CLINICAL STUDY PROTOCOL

Full Study Title:	A feasibility window study of pembrolizumab prior to second evacuation for post-molar gestational trophoblastic neoplasia.
Short Study title / Acronym:	RESOLVE
Product:	Pembrolizumab
Development Phase:	Phase II
Sponsor:	Imperial College London
ClinicalTrials.gov ID:	NCT05635344
Version no:	2.0
Protocol Date:	10th July 2023

This protocol has regard for the HRA guidance

RESEARCH REFERENCE NUMBERS

Include all relevant reference numbers in the table below, delete/amend any that are not applicable.

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CONTACT LIST

Chief Investigator

Dr. Ehsan Ghorani
CRUK Clinician Scientist
1st Floor, Imperial Centre for Translational and Experimental Medicine
Department of Surgery and Cancer
Imperial College London
Hammersmith Campus
Du Cane Road
London W12 0NN
UNITED KINGDOM

Tel: +44 (0)20 3311 1421
Email: e.ghorani@imperial.ac.uk

Sponsor

Research Governance and Integrity Team Imperial College London
Room 221, Level 2, Medical School Building
St Mary's Campus
Norfolk Place
London W2 1PG
UNITED KINGDOM

Contact: Rinat Ezra
Head of Research Governance and Integrity
Email: rrgit.ctimp.team@imperial.ac.uk
Tel: +44 (0)20 7594 1862

Funder

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ICTU Trial Coordinator

Aaron Clarke
Clinical Trial Coordinator
Cancer Research UK Imperial Centre: Clinical Trials Section (CCTS)
Cancer Research UK Convergence Science Centre
Department of Surgery and Cancer
Imperial College London
5th Floor Roderick Hill Building, South Kensington Campus
Prince Consort Road, London, SW7 2AZ

Tel: 02033117740
Email: Aaron.Clarke@Imperial.ac.uk

Study Statistician

Dr Jingky Pamesa Lozano-Kuehne
Email: j.lozano-kuehne@academicians.eu

Laboratories *(delete if not applicable)*

Experimental Cancer Medicine (ECMC) /ICBRC Laboratory
2nd Floor, B Block North
Department of Surgery and Cancer
Imperial College London
Hammersmith Campus
Du Cane Road
London W12 0NN
UNITED KINGDOM

Email: ecmcbiobank@imperial.ac.uk
Tel: +44 (0)20 3313 2349

Protocol development group

Ehsan Ghorani **CRUK Clinician Scientist**	Imperial College London
Michael Seckl **Professor of Molecular Cancer Medicine**	Imperial College London
Naveed Sarwar **Consultant Medical Oncologist**	Imperial College Healthcare NHS Trust
Xianne Aguiar **Lead Gestational Trophoblastic Disease Nurse**	Imperial College Healthcare NHS Trust
Matthew Winter **Consultant Medical Oncologist and Honorary Reader in Medical Oncology**	Sheffield University
Tom Bourne **Professor of Gynaecology**	Imperial College London
Philip Badman **CRUK Centre Cancer Clinical Trials Operations Manager**	Imperial College London
Aaron Clarke **CRUK Centre Cancer Clinical Trials Coordinator**	Imperial College London

Clinical queries

Clinical queries should be directed to the Chief Investigator or ICTU Study Manager who will direct the query to the appropriate person.

This protocol describes the RESOLVE trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact the Trial Coordination centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Trial Coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CCTS	Cancer Clinical Trials Section
CEAC	Cost Effectiveness Curve
CXH	Charing Cross Hospital
CI	Chief Investigator
CNS	Central Nervous System
CR	Complete response
CRF	Case Report Form
CRUK	Cancer Research UK
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of response
DSUR	Development Safety Update Report
EC	Database hosted by the Experimental Cancer Medicine Centre
ECMC	Experimental Cancer Medicine Centre
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
GMP	Good Manufacturing Practice
Hct	Haematocrit
Hgb	Haemoglobin
HRA	Health Research Authority
ICBRC	Imperial Cancer Biomarker Resource Centre
ICER	Incremental cost effectiveness ratio

ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
ITT	Intention to Treat
IUD	Intrauterine device
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Lung function test
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NIHR HTA	National Institute for Health Research: Health Technology Assessment Programme
NIMP	Non- Investigational Medicinal Product
NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression free survival
PPIE	Patient and Public Involvement and Engagement
PR	Partial response
QA	Quality Assurance
QALY	Quality adjusted life year
QC	Quality Control
QoL	Quality of life
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RGIT	Research Governance and Integrity Team
RSI	Reference Safety Information

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TMG	Trial Management Group
TST	Thyroid function test
TSC	Trial Steering Committee
TSH	Thyroid-stimulating hormone
ULN	Upper Limit of Normal
WBC	White blood cell

Table of Contents

TRIAL SUMMARY

TITLE	RESOLVE: A feasibility window study of pembrolizumab prior to second evacuation for post-molar gestational trophoblastic neoplasia.
PRIMARY OBJECTIVE	1. To determine the feasibility of conducting a definitive study of neoadjuvant pembrolizumab prior to 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	To assess the rate of surgical cure with and without pembrolizumab. To assess the safety of a single dose of pembrolizumab prior to second evacuation versus second evacuation alone.
PHASE	II
DESIGN	Single-centre randomised open-label study of neoadjuvant pembrolizumab vs standard of care (SOC)
SAMPLE SIZE	20 patients; randomised 1:1 to standard of care control or single dose of neoadjuvant pembrolizumab.
STUDY POPULATION	Adults (≥18yrs) with pathologically confirmed complete hydatidiform mole (CHM) who have developed low risk postmolar GTN after primary evacuation.
INCLUSION CRITERIA SUMMARY	1. Written informed consent prior to initiation of any study procedures and willingness and ability to comply with the study schedule. 2. Age ≥18yrs 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 5mm of the serosal surface. Adequate organ function as defined in the following: 10. Adequate bone marrow function measured within 28 days prior to administration of study treatment as defined below: Absolute granulocyte count ≥ 1.5 x 10^9/L ; Platelet count ≥ 100 x 10^9/L ; Haemoglobin ≥ 9.0 g/dL (may have been blood transfused) 11. Adequate renal function: Calculated creatinine clearance ≥ 30 ml/min according to the Cockcroft-Gault formula. 12. Adequate hepatic function: Serum bilirubin ≤ 1.5 x Upper normal limit (ULN) and AST/ALT ≤ 2.5 X ULN
EXCLUSION CRITERIA SUMMARY	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.
TREATMENT, FOLLOW UP AND MAIN STUDY PROCEDURES	Patients who undergo primary evacuation for CHM, followed up at the Charing Cross Hospital (CXH) national GTD registration centre will be approached with information about the study. Post primary evacuation, hCG levels are routinely monitored. Those diagnosed with postmolar GTN based on rising or plateaued hCG are routinely invited to CXH for further treatment. Patients will undergo screening procedures and if eligible be recruited into the study at this point. Randomisation will be 1:1 to one of two arms: 1. Standard of care (SOC): second evacuation by ultrasound guided suction evacuation and curettage (n=10) 2. Neoadjuvant pembrolizumab followed by second evacuation (n=10)

