BALLAD
A TRIAL TO EVALUATE THE POTENTIAL BENEFIT OF ADJUVANT CHEMOTHERAPY FOR SMALL BOWEL ADENOCARCINOMA (IRCI-002)

Study Details

- Coordinated by CRUK Clinical Trials Unit, Glasgow
- Sponsor - Greater Glasgow and Clyde Health Board (GGCHB) and University of Glasgow
- Chief Investigators - Professor Jeff Evans & Dr Richard Wilson
- Funded by CRUK as part of the International Rare Cancers Initiative
- Study will be conducted according to ICH GCP guidelines
- Study conducted in accordance with the EU Directive 2001/20/EC

Please note that 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 study requirements prior to signing off the initiation acknowledgement sheet.
Study Team

Chief Investigators:  Professor Jeff Evans & Dr Richard Wilson
Trial Statisticians:  Jim Paul & Caroline Bray
Project Management:  Judith Dixon-Hughes
Clinical Trial Co-ordinator:  Cheryl Wilson
Sponsor Pharmacy Team:  Paula Morrison/Eliza Valentine
Pharmacovigilance:  Lindsey Connery
Clinical Trial Monitor:  Barbara Ross
Pharmacovigilance CTC:  Jennifer Flach
Sponsor Representative:  Paul Dearie

BALLAD Pharmacy Initiation Slides V1.3
18.01.16
Pharmacy Initiation

- Protocol and treatment overview
- IMP Presentation
- BALLAD site file and documentation
- Site initiation process
BALLAD Protocol and treatment overview
Study Design/Objectives

Study Design:

An open-label, randomised, controlled, multi-centre, global trial with disease free survival as the primary end point.

Objectives:

• Assessment of the efficacy of observation versus 24 weeks of adjuvant post-operative chemotherapy in resected stage I-III small bowel adenocarcinoma (SBA).

• Assessment of the efficacy of 24 weeks of adjuvant post-operative fluoropyrimidine ‘monotherapy’ regimen versus fluoropyrimidine plus Oxaliplatin combination chemotherapy regimen in resected stage I-III small bowel adenocarcinoma (SBA).
Primary Endpoint:
  • Disease free survival (defined as time from randomisation to recurrence, development of new primary or death from any cause).

Secondary Endpoints:
  • Overall survival, cost-effectiveness, toxicity, clinico-pathological and molecular profiling of SBA.
Treatment Options

• Group 1 patients, where there is uncertain value of adjuvant chemotherapy, will be randomised to observation versus chemotherapy. For those patients randomised to receive chemotherapy a choice can be made by clinician or patient as to whether they will receive either monotherapy, combination therapy or be randomised to either (as per Group 2 patients). The chemotherapy will be 24 weeks fluoropyrimidine (5FU or Capecitabine) with or without Oxaliplatin. The choice of chemotherapy must be specified prior to randomisation.

• Group 2 patients, where there is certain value of adjuvant chemotherapy, will be randomised to receive 24 weeks fluoropyrimidine chemotherapy either with or without Oxaliplatin. The choice of fluoropyrimidine must be specified prior to randomisation.

• Patients can be randomised into both groups at the one time if they so wish (e.g. can be randomised to receive either observation or monotherapy or doublet therapy)

• For patients that are ineligible to participate in the randomised trial or do not wish to do so then they should be offered patient registration to allow collection of tumour and blood samples for translational research
The choice of regimen should be notified to CRUK CTU at the time of randomisation. The suggestions below are for guidance and differences in standard practice are permitted which must be notified to sponsor at the time of initiation.

- **IV Fluoropyrimidine regimens (every 2 weeks):**
  - Folinic acid 350mg IV over 2 hrs
  - 5-FU 400mg/m² IV over 10 mins
  - 5-FU 2400mg/m² IV over 46 hrs

- **Oral Fluoropyrimidine regimens (every 3 weeks):**
  - Capecitabine 1250mg/m² PO BD for 14 days

- **IV Combination Fluoropyrimidine regimens (every 2 weeks):**
  - Oxaliplatin 85mg/m² IV over 2 hours
  - Folinic acid 350mg IV over 2 hrs
  - 5-FU 400mg/m² IV over 10 mins
  - 5-FU 2400mg/m² IV over 46 hrs

