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An open-label Phase Ib time-to-event continual reassessment method of dose-escalation of tolinapant (ASTX660) in combination with standard radical chemotherapy and radiotherapy in patients with cervical cancer

Submission date
25/06/2022

Recruitment status
No longer recruiting

Registration date
30/08/2022

Overall study status
Completed

Last Edited
12/11/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[X] 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-tolinapant-and-chemoradiotherapy-for-cervical-cancer-that-has-spread-crain

Background and study aims
Cervical cancer affects over 3,000 women a year in the UK. Half of these women are below the age of 45 years. With current treatment, 1 in 3 women will die within 5 years. Current treatment for advanced cervical cancer combines external radiotherapy and chemotherapy (chemoradiation) followed by internal radiotherapy (brachytherapy). The chemotherapy agent used is cisplatin. The drug to be tested, tolinapant, works by blocking the activity of certain proteins that help cancer cells to survive. These proteins can cause cancer cells to die (known as apoptosis). The purpose of this study is to find the best dose of tolinapant to use with radiotherapy. This trial will also look at the side effects of this drug and ensure that the combination is worthwhile.

Who can participate?
Women aged 16 or over, who are scheduled to receive chemoradiotherapy treatment for cervical cancer

What does the study involve?
Patients providing their informed consent for the trial will all receive tolinapant with chemoradiotherapy. Patients will receive chemoradiotherapy as a normal treatment for 5 weeks. On weeks 1, 3 and 5 they will receive tolinapant treatment taken as a tablet. This will be followed by 2 weeks of brachytherapy. The patients will then be followed up 6 weeks and 12 weeks after finishing brachytherapy treatment.

There is also a translational aspect to the study, patients will be asked to provide blood samples at each visit for the translational analysis. Patients will be asked for their consent to send their pre-treatment diagnostic biopsy and to provide an additional biopsy following tolinapant and chemoradiation treatment. Patients will also undergo MRI scans with specific sequences which will be shared for research purposes if they chose to consent to this aspect of the trial.

What are the possible benefits and risks of participating?
We cannot guarantee any specific treatment benefits when taking part in a clinical trial. However possible trial benefits are:
1. You will have access to a drug that would not be available to you outside of the study. Your condition may improve and you may benefit from more frequent medical supervision.
2. The outcome of this trial may find that the combination of tolinapant and CRT works better than the standard CRT alone. This could help change the standard treatment given to patients with the same type of cancer as you in the future.

The main risks are potential side effects from the drug combination, as outlined in the patient information sheet. Patients will be encouraged to discuss these with the research team and the patient will be monitored regularly to assess any side effects of the treatment. The reason for this initial study is to be sure that we have a safe and tolerable treatment before further testing. During the study, additional blood will be collected from a vein, which may cause pain where the needle is inserted. There is a small risk of bruising or infection at the site of insertion. Some people may experience dizziness, an upset stomach or fainting when blood is taken, however, every effort will be made by hospital staff to minimise this.

Where is the study run from?
University of Southampton (UK)

When is the study starting and how long is it expected to run for?
June 2022 to January 2026

Who is funding the study?
Cancer Research UK

Who is the main contact?
Mrs Marina Lee (UK)
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-006555-34

Integrated Research Application System (IRAS)
1004372

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RHMCAN1680

Central Portfolio Management System (CPMS)
51584

Study information

Scientific Title
A Phase Ib TiTE-CRM dose-escalation clinical trial of tolinapant (ASTX660) in combination with standard radical chemoradiotherapy in cervical cancer

Acronym
CRAIN

Study objectives
1. To establish the maximum tolerated safe dose of tolinapant in combination with cisplatin and radiotherapy (CRT) to aid dose selection for a phase II trial
2. To determine the safety and tolerability of tolinapant in combination with CRT
3. To assess how the tumour responds to tolinapant in combination with CRT
4. To ensure the addition of tolinapant does not interfere with planned delivery of CRT

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/08/2022, North West - Haydock Research Ethics Committee (3rd Floor - Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048248; haydock.rec@hra.nhs.uk), ref: 22/NW/0235

Study design
Open-label dose-escalation phase Ib

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Adenocarcinoma or squamous cell carcinoma of the cervix

Interventions
Cisplatin and radiotherapy (CRT) will be given using a standard dose of 45 Gy in 25 daily fractions over 5 weeks with once weekly cisplatin of 40 mg/m2. This is followed by brachytherapy for which common schedules will be a further 28 Gy in 4 fractions high-dose-rate or 34 Gy in 2 fractions pulsed-dose-rate. Tolinapant will be administered in fixed-dose capsules of 30 mg or 90 mg taken orally daily for seven consecutive days as an outpatient (followed by seven consecutive days off) prior to radiotherapy on alternate weeks (weeks 1, 3, 5) during chemoradiation. Patients will be followed up 6 and 12 weeks after radiotherapy treatment.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Tolinapant (ASTX660), cisplatin

Primary outcome(s)
1. The rate of dose-limiting toxicities (DLTs), identified using CTCAE v5 as defined as per the protocol, at each dose level measured using a TiTE-CRM Bayesian model and assessed continually for 12 weeks from the start of treatment. Any of the following events occurring after the first dose of tolinapant will constitute a DLT if, in the opinion of the investigator, the event is defined as definitely or probably related to tolinapant:
1.1. Grade 4 neutropenia ≥7 days duration
1.2. Grade 3 or 4 febrile neutropenia (neutrophils <1000/mm3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour AND/OR life-threatening consequences with urgent intervention indicated)
1.3. Grade 3 or 4 neutropenia associated with a separate event of bacteriologically proven sepsis happening at the same time
1.4. Grade 3 or 4 thrombocytopenia
1.5. Death
1.6. Any other grade 3 or 4 adverse event will constitute a DLT if, in the opinion of the investigator, the event is defined as definitely or probably related to tolinapant

