reports these must be filed in the source documents
- If a site is using electronic data reporting systems or electronic records & hard copies are not available the clinical trial monitor must be permitted access to the system either by being issued with a temporary login or a member of staff available for the duration of the visit to facilitate electronic access to authorised reports/results
- The pharmacy department responsible for the trial will be visited to allow monitoring of the pharmacy site file and review of security, storage and accountability of trial drugs.
- All findings will be discussed at an end of visit and any unresolved issues raised as Action Points
- Action Points will be followed up by the monitor until resolved

DATA MANAGEMENT

CRFs for the trial:

- Screening Registration Form
- MGMT Testing Result Form
- Registration Form
- Pre-Treatment form
- Treatment Form
- Adjuvant Temozolomide Treatment Form
- End of Treatment Form
- Follow–Up Form
- Consent Withdrawal Notification Form
- Pregnancy Notification Form

CRF completion timelines:

- Data entry – within 4 weeks of the patient visit
- DLT Forms immediately after visit
- Resolution of queries – within 4 weeks of receipt
- All data should be returned to CRUK CTU Glasgow within 1 week of sign off

DATA ESCALATION PROCESS

- CRUK CTU will regularly chase outstanding data from participating sites. Routine requests for outstanding data and data queries will be performed quarterly or more regularly if required.
- Sites will be routinely requested to return outstanding data and data queries within 6 weeks of receiving the queries or the CRF being due for completion.
- Trigger reports will be run quarterly at the same point as the routine requests for data. If 20% of forms are overdue for more than 3 months (at least 10 forms meeting this criteria) or any forms greater than 6 months overdue the site will be contacted. A log will be kept of any sites meeting a trigger point.
- If a site consistently meets a trigger point an escalation process will begin. See the protocol for further information.

SITE SET UP

CRUK CTU GLASGOW

Main REC approval - MHRA approval – HRA Document Package - Site Initiation Slides - Investigator Site File - Pharmacy Site File

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SITE

Delegation and Study Specific Training Log – SSI (if required) – R&D Approval/ confirmation – Clinical Trial Agreement – Investigator and Lead Pharmacist CVs - GCP Certificates for PIs – PIS/CF, GP Letter etc. on Trust headed paper - Lab normal ranges and accreditation certificates (haem and biochem)

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INITIATION PROCESS

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DRUG SUPPLY

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SITE ACTIVATED

CONFIDENTIALITY

- All information collected during the course of the study will be kept strictly confidential. Information will be held securely on paper and/ or electronically at CRUK CTU Glasgow. CRUK CTU Glasgow will comply with all aspects of the 1998 Data Protection Act and National Health Service Guidelines for storage, transmittal and disclosure of patient information.

- Data on patients treated on the study will be held in study case report forms (CRFs), these files will be identified by a trial number and patient initials only.

- Patient identifiable data (such as full name/ or initials with date of birth) should not be sent on email correspondence- if you need to refer to a patient use trial name and patient number.

- Where central monitoring of source documents by CRUK CTU (or copies of source documents) are required (eg. scan results, blood results) the personal data of the patient must be anonymised on the report eg. black out the patient's name and any other identifiable information.

- Where anonymisation of documentation is required, sites are responsible for ensuring no patient identifiable data is present before sending it to CRUK CTU Glasgow.

RECORD RETENTION AND ARCHIVING ARRANGEMENTS

- Archiving of the trial essential documents should be performed by both the participating trial site and Sponsor/ CRUK CTU Glasgow.

- Participating sites are responsible for archiving their trial related documentation and should follow the requirements of their R&D office in conjunction with advice from CRUK CTU Glasgow and Sponsor regarding the duration of document retention.

- Sites should not archive their trial documentation until they have been instructed to do so by CRUK CTU/ Sponsor. Where possible, at the time of archiving sites will be notified of the archiving retention period. If this is not confirmed at the time of archiving, sites should not destroy archived documentation until authorisation is given from the Sponsor.

- The Sponsor and CRUK CTU Glasgow will be responsible for archiving the Trial Master File (TMF) and all other essential trial documentation that is not held at participating trial sites as per their applicable Standard Operating Procedures.

