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This study is investigating whether a new drug called ASTX660 can be combined with FOLFOX chemotherapy, a combination of two chemotherapy drugs (oxaliplatin and 5-fluorouracil) routinely used in the treatment of advanced bowel cancer. The purpose of this study is to find the dose of ASTX660 that can be given with FOLFOX chemotherapy, without producing side effects that are serious or detrimental to patients' day-to-day life.

Submission date
16/05/2023

Recruitment status
Suspended

Registration date
09/02/2024

Overall study status
Ongoing

Last Edited
02/05/2025

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims

In this study, we are investigating whether a new drug called ASTX660 can be safely combined with FOLFOX chemotherapy, a combination of two chemotherapy drugs (oxaliplatin and 5-fluorouracil) that are routinely used in the treatment of bowel cancer. The study will also establish the best dose of ASTX660 to use in this combination.

Chemotherapy damages cancer cells causing them to 'self-destruct' by a process known as apoptosis. Unfortunately, cancer cells can find ways to 'switch off' apoptosis and therefore become resistant to chemotherapy. This can lead to growth or spread of the cancer. In the laboratory it has been shown that ASTX660 can 'switch on' apoptosis so that colorectal cancer cells die in response to FOLFOX chemotherapy. Additional laboratory tests suggest that this combination treatment could lead to cancer cell death by other processes, not just apoptosis.

ASTX660 is an experimental unlicensed drug. It has been tested on its own in clinical trials but has not been tested in combination with FOLFOX chemotherapy. The purpose of this study is to find out whether combining ASTX660 and FOLFOX chemotherapy is safe and well tolerated, without producing side effects that are detrimental to patients' day-to-day life. In the study, the dose of ASTX660 will be increased in a stepwise manner (up to the dose identified in previous

trials where this drug was given on its own). The dose of ASTX660 that has the most acceptable side effect profile will be selected as the dose to use in combination with FOLFOX chemotherapy. Up to 30 patients will be treated within the study.

Who can participate?
Participants aged 16 or over with metastatic colorectal cancer in whom second-line palliative FOLFOX chemotherapy is an appropriate treatment option

What does the study involve?
All participants will receive both ASTX660 and FOLFOX chemotherapy. Treatment is given every 2 weeks for up to 12 cycles in total (24 weeks or approximately 6 months total duration) depending on side effects and how the cancer is responding to treatment. FOLFOX is a chemotherapy treatment. ASTX660 is a capsule taken by mouth once a day on a 7 days on/7 days off schedule. Participants will start taking the capsules on the day chemotherapy starts for 7 days and then stop for the next 7 days.
There will be additional blood tests to check for side effects of the drug and to check the levels of the drug in the blood at different times after it is taken. These blood tests will be in addition to the blood tests that are taken as part of routine care. There will also be additional tests on the heart to check the heart rhythm (up to 4 electrocardiograms) and the pumping of the heart (one echocardiogram or MUGA). Some participants will have a biopsy or sample of tumour taken before and during treatment to help investigate findings in the tumour. There will be CT or MRI scans to check how the cancer is responding to treatment. These will be done every 6 weeks during treatment, which may or may not be more frequent than scans done during standard care treatment, meaning it is possible you may have 1 or 2 extra scans over the course of treatment.

What are the possible benefits and risks of participating?
There may or may not be direct medical benefits from taking part in this trial. While we hope that adding the experimental drug ASTX660 to chemotherapy may increase the likelihood of tumour shrinkage compared to chemotherapy alone, we won't be able to show this definitively from this study. Some participants benefit from the increased monitoring on trial and regular contact with the trial team.
The main risks are the potential side effects associated with both the ASTX660 and FOLFOX treatment. Participants will be monitored for these side effects and may need to take additional treatment to control any side effects that develop. However, participants can stop treatment at any time. Side effects will be closely monitored by the doctors involved in the trial.

Where is the study run from?
Cancer Research UK Glasgow Clinical Trials Unit

When is the study starting and how long is it expected to run for?
May 2023 to May 2027

Who is funding the study?
1. Cancer Research UK
2. Taiho Oncology Inc. (USA)

Who is the main contact?
Prof. Victoria Coyle, v.coyle@qub.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Prof Victoria Coyle

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Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-006411-28

Integrated Research Application System (IRAS)
1004428

Protocol serial number
ASTFOX-2021, IRAS 1004428, CPMS 56649

Study information

Scientific Title
ASTFOX : A Phase I study of IAP antagonist, ASTX660 (tolinapant), in combination with standard of care FOLFOX chemotherapy in metastatic colorectal cancer

Acronym
ASTFOX

Study objectives

Primary objective:
To determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of ASTX660 in combination with mFOLFOX 6.

