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A Phase I clinical trial to determine the safety of gemcitabine and nab-paclitaxel administered in combination with ATRA in patients with locally advanced or metastatic pancreatic cancer

Submission date
01/04/2021

Recruitment status
No longer recruiting

Registration date
27/04/2021

Overall study status
Completed

Last Edited
31/01/2024

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-atra-and-chemotherapy-for-pancreatic-cancer-starpac

Background and study aims
The majority of pancreatic cancer patients are diagnosed at a later stage when their cancer is too advanced for surgery. Around 50% (1 in 2) have cancer that has spread to other organs, meaning it cannot be removed through surgery. For these patients, chemotherapy is given to stop the cancer from developing further. In another 30% (1 in 3) of patients, whilst the cancer has not yet spread from the pancreas, it is not possible to have it surgically removed since the cancer involves vital blood vessels around the pancreas. For these patients, there are currently no chemotherapy or radiotherapy treatments available that will shrink the tumour to a size that can be removed by surgery.
Pancreatic cancer is surrounded by a thick scar tissue, called the stroma, which blocks chemotherapy drugs from reaching the tumour and shrinking it. Specific types of cells, called pancreatic stellate cells (PSCs), are an important part of the stroma. Cancer cells activate PSCs allowing the cancer cells to survive longer and spread faster. Studies carried out by the research team have shown that it is possible to de-activate PSCs using vitamin A. In their normal state PSCs store vitamin A, however, this is lost in their activated state (pancreatic cancer). Pancreatic patients do not have enough vitamin A in their body and are therefore unable to change PSCs back to normal. All Trans Retinoic Acid (ATRA) is similar to vitamin A and is commonly given to patients with a specific type of leukaemia or blood cancer. This study is investigating the combination of two chemotherapy drugs (gemcitabine and nab-paclitaxel) plus ATRA. Patients taking both gemcitabine and nab-paclitaxel chemotherapy drugs together have shown a better response to treatment than patients who took only gemcitabine for the treatment of their pancreatic cancer. Research shows that ATRA can target and weaken the stroma (the tissue surrounding the cancer), allowing the chemotherapy treatment to get to the cancer cells. It is

hoped that following this course of treatment the tumour will shrink to a size that may make it suitable for removal by surgery. The aim of this study is to find out whether it is safe to combine these three drugs (ATRA, gemcitabine and nab-paclitaxel) without increasing side effects.

Who can participate?
Patients aged 18 and over with locally advanced or metastatic pancreatic cancer that cannot be removed by surgery

What does the study involve?
There are two parts to the study; the first will test different doses of the drugs to find the highest dose patients can take without too many side effects. The second part will test this dose to find the dose that will produce the desired effect with limited side effects. Participants will take ATRA for up to 6 cycles and chemotherapy until their cancer worsens and will be followed up for 12 months.

What are the possible benefits and risks of participating?
Participants may or may not experience any direct health benefits from taking part in this study. It is hoped that treatment with ATRA in combination with gemcitabine and nab-paclitaxel may decrease the size or stop the progression (growth) of tumours, but this cannot be guaranteed. Participation will provide useful information about the study treatments and cancer that may benefit others in the future.
Participants may have side effects from the drugs or procedures carried out in this study and they will vary from person to person. Everyone taking part in the study will be followed carefully for any side effects through regular checks such as blood tests, vital signs, physical examinations and review of any illnesses or symptoms. Common side-effects (though not an exhaustive list) include hair loss, nausea, vomiting, diarrhoea, low platelets in the blood, low white blood cells, nerve damage that can cause pain, numbness or weakness, lack of energy, body pains, fever, cough and abnormal liver function tests.