	Pembrolizumab will be given as a single 200 mg IV dose with second evacuation 14 days later. In the SOC arm, patients will undergo second evacuation on day 10 post randomisation. Between pembrolizumab administration and second evacuation, patients will have 2 clinical reviews to determine whether any new indication for urgent chemotherapy has arisen and commence this immediately if so. Cancer tissue for research will be collected at the point of second evacuation and patients will subsequently enter a standard of care surveillance protocol.
PRIMARY ENDPOINT	Feasibility of the approach, defined as the proportion of eligible patients who consent to randomisation and the proportion of patients randomised to the intervention arm who complete protocol treatments.
SECONDARY ENDPOINTS	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. 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).
ESTIMATED RECRUITMENT PERIOD	12 months
END OF TRIAL DEFINITION	The end of the trial is defined as collection of the last data point for the last patient
IMP	Name: Pembrolizumab Formulation: Concentrate for solution for infusion Dose: Single 200 mg single dose in the intervention arm. Route of administration: Intravenous (IV)

1. BACKGROUND

1.1 Introduction:

Gestational trophoblastic diseases (GTD) are a variety of rare, pregnancy-related proliferative disorders of placental trophoblasts. GTD ranges from premalignant conditions of partial and complete hydatidiform mole (CHM) to malignant gestational trophoblastic neoplasias (GTN) including invasive mole, choriocarcinoma and the rare placental-site trophoblastic and epithelioid trophoblastic tumours[1].

Patients with GTD are registered at one of three UK centres, of which the largest is Charing Cross Hospital (CXH), London. The CXH Trophoblastic Disease Centre is furthermore the largest of its kind globally with over 1200 registrations per year.

Most patients with GTD are radiologically diagnosed with premalignant hydatidiform mole during early pregnancy and subsequently undergo surgical evacuation of the uterus. Amongst patients with CHM, approximately 15% are not cured by primary evacuation. This is diagnosed usually with rising or plateaued human chorionic gondadotrophin (hCG) levels (a sensitive marker of disease burden)[2]. Patients usually have intrauterine and sometimes extrauterine disease. Postmolar disease at this point is considered to be malignant GTN and requires further therapy, usually with chemotherapy or second evacuation. Chemotherapy carries a number of short and long term toxicities that negatively impact quality of life. Our patient representatives indicate that our predominantly young cohort of women are keen to avoid these toxicities. Approximately one third of patients are cured with second evacuation alone[3].

Immunotherapy with pembolizumab that targets the T cell inhibitory receptor PD1 are highly effective in GTN (~75% cure rate)[4]. In other cancer types that are less sensitive, pembrolizumab delivered prior to disease resection has proven to be highly effective, resulting in high pathological complete response rates (elimination of all viable cancer cells)[5,6]. These observations motivates us to ask whether treatment with pembrolizumab prior to second evacuation of postmolar GTN could enhance the surgical cure rate and represent a powerful approach to cure this disease without requiring chemotherapy.

From a translational research perspective, the unique immune biology of GTN offers an ideal opportunity to deepen our understanding of immune regulation in cancer. GTN arises from placental trophoblasts and as such is a semi- or fully allogeneic transplant with both maternal and paternal genomic contribution[7]. Conventionally, such HLA mismatched transplants are expected to be rapidly rejected by the host immune system that recognises paternal antigens as foreign, yet GTN can be widely metastatic and fatal without therapy. In parallel, the exceptionally high response rate of this disease to immunotherapy offers an opportunity to study the biology of an optimally activated anti-cancer immune response. Thus, GTN represents a model to

study both mechanisms of extreme immune evasion in a highly antigenic environment and the basis of immunotherapy sensitivity.

Here, we propose a feasibility window study of neoadjuvant pembrolizumab vs. no treatment prior to second evacuation of intrauterine postmolar GTN. The trial will enable us to determine whether pembrolizumab prior to second evacuation is acceptable to patients and feasible to deliver. This could directly set a new standard of care or motivate a larger, definitive study. Second evacuation tissues and blood samples will be used to support a CRUK funded study of immune regulation in cancer using GTN as a model, expected to yield novel insights into why the immune response is incapable of rejecting cancers in general and how pembrolizumab overcomes this. These insights will help develop new treatments and approaches to personalised care across cancer types.

1.2 Clinical Rationale: Reducing exposure to chemotherapy amongst patients with low-risk disease

Two broad treatment options are considered for patients with postmolar GTN that has not spread beyond the uterus and who otherwise are considered low risk according to FIGO international criteria[8]. Firstly, further evacuation of intrauterine disease and secondly systemic treatment with chemotherapy. Whilst further treatments may be required, the overall cure rate approaches 100%, thus it is desirable to offer the least toxic approach upfront.

A limitation of second evacuation is the relatively low cure rate of approximately 25-35%[3,9–11]. Recently, immunotherapy with pembrolizumab has emerged as a highly active modality. In more common cancer types that are less immunotherapy responsive than GTN, immunotherapy given prior to surgery has yielded high response rates[5,6]. This hasn't been tested in GTN. We hypothesise that immunotherapy given before second evacuation of recurrent GTN will significantly increase the cure rate resulting in a novel treatment approach that will reduce the need for exposure to toxic chemotherapy.

1.2.1 Chemotherapy

Although adopted as the usual first line choice, chemotherapy is toxic, inconvenient, adversely impacts quality of life and introduces additional financial and social morbidities[12]. Whilst GTN is highly chemotherapy sensitive, up to 40% of all low-risk patients develop resistance to 1st line methotrexate chemotherapy requiring a treatment change, usually to multiagent therapy[13]. These regimens come with considerable toxicities including short term alopecia, mucositis, fatigue and the risk of life threatening neutropenic sepsis[14]. Long term, there is an increased risk of second malignancy and early menopause[15]. Treatment requires overnight admissions away from home which many young patients find challenging. This view

is reiterated by our expert patient representative, who believes patients are generally strongly motivated to participate in trials that limit the need for chemotherapy.

1.2.2 Second evacuation

Second evacuation by suction curettage[16] of recurrent intrauterine disease is an alternative approach for patients with no spread of disease beyond the uterus. Following early work suggesting that second evacuation alone may be a sufficient treatment for some patients[17], this option has been explored in further retrospective studies[3,10,11,18,19], two single arm prospective studies[20,21] and one randomised phase II trial of evacuation vs. chemotherapy[22]. Collectively, these studies have established that second evacuation is a safe procedure that spares at least on quarter of patients the need for further treatment, depending on the hCG prior to evacuation.

Globally, the largest study of second evacuation to date was carried out at CXH and reviewed the outcomes of 111 patients with disease recurrence following primary evacuation[3]. Amongst those with an hCG of 10,000 to 20,000 IU/L, the cure rate was 25% (n=6 cured / 24 treated). Amongst all patients with an hCG less than 20 000 IU/L, a cure rate of 35% was observed (n=20 cured / 57 treated). Since the overall cure rate remains close to 100%, it is arguable that minimisation of toxicity should be a key goal and some advocate second evacuation as a preferred, lower toxicity, option to chemotherapy particularly amongst those with lower hCG levels. In the era of immunotherapy agents that activate anti-tumour immune responses, it is possible that combining this modality with second resection may further reduce the need for chemotherapy.

1.2.3 Immunotherapy before second evacuation may greatly enhance cure rates

T cells of the immune system can recognise and control tumours, but their function is limited by inhibitory receptors (checkpoints). Monoclonal antibodies directed against these receptors (checkpoint blockade immunotherapy [CPI]) have proven to be effective across cancer types[23–25]. We have recently shown that GTN is profoundly CPI sensitive**.** Complete responses occur in ~70% of anti-PD1 treated patients[4], the highest rate across all human cancers.

