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A Phase 1b/IIa trial to explore the combination of a new drug, PLX-7486, with gemcitabine in patients with advanced cancer (part 1b) and with advanced pancreatic ductal cancer and cancer-related pain (Part IIa)

Submission date
29/01/2018

Recruitment status
Stopped

Registration date
01/02/2018

Overall study status
Stopped

Last Edited
08/08/2019

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
PLX-7486 is a drug that has been shown to suppress the growth of cancer cells in the laboratory, and may help to treat cancers. Gemcitabine is a chemotherapy drug that is widely used for the treatment of several cancers, including pancreatic cancer, lung cancer, ovarian cancer, breast cancer and bladder cancer. Both PLX-7486 and gemcitabine have been tested on their own. However this is the first time they have been tested together. This is being done because PLX-7486 in combination with gemcitabine has been shown to prolong survival in animal models compared with gemcitabine alone. The aim of this study is to see what dose of these two drugs can be given together safely and provide initial data on whether the combination may be more effective than gemcitabine alone in humans.

Who can participate?
Males and females aged 16 or over who have an advanced solid cancerous tumour

What does the study involve?
All patients are given both the new drug, PLX-7486, and gemcitabine. Gemcitabine is given as an infusion through a vein in the arm, once a week on days 1,8 and 15 of a 28 day treatment period (known as a 'cycle'). PLX-7486 is taken orally (by mouth), and patients will be given a supply of capsules to take home, to be taken once a day. Full instructions are given for how to take the drug, along with a diary card to help patients keep track of their medication. Patients attend hospital regularly to see the study doctor and/or nurse to make sure the treatment is not causing side-effects. This involves some tests such as blood and urine samples, weight, pulse, temperature and blood pressure, and ECG (tracing of the heart). Computed tomography (CT) or magnetic resonance imaging (MRI) (scans that use either computers or magnetics to create images) are performed every 8 weeks during treatment. Patients in the dose finding part of the study have extra blood samples taken on day 15 of the first cycle of treatment. The extra

samples are taken before the drug is given, and then 2, 4, 8 and 10-12 hours afterwards. Patients in the dose expansion part of the study complete a questionnaire about their pain at the beginning of the study and every few weeks during treatment. Additionally, patients who agree to have a biopsy (which involves some tumour tissue being taken from the site of the cancer) have this done before treatment begins, and at cycle 2 of treatment. This is optional, and patients can still enter the study if they do not agree to this. Treatment continues until the patient's cancer worsens, or the side effects are not tolerable, or the patient decides they no longer want to participate in the study.

What are the possible benefits and risks of participating?
Participants may benefit from improved symptom control, quality of life and survival although this is unknown. Participants will be more closely monitored than if they were not in a clinical trial. Participants may be at risk from potential side effects associated with the study drug. Undertaking more CT scans means they have more exposure to radiation (X-rays) which may cause another cancer later in life although this is unlikely. The contrast used in CT scans may cause kidney damage or in some cases an allergic reaction. The addition of PLX-7486 may cause the cancer to worsen.

Where is the study run from?
1. Beatson West of Scotland Cancer centre (UK)
2. The Christie Hospital (UK)
3. The Clatterbridge Cancer Centre (UK)
4. Addenbrooke's Hospital (UK)

When is the study starting and how long is it expected to run for?
July 2019 to June 2020 (updated 10/06/2019, previously: July 2016 to June 2020)

Who is funding the study?
1. Plexxikon (UK)
2. Cancer Research UK (UK)

Who is the main contact?
Mrs Carol Evans (Public)
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Contact information

Type(s)
Public

Contact name
Mrs Carol Evans

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-003267-19

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PAGoDA-2016

Study information

Scientific Title
PAGoDA: A Phase Ib/IIa Trial Combining the Selective Dual Trk/CSF1R Kinase Inhibitor PLX7486 with Gemcitabine in Patients with Advanced Solid Tumours, or as First or Second-line Treatment for Locally Advanced or Metastatic Pancreatic Ductal Adenocarcinoma (PDAC)

Acronym
PAGoDA

Study objectives
The overall study aim is to determine the recommended Phase II dose of the selective dual Trk /Fms kinase inhibitor PLX-7486 when given in combination with gemcitabine, and to determine preliminarily evidence of anti-tumour efficacy and assess the effects of the combination on tumour-related pain and Quality of Life in with advanced pancreatic ductal adenocarcinoma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/07/2018, NHS HRA South Central - Oxford C Research Ethics Committee (Level 3, Block B Whitefriars Building, Lewins Mead, Bristol BS1 2NT; 0207 104 8241; nrescommittee.southcentral-oxfordc@nhs.net), ref: 18/SC/0336.

