PARADIGM (BR32)

OlaPArib And RADiotherapy In newly-diagnosed GlioblastoMa:

Short-course radiotherapy plus olaparib for newly diagnosed glioblastoma in patients unsuitable for radical chemoradiation: a randomised phase II clinical trial preceded by a lead-in phase I dose escalation study.

PHASE I PHARMACY INITIATION SLIDES

(VERSION 2.0 09.03.2016)

STUDY 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 Astra Zeneca 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 compliment 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

STUDY TEAM

• Chief Investigator :	Professor Anthony Chalmers
• Trial Statisticians:	Caroline Bray/Jamie Stobo
• Project Manager:	Anna Morris
• Sponsor Pharmacist	Dr Samantha Carmichael
• Pharmacovigilance Manager:	Lindsey Connery
• Clinical Trial Coordinator:	Susan Dillon
• Trial Monitor:	Michaela Rodger
• Co-Sponsor Representative:	Paul Dearie

PHARMACY INITIATION

- Protocol and treatment overview
- IMP presentation

- PARADIGM site file and documentation
- Site initiation process

STUDY DESIGN AND OBJECTIVES

Study Design

This trial is a multi-centre, two-stage, clinical trial of Olaparib in combination with radiotherapy. Phase I is a dose escalation trial of Olaparib in combination with short course radiotherapy and will follow a 3+3 cohort design.

This will be followed by a randomised, placebo controlled, double-blind phase II trial of radiotherapy plus placebo versus radiotherapy plus Olaparib (at the dose determined in phase I).

Study Objectives

The objective of phase I is to establish the maximum tolerated dose of Olaparib when given in combination with radiotherapy. The objectives of phase II are to obtain evidence that adding Olaparib to radiotherapy improves overall survival in this patient population, and to justify a subsequent phase III trial. Additional objectives are to document the safety, toxicity and quality of life associated with this combination

STUDY POPULATION

The trial includes a population of newly diagnosed glioblastoma patients who would not be eligible for treatment with standard radical radiotherapy with concomitant and adjuvant temozolomide

Treatment and Duration

- All patients will receive hypofractionated, short-course radiotherapy (40 Gray in 15 fractions) over 19 – 21 days.

- All patients will commence Olaparib 3 days prior to radiation and will continue throughout radiotherapy treatment and then for a further four weeks.

- The Olaparib dose will be dependant on the dose cohort to which the patient has been enrolled.

Planned Dose Escalation Cohorts

The starting dose of Olaparib will be 50mg orally once daily and if tolerated will be increased for subsequent cohorts as show below:

Dose Level	Olaparib Dose PO (starting 3 days prior to radiotherapy)
-1	There will be no dose reduction permitted if the starting dose is not tolerated. Subjects who do not tolerate the starting dose must be removed from the study
1	50mg once daily
2	100mg once daily
3	100mg twice daily
4	200mg twice daily

IMP PRESENTATION AND MANAGEMENT

Investigational Medicinal Products

Olaparib for Phase I

- Olaparib for use in the Phase I part of the study will be supplied free of charge from Astra-Zeneca and distributed to sites by Fisher Clinical Services (FCS) for use in the PARADIGM study.
- Study sites are responsible for monitoring stock levels and will order additional supplies via sponsor using the PARADIGM re-order form.
- Olaparib is considered IMP for the purpose of this study.
- Olaparib will be supplied by FCS as a green film coated tablet containing either 25mg or 100mg of active drug substance.

Full instructions regarding management, labelling and accountability of all study drugs is given in a separate IMP Management Document for the Study

Prescribing and Dispensing Arrangements

- Study specific prescriptions must be used – a master copy must be placed in the pharmacy file
  - electronic prescribing can be used but must clearly state that use is within the PARADIGM study.
- Prescription must
  - clearly identify prescribing as part of the PARADIGM study
  - patients study number
- Sites are required to include the following information when labelling dispensed supplies for this study.
  - PARADIGM Study
  - Principal Investigator: xxxx
  - EudraCT Number: 2014-001216-19

- UK Sponsor: NHS Greater Glasgow and Clyde & University of Glasgow
- For Clinical Trial Use Only
- Patient Trial Number: xxxx
- (xxxx – to be completed locally as appropriate)

There is no stipulation on the format or layout of the labels. Any other additional labelling on dispensing can be added as per local practice.