Whilst CPI is mostly utilised in the setting of advanced, metastatic disease, it is increasingly studied in other settings. Several studies have now shown that neoadjuvant immunotherapy prior to cancer resection is a powerful approach, resulting in complete pathological responses amongst patients with melanoma[6] and lung cancer[5] amongst other cancer types. Given that the efficacy of anti-PD1 therapy is higher in GTN than these other tumour types that are conventionally considered to be most immunotherapy response, we hypothesise that neoadjuvant pembrolizumab prior to second evacuation could significantly enhance the cure rate over second evacuation alone.

1.3 Scientific Rationale

Tumour infiltrating T-cells (TILs) recognise cancer cells[26–30], but untreated malignancies usually progress, indicating tumour microenvironmental (TME) immune dysfunction[31]. The mechanisms of immune suppression within the tumour environment are not well understood.

In parallel, CPI has transformed the management of patients with multiple cancer types, but only a minority of patients benefit. The reasons for this are likewise unknown and underscore our limited understanding of the mechanisms governing TIL activity.

In summary, we propose GTN to be a unique model of human cancer immune regulation. Comparative study of tissues obtained from the control and intervention arms of this trial will elucidate fundamental mechanisms of cancer immune suppression and how this is reversed by immunotherapy. This understanding will help develop new treatments and tools to better personalise treatment of patients with GTN and more common cancers. The translational aims are supported by a CRUK Clinician Scientist Fellowship awarded to the CI. Input from an expert patient representative suggests that this cohort are motivated to participate in research that will potentially result in treatment advances in GTN and other cancers.

1.3.1 GTN as an extreme model of immune suppression: how do cancers escape immune control?

T cells distinguish cancer from normal self by detecting differences in protein fragments (antigens) presented on MHC molecules. Cancers are antigenically different from self in that they overexpress certain non-mutated proteins and in most cases additionally present mutated or neo-antigens. The immune response is stronger against cancer cells that are antigenically more different to self[32]. GTN is a unique cancer type since it is genomically composed of both maternal and paternal contributions, and in many cases only from paternal DNA. Thus, GTN represents a semi- or fully-allogeneic transplant.

Because of antigenic diversity particularly in MHC proteins, mismatched tissue transplants are usually rapidly rejected by the host immune system, yet GTN avoids this fate. Since it so strongly antigenic, this disease must employ very powerful mechanisms to suppress the immune response. Studying GTN as an extreme model of how a highly antigenic cancer type escapes immune destruction will thus shed light on mechanisms employed by other cancer types and drive research into new therapeutic approaches in this and other more common cancers.

1.3.2 GTN as an extreme model of tumour rejection triggered by pembrolizumab: how does immunotherapy work?

Across cancer types, it remains unknown why some but not all patients respond to immunotherapy. An essential piece of missing information is precisely how agents such as pembrolizumab work, and in which immune cell population this drug acts on.

T cells are broadly divided into CD4 T helper (Th) and CD8 T cytotoxic cells. These populations recognise antigens presented on MHC class I and class II respectively.

Whilst relatively understudied, Th cells are central to the anti-tumour immune response. This population can adopt a variety of fates to play an important role in recruiting, activating and sustaining the activity of anti-cancer CD8 cytotoxic T cells. Th cells can additionally mediate tumour rejection both directly and indirectly.

In parallel to employing strong mechanisms to prevent immune rejection, GTN is the most immunotherapy responsive cancer type described to date with a cure rate of ~75%. This contrasts with 5 year survival rates of ~40% with the anti-PD1 directed agent nivolumab in advanced melanoma[33] and ~30% with pembrolizumab in lung cancer respectively[34]. Notably, like many cancer types, GTN has suppressed or absent expression of MHC I required for CD8 T cell recognition, indicating a potentially important but unknown role of Th cells. This disease thus offers a unique opportunity to better understand the mechanisms of immune rejection triggered by anti-PD1 immunotherapy and in particular the CD4 T cell contribution to this. By studying the optimally activated intratumour immune response amongst patients with GTN treated with pembrolizumab in the intervention arm, we expect to greatly advance our understanding of how pembrolizumab acts, which are the effector populations and how they are regulated.

1.4 Safety Considerations

Individually, both pembrolizumab and second evacuation are characterised by a very low complication rate.

1.4.1 Pembrolizumab for GTN

Amongst patients with advanced GTN, pembrolizumab has proven to be a remarkably low toxicity agent. In CXH led global cohort of 58 patients treated over the past 7 years, only one patient discontinued therapy because of toxicity and there have otherwise been no grade 3 or higher events. The single patient who stopped treatment had a renal transplant that unfortunately was rejected following pembrolizumab therapy. Patients with organ transplant are excluded from this study and with a single dose of pembrolizumab we anticipate no safety concerns.

1.4.2 Pembrolizumab delivery with respect to second evacuation

As a standard of care, pembrolizumab is given at a flat dose of 200 mg IV once every 3 weeks or 400 mg once every 6 weeks. Usually, patients are commenced on 200 mg before switching to the higher dose once established. Although recent data suggest there is no difference in toxicity between the two regimens[35], we propose to offer the lower dose as a precaution.

In the intervention arm, we propose to carry out second evacuation 14 days following a single dose of pembrolizumab. We will allow a 2-day margin either side of the target to accommodate surgical theatre availability. To determine the number of doses and time to second evacuation, we have primarily aimed to balance two competing factors. Firstly, since patients have already been determined to require treatment for disease recurrence, the time between randomisation and evacuation should be minimised to reduce the risk of complications such as vaginal bleeding. Secondly, a period of time is required for maximal pembrolizumab effect in the tumour environment. In deciding on 14 days between pembrolizumab treatment and evacuation, we have considered data from patients with lung cancer treated with a single dose of pembrolizumab, which has shown a maximal effect on circulating T cell activation between 2-3 weeks post dose. In patients with advanced disease, 14 days is considered the minimal time period before a tumour response is seen with hCG decline. Thus a 14 day window ensures sufficient time for pembrolizumab effect whilst minimising the risks associated with tumour progression if therapy is ineffective.

1.4.3 Second evacuation

Second evacuation by ultrasound guided suction curettage is considered to be a safe approach in suitably selected patients. In three contemporary prospective studies recruiting 134 patients with disease recurrence after primary evacuation[21,22,36], a total of four grade 1 (3%) and one grade 3 (0.7%; requiring transfusion to support) cases of uterine haemorrhage were observed. In contrast, patients treated with 1st line methotrexate chemotherapy for low risk GTN have a reported rate of grade 3 haemorrhage of approximately 2%[37]. Amongst patients undergoing second evacuation in the studies noted above, one case of grade 1 uterine perforation (0.7%) was managed conservatively.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Endpoints

Objectives	Endpoints
To determine the feasibility of conducting a definitive study of neoadjuvant pembrolizumab prior to second evacuation of low risk postmolar gestational trophoblastic neoplasia (GTN)	1. The proportion of eligible patients who consent to randomisation. 2. The proportion of patients randomised to the intervention arm who complete protocol treatments.
To collect tissues at the point of second evacuation and blood to support translational research into the mechanisms of immune evasion and immunotherapy sensitivity in this disease	

2.2 Secondary Objective and Endpoint

Objectives	Endpoints
To assess the rate of surgical cure with and without pembrolizumab.	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.
To assess the safety of a single dose of pembrolizumab prior to second evacuation versus second evacuation alone.	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).