Secondary objectives:
1. To assess the safety and tolerability of ASTX660 in combination with mFOLFOX6.
2. To assess the preliminary anti-tumour activity of ASTX660 in combination with mFOLFOX6
3. To describe the pharmacokinetics of ASTX660 when given in combination with mFOLFOX6

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 05/09/2023, Wales Research Ethics Committee 1 (Health and Care Research Wales Support and Delivery Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 292 2940931; Wales.REC1@wales.nhs.uk), ref: 23/WA/0173

Study design
Interventional non-randomized

Primary study design
Interventional

Study type(s)
Treatment, Safety, Efficacy

Health condition(s) or problem(s) studied
Metastatic colorectal cancer

Interventions
This study is a single-arm phase I study for participants with metastatic colorectal cancer in whom second-line palliative FOLFOX chemotherapy is an appropriate treatment option. Participants will be treated with combination ASTX660 (tolinapant) plus FOLFOX. Treatment will be administered on an outpatient basis. Treatment dose levels are as follows;

Dose level ASTX660 Fluorouracil Folinic acid (mg) Oxaliplatin (mg/m²)
(tolinapant) (mg) (mg/m²)
1 (starting) 60 320mg/m² IV bolus 350 68
1920mg/m² IV infusion
2 60 400mg/m² IV bolus 350 85
2400mg/m² IV infusion
3 90 400mg/m² IV bolus 350 85
2400mg/m² IV infusion
4 120 400mg/m² IV bolus 350 85
2400mg/m² IV infusion
5 180 400mg/m² IV bolus 350 85
2400mg/m² IV infusion

FOLFOX is given every 2 weeks for up to 12 cycles in total (24 weeks or approximately 6 months total duration) depending on side effects and how the cancer is responding to treatment. ASTX660 is a capsule taken by mouth once a day on a 7 days on/7 days off schedule. Participants

will start taking the capsules on the day chemotherapy starts for 7 days and then stop for the next 7 days.
Treatment will be continued for up to 12 cycles (24 weeks in the absence of treatment delays due to adverse event(s)) or until one of the following criteria applies:

• Disease progression,
• Intercurrent illness that prevents further administration of treatment,
• Unacceptable adverse event(s) which fail to resolve within 2 weeks (6 weeks for neurotoxicity)
• Participant decides to withdraw from the study, or
• General or specific changes in the participant's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Participants who discontinue study treatment due to disease progression will no longer be followed up. Participants who complete 12 cycles of study treatment OR discontinue study treatment prior to 12 cycles for any reasons other than disease progression, will continue to be followed up for up to 52 weeks from cycle 1 day 1 of treatment, or until disease progression or death (whichever occurs first).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
ASTX660, fluorouracil, oxaliplatin, folinic acid, levofolinic acid

Primary outcome(s)
The maximal dose of ASTX660 which can be administered in combination with mFOLFOX6 for which toxicity rate is closest to target toxicity rate of 25%. This will be defined the maximum tolerated dose (MTD) determined by dose limiting toxicities as measured by clinical and laboratory toxicities (NCI-CTC AE version 5) during the first 2 - 2 weekly cycles of treatment.

Key secondary outcome(s))
1. Toxicity of the combination which will be measured by clinical and laboratory toxicities (NCI-CTC AE version 5) for patients throughout the duration of their treatment and for 30 days following completion of their study treatment
2. Objective response rate (defined as the proportion of patients with a complete response or partial response according to RECIST v1.1)
3. Progression free survival (determined as the time from patient registration to subsequent radiological disease progression according to RECIST v1.1)
4. Pharmacokinetic profile of ASTX660 in patients with metastatic colorectal cancer (Cmax, Tmax, AUC, T1/2, volume of distribution, and clearance of ASTX660 (through measurement of plasma concentration of ASTX660))