IMP Accountability

- Each patient taking part in the PARADIGM study must have a patient log detailing the following information:

  - ➢ Date of Issue
  - ➢ Dose
  - ➢ Bottle number
  - ➢ Batch Number
  - ➢ Expiry Date

- The tear off label from the tablet bottle must be stuck on the individual patient accountability form.
- A Bulk IMP Accountability log must also be maintained by site for each strength of tablets
- Logs must be kept up to date at time of each dispensing and made available if requested for remote monitoring
- Logs can be provided by CRUK CTU for use in this study but local documentation can be used after approval by CRUK CTU

Returns and Destruction

- Sites must request permission from sponsor to destroy any Expired, Damaged or Unused stock of Olaparib. Destruction of unused or expired Olaparib, should be undertaken after the Sponsor has given written

permission, in line with local policies and procedures and a destruction log completed

- A destruction log will be provided for use.

Storage of IMP

Olaparib/Placebo

- Olaparib /placebo must be stored at the correct storage conditions defined as storage below $30^{o}C$.
- Temperatures below the lower limit of $15^{0}C$ are classed as a temperature deviation

Defects, Recalls & Temperature Deviations

- Complaints or defects regarding Olaparib
  - ➢ Complete a copy of the PARADIGM temperature deviation and defect reporting form and forward to CR-UK CTU.

- Temperature deviations regarding Olaparib
  - ➢ Complete the PARADIGM temperature deviation and defect reporting form and forward to CR-UK CTU providing the following information:

  – Duration of temperature deviation: please provide the maximum period of time the IMP may have been exposed to temperatures out with those indicated
  – Maximum/ minimum temperature achieved
  – Quantity of packs and batch number of affected stock
  – Reason for temperature excursion/any action already taken
  – Wherever possible please include a copy of the temperature log

Site Set-Up

CTU GLASGOW

Main REC approval - MHRA approval - Site Initiation Slides - Investigator File - Pharmacy File - Sample Collection Supplies

SITE

Delegation & Study Specific Training Log– SSI - R&D Approval - Investigator CVs and Lead Pharmacist – Pharmacy Site Assessment Form - Delegation log - Clinical Trial Agreement - GCP Certificates for PIs - PIS, Consent, GP Letter etc on Trust headed paper Lab normal ranges (Haem + biochem), Accreditation certificates.

INITIATION PROCESS SITE ACTIVATED DRUG SUPPLY

Pharmacy Initiation Process

- Overall Site initiation process - Each member of the study team is required to participate in site initiation to ensure compliance with the protocol and training on study procedures. Initiation for the study will be done by site staff accessing on line initiation slides via CRUK CTU website.

- Pharmacy Site initiation process - Each member of the pharmacy study team is required to access the on line Pharmacy Initiation slides via CRUK CTU website.

- Lead pharmacist for the PARADIGM study will complete a Pharmacy Site Assessment Form and return to CRUK CTU.

- A Delegation and Study Specific Training log must be completed for the lead pharmacist and any other pharmacy clinical trial staff who are delegated IMP management responsibilities. These staff will be required to provided evidence of GCP training and current CV's.

- Acknowledgement sheet - Each member of the study who has viewed the initiation slide presentation requires to complete an acknowledgement sheet to confirm this.

- Initiation Accreditation call - Prior to activation of the site a short initiation call will be completed with the main contact for the site.

Post Approval

- Site Responsibilities
  - Ensure Pharmacy file contents are kept up to date
  - Ensure accountability logs are kept up to date
  - Inform CR-UK CTU Glasgow of any changes in contacts or arrangements for pharmacy
  - Action amendments where required.

- Sponsor Responsibilities
  - Forward amendments in a timely manner
  - Review and amend IMP management process as required
  - Help solve problems & provide support as required

Contact Details for CRUK CTU, Glasgow

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