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A study to assess the feasibility of treating patients with gestational trophoblastic neoplasia with pre-surgical pembrolizumab prior to their second evacuation and determine if this is a desirable alternative

Submission date
24/02/2023

Recruitment status
Recruiting

Registration date
27/07/2023

Overall study status
Ongoing

Last Edited
13/02/2026

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Gestational trophoblastic diseases (GTD) are a group of rare, pregnancy-related diseases of the placenta which can range from pre-cancerous growths to cancers that can be fatal if left untreated. Most patients with GTD are diagnosed at the precancerous stage early in pregnancy and undergo surgical removal of the disease from the womb. Around 15% of patients are not cured by surgical removal alone and need further treatment with chemotherapy or second surgery. Roughly one-third of patients are cured with a second surgery. Anticancer treatment with chemotherapy carries many short- and long-term side effects that can negatively affect a person's quality of life. Finding less harmful therapies that can be paired with surgery could therefore be of great benefit to patients with recurrent GTD. One alternative is to pair surgery with another class of anticancer treatment, known as immunotherapy. Immunotherapy drugs such as pembrolizumab work by activating the body's natural immune defences to fight the cancer. Pembrolizumab is an extremely effective and safe treatment for patients with more advanced GTD and an attractive alternative to more toxic chemotherapies. This study aims to determine how feasible it is to give pembrolizumab prior to the second surgery. The study will determine if we are able to recruit patients and if treatment can be safely delivered. Patients will be closely monitored and the researchers will collect tissues that will help them to understand better how cancers escape the immune system and how immunotherapy works.

Who can participate?
Patients aged 18 years and over with gestational trophoblastic neoplasia

What does the study involve?
Participants are randomly allocated to receive second surgery alone or to receive a single dose of pembrolizumab followed by surgery. All participants will be followed up for a year after the date of their surgery.

What are the possible benefits and risks of participating?
There is a possibility of redness, swelling and bruising after collection and participants may feel lightheaded or faint. For the second evacuation only arm the blood sample taken during pre-screening is what would usually be performed if the patient was undergoing standard-of-care treatment. No further blood samples are to be performed beyond this point besides blood collection for research. Only one small tube of blood will be collected at these time points. For the pembrolizumab group, blood sampling will be performed at pre-screening and the Day 11, 6-week and 12-week visits. These blood tests are important to ensure no adverse consequences of the IMP and to ensure patient safety. Furthermore, as the surgical evacuation in this arm is being performed at 14 days instead of the 7 as in the second evacuation arm, it is important to ensure hCG levels have not increased to a level where more prompt and aggressive treatment is needed.
Pembrolizumab is a common treatment for NSCLC. The common side effects are related to the immune system and include itching/rash, diarrhoea, cough, muscle/joint pain, fever, abdominal pain, sickness, headache and tiredness. This treatment is not yet licenced to be used in this setting, however, a global cohort of 58 patients with advanced gestational trophoblastic neoplasia (GTN) who were treated with pembrolizumab demonstrated a 70% cure rate. Furthermore, in the standard of care setting, pembrolizumab is given at a dose of 200 mg IV every 3 weeks or 400 mg every 6 weeks. In this study the patients will simply be received a single 200 mg IV dose, limiting the chance of any toxicities or adverse reactions.
Being exposed to X-rays does carry a risk of causing cancer many years or decades later, but this risk is thought to be very small. For example, an X-ray of the chest, limbs or teeth is equivalent to a few days' worth of background radiation and has less than a 1 in 1,000,000 chance of causing cancer. Participants will only undergo a single x-ray during the screening portion of the study.
Second evacuation by ultrasound-guided suction curettage is considered to be a safe approach in suitably selected patients and adverse side effects are deemed extremely unlikely but can include bleeding from the cervix or infection of the uterus; again, both are deemed very rare. All patients that undergo evacuation will be closely monitored.
MRI scans use powerful magnets and a computer to produce detailed images of any part of the body; these scans do not use X-rays. No short-term side effects have been found with MRI scans however patients may feel uncomfortable during a scan as they will have to remain very still throughout the procedure and may have feelings of claustrophobia whilst within the MRI machine. In some cases, a contrast medium/dye will be injected intravenously (into a vein) as part of the scan; this dye is used to improve the quality of the images. MRI contrast medium is generally very safe and side effects are uncommon but can occur.
Incidental findings are defined as observations of potential clinical significance unexpectedly discovered in research participants and unrelated to the purpose of the study. These may include for example abnormal or unexpected findings from laboratory samples or from radiology images.
The researchers do not expect many incidental findings to be identified during this study. However, any incidental findings discovered would be reported back by the Chief Investigator and study team to the participant's treating oncologist and the participant themselves in writing. This may for example include any results from the translational analysis conducted.
If an incidental finding is observed during the study, and it is considered a significant abnormality, then the study team should report these to the PI who should take action accordingly. It is the PI's responsibility to ensure findings are communicated to the participant, GPs or other clinicians as appropriate. Incidental findings should be reported to the sponsor trials team.
The patient population for this study will be women of childbearing age. All of the cohort have an elevated hCG, which is the marker normally used to define pregnancy but is also high in gestational cancer. At pre-screening, elevated hCG is confirmed with a blood test. Pregnancy is

ruled out with the USS also done during pre-screening: the USS shows there is cancer and not a fetus in the uterus. The researchers have also included “pregnancy” as an exclusion criterion.