- **Oral Combination Fluoropyrimidine regimens (every 3 weeks):**
  - Oxaliplatin 130mg/m² IV over 2 hours
  - Capecitabine 1000mg/m² PO BD for 14 days
Key Inclusion Criteria

- R0 resected stage I, II or III SBA
- No evidence of residual or metastatic disease at laparotomy or on CT/MRI imaging of chest, abdomen and pelvis.
- Patients must be registered and randomised within 12 weeks of surgery and commence chemotherapy within 14 weeks of surgery
- ECOG Performance Status of 0 or 1
- Absolute neutrophil count ≥ 1.5 x10⁹/l
- Platelet count ≥ 100 x 10⁹/l
- Haemoglobin ≥ 90 g/l (previous transfusion is allowed)
- AST and ALT ≤ 2.5 x upper limit of normal (ULN). (At least one of ALT or AST MUST be performed)
- Creatinine clearance > 50 ml/min (calculated by Cockcroft Gault or Wright equation) or measured by EDTA
- Serum bilirubin ≤ 1.5 x ULN
- Signed and dated informed consent indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrolment.
- Age ≥ 16 years
- Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other trial procedures.

PLEASE REFER TO PROTOCOL FOR FULL LIST OF INCLUSION/ EXCLUSION CRITERIA

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Key Exclusion Criteria (1)

- Non-adenocarcinoma histology of small bowel tumour which includes but is not confined to lymphoma, GIST, carcinoid or other neuroendocrine tumour, squamous carcinoma, melanoma or sarcoma.
- Previous neo-adjuvant chemo(radio)therapy for SBA
- Clinically significant cardiovascular disease (i.e. active or < 12 months since cerebrovascular accident, myocardial infarction, unstable angina, New York Heart Association [NYHA] grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, uncontrolled hypertension)
- Pregnancy/lactation or of child bearing potential and not using medically approved contraception. (Postmenopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential)
- Previous malignancy other than adequately treated in situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin, unless there has been a disease free interval of at least 3 years and treatment was with curative intent
- Known or suspected dihydropyrimidine dehydrogenase (DPD) deficiency

PLEASE REFER TO PROTOCOL FOR FULL LIST OF INCLUSION/ EXCLUSION CRITERIA
Key Exclusion Criteria (2)

- Known untreated coeliac disease (may be enrolled if diet controlled), untreated chronic inflammatory bowel disease or other cause of malabsorption or intestinal obstruction
- Grade ≥ 2 peripheral neuropathy
- Administration of any investigational drug within 28 days or 5 half-lives, whichever is longer, prior to receiving the first dose of trial treatment.
- Previous hypersensitivity to platinum salts
- Patients with clinically significant, active infections, or any other serious medical condition in which chemotherapy is contraindicated will be excluded
- Patients with untreated vitamin B12 deficiency are excluded from receiving folinic acid as part of their chemotherapy regimen. However, these patients may be eligible for treatment with capecitabine fluoropyrimidine therapy, where no folinic acid is administered as part of the treatment regimen
- Patients with clinically significant sensorineural hearing impairment are excluded from receiving oxaliplatin but will be eligible for the fluoropyrimidine monotherapy provided as a clinician’s choice for patients in group 1 randomised to either observation or chemotherapy

PLEASE REFER TO PROTOCOL FOR FULL LIST OF INCLUSION/ EXCLUSION CRITERIA
IMP Presentation and Management
The Investigational Medicinal product (IMP) in this study are:

- Fluorouracil
- Folinic Acid/L Folinic Acid
- Capecitabine
- Oxaliplatin

All drugs administered as part of the Group 1 & 2 randomisations are considered Investigational Medicinal Products (IMPs) for the purposes of this protocol.

All trial drugs for use in the trial should be taken from usual pharmacy stock; there is no provision for funding, reimbursement or discounted stock. Shelf stock will not require IMP labelling but all IMP being dispensed to patients must be labelled at site, at the time of dispensing, in accordance with all applicable regulatory requirements.