Key secondary outcome(s))
1. Drug-related adverse events (AEs) and serious AEs (SAEs), graded using CTCAE v5, assessed 3 months from completion of chemoradiation treatment
2. Response rate measured using MRI categorised using RECIST version 1.1 criteria at baseline, treatment week 5 and follow-up 2
3. Relative dose intensity of planned courses of CRT will be calculated and total chemotherapy delays will be assessed 3 months after the completion of chemoradiation treatment

Completion date
31/01/2026

Eligibility

Key inclusion criteria
1. Histologically confirmed adenocarcinoma or squamous cell carcinoma of the cervix stage IB2/IIB/IIIB
2. Suitable for radical treatment with radiotherapy and cisplatin (using a standard dose of 45 Gy in 25 daily fractions over 5 weeks with weekly cisplatin 40 mg/m2)
3. Adequate haematological parameters:
3.1. Haemoglobin ≥ 90 g/l
3.2. Neutrophil count ≥ 1.5 x 109/l
3.3. Platelets ≥ 100 x 109/l
4. Adequate biochemical parameters:
4.1. Bilirubin ≤ 1.5 x ULN

4.2. AST and ALT ≤2.0 x ULN
4.3. ALP ≤ 2.5 x ULN
5. Lipase and Amylase ≤1.2 x ULN
6. GFR calculated (by Cockcroft-Gault formula or other accepted formula) or measured directly as ≥ 50 mL/min
7. Aged 16 years and over
8. ECOG Performance Status of 0-1
9. Willing and able to give written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Upper age limit
100 years

Sex
Female

Total final enrolment
11

Key exclusion criteria
1. Previous pelvic radiotherapy
2. Liver cirrhosis, or chronic liver disease Child-Pugh Class B or C
3. Pregnancy or breastfeeding (Women of child bearing potential (WOCBP) must have a negative serum pregnancy test at screening)
4. Patients of child-bearing potential who are not able to use a highly effective method of contraception
5. Any investigational medicinal product (IMP) within 30 days prior to consent
6. Major surgery within 30 days prior to enrolment
7. Hypersensitivity to tolinapant, excipients of the drug product, or other components of the study treatment regimen
8. Patients with known HIV infection
9. Patients with known active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test) or hepatitis C. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody and the 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
10. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable arrhythmias, unstable angina, left bundle branch block, third-degree heart block, pacemakers or congestive cardiac failure (New York Heart Association ≥ grade 2) within 6 months prior to enrolment

11. Any patient who has received a live vaccine within 4 weeks of initiation of their treatment (COVID-19 vaccination is allowed)
12. Conditions requiring systemic treatment with either corticosteroid (≥ 20 mg daily prednisolone or equivalent) or other immunosuppressive medications within 14 days of study drug administration.
13. Prior anticancer treatments or therapies within the indicated time window prior to the first dose of study treatment (tolinapant), as follows:
13.1.Cytotoxic chemotherapy or radiotherapy within 3 weeks prior and any encountered treatment-related toxicities (excepting alopecia) not resolved to Grade 1 or less.
13.2. Skin-directed treatments, including topicals and radiation within 2 weeks prior
13.3. Monoclonal antibodies within 4 weeks prior and any encountered treatment-related toxicities not resolved to Grade 1 or less
13.4. Small molecules or biologics (investigational or approved) within the longer of 2 weeks or 5 half-lives prior to study treatment and any encountered treatment-related toxicities not resolved to Grade 1 or less
13.5. At least 6 weeks must have elapsed since CAR-T infusion and subjects must have experienced disease progression, and not have residual circulating CAR-T cells in peripheral blood (based on a local assessment). Any encountered treatment-related toxicities must have resolved to Grade ≤1.
14. Patients taking a QT-prolonging agent
15. Use of a concomitant medication which is a strong CYP3A4 inhibitor
16. Abnormal left ventricular ejection fraction (LVEF) of <50% on echocardiogram (ECHO)
17. History of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy
18. Screening 12-lead electrocardiogram (ECG) with measurable QTc interval of ≥470 msec (according to either Fridericia's or Bazett's correction)
19. Any other active malignancy

Date of first enrolment
30/09/2022

Date of final enrolment
31/01/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
The Christie Hospital
550 Wilmslow Road
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Study participating centre
Southampton General Hospital
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
University of Southampton

ROR
https://ror.org/01ryk1543

Funder(s)

Funder type
Charity

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 available upon request from Southampton Clinical Trials Unit (ctu@soton.ac.uk). As a minimum, anonymous data will be available for request from three months after the publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data-sharing documentation. Researchers interested in the trial data are asked to complete the Request for Data Sharing form [template located on the SCTU website, www.southampton.ac.uk /ctu] to provide a brief research proposal on how they wish to use the data. It will include; the

objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		07/06/2024	11/06/2024	Yes	No
Basic results		12/11/2025	12/11/2025	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 7	06/09/2024	12/11/2025	No	No
Statistical Analysis Plan	version 1	24/10/2024	12/11/2025	No	No
Study website		11/11/2025	11/11/2025	No	Yes