Where is the study run from?
Barts Health NHS Trust (UK)

When is the study starting and how long is it expected to run for?
March 2015 to March 2019

Who is funding the study?
1. Medical Research Council (MRC) (UK)
2. Celgene (USA)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-002662-23

Integrated Research Application System (IRAS)
174496

Protocol serial number
CPMS 20118, IRAS 174496

Study information

Scientific Title
A Phase 1B study repurposing ATRA as stromal targeting agent along with gemcitabine and nab--paclitaxel for pancreatic cancer (STAR_PAC)

Acronym
STAR_PAC

Study objectives
Part 1: To determine the maximum tolerated dose (MTD) of the combination of gemcitabine, nab-paclitaxel and all-trans retinoic acid (ATRA)
Part 2: To determine the optimal biological dose (OBD) of ATRA when given in combination with gemcitabine and nab-paclitaxel

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/10/2015, South Central – Berkshire (Bristol REC Centre, Whitefriars, Level 3, Block B, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8224; berkshire.rec@hra.nhs.uk), REC ref: 15/SC/0548

Study design
Non-randomized; Interventional; Design type: Treatment, Drug, Imaging

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Pancreatic cancer

Interventions
This open-label, multi-centre phase IB study has two parts:

Part 1 is the dose-escalation stage which will test different doses of the combination of ATRA, gemcitabine and nab-paclitaxel. The number of patients treated in this part of the study will depend on the incoming data regarding the side effects of the drugs and how many different doses are tested. At the end of this part, the maximum dose patients can receive with reasonable levels of side effects (the maximum tolerated dose, MTD) will be defined. Doses and the dose escalation plan may be altered according to incoming data from monitoring the side effects patients experience.

The second part of the study aims to explore whether the combination of treatments has an effect on the cancer. This part of the study will be dependent on confirming the MTD from the first part of the study. Participants will receive a dose level based on the MTD established during Part 1 of the study; however, the dose of ATRA given to patients may be altered to make sure they have the required levels of Vitamin A in their blood.

Study timelines:
Recruitment for part 1 of the study is planned to begin in October 2015 and data analysis will take place in January 2017. Recruitment for part 2 is planned to begin in July 2017 and data analysis will take place in September 2017. The study final report will be completed and the study closed by March 2018.

Patient visits:
Participants will receive up to six cycles (28 days each) of ATRA. Patients will receive the two chemotherapy drugs gemcitabine and nab-paclitaxel until their cancer worsens or beyond at the Investigator's discretion. Patients will be followed up for 12 months from the date of enrolment.

Screening:
After reading the Patient Information Sheet/Informed Consent Form (PIS/ICF), patients will be given as long as they need to decide whether to take part. If the patient decides to participate, they will be asked to sign the Informed Consent Form (ICF). No study tests or evaluations will be done before the patient signs the ICF.

Before being enrolled into the study, patients will need to have medical examinations, tests, or procedures to find out if they are eligible. Some of these examinations, tests, or procedures may be part of their regular medical care. If the patient has had any of these recently, they may not need to be repeated. This will be up to the study doctor. The following tests and assessments will be done as part of the screening assessment:
• Confirmation of diagnosis and recording of their medical history including specific information regarding any previous treatment and heart problems
• Recording of the patient's height, weight and vital signs (heart rate, blood pressure, breathing

rate and temperature)
• The patients ECOG performance status (a rating of how well they are able to perform everyday tasks and activities) will be assessed and recorded
• Full physical examination by a physician
• Peripheral Neuropathy Assessment to test for any nerve damage
• An ECG (12-lead) to check the electrical activity of their heart
• Patients who are able to become pregnant will have a pregnancy test within 7 days prior to first study drug administration which must be negative for them to participate in the trial
• Routine blood tests will be done to check overall health and to check for specific health issues which may prevent them from taking part in the study
• Patients will also have their blood levels of the tumour marker CA19.9 recorded and their levels of Vitamin A
• Patients will have a CT scan (or MRI if allergic to contrast agent) of their tumour within 28 days prior to Cycle 1 Day which will be part of standard clinical care
• Recording of any other medications the patient may currently be taking.
• Patients will be asked to provide consent for their archived formalin-fixed, paraffin-embedded (FFPE) tumour biopsy sample to be sent to the study laboratory for research tests. If this archived sample is unavailable patients will be asked to undergo an extra biopsy to provide this sample to the study. Patients must agree to this in order to participate in the study.