Where is the study run from?
Imperial College London (UK)

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

Who is funding the study?
1. NIHR Imperial Biomedical Research Centre (UK)
2. Cancer Treatment and Research Trust (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05635344

Clinical Trials Information System (CTIS)
2022-002986-14

Integrated Research Application System (IRAS)
1006984

Central Portfolio Management System (CPMS)
56206

Protocol serial number
C/43/2022

Study information

Scientific Title
A feasibility window study of pembrolizumab prior to second evacuation for post-molar gestational trophoblastic neoplasia

Acronym
RESOLVE

Study objectives
Primary objectives:
1. To determine the feasibility of conducting a definitive study of neoadjuvant pembrolizumab prior to the second evacuation of low-risk postmolar gestational trophoblastic neoplasia (GTN)
2. To collect tissue at the point of second evacuation and blood to support translational research into the mechanisms of immune evasion and immunotherapy sensitivity in this disease

Secondary objectives:
1. To assess the rate of surgical cure with and without pembrolizumab
2. To assess the safety of a single dose of pembrolizumab prior to the second evacuation versus the second evacuation alone

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 25/07/2023, Westminster Research Ethics Committee (Nottingham HRA Centre, Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; None available; westminster.rec@hra.nhs.uk), ref: 23/LO/0260

Primary study design
Interventional

Study design
Randomized controlled open parallel-group trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Low-risk post-molar gestational trophoblastic neoplasia

Interventions
This will be a single-centre, open-label study that will aim to recruit 20 patients with low-risk post-molar gestational trophoblastic neoplasia to be randomised at a 1:1 ratio into two arms; standard of care vs neoadjuvant pembrolizumab. The 10 participants that will be randomised onto the standard of care arm will have their GTN treated with a secondary evacuation alone. The patients randomised onto the intervention arm will be given a single neoadjuvant 200 mg dose of pembrolizumab approximately 2 weeks prior to their second evacuation surgery. Following the second evacuation, patients in both arms will undergo standard of care urine and blood hCG monitoring every 2 weeks until hCG normalisation and then monthly urine hCG measurement for up to 1-year post evacuation. Failure of second evacuation to result in disease control is defined as per national guidelines (rise or plateau in hCG, hCG over 20,000 IU/L at 4

weeks, heavy vaginal bleeding). Patients will additionally have a clinical review and toxicity check at 2, 6 and 12 weeks post-evacuation. Randomisation will be done through sealed envelope.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Pembrolizumab

Primary outcome(s)
1. The proportion of eligible patients who consent to randomisation
2. The proportion of patients randomised to the intervention arm who complete protocol treatments
Recorded at 1 year post surgical evacuation

Key secondary outcome(s)
1. Proportion of patients who achieve a sustained complete response following second evacuation and no further anti-cancer therapy, defined as normalisation of hCG and no rise by 1 year post procedure
2. Incidence of adverse effects of second evacuation and pembrolizumab within 30 days and 12 weeks respectively, assessed by Common Terminology Criteria for Adverse Events (CTCAE v5.0, 27 Nov 2017)

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Written informed consent prior to initiation of any study procedures and willingness and ability to comply with the study schedule
2. Age ≥18 years
3. Postmolar GTN defined as recurrence or persistence of histologically confirmed CHM after primary surgical evacuation with no intervening treatment
4. Postmolar GTN defined as plateau or rising human chorionic gonadotropin (hCG). Plateaued hCG is defined as four or more equivalent values of hCG over at least 3 weeks. Rising hCG is defined as two consecutive rises in hCG of 10% or greater over at least 2 weeks
5. hCG under 20,000 IU/L
6. Low risk disease as defined by the Federation of Obstetrics and Gynecology (FIGO) 2000 risk scoring criteria (score of 6 or less)
7. No metastatic disease on chest X-ray
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
9. Disease present within the uterine cavity and not within 5 mm of the serosal surface
10. Adequate bone marrow reserve or organ function as defined by any one of the following parameters:
10.1. Absolute granulocyte count ≥1.5 x 109/L
10.2 Platelet count ≥100 x 109/L
10.3 Haemoglobin ≥9.0 g/dL (may have been blood transfused)

10.4. Creatinine clearance ≥ 30 ml/min (Cockcroft-Gault formula)
10.5. Serum bilirubin ≤1.5 x ULN
11. All patients must agree to a highly effective method of contraception, or to complete abstinence* for 1 year following second evacuation. This is standard practice following second evacuation of GTN because hCG levels rise in pregnancy thus masking a potential cancer recurrence

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
Female

Total final enrolment
0

Key exclusion criteria
1. Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, patients who have had any evidence of the other cancer present within the last 2 years or patients whose previous cancer treatment contraindicates this protocol therapy
2. Patients with histologically confirmed choriocarcinoma, placental site trophoblastic tumour (PSTT) or epithelioid trophoblastic tumour (ETT) on the first curettage
3. Pregnant women
4. Uncontrolled vaginal bleeding
5. Administration of live vaccine within 30 days prior to the first dose of study drug
6. History of immunodeficiency or receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
7. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
8. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis
9. History of Human Immunodeficiency Virus (HIV) infection
10. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection
11. History of active Bacillus Tuberculosis (TB)
12. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration

of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator
13. History of allogenic tissue/solid organ transplant

Date of first enrolment
14/02/2024

Date of final enrolment
31/12/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
England
W6 8RF

Sponsor information

Organisation
Imperial College London

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
NIHR Imperial Biomedical Research Centre

Alternative Name(s)
NIHR Imperial BRC, Imperial Biomedical Research Centre, BRC

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Funder Name
Cancer Treatment and Research Trust

Alternative Name(s)
Cancer Treatment & Research Trust, The Cancer Treatment & Research Trust, The Cancer Treatment and Research Trust, CTRT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

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?
Protocol file	version 2.0	10/07/2023	14/08/2023	No	No