Completion date
17/05/2027

Eligibility

Key inclusion criteria

1. Willing and able to provide written informed consent and be capable of co-operating with treatment and follow-up
2. Histologically confirmed unresectable metastatic colorectal adenocarcinoma
3. Clinically and/or radiographically documented measurable disease (as per RECIST v1.1)
4. Have had 1 previous line of systemic therapy for treatment of metastatic disease, and for whom FOLFOX alone would otherwise be a
reasonable second-line treatment option. This includes patients with progressive disease on or within 6 months of completion of neoadjuvant or adjuvant therapy
5. Disease which is amenable to biopsy and provides consent to pre- and on-treatment tumour biopsies (applies to participants who are to be treated at dose levels 3-5 only)
6. Provides consent for use of archival tumour tissue
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 - 2 and stable over preceding 4 weeks.
8. Life expectancy > 6 months
9. Age 16 years or older
10. Haematological and biochemical indices within the ranges shown
- Haemoglobin (Hb) ≥9.0 g/dL / 90g/L (no prior transfusion within last 4 weeks) or ≥10.0 g/dL / 100g/L (transfusion within last 4 weeks)
- Absolute neutrophil count (ANC) ≥1.5 x 109/L
- Platelet count ≥100 x 109/L
- Serum bilirubin ≤1.5 x upper limit of normal (ULN)
- Alanine amino-transferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x (ULN) (or ≤5 x ULN in the presence of liver metastases)
- Calculated creatinine clearance (using the Cockcroft & Gault formula or other mathemtaical calculation e.g. Wright formula if used as standard of care at site) ≥ 50 mL/min
- PT and aPTT ≤1.5 x ULN
- Albumin ≥ 80% of the lower limit of normal
- Amylase ≤ ULN
- Lipase ≤ 1.2 ULN

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 12/02/2025:
1. Anti-cancer therapy consisting of endocrine therapy, immunotherapy, chemotherapy or another investigational agent during the previous 4 weeks (6 weeks for nitrosureas, Mitomycin-C) is not permitted with the exception of LHRH agonists for treated/biochemically-stable, organ-confined prostate cancer in the preceding 3 years. Previous use of palliative radiotherapy within

the preceding 4 weeks is permitted except where there has been a large volume of bone marrow irradiated or where the irradiated lesion is the only one suitable for RECIST measurability or biopsy. Previous short course or long course radiotherapy more than 4 weeks before trial registration for rectal cancer is permitted provided the criteria for RECIST measurability and biopsy are met.
2. Major surgery within 4 weeks of trial registration
3. Ongoing toxic manifestations of previous treatments that are ≥ Grade 2 according to NCI-CTCAE v5.0 with the exception of alopecia or certain Grade 2 toxicities, which in the opinion of the investigator and Sponsor should not exclude the patient – these should be discussed on a case by case basis
4. Symptomatic brain metastases or spinal cord compression. Participants with brain metastases that have been radiologically stable post treatment over an 8-week period may be included (provided corticosteroid use is equal to or less than 10mg/day prednisolone equivalent)
5. Uncontrolled hypertension (>160 mmHg systolic or >100 mmHg diastolic in a relaxed, temperate setting with patient quiet and seated with their arm outstretched and supported)
6. Participants with a known left ventricular ejection fraction (LVEF) <50%. An echocardiogram (ECHO) must be performed in all participants during screening. An alternative such as MUGA is acceptable if this is used as standard of care in place of echocardiogram at site.
7. Concomitant use of known strong inhibitors or inducers of CYP3A4. The required washout period is 4 weeks or 5 half-lives, whichever is longer.
8. Participants who are allergic or are intolerant to any of the study medications
9. Complete dihydropyrimidine dehydrogenase (DPD) deficiency. Participants with partial DPD deficiency may still be eligible for study treatment with FOLFOX provided they have previously tolderated escalation to the cohort-assigned dose of flurouracil. If patients have previously received capecitabine then they must have previous tolerated escalation of capecitabine to 80% BSA dosing of capecitabine (if allocated to dose level 1) or 100% BSA dosing (if allocated to dose levels 2-5).
10. Any participants receiving treatment with brivudine, sorivudine and analogues or participants who have not stopped these drugs at least 4 weeks prior to the start of study treatment.
11. Significant cardiovascular disease as defined by:
11.1. History of congestive heart failure requiring therapy (NYHA III or IV – Appendix IV)
11.2. History of unstable angina pectoris or myocardial infarction up to 6 months prior to trial entry
11.3. Presence of severe valvular heart disease
11.4. Presence of a ventricular arrhythmia requiring treatment
11.5. Screening 12-lead electrocardiogram with measurable QTc interval (Fridericia's correction) of >=470 msec).
11.6. Presence of complete Left Bundle Branch Block or 3rd degree heart block
12. Known to be serologically positive for Hepatitis B, Hepatitis C or Human Immunodeficiency Virus (HIV) (mandatory testing not required)
13. Pregnant or breast-feeding females or females of childbearing potential and males unwilling to use a highly effective method of contraception. Women of childbearing potential* and men with female partners of childbearing potential*, must agree to use adequate contraceptive measures for the duration of the study and for 6 months after the completion of study treatment (females) and 90 days after completion for males
14. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase I study of ASTX660 (tolinapant) plus FOLFOX.
15. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial, including any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

