PRIMUS 001
A PRECISION PANC CLINICAL STUDY
An adaptive phase II study of FOLFOX-A (FOLFOX and nab-paclitaxel) versus AG (nab-paclitaxel and gemcitabine) in patients with metastatic pancreatic cancer, with integrated biomarker evaluation

Initiation Slides (Version 1.2: 14th February 2019)
EudraCT Ref: 2016-004155-67
ISRCTN No: 75002153
Sponsor: NHS Greater Glasgow and Clyde
Chief Investigators: Dr Janet Graham and Dr David Chang
Study Details

- The trial is being co-ordinated by CRUK via the CRUK Clinical Trials Unit, Glasgow
- Sponsor of the trial is NHS Greater Glasgow and Clyde
- Co Chief Investigators are Dr Janet Graham and Dr David Chang
- Trial is being funded by a grant from Celgene, and CRUK.

**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 study requirements prior to signing off the initiation acknowledgement sheet.**

- Study will be conducted according to ICH GCP guidelines E6
- Study conducted in accordance with the EU Directive 2001/20/EC & amendments
- Study carried out in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research involving Human Subject 1964 (as amended)
# Study Team

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
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<tbody>
<tr>
<td>Chief Investigators:</td>
<td>Dr Janet Graham (oncology lead) and Dr David Chang (translational lead)</td>
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<td>Clinical Trial Co-ordinator:</td>
<td>Craig Campbell</td>
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<td>Clinical Trial Monitor:</td>
<td>Louise Dinnett</td>
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Study Design

• **PRIMUS 001** is a multicentre, randomised, open label, two arm, phase II interventional trial with pre-clinical and translational work including in-depth molecular profiling and biomarker discovery/development.

• **Primary objective:** To provide a phase II assessment of efficacy of FOLFOX-A when compared to AG in all (unselected) patients and the biomarker-positive group (putative biomarker of DNA-damaging agent responsiveness) using PFS as the primary endpoint. The trial results will inform the predictive value of the biomarker (estimated prevalence 20%) and guide the ultimate phase III design.

• **Secondary objectives:** To assess response rate, overall survival, safety, tolerability (specifically neurotoxicity), quality of life and health economics. Biomarker discovery and development will also be ongoing as part of the study.

• The trial will open in approximately 20 UK sites and recruit 500 patients over 46 months
RECIST Reporting Requirements

- All radiological investigations **MUST** be reported as per protocol / RECIST version 1.1.

- Source documentation of this must be available for review if the original report has had to be supplemented to bring it in line with protocol requirements.

- CRUK CTU, Glasgow have produced a worksheet to assist with the documentation of study specific reporting and will make this available to all participating sites.
Eligibility Criteria

**Please refer to section 3.2 of the protocol for full details of the eligibility criteria for the study (Brief details of the key selection criteria only is detailed on this slide)**

1. Patient has been registered to Precision-Panc Master Protocol and their tissue has been deemed suitable for NGS analysis
2. ≥16 years old
3. Histologically confirmed metastatic PDAC with measurable metastatic lesions
4. ECOG 0 or 1 with life expectancy of no less than 12 weeks
5. No previous chemo for metastatic disease and no prior treatment with nab-paclitaxel or oxaliplatin
6. Adequate liver and bone marrow function
7. Negative pregnancy test and patients willing to use contraception as required
8. No active infection
9. Patient must not have grade 2 or above neuropathy
10. Patient must not have received any investigational or anti-cancer therapy drug within 28 days or first dose of trial treatment and patient must not have had major surgery
11. Patient must not have had minor surgery or radiotherapy within 7 days of randomisation
12. Patient must not have ongoing severe diarrhoea (grade 3 or above despite best supportive measures)

Please note there will be no exception to the eligibility requirements at the time of registration/randomisation. Queries in relation to the eligibility criteria should be addressed via contact with the CTU prior to registration/randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.
Pre-Randomisation Assessment Requirements

Within 28 days of randomisation
- Confirmation that patients has been registered to Precision-Panc Master Protocol and has an adequate tumour sample for molecular analysis
- Written, informed consent for PRIMUS 001 study, once the patient has signed consent a screening form should be completed and sent to CRUK CTU Glasgow
- Medical history, demographic details
- Review of concomitant medications
- Full physical exam including height, weight, BP and pulse
- ECOG PS
- ECG
- FBC – Hb, WBC, platelets, ANC, lymphocytes
- Biochem – Na, K, calcium, phosphate, mg, CRP, urea, creatinine, protein, albumin, bili, Alk phos, AST/ALR and LDH
- CA19.9
- CT CAP

Within 14 days of randomisation
- Pregnancy test if required

Prior to randomisation
- Completion of all QoL – EORTC QLQ C30, PAN26, EQ-5D-5L and GOG NTOX
- Translational blood sample
Screening Process

All patients MUST have been registered on the Precision-Panc Master Protocol to take part in PRIMUS 001.