PHARMACOVIGILANCE

Clinical Trial Regulations require:

- Investigators document all Adverse Events (AEs) in patient notes and as required by the CRF
- Investigators report Serious Adverse Events (SAEs) immediately to the CRUK CTU
- The CRUK CTU (on behalf of the Sponsor) will make expedited reports of SAEs that meet the criteria for SUSARs to the Regulatory Authority (MHRA), REC, Sponsor and AstraZeneca
- The CRUK CTU will produce Development Safety Update Reports in conjunction with the Chief Investigator

PHARMACOVIGILANCE DOCUMENTATION

The Pharmacovigilance section of the site file must be maintained and contain the following documentation:

- Copy of all SUSAR and DSUR reports
- All SAE reports that have been submitted by the site (these may be filed with the CRFs if a file note produced by your site, recording the location of SAE reports, is filed in the site file)
- Copies of the current and previous RSI (Investigator Brochure for olaparib) with other related documentation such as the front sheet document
- All other correspondence from Pharmacovigilance

CRUK CTU PHARMACOVIGILANCE TEAM

If you have any queries about safety reporting please contact the CRUK CTU Pharmacovigilance team who will be happy to provide assistance:

Email: mvls-ctu-pv@glasgow.ac.uk Telephone: 0141 211 3567/0203/3968/0352

REPORTING REQUIREMENTS[1]

ADVERSE EVENTS (AEs)

- All AEs must be followed;
  - until resolution,
  - or for at least 30 days after discontinuation of trial medication,
  - or until toxicity has resolved to baseline,
  - or ≤ Grade 1,
  - or until toxicity is considered to be irreversible
- All AE and toxicities must be graded according to the NCI-CTCAE Version 4.03
- An exacerbation of a pre-existing condition is an AE

SERIOUS ADVERSE EVENTS (SAEs)

- Serious Adverse Events (SAEs) must be reported immediately (within 24 hours of knowledge of the event) using the current version of the PARADIGM-2 SAE report form.
- Sites must complete and fax the report to CRUK CTU Glasgow Pharmacovigilance (PV) on fax number **0141 232 2157.**

  SAE report forms may also be emailed to mvls-ct-pv@glasgow.ac.uk if fax facilities are not available.
- The CRUK CTU PV will create a SAE reference number and will send an acknowledgement fax to confirm receipt of the initial report. Please contact PV if you do not receive an acknowledgement.
- The CRUK CTU PV will request additional information if the event is unexpected and will raise queries for any inconsistent or missing information . Completed queries must be returned within 5 working days.
- **SAEs are required to be reported for up to 30 days after discontinuation of trial treatment**. Any SAE that occurs after 30 days post treatment is also required to be reported if the PI thinks the SAE is related to the protocol treatment, and is medically important.
- **PARALLEL 1 only**: events that meet the definition of a SAE but are related to temozolomide (nIMP) only, do not require reporting. However any **events considered to be a result of interactions between olaparib and temozolomide and / or radiotherapy will require reporting as SAEs.**

REPORTING REQUIREMENTS(2)

EXPEDITED REPORTING

The assessment of expectedness for SAEs and regulatory reporting will be undertaken by the CRUK CTU PV and CI. SAEs that meet the criteria for SUSARs will be reported to the MHRA, REC, Sponsor and AstraZeneca where in the opinion of the Chief Investigator the event was:

- Related – that is, resulted from administration of any of the research procedures **AND**
- Unexpected – that is the type of event not listed as an expected occurrence in the Reference Safety Information (RSI). The RSI is section 5.4 of the Investigator Brochure that has regulatory approval to assess the expectedness of SAEs **OR**
- Is an interaction between olaparib and the radiotherapy treatment and /or temozolomide

CRUK CTU on behalf of the Sponsor is responsible for the expedited reporting of all SUSARs to the required Regulatory Authorities, Research Ethics Committee (REC), PI at trial sites and the trial Sponsor(s) as well as AZ.

- Fatal or life threatening SUSARs will be reported within 7 days of the CRUK CTU PV receiving the first notification of the unexpected event. Any additional information will be reported within eight days of sending the initial report
- All other SUSARs will be reported within 15 days of the CRUK CTU PV receiving the first notification of the unexpected reaction.
- If the SAE is a suspected SUSAR then follow up information must be provided as quickly as possible and in the timeframe requested by the CRUK CTU and CI. All follow-up information is required to be reported promptly and follow up reports are required to be submitted until all AEs listed on the initial SAE report resolve.

REPORTING REQUIREMENTS[3]

PREGNANCY REPORTING

Pregnancy occurring in a clinical trial participant, or the partner of a participant, while not considered an AE or a SAE, requires monitoring and follow-up.

- Any pregnancy occurring in a patient or a patient's partner during treatment with olaparib or occurring within three months of last administration of IMP must be reported to Pharmacovigilance within 24 hours of the site staff becoming aware of it by faxing a completed Pregnancy Notification Form (PNF) to Pharmacovigilance 0141 232 2157.