16. Participants who have received a live attenuated vaccine from 28 days prior to first dose of trial treatment.
17. History of another malignancy in the last 3 years (other than adequately treated squamous /basal cell skin cancer, treated DCIS of the breast, treated early-stage cervical cancer or treated /biochemically-stable, organ-confined prostate cancer)
18. Participants with known malabsorption or inability to comply with oral medication

Previous exclusion criteria:
1. Anti-cancer therapy consisting of endocrine therapy, immunotherapy, chemotherapy or another investigational agent during the previous 4 weeks (6 weeks for nitrosureas, Mitomycin-C) is not permitted with the exception of LHRH agonists for treated/biochemically-stable, organ-confined prostate cancer in the preceding 3 years. Previous use of palliative radiotherapy within the preceding 4 weeks is permitted except where there has been a large volume of bone marrow irradiated or where the irradiated lesion is the only one suitable for RECIST measurability or biopsy. Previous short course or long course radiotherapy more than 4 weeks before trial registration for rectal cancer is permitted provided the criteria for RECIST measurability and biopsy are met.
2. Major surgery within 4 weeks of trial registration
3. Ongoing toxic manifestations of previous treatments (≥ Grade 2 according to NCI-CTCAE v5.0, or ≥ Grade 1 for peripheral sensory or motor neuropathy) with the exception of alopecia or certain Grade 2 toxicities, which in the opinion of the investigator and Sponsor should not exclude the patient – these should be discussed on a case by case basis
4. Symptomatic brain metastases or spinal cord compression. Participants with brain metastases that have been radiologically stable post treatment over an 8-week period may be included (provided corticosteroid use is equal to or less than 10mg/day prednisolone equivalent)
5. Uncontrolled hypertension (>160 mmHg systolic or >100 mmHg diastolic in a relaxed, temperate setting with patient quiet and seated with their arm outstretched and supported)
6. Participants with a known left ventricular ejection fraction (LVEF) <50%. An echocardiogram (ECHO) must be performed in all participants during screening. An alternative such as MUGA is acceptable if this is used as standard of care in place of echocardiogram at site.
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Virus (HIV) (mandatory testing not required)
13. Pregnant or breast-feeding females or females of childbearing potential and males unwilling to use a highly effective method of contraception. Women of childbearing potential* and men with female partners of childbearing potential*, must agree to use adequate contraceptive measures for the duration of the study and for 6 months after the completion of study treatment (females) and 90 days after completion for males
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18. Participants with known malabsorption or inability to comply with oral medication

Date of first enrolment
17/07/2024

Date of final enrolment
17/05/2026

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Study participating centre
Northern Ireland Cancer Centre
Belfast City Hospital
Belfast
United Kingdom
BT9 7AB

Study participating centre
Beatson West of Scotland Cancer Centre
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Study participating centre
Leicester Royal Infirmary
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LE1 5WW

Sponsor information

Organisation
NHS Greater Glasgow and Clyde

ROR
https://ror.org/05kdz4d87

Organisation
University of Glasgow

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

Funder Name
Taiho Oncology Inc.

Results and Publications

Individual participant data (IPD) sharing plan
Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
Data arising from this study will be available for sharing after the main outcomes have been published. The Clinical Trials Unit is committed to furthering cancer research by sharing de-identified individual-patient data (IPD) from its studies with others in the field who wish to use the data for high quality science. All proposals will be reviewed for their scientific merit by the TMG and CTU. Data sharing agreements will be put in place prior to any data transfer.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1	31/08/2023	08/03/2024	No	Yes