Study design
Multi-centre open-label phase Ib trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Advanced cancer/ Pancreatic Ductal Adenocarcinoma

Interventions

All patients are given gemcitabine and the new drug PLX-7486. Gemcitabine is given intravenously (starting dose of 1000mg/m2) once a week on days 1, 8 and 15 of a 28 day treatment cycle. PLX-7486 is taken orally once a day. The first cohort uses a dose of 600mg PLX-7486 daily. If this dose is tolerated with no Dose Limiting Toxicities (DLTs), then a cohort with a dose of 750mg once daily is opened. 3 patients are treated at each dose, unless a DLT (as defined in the protocol) is observed, in which case the cohort is expanded to include a further 3 patients. If 2 or more patients experience a DLT, then no more patients are treated at that dose level, and the dose level below is expanded to 6 patients (unless already done so). If less than 2 patients experience a DLT, this is declared the Maximum Tolerated Dose (MTD). There is also an option to decrease the dose level if required.
Once the MTD is determined an expansion cohort is opened which enrols 12 patients with Pancreatic Ductal Adenocarcinoma (PDAC), and cancer related pain, at the MTD.
In both the escalation and expansion phase, treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent. Patients are followed up for 28 days after the last administration of study drug. Thereafter, follow up is three monthly for survival only, by telephone or review of medical notes. If the patient experiences toxicity related to the study drug, they are followed up until resolution or stabilisation of the toxicity, or until a new anti-cancer treatment is started.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
PLX-7486

Primary outcome(s)
1. Safety and tolerability profile is measured by reviewing adverse events (using NCI CTCAE v4.03)at weekly intervals. Sites will be asked to submit weekly DLT forms and these will be discussed at regular Safety Review Committee meetings.
2. Recommended Phase II dose of PLX-7486 in combination with gemcitabine is measured using a standard 3+3 design as described above. The Recommended Phase II dose of PLX-7486 with gemcitabine will be that which results in no more than 1 DLT in 6 patients.

Key secondary outcome(s))
1. Pharmacokinetic (PK) profile of PLX-7486 is measured by taking blood samples from patients enrolled in the escalation phase of the study at defined timepoints on Cycle 1 day 15. These will be analysed by PPD Bioanalytical laboratories to determine the PK profile of PLX-7486.
2. Preliminary anti-tumour activity of PLX-7486 in combination with gemcitabine is measured using RECIST 1.1 every 8 weeks during treatment.

Completion date
01/06/2020

Reason abandoned (if study stopped)
Unforeseen issues with IMP supply

Eligibility

Key inclusion criteria

1. Age ≥ 16 years
2. Able to give written informed consent prior to participating in the trial and any trial related procedures being performed
3. Willingness to comply with scheduled visits, treatment plans, laboratory tests and other trial procedures
4. Karnofsky Performance Score ≥ 70
5. Measurable or evaluable disease. Patient enrolled in the expansion phase should have measurable disease by RECIST v1.1 criteria
6. Dose escalation phase:
6.1. Patients with a histologically or cytologically proven advanced solid tumour refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient, and where treatment with gemcitabine is an appropriate option.
6.2. Any number of prior lines of therapy permitted
7. Dose expansion phase:
7.1. Patients with histologically or cytologically proven locally advanced or metastatic PDAC with the primary tumour in-situ, in whom single-agent gemcitabine is indicated, either as first-line palliative chemotherapy or second-line chemotherapy following FOLFIRINOX treatment. Previous FOLFIRINOX must be completed ≥ 28 days prior to cycle 1 day
7.2. Patients who have an average cancer-related pain score of 3-8 on the Short Form Brief Pain Inventory within 3 weeks of Cycle 1 Day 1
8. Adequate haematological and biochemical indices as below performed within one week (Day -7 to Day 1) before the patient receives study drug (note: patients must not have received recent red blood cell transfusions within 4 weeks, platelet transfusions within 1 week, or growth factors within 1 week of screening tests)
9. Females of childbearing potential must have a negative pregnancy test within 7 days prior to start of dosing, agree to use adequate contraceptive measures (see section 7.1.7) from the time of the negative pregnancy test up to 6 months after the last dose of study drug, and should not be breast feeding. Non-childbearing potential must be evidenced by fulfilling one of the following criteria at screening:
9.1. Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
9.2. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
10. Male patients should be willing to use barrier contraception i.e. condoms and female partners of child bearing potential must agree to use adequate contraceptive measures for the duration of the study and up to 6 months after the completion of the study treatment
11. Able to swallow and absorb oral medications
12. Life expectancy of at least 12 weeks