3. STUDY DESIGN

3.1 Design

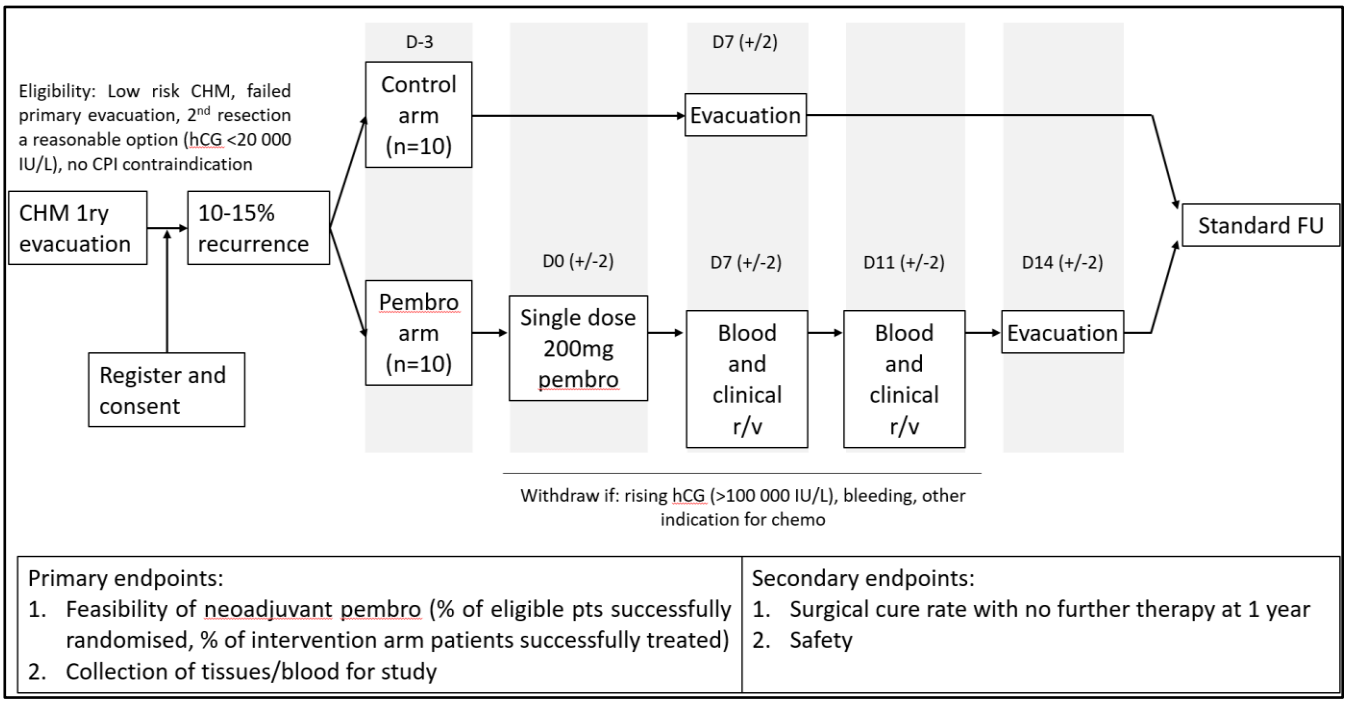
This is a single centre, randomised, open-label study of a single dose of 200 mg IV pembrolizumab followed by second evacuation 14 days later, or second evacuation alone for patients with low risk GTN who have failed primary surgical evacuation (Figure 1).

3.2 Treatment regimens

Table 1: Summary of treatment groups

Treatment arm	Number of participants
Second evacuation alone (control)	10
Pembrolizumab followed by second evacuation (Intervention)	10
Total number of participants	20

Figure 1: Study Flowchart



Key:
CHM – Complete Hydatidiform mole; **1ry** – Primary; **CPI** – Checkpoint inhibitor; **Pembro** – Pembrolizumab; **FU** – Follow up Visit

4. PARTICIPANT ENTRY

4.1 Study setting and population

The study will recruit patients aged 18 and above with untreated low risk GTN following primary uterine evacuation of CHM. Recruitment, treatment and follow-up will be at Charing Cross Hospital with the option of opening a second site if recruitment targets are not met.

All potential patients recruited onto study must meet all the inclusion and none of the exclusion points listed below:

(i) 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 ≥18yrs

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 not within 5mm of the serosal surface.

10. Adequate bone marrow reserve or organ function as defined by any one of the following parameters:
    - Absolute neutrophil count ≥ 1.5 x 10^9 /L;

- Platelet count ≥ 100 x 10^9 /L;
- Haemoglobin ≥ 9.0 g/dL (may have been blood transfused)
- Creatinine clearance ≥ 30 ml/min (Cockcroft-Gault formula)
- Serum bilirubin ≤ 1.5 x ULN
- AST/ALT ≤ 2.5 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.

**Complete abstinence (defined as refraining from heterosexual intercourse) must be in line with the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.*

(ii) 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 tumor (PSTT) or epithelioid trophoblastic tumor (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. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

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 (eg., 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. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

11. History of active TB (Bacillus Tuberculosis).

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.

5. PROCEDURES AND MEASUREMENTS

5.1 Identification and recruitment of participants

Patients diagnosed with GTD are routinely registered at one of two centres covering England and Wales: Charing Cross Hospital, London (CXH) and Weston Park Hospital, Sheffield. Patients with a diagnosis of CHM following primary evacuation of intrauterine disease registered at CXH will be identified and sent information about the trial to provide time to consider participation. Following primary diagnosis, patients routinely undergo hCG monitoring (2-weekly urine and blood until hCG normalisation and then monthly urine hCG). In approximately 10-15% of cases a rise or plateau in hCG occurs, indicating failure of primary evacuation resulting in development of postmolar GTN and the need for further therapy. At this point, patients are routinely invited to CXH for further evaluation and can be enrolled into the study.

5.2 Pre-screening

As part of routine evaluation of suspected postmolar GTN, patients undergo assessments to determine whether the disease is low or high risk based on the FIGO 2000 international guidelines. These tests include:

- Thoracic x-ray,
- Uterine ultrasound scan of the uterus
- Blood tests to determine hCG level, organ function and viral status.

Whilst low risk patients would be considered for single agent chemotherapy with methotrexate or second evacuation, high risk patients start multiagent chemotherapy.

All patients in this cohort will have elevated hCG due to the nature of the disease and hCG is a marker that is also elevated during pregnancy. To rule pregnancy out, blood hCG testing will be paired with an uterine ultrasound scan to confirm presence of cancer and absence of a foetus.

To reduce the number of patients we unnecessarily approach with further study information (which has the risk of increasing anxiety around the decision making process), we will offer the trial only to patients we have established to have low-risk disease amenable to second evacuation after the above standard of care investigations have been completed.

5.3 On Study Screening (pre-randomisation)

Pre-screening test results remain valid for 7 days prior to randomisation. Patients who are considered eligible based on pre-screening results will be invited to provide written informed consent before further study screening procedures.

We will obtain consent followed by on study screening procedures commencing on the day of attending CXH. These processes are expedited for the following reasons: firstly, to minimise the time between diagnosis and definitive therapy since delays introduce additional risks; secondly, as a national service, patients may travel long distances to attend CXH and we aim to reduce the inconvenience of additional attendances.

Data obtained as standard of care prior to written informed consent may be used for the study provided they comply with the protocol specified timelines.