Once a patient has signed the informed consent firm site must complete a screening form and either telephone or fax this to the following numbers to received a screening ID:

Telephone Number: 0141 301 7201
Fax Number: 0141 301 7946
Randomisation Process

All patients MUST have been registered on the Precision-Panc Master Protocol to take part in PRIMUS 001.

Randomisation to the trial can be performed by either telephone or fax on the following numbers:

Telephone Number: 0141 301 7201  
Fax Number: 0141 301 7946

Minimisation (including a random factor) will be used to allocate patients between treatment arms. The following factors will be used:

• Treatment centre
• Presence of absence of liver metastases
• Primary tumour location (head vs body/tail)
• Baseline CA19.9 (normal vs >ULN-59 U/mL vs >59 U/mL)
Informed Consent Process

Informed consent process:
• Consent Forms must be completed by a clinician (or deputy listed on delegation log)
• At least one original consent must signed and completed by the patient
• Date must be prior to registration
• Make one/two photocopies
  - Original to be filed in Investigator File
  - Original or photocopy to be given to patient (+PIS)
  - Photocopy to be filed in hospital notes

• Consent Form must not be sent to your coordinating trials office

CONSENT WITHDRAWAL

This is when the patient specifically asks to withdraw their consent at any point in the study. 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 with full details of withdrawal
  — Where applicable the CTU will request site completes a Consent Withdrawal Form
  — No further follow-up should be collected on the patient from the date of consent withdrawal onwards.

Please remember that stopping treatment is NOT the same as withdrawing consent!
Study Treatment Details

Patients will receive either:

**Nab-Paclitaxel + gemcitabine (AG) arm (28-day cycle)**
- *nab*-paclitaxel: 125 mg/m² IV over 30 minutes, day 1, 8, and 15 (administered first)
- Gemcitabine 1000 mg/m² IV over 30 mins on days 1, 8, and 15 (immediately following *nab*-paclitaxel)

Or

**FOLFOX A arm (14-day cycle)**
- *nab*-paclitaxel: 150mg/m² IV over 30 minutes, day 1 (administered first)
- Oxaliplatin: 85mg/m², IV over 2 hours, day 1
- Folinic acid: 350 mg flat dose, IV over 2 hours, day 1
- 5-FU infusion: 1200mg/m²/day, as a continuous IV infusion over 2 days, day 1 and day 2 (for a total dose of 2400mg/m² over 46 hours (or 48 hours as per standard practice))
- Patients in the FOLFOX-A arm will also receive daily G-CSF as primary prophylaxis against neutropenic events for all cycles. This should be given as per local policy for 14 days chemotherapy regimens i.e. it may be started on day 4 for 7 days (preparation and dose should be given as per local policy).

Patients will continue treatment until disease progression or unacceptable toxicity or patient withdrawal.

**Please refer to study protocol for detailed information on study treatments, including administration of treatment, prohibited therapies and potential drug interactions.**
Treatment/Dose Modifications

All dose adjustments to be made based upon the worst or most clinically significant preceding toxicity.

For FOLFOX-A only two dose reductions are permitted

For AG three dose reductions are permitted

If the patient’s treatment is delayed for more than 3 weeks the patient should stop treatment (apart from hepatic toxicity related to biliary obstruction)

Day 1 treatment may be delayed or brought forward for up to 48 hours for administrative reasons, day 8 or day 15 treatment may be delayed or brought forward by up to 24 hours.

**Please refer to section 5.10.1 and 5.10.2 of the study protocol for full details of treatment modifications/dose reductions/delays (Brief details in relation to treatment modifications are provided on these slides). **
Process for notification of protocol deviations by sites

• All participating sites must notify the Sponsor (via CRUK CTU) of all deviations from the protocol or GCP immediately.

• The Sponsor requires a report on the incident(s) 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.

- The 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 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 plan and visits

**Monitoring Visits/Schedule:**

Sites will receive a monitoring call on a yearly basis by the CRUK CTU monitoring team. Each site will be visited once during the study. For cause monitoring will be arranged on an ad hoc basis.

**Telephone & Remote Monitoring:**

- The time & date will be agreed with a member of the Site Study 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 agreed date.
- Please set aside 50 to 70 minutes for this call.

**On Site Monitoring:**

- 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.
- Pharmacy visits will include review of Pharmacy Site File – Temperature Logs – Drug Returns – Drug Accountability Logs and Destruction of Drug.
- All findings will be discussed at an end of visit meeting and any unresolved issues raised as Action Points.
- Action Points will be followed up by the monitor until resolved.
Data Management

The trial uses the electronic data capture system MACRO and paper randomisation and quality of life forms.