Treatment:
Patients will take oral capsules of ATRA twice daily on Days 1-15 of each 28-day cycle, and the two chemotherapy drugs (gemcitabine and nab-paclitaxel) will be given to patients in hospital through a drip into the arm on Days 1, 8 and 15 of each cycle. Patients will receive up to 6 cycles of ATRA and will receive gemcitabine and nab-paclitaxel for as long as they are benefitting from it. Patients may stop treatment (of any of the drugs) if their cancer worsens, or the patient decides to withdraw consent or the study physician decides it is in their best interest.

The following tests and/or procedures will be carried out prior to treatment on Day 1 of each Cycle:
• The patient's weight, vital signs and Eastern Cooperative Oncology Group (ECOG) Performance status assessed and recorded*
• Physical examination based on any health issues the patient has*
• Routine blood tests to check overall health and to check for specific health issues relevant to the study drugs*
• Blood test to measure levels of the tumour marker CA19.9 and Vitamin A*
• Additional blood sample will be taken for research purposes
• Patients will be asked about any health issues they are experiencing
* These assessments only need repeating prior to cycle 1 if more than 7 days have elapsed since they were performed for screening purposes, unless there are clinical concerns.

The following tests and/or procedures will be carried out on Day 1 of each Cycle:
• The time that patients take their first dose of ATRA will be recorded and a total of seven blood samples will be taken over a period of 5 h for testing to investigate how the study drugs are processed by the body. Blood samples will be taken 15 min before the patient takes the ATRA dose and 30 min, 1, 2, 3, 4 and 5 h after the dose.
• An additional blood sample will be taken for research purposes

The following tests and/or procedures will be carried out prior to treatment on Day 8 of each Cycle:
• Patients will be asked about any health issues they are experiencing
• Recording of patients vital signs

• An additional blood sample will be taken for research purposes
• Routine blood tests to check overall health and to check for specific health issues relevant to the study drugs*

The following tests and/or procedures will be carried out prior to treatment on Day 15 of each Cycle:

Patients will have the same tests as per Day 8 plus;
• Patients will be asked to bring their study treatment diaries and empty bottles of ATRA to check if they have missed any of their ATRA doses.
• Patients who consent to providing cheek cell and hair samples will have these samples taken.
• Patients will be asked to bring their study treatment diaries and empty bottles of ATRA to check if they have missed any of their ATRA doses.

Cycle specific tests and/or procedures:

Day 1 of Cycles 1-3 and for patients in Part 2 who have had their ATRA dose altered:
• The time that patients take their first dose of ATRA will be recorded and a total of seven blood samples will be taken over a period of 5 h for testing to investigate how the study drugs are processed by the body. Blood samples will be taken 15 min before the patient takes the ATRA dose, and 30 min, 1, 2, 3, 4 and 5 h after the dose.

Day 1 of Cycle 2 onwards:
• Recording of any other medications the patient may currently be taking

Optional procedures:
• Patients who consent to take part in the optional diffusion-weighted magnetic resonance imaging (DW-MRI) scans will have their first scan before beginning study treatment and will have additional scans within one 1 week prior to beginning Cycle 2 and 4 of treatment (within the last week of the previous cycle).
• Patients who consent to provide additional tumour biopsy samples or who do not have sufficient archival tumour sample will have this biopsy done before beginning study treatment, prior to beginning Cycle 3 and if their disease progresses.
• Patients who consent to providing cheek cell and hair samples will have these samples taken prior to starting treatment and 5 h after their first ATRA dose.

CT scans:
As per standard clinical care, patients will undergo CT scans of their tumours every 8weeks and the results will be recorded for the study.

Safety visit:
Patients will have these visits within 30 days(+/=7 days) after stopping treatment of gemcitabine /nab-paclitaxel:
• ECOG Performance status will be assessed and recorded
• Patients will be asked about any health issues they are experiencing
• Routine blood tests to check overall health and to check for specific health issues relevant to the study drugs

Disease progression:
If the patient’s cancer worsens they will have the following tests done. If the patient is unable to attend hospital they will be contacted via telephone and only details about the overall health will be recorded for the study.