Once written informed consent has been obtained, patients will be added to the study database, where a unique Screening ID will be allocated. This should be used in all correspondence during the screening period.

Screening procedures and assessments are as follows:

- Collection of demographic data
- Review of medical history to include cancer history and treatment
- Physical examination and performance status
- Blood tests to confirm eligibility: thyroid function test, cortisol.
- Record of vital signs (including height and weight)
- Assessment of concomitant medications
- Collection of research bloods
- Recording of blood test results done as part of pre-screening: renal/liver function, full blood count, viral screen, coagulation screen, hCG
- Recording of ultrasound scan and chest x-ray results done as part of pre-screening

A complete record of all patients who enter screening for the study, and those who go on to be enrolled, must be maintained at each site. The site investigators are responsible for ensuring that this record includes the allocated ID as well as the patient identifiable data including name, hospital number and date of birth.

Eligible patients who take part in the study must meet all the listed inclusion criteria and none of the exclusion criteria (section 4.1).

5.4 Randomisation

After eligibility has been confirmed, patients will be randomised to the trial. Randomisation will be performed centrally by Imperial Cancer Clinical Trials Section (CCTS) using the study database. There will be no option for manual randomisation. Upon randomisation each patient will be allocated a unique subject ID which should be used in all future correspondence. Please refer to the eCRF Completion Manual for further details on patient randomisation.

In this open-label study, randomisation will be on a 1:1 basis between second evacuation and pembrolizumab prior to second evacuation arms. Randomisation will be stratified according tp baseline hCG since this has been shown to strongly influence the probability of cure following second evacuation. Based on historical data, we have carried out simulations to show that randomising patients within pre-defined hCG values corresponding to expected median or quartile limits results in balanced distribution of hCG values between the two arms in over 95% of simulated trials. The Trial Statistician will be responsible for holding the randomisation code securely until the final analysis of the study but also to enable the interim analysis.

After eligibility has been confirmed, an archival tissue sample in the form of formalin fixed paraffin embedded (FFPE) tumour block and/or diagnostic tissue section will be collected from each patient.

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5.5 Visit Schedule

Table 2: Schedule of Assessments: Second evacuation only

Procedure	Pre-screening	Baseline/ screening Day -3 to 0	Day 7[1]	2 weeks post evacuation[2]	6 weeks post evacuation[2]	12 weeks post evacuation[2]	Every 2 weeks post evacuation until normalisation of hCG	Every month following normal hCG and until 1 year post evacuation
Informed Consent		X						
Medical History & Demographics		X						
Physical Exam		X		X	X			
Performance Status		X		X	X			
Vital Signs		X						
Haematology	X							
Biochemistry	X							
Coagulation	X							
Viral Screen (Hep B, Hep C, HIV)	X							
Thyroid Function Tests and Cortisol		X						
Tumour marker blood hCG	X						X	
Research Blood Sample		X		X	X	X		
Archival Tissue		X						
Imaging - Chest X-ray	X							
Imaging - Uterine ultrasound scan	X		X					
Randomisation		X						
Surgical evacuation			X					
Urine hCG							X	X
Adverse Events				X	X	X		
Concomitant Medications		X						

1. Visit is permitted to be performed two days prior or after scheduled timepoint.
2. Visit is permitted to be performed three days prior or after scheduled timepoint.

Table 3: Schedule of Assessments: Pembrolizumab arm

Procedure	Pre-screening	Baseline/ Screening Day -3 to 0	Day 0	Day +7[1]	Day +11[1]	Day +14[1]	2 weeks post evacuation [2]	6 weeks post evacuation [2]	12 weeks post evacuation [2]	Every 2 weeks post evacuation until normalisation of hCG	Every month following normal hCG and until 1 year post evacuation
Informed Consent		X									
Medical History & Demographics		X									
Physical Exam		X			X		X	X	X		
Performance Status		X			X		X	X	X		
Vital Signs		X			X						
Haematology	X				X			X	X		
Biochemistry	X				X			X	X		
Coagulation	X				X			X	X		
Viral screen (Hep B, Hep C, HIV)	X										
Thyroid Function Tests and Cortisol		X						X	X		
Tumour marker blood hCG	X			X	X					X	
Research Blood sample		X				X	X	X	X		
Archival Tissue		X									
Imaging – Chest X-ray	X										
Imaging – Uterine ultrasound scan	X					X					
Imaging – Optional Magnetic Resonance Imaging			X[3]			X[4]					
Randomisation		X									
Pembrolizumab			X								

Surgical evacuation						X					
Urine hCG										X	X
Adverse Events					X		X	X	X		
Concomitant Medications		X									

1. Visit is permitted to be performed two days prior or after scheduled timepoint.
2. Visit is permitted to be performed three days prior or after scheduled timepoint.
3. Visit is permitted to be performed anytime from randomisation to before Pembro administration.
4. Visit is permitted to be performed within two days prior to the second evacuation

5.6 Study Schedules

Scheduled visits, and their relevant assessments, will be conducted according to the randomised treatment arm – please refer to tables 2 and 3.

5.7 Follow-up

Following 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.

5.8 Procedures, Assessments and Laboratory Evaluations

(i) Demographic data

Patient month and year of birth will be collected at screening. For equality and diversity purposes, gender including gender reassignment; sexual orientation; marital status; disability; ethnicity, religion; geographical location and socioeconomic status and smoking status/history) will also be collected with all questions being optional to answer.

(ii) Medical history to include cancer history and treatment

A medical history will be taken. This history will detail the patient's cancer, including details of prior anti-cancer therapies. Any other relevant medical history and treatments will also be recorded. Concurrent diseases, i.e., other medical conditions that are ongoing from the start of the study, will be documented as adverse events if they worsen.

(iii) Vital signs

Vital signs including height (screening only), weight, body temperature, pulse, blood pressure and BMI will be recorded as indicated in the schedule of assessment tables. Vital signs may be assessed at any time during the visit; however, pulse and blood pressure should be measured after at least 10 minutes rest.

(iv) Physical exam

A complete physical examination will be performed as indicated in the schedule of assessment tables. The following examinations should be undertaken: general

appearance; skin; eyes, ears, nose, mouth and throat; head, neck and thyroid; chest; cardiovascular; abdomen; extremities; genitalia; spine; musculoskeletal; lymph nodes; neurological; other. The outcome of the examinations will be assessed to include whether normal, abnormal (clinically significant or not clinically significant) or not done.

(v) ECOG performance status

ECOG performance status will be performed as indicated in the schedule of assessments tables according to criteria as follows:

Table 4: ECOG Performance status

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

(vi) Laboratory evaluations:

The following laboratory evaluations will be conducted as indicated in the schedule of assessments tables, with collection and analysis according to standard practice at the relevant site.

- **Haematology:** White blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct) and platelet count.
- **Biochemistry:** Chem 7 (sodium [Na], potassium [K], chloride [Cl], bicarbonate [CO2], creatinine [Cr], glucose), calcium, phosphate, magnesium, urea and electrolytes. Creatinine clearance calculated based on Cockcroft-Gault estimate.
- **Liver function tests (LFTs):** ALT or AST (either or both as per local practice), alkaline phosphatase (ALP), albumin, lactate dehydrogenase (LDH) and total bilirubin.
- **Coagulation screen:** APTT, PT
- **Thyroid function tests (TFTs):** TSH, free T3, free T4.
- **Viral Screen:** Hepatitis B, Hepatitis C and Human Immunodeficiency virus (HIV)
- Human Chorionic Gonadotropin (hCG) blood or urine test

(vii) Tumour assessment

Tumour assessment will be performed by serial hCG measurement. Complete response is defined as normalisation of hCG levels (<5 IU/L) post second evacuation.