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Sex

All

Key exclusion criteria
1. Any systemic anti-cancer therapy (including investigational medicinal products) within 21 days prior to cycle 1 day 1 (6 weeks for nitrosureas and Mitomycin-C); within 5 half-lives for biological therapy and within 14 days for palliative radiotherapy.
1.1. Dose expansion phase: Prior gemcitabine-based chemotherapy for advanced disease. Prior neo-/adjuvant gemcitabine completed ≥ 6 months prior to cycle 1 day 1 is permitted.
2. Unresolved significant toxicity from prior therapy (except alopecia and Grade 1 toxicities, which in the opinion of the Investigator should not exclude patients). If uncertain, please contact the CTU to raise with the Chief Investigator.
3. Known leptomeningeal involvement, brain metastases or spinal cord compression, history of seizures or any condition that may predispose to seizure, including alcoholism
4. Known hypersensitivity (> Grade 2) to pyrimidine antimetabolites, PLX-7486 or structurally/ chemically similar drugs
5. Any gastrointestinal condition that may affect drug absorption of PLX-7486: malabsorption syndrome, previous gastrointestinal surgery (previous Whipples resection permitted), bowel obstruction, current refractory nausea or vomiting
6. Patients with uncontrolled diabetes
7. Treatment with warfarin. Patients on warfarin for DVT-PE can be converted to LMWH or oral Factor Xa inhibitors e.g. Rivaroxaban
8. Any severe or uncontrolled systemic disease (including active infection) or evidence of any other significant disorder or lab finding that the Investigator considers would make it undesirable for the patient to participate in the trial e.g. interstitial lung disease, severe hepatic impairment, uncontrolled chronic renal disease.
9. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
10. Resting ECG with measurable QTcF ≥ 450 msec (for males) or ≥470 msec (for females) at screening. Known Left ventricular (LV) dysfunction outside the institutional range of normal (testing not required)
11. Current malignancies other types, with the exception of adequately treated cone-biopsied in-situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin. Cancer survivors, who have undergone potentially curative therapy for a prior malignancy who have no evidence of that disease for the last 3 years are eligible for the study.
12. Patients participating in or planning to participate in another interventional clinical trial whilst on this study. Participation in an observational trial is acceptable.
13.In the Investigator’s opinion, any other condition which would not make the patient a good candidate for the clinical trial

Date of first enrolment
16/07/2019

Date of final enrolment
16/07/2020

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
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G12 0YN

Study participating centre
The Christie
Wilmslow Road
Manchester
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M20 4BX

Study participating centre
The Clatterbridge Cancer Centre
Clatterbridge Road
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Liverpool
United Kingdom
CH63 4JY

Study participating centre
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
NHS Greater Glasgow and Clyde

Organisation

University of Glasgow

Organisation
NHS Greater Glasgow and Clyde

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Industry

Funder Name
Plexxikon

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. All data will be archived and preserved on an NHS secure server in line with NHS trust policies. The database program will be archived to allow reconstruction as required. Data generated will be made available to all parties as agreed in the terms of the ECMC Combinations Alliance agreement. Other researchers may have access to data generated through collaboration. Restrictions to data sharing are unlikely as all data will be anonymised. All patients will provide informed consent for use of their anonymised data.

IPD sharing plan summary

Study outputs

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