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A multi-arm non-comparative platform trial of new second-line treatments for metastatic pancreatic cancer patients based on a patient's individual biomarkers

Submission date 13/09/2019	**Recruitment status** Stopped	[X] Prospectively registered [ ] Protocol
Registration date 15/10/2019	**Overall study status** Stopped	[ ] Statistical analysis plan [ ] Results
Last Edited 01/05/2024	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

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Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-003971-37

Central Portfolio Management System (CPMS)
43749

Protocol serial number
PRIMUS0042018

Study information

Scientific Title
A multi-arm non-comparative signal seeking phase II platform umbrella trial of biomarker-directed novel second-line treatments in metastatic pancreatic cancer

Acronym
PRIMUS-004

Study objectives
Therapeutic hypothesis targeting replication stress and DDR deficiency in PDAC. Patients that are DDR deficient can be targeted with platinum based chemotherapy (good performance status) or PARP inhibitors (poor performance status, or after 1st line platinum therapy). High replication stress can be targeted with either ATR or WEE1 inhibitors. In cases where both high replication stress and DDR deficiency co-exist, ATR / WEE1 inhibition can be used after platinum resistance develops.

The aim of PRIMUS-004 is to offer a range of second-line treatment arms with extensive molecular profiling and evaluation of candidate selection biomarkers, as outlined in the Precision-Panc Master Protocol. Suitable patients would be those with advanced pancreatic cancer, previously treated with chemotherapy. The umbrella platform structure, under which will sit multiple individual signal seeking trial components arms/appendices, will provide a framework for second-line treatments to be investigated with a flexible, yet statistically-structured design. Initially, treatment arms will include all biomarker subgroups, but an adaptive and flexible design will allow subsequent focused recruitment or stoppage in particular subgroups based on the observed results. The outcomes of the signal seeking arms will provide “clear line of sight” on the design of larger, later phase randomised trial. This design also provides patients and clinicians with attractive treatment options in a situation where current

best treatment options are limited and studies are hampered by the aggressiveness of pancreatic cancer, where a majority of patients deteriorate rapidly upon progression on first-line therapy. This will be a multi-centered study.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/07/2020, West of Scotland Research Ethics Committee 1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 3140212; WoSREC1@ggc.scot.nhs.uk), ref: 20/WS/0091

Primary study design
Interventional

Study design
Interventional non-randomised study

Study type(s)
Treatment

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

Interventions
As this is a rolling platform study at present, the researchers have one appendix open.
Single-arm, signal seeking study investigating the objective response rate to second-line combination treatment of olaparib and AZD6738 in candidate biomarker subgroups in patients with advanced pancreatic cancer who had stable disease or better response to at least 1612 weeks of 1st line platinum-based therapy. Response of stable disease or better must be confirmed by repeat scan performed at a minimum of 4 weeks from previous scan.

The treatment regimen for appendix 1:
Olaparib 300mg twice daily continuously for 28 days
AZD6738 160mg once daily on days 1 – 7 for 28 days
Treatment will continue until disease progression, patient withdrawal or clinician withdraws patient due to toxicities

The pre-specified candidate biomarkers to be assessed are:
1. Response to previous platinum therapy
2. Pre-platinum HRR mutation status

Exploratory (retrospective) biomarkers are:
1. GPOL HRD signature
2. Replication stress transcriptomic signature
3. Transcriptome subtype

As the study proceeds, recruitment to certain subgroups may be closed (platinum responsiveness CR/PR v SD; HRR mutant vs HRR non-mutant) depending on recruitment rate or response rate (as advised by the independent Data Monitoring Committee).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Olaparib, AZD6738

Primary outcome(s)
Objective response rate (ORR) based on RECIST V1.1 at baseline, 8 weekly from randomisation until disease progression

Key secondary outcome(s)
1. Progression free survival (PFS) and overall survival (OS) based on RECIST V1.1 at baseline, 8 weekly from randomisation until disease progression
2. Safety profile based on CTCAE V5.0 at day 1 of each cycle (every 4 weeks)
3. Analysis of tumour and blood samples to determine the molecular profile and hypothesised biomarkers of therapeutic responsiveness with correlation to ORR, PFS & OS at baseline, 2 months after registration and on progression

Completion date
01/02/2025

Reason abandoned (if study stopped)
Lack of staff/facilities/resources

Eligibility

Key inclusion criteria
Core Inclusion Criteria:
1. Patient has been enrolled in the Precision- Panc- Master Protocol and their tissue taken post first line treatment has been deemed suitable for NGS analysis
2. Patient has provided signed informed consent for the appropriate PRIMUS-004 Appendix prior to any trial procedures being carried out
3. Age ≥ 16 years
4. Histologically confirmed metastatic pancreatic ductal adenocarcinoma and its variants
5. Measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) V1.1
6. Adequate organ and bone marrow function as defined below (also refer to adequate organ function as defined in relevant drug-specific appendix):
6.1. Absolute neutrophil count ≥ 1.5 x109/L
6.2. Platelet count ≥ 100 x109/L
6.3. Total bilirubin ≤ 1.5 x ULN, unless the patient has documented Gilbert’s syndrome
6.4. AST and/or ALT ≤ 2.5 x ULN, or ≤ 5 x ULN if the patient has liver metastases
6.5. GFR ≥ 51 ml/min as assessed using the Cockroft Gault equation, or Wright formula or measured by EDTA clearance
7. Negative serum or urine HCG test for females with child-bearing potential. Postmenopausal women must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential
8. Woman of child-bearing potential, and men with female partners of child bearing potential,

must agree to use adequate contraceptive measures (see specific appendixsection 4.1.8.1) for the duration of the study and for up to 6 months after the completion of study treatment. Men with pregnant or lactating partners should be advised to use barrier method contraception to prevent exposure to the foetus or neonate
9. Compliant, and can be followed up regularly