(viii) Thoracic x-ray and uterine ultrasound Scan (USS)

A thoracic x-ray and uterine ultrasound scan (USS) will be undertaken as part of pre-screening to ascertain if disease is low or high risk. The USS will be transvaginal, unless adequate imaging to determine eligibility criteria can be obtained by a transabdominal scan.

Additionally, a second uterine USS will be undertaken prior to second evacuation to ensure the disease remains amenable to second evacuation (disease within the uterine cavity and not within 5mm of the serosal surface). The second scan will routinely be carried out as a transvaginal study.

For the Pembrolizumab arm only, two optional MRI scans may be performed (funding permitted); the first of which would be given during the screening period and the second within two days before the second evacuation visit. The MRIs will be used for exploratory analysis separate from the main study.

(ix) Assessment of adverse events

Adverse events will be assessed as indicated in the schedule of assessments table, according to the data detailed in section 7.1.

(x) Assessment of concomitant medications

Concomitant medications will be assessed as indicated in schedule of assessments table, with the following data recorded for each medication:

- Name
- Start date / whether ongoing / end date
- Indication
- Dosage
- Frequency
- Route of administration

If a COVID-19 vaccine is administered during treatment, this will be recorded as a concomitant medication, with each dose recorded separately

(xi) Research samples

An archival tissue sample in the form of formalin fixed paraffin embedded (FFPE) tumour block will be collected from each patient, as well as blood (up to 20 ml) at baseline. Further blood for research and fresh tissue from second evacuation will be collected as indicated in schedule of assessments table. Tissues will be studied in an ongoing research project to better understand the mechanisms of immune evasion and sensitivity in GTN.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

(xii) Sample storage and analysis

Written informed consent which include the collection and use of specified biological samples and a full chain of custody will be maintained for all samples throughout the study.

PIs are responsible for maintaining full traceability of biological samples collected from patients while these are in storage at their site, until shipment to Imperial College London ECMC Laboratory and from return to site and/or disposal. Any person(s) responsible for temporarily holding samples, e.g. sub-contracted service provider must keep full traceability of samples from initial receipt of sample to onward shipment, return or disposal as appropriate.

Samples shipped to the ECMC Laboratory will be stored and analysed according to this protocol, a separate study laboratory manual, and any additional documentation produced by CCTS as required.

Imperial College London, CCTS has oversight of each sample's lifecycle through internal procedures and monitoring of study sites.

Archival tissue samples will be retained for further study and will be registered with the Imperial College Healthcare NHS Tissue Bank (ICHTB). Samples will be returned once the planned translational project is complete or earlier upon written request.

5.9 Incidental Findings

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.

We would not expect many incidental findings to be identified during this study. However, any incidental findings that were discovered would be reported back by the Chief Investigator and study team to the treating oncologist and participant.

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.

6. TREATMENTS

6.1 Investigational Medicinal Product Details

Pembrolizumab is an IMP for the purposes of this study. It is currently approved by NHS England for treatment of patients with GTN who have failed chemotherapy.

The Summary of Product Characteristics (SmPC) will be used as reference safety information (RSI) for the study, as submitted for CTA and amended where required during the trial e.g., when submitting DSURs, substantial amendment to study etc.

6.2 Labelling and Packaging

Packaging and labelling of pembrolizumab should be according to local practice. There are no trial-specific requirements.

6.3 Storage and Dispensing

Storage of pembrolizumab must be in line with the current relevant SmPC.

Once the pembrolizumab has been diluted for infusion, it should ideally be used immediately. If not used immediately it should be refrigerated at 2-8^{o}C for a maximum of 96 hours (including up to 6 hours at ≤ 25^{o}C) and not frozen. If refrigerated, the vials and/or IV bags must be allowed to come to room temperature prior to use.

Dispensing will be according to local standard practice.

6.4 Dosage, Duration and Compliance

A single 200 mg IV dose of pembrolizumab will be administered in the treatment arm.

6.5 Accountability

The investigator and appropriately trained and delegated staff will document the receipt, dispensing, administration and destruction of pembrolizumab as per local policy.

Please refer to the IMP Handling Manual for further details.

6.6 Drug interactions / Precautions / Contraindications

Interactions

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

Precautions

None. Management of specific adverse events is detailed in section 6.9.

Contraindications

Hypersensitivity to the active substance or to any of the excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

6.7 Overdose of IMP

There is no information on overdose with pembrolizumab.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

6.8 Dose Modifications for Toxicity

The pembrolizumab dose given will be a single dose before second evacuation. Any toxicity resulting from the Pembrolizumab should be treated as per standard of care.

6.9 Study drug administration

Drug administration is as per local standard procedures.

6.10 Pre-medications / Non-IMP details

There are no premedications.

6.11 Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Participant decision
- In the intervention arm, development of indications for urgent chemotherapy in the period between receiving pembrolizumab and awaiting second evacuation, discussed further below*

**Patients who develop vaginal bleeding, rising hCG >100,000 IU/L or any other indication for urgent chemotherapy will be withdrawn from the study to commence chemotherapy as determined by the treating team.*

(i) Procedures for Withdrawal from Study

In the event of a patient withdrawing from the study, no further visits or follow up will be conducted. The primary reason must be recorded in the eCRF and the patient's medical records. Any data and samples already collected will be retained and analysed.

Where the patient has withdrawn due to an AE, the investigator should follow the procedures in section 7.0.

6.12 Lost To Follow Up

In the event that a patient has been lost to follow up, this should be recorded on the eCRF with their last known contact date and survival status at the time. Lost to follow up status and steps taken to try to contact patient should also be noted in the patient's medical notes.

6.13 Trial Closure

End of trial is defined as collection of the last data point of the last patient, which is 1 year after their second evacuation visit. Samples taken for ongoing research will be registered with the Imperial College Tissue Bank at this point to support ongoing work. In the event that the study is closed early or terminated, the sponsor will notify the participating site that all study related activities will need to stop. Patients are to continue being cared for as per Trusts standard procedures.

7. PHARMACOVIGILANCE

7.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not listed in the reference safety information (RSI) e.g. list of expected medical events within investigator's brochure for an unapproved investigational product or section 4.8 of the summary of product characteristics (SmPC) for an authorised product. *When the outcome occurs this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose:

- **Results in death.**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly or birth defect.**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious

7.2 Causality

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.3 Severity of Adverse Events

Severity of AEs will be assessed using the grading scales found in the National Cancer Institute CTCAE version 5.0 (27th November 2017), by attributing the most relevant CTCAE term. Where it is not possible to attribute a specific CTCAE term, a term may be attributed by the investigator and assessed according to the introduction under Grades in CTAE version 5.0 i.e., grade 1=mild; grade 2=moderate; grade 3=severe; grade 4=life-threatening; grade 5= fatal.

CTCAE version 5.0 is accessible online here:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

7.4 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

(i) 7.4.1 Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form and sent to the study coordination centre within one month of the form being due.