MACRO log ins will be required for members of staff entering data and the PI and can be requested from the CTC/PM

Data Escalation Process:

• CRUK CTU will regularly chase outstanding data from participating sites. Routine requests for outstanding data and outstanding data queries will be performed quarterly or more regularly if required for a specific study.
• 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 any site has 20% of forms 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 be begin. See protocol for further information.
CRUK CTU GLASGOW will provide
REC approval - MHRA approval – HRA Document Package - Site Initiation Slides - Investigator Site File - Pharmacy Site File

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SITE to submit
Delegation and Study Specific Training Log – SSI (if required) – R&D Approval/ confirmation – Clinical Trial Agreement – Principle Investigator and Lead Pharmacist CVs - GCP Certificate for PI and Lead Pharmacist – PIS/CF, GP Letter etc. on Trust headed paper - Lab normal ranges and accreditation certificates (haem and biochem) – Pharmacy Site Assessment Form

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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 the CRUK CTU. The CRUK CTU 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 electronic case report forms (eCRFs), 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 and patient number.

• Where central monitoring of source documents by CRUK CTU (or copies of source documents) are required (e.g. scan results of blood results) the personal data of the patients must anonymised on the report e.g. 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 to CRUK CTU.
Record Retention and Archiving Arrangements for study

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

• 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 the CRUK CTU and Sponsor regarding the duration of document retention.

• Sites should not archive their trial documentation until they have been instructed by the CRUK CTU or Sponsor that they are able to do so. 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 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 SOPs.
Clinical Trial Regulations require:

• Investigators document Adverse Events (AEs) in patient notes and the CRF as required
• Investigators report Serious Adverse Events (SAEs) immediately to the CRUK Clinical Trials Unit Glasgow
• The 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 + applicable pharmaceutical company
• The 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 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/ 0352/ 3968
Safety Reporting Requirements

ADVERSE EVENTS (AEs)

- All AEs must be followed;
  - until resolution,
  - or for the time period specified in the drug-specific appendix,
  - or until toxicity has resolved to baseline,
  - or ≤ Grade 1,
  - or until toxicity is considered to be irreversible
- All AEs and toxicities must be graded according to the NCI-CTCAE Version 4.03
- An exacerbation of a pre-existing condition is an AE
- AEs occurring between signing pre-screening consent and drug subgroup consent should only be recorded on the eCRF if they are a result of a study related procedure
- All AEs occurring after drug subgroup consent prior to the start of study IMP require to be recorded on the eCRF

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 PRIMUS 001 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-ctu-pv@glasgow.ac.uk
- The CRUK CTU PV will create a SAE reference number and will send an acknowledgement email or 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 from consent up to 30 days after final study treatment.
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, Sites and pharma company.

- 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 whether the event is a SUSAR or not.
Safety 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 IMP treatment or occurring within 6 months of last administration of IMP must be reported to Pharmacovigilance within 24 hours of the site staff becoming aware of it by completing the Pregnancy Notification eCRF and also sending a completed Pregnancy Notification Form (PNF) to Pharmacovigilance by fax 0141 232 2157 or emailed to mvls-ctu-pv@glasgow.ac.uk.
- 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 queries for further SAE information are responded to promptly to enable the gathering of required safety data for the Sponsor to make decisions regards patient safety for this trial.
General Pharmacy Information

For the purposes of this trial, the following are considered IMP: nab-paclitaxel, oxaliplatin, fluorouracil, gemcitabine and folinic acid.

Patients who are eligible for this trial will be randomised to receive either:

- **Nab-Paclitaxel + gemcitabine (AG) arm (28-day cycle)**
- Or
- **FOLFOX A arm (14-day cycle)**

Treatment will continue until disease progression or unacceptable toxicity.

BSA capping is not recommended but is permitted as per standard practice.

Dose banding is permitted for all drugs (apart from nab-paclitaxel) where it is local practice.

Nab-paclitaxel will be provided FOC from Celgene and distributed by Fisher Clinical Services for all patients on the FOLFOX-A arm and only in selected sites for the AG arm (currently England and NI). Otherwise, nab-paclitaxel (along with oxaliplatin, gemcitabine, fluorouracil and folinic acid) will be taken from hospital's own stock.

For details on dose modifications for toxicities, supportive therapy, prohibited therapy and potential drug interactions please refer to the protocol.

Full instructions regarding management, labelling and accountability of the IMPs are 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.
Translational Research Requirements

- Translational bloods should be taken prior to cycle one day one, two months post randomisation (at time of first CT scan) and at progression.

- Blood will be sent to and analysed at the CRUK Manchester Institute.

- 4x 10ml Streck cell free DNA BCT tubes and 1 x 3ml EDTA tube are required per visit.

- The Streck tubes must arrive at the lab in Manchester within 96 hours of collection (via Royal Mail Safebox).

- The EDTA samples will be frozen at site and collected at the end of the study.

- The study team will supply safeboxes and tubes for the study.

- Please see the PRIMUS 001 lab manual for full details of translational sampling.
Other 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.
- Staff should ensure that their details are available to the Investigator.
- Staff should maintain appropriate confidentiality at all times
Contact Details for CRUK CTU, Glasgow

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