  PNFs may also be emailed to mvls-ct-pv@glasgow.ac.uk if fax facilities are not available.
- It is the Investigator's responsibility to obtain consent from the patient or patient's partner for following-up the pregnancy until outcome. Investigators must also submit an updated PNF with the pregnancy outcome at delivery or if there is a change in condition during pregnancy such as miscarriage or planned termination
- Any pregnancies that result in a congenital anomaly or birth defect will require to be reported by the Investigator as a SAE.

PHARMACOVIGILANCE DATA ESCALATION PROCESS

- CRUK CTU Pharmacovigilance team will regularly chase outstanding data from participating sites in relation to SAE report forms with request for data/ queries to be returned within 5 working days.

- If, following requests, a response is not received from site staff an escalation process will begin.

- Please ensure all PV queries for further information are responded to promptly to enable the gathering of required safety data for the Safety Review Committee to make decisions regards dose escalation of Olaparib and patient safety for this early phase trial.

GENERAL PHARMACY INFORMATION

Olaparib

Olaparib (IMP for the study) will be provided free of charge by AstraZeneca to sites for use of patients in the PARADIGM-2 trial and will be trial specific investigational medicinal product trial stock.

Temozolomide

Temozolomide is considered a non-investigational medical product (NIMP) for the purposes of this study. Temozolomide should be supplied from routine hospital stock. There is no discount scheme or reimbursement in place for temozolomide supplies.

Full instructions regarding management, labelling and accountability of the IMP/ NIMP is given in a separate IMP Management Document, provided to participating sites in the Pharmacy Site File.

Please also see the Pharmacy Initiation slides for further training for Pharmacy staff.

RADIOTHERAPY INFORMATION

- Radiotherapy treatment should start within 6 weeks of surgery. An additional week will be allowed if required.
- The use of CT planning is mandatory.
- Radiotherapy will be delivered to a total dose of 60 Gy in 6 weeks, in a once daily schedule of 2 Gy per fraction, five days per week for a total of 30 fractions.
- Delays of up to 7 days are permitted once the patient has started radiotherapy. This includes breaks in treatment caused by public holidays, transport failure, machine breakdown, intercurrent illness and other potential factors. In the case of delays, dose compensation for any associated increase in overall treatment time is not required.

RADIOTHERAPY QA

- Radiotherapy Quality Assurance will be conducted through the UK RTTQA team.
- Pre-trial Facility Questionnaires will be sent to all participating sites, to collect contact, equipment and delivery technique details.
- Each site will be required to submit a 'Dummy Run' case, comprising a case chosen by the site that has been outlined and planned according to the PARADIGM-2 protocol. The RTTQA team will undertake review of volumes and dose distribution and must approve the Dummy Run case before sites can open the trial.

Please refer to section 5.11 of the trial protocol for full details on radiotherapy treatment.

TRANSLATIONAL RESEARCH

Patients must consent to participate in the translational research

Tissue collection:

- Patients will be asked to consent to use of residual tumour tissue that was removed at the time of their original neurosurgical operation and was not needed for routine diagnosis and treatment for research purposes.

Blood samples:

- Additional blood samples will be taken as per the schedule of assessments and used specifically for translational research purposes.

Blood and tumour samples for translational research will be stored at the Glasgow Biorepository until use, and may be transported to laboratories in the UK or internationally for analysis. Access to these samples for research projects will be managed by the PARADIGM-2 Trial Management Group and the Glasgow Biorepository.

Aims:

The main aims of the translational research projects will be to identify molecular biomarkers that have potential to predict which glioblastoma patients will benefit from the addition of olaparib to radiotherapy, and to investigate whether olaparib has any protective effects on the normal brain. Blood samples will be analysed to look for circulating cells or DNA that has come from the tumour, which can sometimes be used to obtain information about the tumour. This exploratory work is aimed at developing new blood tests that could provide useful information about the tumour without needing a biopsy or operation.

Further details regarding sample handling and sample shipping will be provided in the Laboratory Manual for the trial.

OTHER STUDY STAFF

The Principal Investigator has overall responsibility for the conduct of the clinical trial at the trial site.

BUT

- All staff must comply with GCP
- Staff should only perform tasks delegated to them on the delegation log
- Staff should have the appropriate trial related training on the trial protocol
- Staff should ensure that their details are available to the Investigator
- Staff should maintain appropriate confidentiality at all times

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