(ii) 7.3.2 Serious AR/AEs

Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

SAEs

An SAE form should be completed and emailed to the study coordination centre for all SAEs within 24 hours. However, relapse and death due to disease under study and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

SUSARs

In the case of suspected unexpected serious adverse reactions, the staff at the site should:

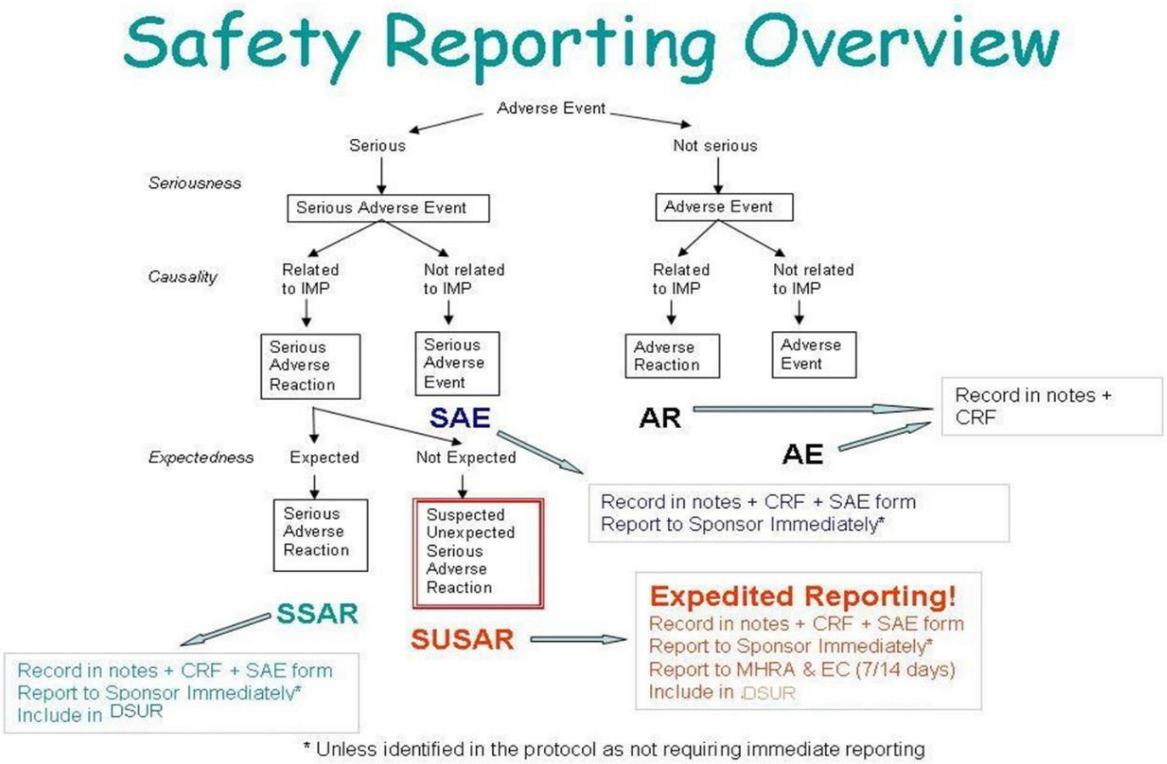
Complete the SAE case report form & send it immediately (within 24 hours,), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.

Or

Contact the study coordination centre by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above.

The study coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office



Contact Details for Reporting SAEs and SUSARs:

RESOLVE@imperial.ac.uk

Tel: 02033117740 (Mon to Fri 09:00 – 17:00)

RGIT.ctimp@imperial.ac.uk

7.5 Developmental Safety Update Reports / Annual Safety Reports

Developmental Safety Update Reports (DSUR) will be submitted to the Sponsor, the Ethics Committee and Regulatory Authority in accordance with local / national regulatory requirements.

7.6 Pregnancy

Pembrolizumab is contraindicated in pregnancy. Pregnancy is not considered an SAE but where the patient gives their consent the pregnancy will be recorded and followed up in the eCRF.

7.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

8.1.1 Feasibility of the treatment strategy

A primary goal of the study is to determine the proportion of patients in the treatment arm who complete the planned protocol of pembrolizumab followed by second evacuation. To justify a larger study of this intervention, we would expect 90% of patients to complete the protocol with a lower bound of 70% below which we would not consider the strategy to be practicable. With 10 patients, assuming 90% complete protocol treatments, the 95% confidence interval is 71 – 100%.

8.1.2 Feasibility of recruitment

Estimated cure rate with second evacuation alone is approximately 25% in our cohort[3]. The cure rate with single agent chemotherapy is approximately 66%. Therefore under conservative assumptions, in order to demonstrate a clinically significant benefit of pembrolizumab prior to second evacuation of 66% cure vs. second evacuation alone (25% cure), 40 patients in total are required (80% power, significance level 0.05). To justify a larger study, this cohort would be recruited in no more than 3 years (14 patients/year).

Based on current caseloads, we estimate approximately 50 patients per year in the UK are eligible for the study, of whom 30 are managed at CXH. With 30 eligible patients, assuming 66% (n=20) are recruited in 1 year, the 95% confidence interval

is 50 – 84%. This is consistent with the recruitment target of at least 15 patients per year at CXH (30 patients/year x 0.5 [lower bound of the 95% confidence interval for the recruitment rate]). Thus recruitment of 20 patients in 1 year would give us confidence that a definitive study would be feasible.

8.1.3 Detection of a clinical meaningful result

Given the challenges of carrying out definitive randomised controlled trials in the rare disease setting, data from small scale studies have been highly influential in driving treatment advances. The global adoption of pembrolizumab for GTN is a case in point. Our initial observation was exceptionally high pembrolizumab efficacy amongst a series of 4 patients. These data were sufficient to result in a change in NHS guidelines to support funding of this agent for patients with resistant disease. As we and the global community have accrued more data, use of pembrolizumab is now recommended in global GTN management guidelines.

While, as per recommendations for feasibility studies, we did not conduct sample size calculations for the pembrolizumab vs control comparison, we note that even with such a small sample size we would have adequate power to detect a clinically significant difference between the arms. Second evacuation for disease recurrence has a complete response (CR) rate of ~25% based on a study done at our centre. Amongst the remainder who relapse, we estimate a 75% CR rate to pembrolizumab based on multicentre data on patients with drug resistant, metastatic disease. We thus estimate the CR rate of neoadjuvant pembrolizumab to be 81% (100*[0.25+(1-0.25)*0.75]). For 80% power with α of 0.05, 9 patients per arm are required. This is consistent with 20 patients in total, randomised 1:1 to the control and neoadjuvant pembrolizumab arms.

8.1.4 Translation aims

A co-primary objective of the study is to obtain second evacuation tissue and blood for translational research. We have carried out sample size estimation to evaluate the number of patients required to identify immunotherapy triggered differences in the transcriptional profile of key tumour infiltrating T cell populations. Assuming 1000 genes are tested with average read count of 50, to identify 50 genes which are differentially expressed with a fold change of 4 or more at a false discovery rate (FDR) of 0.05, requires 9 patients per group (determined using the RnaSeqSampleSize package; Zhao 2018).

In summary, 10 patients per arm is justified to achieve the goals of this study.

8.2 Planned recruitment rate

Analysis of our current caseload reveals approximately 30 cases/year are eligible. We aim to enrol all patients within 12 months of opening and will determine

recruitment rates at a planned 6 month interim review. If recruitment targets are not met (<40% of patients recruited), we will open a second site at Weston Park Hospital (the only other centre for GTN management in England and Wales).