Appendix Specific Inclusion Criteria
1. Patient has the ability to provide written informed consent to participate in the trial and be compliant with the protocol requirements
2. Patient must have measurable disease (pre- and post-platinum chemotherapy) as per RECIST V1.1
3. ECOG Performance status 0-1
4. Life expectancy of at least 12 16 weeks
5. Haemoglobin ≥ 10.0 g/dL, with no blood transfusion in the past 28 days
6. Patient must have completed at least 16 weeks of platinum chemotherapy as first-line treatment for advanced pancreatic cancer
7. Patients must have achieved at least stable disease as a response to platinum .by RECIST V1.1 and this must be confirmed by repeat assessment at a minimum of 4 weeks from previous scan
8. Archival tissue sample taken prior to platinum chemotherapy is available and suitable for Next Generation Sequencing analysis
9. Ability to swallow study medication and no gastrointestinal disorders likely to cause malabsorption of study drug(s).
10. Known HRRm status from pre-first line treatment biopsy

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 Years

Sex
All

Key exclusion criteria
Core Exclusion Criteria
1. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period (no longer receiving experimental treatment) of an interventional study unless that study primary endpoint has been met
2. Patients weighing less than 30 kg:
3. Receipt of last dose of anti-cancer therapy (chemotherapy, targeted therapy, immunotherapy, etc.) within 21 days of Cycle 1 Day 1. A duration of five half lives is allowed for patients treated with non-cytotoxic drugs. If sufficient wash-out time has not occurred within 21 days due to the schedule or pharmacokinetics properties of an agent, a longer washout period will be required as agreed by the Investigator.
4. Palliative radiotherapy must have been completed 21 or more days before Cycle 1 Day 1. The

patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, if appropriate, before and during the study as long as these were started at least 5 days prior to the study treatment
5. Major surgery (as defined by the investigator) within 2 weeks of starting study treatment: patients must have recovered from any effects of any major surgery
6. Any other malignancy which has been active or treated within the past three years, with the exception of cervical intraepithelial neoplasia, non-melanoma skin cancer, ductal carcinoma in situ, stage 1 grade 1 endometrial carcinoma, or other solid tumours curatively treated with no evidence of disease for ≥ 3 years prior to study entry
7. With the exception of alopecia and Common Terminology Criteria for Adverse Events (CTCAE) grade 2 neuropathy, any unresolved toxicities from prior therapy ≥ grade 2
8. History of myocardial ischemia (MI), unstable angina, stroke, or transient ischemia within previous 6 months
9. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases that places the patient at unacceptable risk of toxicity or non-compliance.
10. Patients with symptomatic uncontrolled brain metastases. Patients with a history of treated central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria: disease outside the CNS is present, no clinical evidence of progression since completion of CNS-directed therapy, minimum 3 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥ 3) acute toxicity with no ongoing requirement for >10 mg of prednisolone per day or an equivalent dose of other corticosteroid. If on corticosteroids, the patient should be receiving a stable dose of corticosteroids, started at least 4 weeks prior to treatment
11. Women who are breast feeding

Appendix I Specific Exclusion Criteria:
12. Previous treatment with a PARP inhibitor (including olaparib) or other ATR inhibitor (unless treatment was for less than 3 weeks duration and at least 12 months have elapsed between the last dose and randomisation.
13. Patients with myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML) or with features suggestive of MDS/AML.
14. Mean resting corrected QT interval (QTc) >470 msec for females and >450 for men, obtained from 3 electrocardiograms (ECGs).
15. Patients at risk of brain perfusion problems
16. Patients with relative hypotension(<90/60 mm Hg) or clinically relevant orthostatic hypotension, including a fall in
systolic blood pressure of > 20 mm Hg
17. A known hypersensitivity to olaparib, AZD6738 or any excipient of the product, or any contraindication to the combination anti-cancer agent, as per local prescribing information
18. Immunocompromised patients e.g. known to be serologically positive for human immunodeficiency virus (HIV) or patients with known active hepatitis (Hepatitis B or C). Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
19. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)
20. Whole blood transfusions in the last 120 days prior to entry to the study
21. Involvement in the planning and/or conduct of PRIMUS-004
22. Previously treated in the PRIMUS-004 study

Date of first enrolment

02/11/2020

Date of final enrolment
31/01/2024

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
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Study participating centre
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Churchill Hospital
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Study participating centre
St James' University Hospital
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Ls9 7TF

Sponsor information

Organisation
NHS Greater Glasgow and Clyde

ROR
https://ror.org/05kdz4d87

Organisation
The University of Glasgow

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No