• Recording of vital signs
• Patients will be asked about any health issues they are experiencing
• Routine blood tests to check overall health and to check for specific health issues relevant to the study drugs
• As per standard care, patients who progress will have a CT/MRI scan of their cancer and the results will be recorded for the study
• Optional biopsy for patients who consented to this

Follow-up visits:
Patients will be followed up for 12 months after enrolment into the study. Patients will attend their usual hospital clinics every 3 months and the following will be recorded for the study:
• The patient will be asked to report any health issues they are experiencing
• CA19.9 tumour marker levels will be measured in the blood
• For patients who have not had their cancer progress a CT scan will be performed as per standard care
• Recording of general information about the patient's health and any treatments

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
ATRA, gemcitabine, nab-paclitaxel

Primary outcome(s)
Part 1: Dose Limiting Toxicities (DLT) attributed as possibly, probably or definitely related to the study treatment measured using adverse events recorded within the first 28 days of treatment
Part 2: Determination of optimal biological dose (OBD) based on serum Vitamin A levels measured using blood sample analysis at the end of each treatment cycle - up to 6 cycles of treatment (1 cycle = 28 days)

Key secondary outcome(s))
1. Maximum concentration observed (Cmax) determined using ATRA PK measured using blood sample analysis pre-dose and post-dose up to 5 hours on day 1 of cycles 1-3
2. Time of maximum concentration observed (Tmax) determined using ATRA PK measured using blood sample analysis pre-dose and post-dose up to 5 hours on day 1 of cycles 1-3
3. Area under the curve (AUC) determined using ATRA PK measured using blood sample analysis pre-dose and post-dose up to 5 hours on day 1 of cycles 1-3
4. Serum Vitamin A levels measured using blood sample analysis at baseline and at the end of cycles 1 and 2
5. Incidence of AE (graded by NCI CTCAE v4.03) from the time of consent until end of treatment, an average of 8 months
6. Objective response rate (ORR), defined as the percentage of patients with measurable disease at baseline who have at least one visit response of CR or PR prior to any evidence of progression assessed by the site radiologist using CT scans (RECIST v1.1) 8 weekly until progression or death for a maximum of 12 months
7. Progression-free survival (PFS), defined as the time from the date of registration to the date of first documented tumour progression (as assessed by the site radiologist and/or investigator, using RECIST v1.1) or death from any cause, whichever occurs first - assessed 8 weekly until

progression or death for up to 12 months
8. Overall survival (OS), defined as the time from registration to death from any cause or 12 months follow up, whichever occurs first

Completion date
19/03/2019

Eligibility

Key inclusion criteria
Each patient must meet all of the following inclusion criteria to be enrolled in the study:
1. Written informed consent prior to admission to this study
2. Age ≥18 years. No upper age limit
3. WHO performance status 0 or 1
4. Life expectancy ≥12 weeks
5. Histologically proven Pancreatic ductal adenocarcinoma (PDAC). Formalin-fixed, paraffin-embedded tumour sample from the primary cancer must be available for central testing. If not available or sufficient patients will be asked to undergo a US or CT guided biopsy prior to study entry to satisfy this eligibility criterion.
6. Locally advanced or metastatic disease which is measurable according to the Response Evaluation Criteria in Solid Tumours (RECIST v1.1)
7. Received no prior systemic therapy for metastatic or locally advanced disease. Prior adjuvant chemotherapy (with gemcitabine or any other drug/s) is allowed if completed at least 6 months previously.
8. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:
8.1. Absolute Neutrophil Count ≤1.5 x 109/l (without granulocyte colony-stimulating factor support within 2 weeks prior to the first study treatment)
8.2. Platelet count ≤100 x 109/l (without transfusion within 2 weeks prior to the first study treatment)
8.3. Haemoglobin ≤10 g/dl (transfusion permitted to establish target haemoglobin levels prior to the first study treatment)
8.4. Calculated creatinine clearance (e.g. Cockcroft-Gault) ≤50 ml/min
8.5. Bilirubin level ≤1.5 ULN (patients with known Gilbert disease who have bilirubin levels ≤3 x ULN may be enrolled). Patients must be able to undergo biliary stenting if required before or, if required, during the trial
8.6. AST or ALT <2.5 x ULN or <5 x ULN in the presence of liver metastases
8.7. Alkaline phosphatase (ALP) <2.5 x ULN or <5 x ULN in the presence of liver and/or bone metastases
8.8. INR and aPTT ≤1.5 x ULN; this applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose
9. Female patients of child-bearing potential are eligible, provided they have a negative serum or urine pregnancy test within 7 days prior to the first dose of study treatment, preferably as close to the first dose as possible. All patients with reproductive potential must agree to use a medically acceptable method of contraception throughout the treatment period and for 1 month after discontinuation of ATRA and /or gemcitabine/nab-paclitaxel (whichever is the latest) and for 6 months after discontinuation for male patients. Acceptable methods of contraception include IUD, oral contraceptive, sub-dermal implant and double barrier (condom with a contraceptive sponge or contraceptive pessary). Micro-dosed progesterone preparations (“mini-pill”) are an inadequate method of contraception during treatment with ATRA. If patients are taking this pill they should be instructed to stop and another form of contraceptive should