8.3 Statistical analysis

8.3.1 Analysis populations

In order to describe feasibility of the approach and collect tissue for translational activities, the primary analysis population will be Intention to Treat (ITT). To determine patient interest as a second measure of feasibility, we will additionally consider the population of patients assessed for eligibility

8.3.2 Primary Endpoint Analysis

We will carry out descriptive data analyses with respect to the feasibility of recruitment and completing protocoled treatments on the intervention arm.

Firstly, participant flows will be evaluated using a CONSORT diagram adapted for feasibility studies[38]. We will record the numbers of patients:

1. With low risk GTN following primary evacuation of CHM
2. Consented
3. Screened
4. Eligible
5. Randomised
6. Who complete per protocol treatments

The number of patients who drop-out at each stage will additionally be recorded.

We will calculate the proportion of eligible patients who consent to participation as a measure of the potential to recruit to a larger study, along with the proportion of patients randomised to the intervention arm who complete per protocol treatments. In the intervention arm, the proportion of patients who are withdrawn from the study after pembrolizumab but before second evacuation and the reasons for this. The 95% confidence intervals will be calculated along with these proportions.

8.3.3 Secondary Endpoint Analysis

Recurrence free survival rate will be evaluated at the 1 year landmark post second evacuation. Safety data analysis will be conducted as below (8.3.4).

8.3.4 Safety Analysis

Safety data analysis will be conducted on all subjects randomised within the trial. Data will be collected on the number of patients who are withdrawn from the study in order to commence chemotherapy due to tumour progression. The number and proportion of patients who experience complications arising from second evacuation will be reported. In the intervention arm, the number and percentage of subjects experiencing an AE and the number of events will be reported. Information regarding severity will be examined with a focus on Grade 3-5 events using the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the shipment of IMP and the enrolment of participants, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The sponsor trials team will make amendments and make the decision to amend the protocol and decide whether changes are substantial or non-substantial, with support from the Protocol Development Group where applicable. Changes will be communicated to stakeholders, including participating sites, electronically and be version controlled according to tracked changes and in accordance with the relevant standard operating procedures. The amended protocol will be reviewed by all members of the Protocol Development Group prior to finalising.

(iii) Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local / national requirements. The Annual Progress Report will also detail all SAEs recorded.

(iv) End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.
The end of trial notification will be submitted within 90 days of the end of trial definition being met. In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.

9.4 Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory Authority must be obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and DSURs, and be notified of the end of the trial.
This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: CTA 19174/0438/001-0001

9.5 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.
The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.6 Other Required Approvals

The procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert will be undertaken before the study commences.

9.7 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the Research Governance and Integrity Team (RGIT) on a monthly basis.
An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.
A serious breach is defined as:
A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

RGIT will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

9.8 Insurance and Indemnity and Sponsor

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.
Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

9.9 Funding

Funding for this study has been provided by the Imperial Biomedical Research Centre and the Cancer Treatment and Research Trust Charity. Funding for the translational aspects of the study will be from Cancer Research UK. Funding allocated to the sites is detailed in the participant site agreement. Requests and queries regarding payment should be sent to resolve@imperial.ac.uk,

9.10 Trial Registration

The study will be registered on the following trial databases in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations:

- Clinicaltrials.gov
- Cancer Research UK
- EC Trial Finder

9.11 Informed Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.12 Contact with General Practitioner

It is the investigator's responsibility to inform the participant's General Practitioner *(where applicable)* by letter that the participant is taking part in the study provided the participant agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

9.13 Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

Data will be transferred to (insert third party name as appropriate or delete)

9.14 Data Protection and Participant Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9.15 End of Trial

The end of the trial is defined as collection of the last data point for the last participant. Samples taken for translational research will be held under Imperial College Tissue Bank ethics for ongoing work.

9.16 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial are classified as source data.

Source data are contained in source documents; these are defined as: original documents, data, and records e.g. hospital medical records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, radiological imaging, patient files, and records kept at the pharmacy, laboratories and any medico-technical departments involved in the clinical trial.

10.2 Language

eCRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

10.3 Database

The electronic case report form (eCRF) is in OpenClinica.

The method of entry and validation, procedure for raising queries, and other core data entry aspects will be detailed in a separate Data Management Plan held by CCTS and in eCRF Completion Guidelines circulated to participating sites.

10.4 Data Collection

In compliance with GCP, the medical records/notes should be clearly marked and allow easy identification of a patient's participation in the clinical trial.
The Investigator (or delegated member of the site study team) must record all data relating to protocol assessments and procedures, laboratory, safety and efficacy data in the eCRF. Details of procedures for eCRF completion will be provided in eCRF Completion Guidelines circulated to participating sites.
Details of procedures for eCRF/CRF completion will be provided in a study manual.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

11. STUDY MANAGEMENT STRUCTURE

11.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened as a joint Committee with the Independent Data Monitoring Committee (IDMC)

11.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial co-ordinator. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.3 Data Monitoring Committee

An IDMC will be convened as a joint committee with the TSC to monitor data collected during the study and to make recommendations to the TMG on whether there are any ethical or safety reasons as to why the trial should not continue. It will consist of at least an independent Chair, an independent statistician, an independent clinician, the Chief Investigator and Trial Coordinator. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter

11.4 Early Discontinuation of the Study

Any stopping criteria will be defined by the IDMC, including a required procedure for future visits / assessments if the study needs to be discontinued early.

11.5 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of ‘low’, ‘medium’ or ‘high’ to the trial. The risk assessment will be carried out by RGIT in collaboration with the Study co-ordinator and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.6 Monitoring

The study will be monitored periodically by the trial co-ordinator to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring will incorporate central, remote and on-site elements.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

11.7 Quality Control and Quality Assurance

Quality Control will be performed according to Sponsor internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

The study may be participant to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.8 Peer review

Internal review has been conducted by Imperial College London as follows:

- Imperial College Trials Unit - Cancer Peer Review Committee

The study has furthermore been presented and discussed at 2022 EOTTD and ISSTD international meetings.

11.9 Public Involvement

This study will use public involvement throughout the life cycle of the study. Public involvement will include:

- Design of the research – review of protocol and all patient facing documentation;
- Management and undertaking of the research – advising on recruitment strategies and contribution to TSC meetings;
- Dissemination of results – production of a plain English summary and advising on avenues for dissemination.

11.10 Publication and Dissemination policy

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP/device and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study,

the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the joint TSC / IDMC.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study. The results will also be submitted to the EudraCT results database in accordance with regulatory requirements.

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13. REVISION HISTORY

Version	Date	Summary of changes
1.0	14/Feb/2023	First version
2.0	10/Jul/2023	Second version drafted post initial REC/MHRA review and addressed a number of changes required to conform with PIS as well as a number of wording and formatting changes.

SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: RESOLVE: A feasibility window study of pembrolizumab prior to second evacuation for post-molar gestational trophoblastic neoplasia.

Protocol Number: C/43/2022

Signed: _____

Name of Chief Investigator
Title

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: RESOLVE: A feasibility window study of pembrolizumab prior to second evacuation for post-molar gestational trophoblastic neoplasia.

Protocol Number: C/43/2022

Signed: _____

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: RESOLVE: A feasibility window study of pembrolizumab prior to second evacuation for post-molar gestational trophoblastic neoplasia.

Protocol Number: C/43/2022

Signed: _____

Name of Statistician
Title
Organisation/Company

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: RESOLVE: A feasibility window study of pembrolizumab prior to second evacuation for post-molar gestational trophoblastic neoplasia.

Protocol Number: C/43/2022

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____