Chemotherapy regimens will be administered as per institutional standard care and are the choice of the Principal Investigator at that site.
Prescribing and Dispensing Arrangements

• Study specific prescriptions must be used – a master copy must be placed in the pharmacy file

• Prescriptions must
  – Clearly identify prescribing as part of the BALLAD study including protocol number
  – Patient study number

• Sites are required to include the following information when labelling dispensed supplies for this study:
  – BALLAD Study
  – Principal Investigator
  – Eudract Number
  – Sponsor: NHS Greater Glasgow and Clyde and University of Glasgow
  – For Clinical Trials Use Only
  – Patient Trial Number: xxxx
  – Cycle No: xxxx(if this is local practice to do so)
  (xxxx – to be completed locally as appropriate)

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

- Please refer to the SmPC for formulation and presentation of all IMP for use in the BALLAD study.

- All IMPs should be stored and handled as per SmPC and as per local policies and procedures.
BALLAD site file and documentation
Pharmacy Site File

- All pharmacy sites will be provided with a pharmacy file containing key documentation and initiation training slides. The pharmacy file must be kept up-to-date and be available for inspection by the study monitors at monitoring visits, regulatory authorities and on request from the sponsor if required.

- Pharmacy Site File will include the following as a minimum:
  - BALLAD Patient specific Capecitabine accountability Log for 150mg and 500mg tabs
  - BALLAD Patient specific Fluorouacil Accountability Log for IV loading dose and 46hr infusion
  - BALLAD Patient Specific Folinic Acid Accountability Log
  - BALLAD Patient Specific L-Folinic Acid Accountability Log
  - BALLAD Patient Specific Oxaliplatin Accountability Log
  - BALLAD Study Specific Training Record
  - BALLAD study subject identification log
Accountability Logs

• 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 CTC for use in this study but local documentation can be used only after approval by CRUK CTC and R&D Sponsor Pharmacy Team.
• Each patient taking part in the study must have a patient log detailing the following information for traceability purposes:
  – Date of Issue
  – Cycle
  – Dose
  – Quantity and strength dispensed
  – Batch number and expiry date

  – There will be a separate log for each strength of capecitabine
IMP Accountability (Fluorouracil)

- Each patient taking part in the study must have a patient log detailing the following information for traceability purposes:
  - Date of Issue
  - Cycle/day
  - Dose
  - Batch number and expiry date
  - Vehicle, manufacturer batch number and expiry date
  - Dose banding

- There will be separate logs for both the IV loading dose and IV 46hr infusion of 5FU
Each patient taking part in the study must have a patient log detailing the following information for traceability purposes:

- Date of Issue
- Cycle
- Dose
- Manufacturer
- Batch number and expiry date
- Vehicle
- Manufacturer
- Batch number and expiry date
- Dose banding manufacturer
- Batch number and expiry date

- A log will be required for EITHER Folinic Acid or L-Folinic Acid
• Each patient taking part in the study must have a patient log detailing the following information for traceability purposes:
  – Date of Issue
  – Cycle
  – Dose
  – Manufacturer, batch number and expiry date of product
  – Diluent
  – Manufacturer, batch number and expiry date of diluent
  – Vehicle
  – Manufacturer, batch number and expiry date of vehicle
  – Dose banding manufacturer
  – Batch number and expiry date of dose-banded product
Returns and Destruction

Patient Returns:
- Tablet counts for Capecitabine must be performed and recorded on the Patient specific Subject Accountability Log.

Destructions:
- Patient returns can be destroyed once all accountability has been completed and any discrepancies resolved.
Defects and Temperature Deviations

• Complaints or Defects regarding all IMP:
  ➢ Should be dealt with by following local hospital procedures.

• Temperature deviation regarding all IMP:
  ➢ follow local department procedure but must be notified to the CTU. Further advice will be given as appropriate on a case by case basis.
BALLAD Pharmacy Site Initiation Process
Site Set-up

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

SITE
Staff Contact & Responsibilities Sheets – SSI - R&D Approval
- Investigator CVs and Lead Pharmacist - 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

DRUG SUPPLY

SITE ACTIVATED

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Pharmacy Initiation Process

- **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 online initiation slides via CRUK CTU website.

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

- A Staff Contact and Responsibilities Sheet 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 provide 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 Site File contents are kept up to date
  – Ensure accountability logs are kept up to date
  – Inform CRUK 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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