be prescribed instead.
10. Able to follow protocol requirements as assessed by the Principal Investigator

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
27

Key exclusion criteria
A patient will not be eligible for inclusion in this study if any of the following criteria apply:
1. Patient has known brain metastases
2. Patient has experienced a significant reduction in performance status between the screening/ baseline visit and within 72 hours prior to commencement of treatment as per trial protocol, as per the Investigator's assessment
3. Patients with pre-existing sensory neuropathy >grade 1
4. History of malignancy in the last 5 years; with the exception of:
4.1. Patients with prior history of in situ cancer or basal or squamous cell skin cancer are eligible
4.2. Patients with other malignancies are eligible if they were cured by surgery alone or surgery plus radiotherapy and have been continuously disease-free for at least 5 years
5. Patient has active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy
6. Patient has HIV, or active hepatitis B or C infection
7. Patient has undergone major surgery, other than diagnostic surgery (i.e., surgery to obtain a biopsy for diagnosis without removal of an organ), within 4 weeks prior to Day 1 of treatment in this study
8. Patient has a history of allergy (including soya bean or peanut allergies) or hypersensitivity to any of the study drugs or any of their excipients, or the patient exhibits any of the events outlined in the Contraindications or Special Warnings and Precautions sections of the products or comparator SmPC or Prescribing Information
9. History of connective tissue disorders (e.g., lupus, scleroderma, arteritis nodosa)
10. Patient with a history of interstitial lung disease, history of slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies
11. Patient with high cardiovascular risk, including, but not limited to, recent coronary stenting or myocardial infarction in the past year
12. History of Peripheral Artery Disease (e.g., claudication, Leo-Buerger's disease)
13. Patient has serious medical risk factors involving any of the major organ systems, or serious psychiatric disorders, which could compromise the patient's safety or the study data integrity

14. Concurrent treatment with other experimental drugs or participation in another clinical trial with any investigational drug ≤30 days prior to study entry depending on the half-life of the investigational drug and/or guidance issued by the IMP manufacturer. Please contact the STARPAC Coordinating team for further information
15. Patient is taking any prohibited concurrent medication, including Vitamin A supplements and is unwilling to stop use prior to and during the trial
16. Patient is pregnant, planning to become pregnant or breastfeeding
17. Patient has received a live vaccine within 4 weeks prior to receiving their first dose of study treatment
18. Patient is unwilling or unable to comply with study procedures, as assessed by the Principal Investigator

Date of first enrolment
08/02/2016

Date of final enrolment
27/02/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Bartholomew's Hospital
Barts Health NHS Trust
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Guy's Hospital
Guy's and St Thomas' NHS Foundation Trust
Great Maze Pond

London
United Kingdom
SE1 9RT

Study participating centre
Hammersmith Hospital
Imperial College Healthcare NHS Trust
72 Du Cane Road
London
United Kingdom
W12 0HS

Sponsor information

Organisation
Barts Health NHS Trust

ROR
https://ror.org/00b31g692

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/M015610/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Celgene

Alternative Name(s)
Celgene Corporation

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		24/09/2020	26/04/2021	Yes	No
HRA research summary			28/06/2023	No	No
Plain English results			31/01/2024	No	Yes