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Study of etoposide carboplatin chemotherapy in combination with pembrolizumab and lenvatinib therapy in advanced high-grade neuroendocrine tumours

Submission date
05/07/2023

Recruitment status
Recruiting

Registration date
16/11/2023

Overall study status
Ongoing

Last Edited
24/10/2024

Condition category
Cancer

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

Plain English Summary

Background and study aims
This is a single-arm, open-label phase II study for chemotherapy naïve patients with confirmed high-grade neuroendocrine tumours (HG-NETs). Patients enrolled on the study will receive carboplatin, etoposide and pembrolizumab as induction treatment before moving on to pembrolizumab and lenvatinib for maintenance treatment. The study will aim to assess the safety and efficacy of this combination of drugs, and this two-part treatment. Carboplatin plus etoposide is an already proven effective regimen against HG-NETs. However, a recognised challenge of this treatment is the development of resistance to these drugs. The addition of pembrolizumab to this treatment course is thought to have a synergistic effect and increase long-term disease control. Pembrolizumab is a monoclonal antibody designed to block the PD-1 receptor, which binds PDL-1 and PDL-2 ligands to counteract their anti-tumour response, thereby activating the body's immune system to fight cancer cells. Lenvatinib blocks the activation of all Vascular Endothelial Growth Factors (VEGF) receptors to prevent the growth and proliferation of blood vessels in and around tumours cutting their supply of nutrients and oxygen thereby preventing further tumour growth.

Who can participate?
Patients aged 18 years old and over with neuroendocrine carcinoma will be recruited across 4 sites.

What does the study involve?
Induction treatment will consist of a three-weekly cycle of carboplatin at 5AUC administered intravenously on day 1 of the cycle, followed by etoposide 100mg/m2 on days 2 and 3, and pembrolizumab at 200mg on all 3 days. After 4 cycles, the patients will then move onto the maintenance treatment phase and be given 200mg pembrolizumab (via IV again) every 3 weeks whilst taking oral lenvatinib 20mg daily. Patients will continue on this course until unacceptable

toxicity, disease progression, withdrawal or completion of 2 years. A form of imaging scan known as CT will be performed 21 days after induction treatment and then 9 weekly thereafter to assess disease response.

What are the possible benefits and risks of participating?
Very common side effects seen in ≥10% to 20% of patients treated with pembrolizumab /KEYTRUDA include the following: Joint pain, fever, back pain, rash.
Many adverse effects of lenvatinib have been reported, including hypertension, hand-foot syndrome, diarrhea, and thrombocytopenia. Zhu et al analyzed the safety and efficacy profiles of lenvatinib in patients with cancer in a systematic review and meta-analysis. In this analysis of lenvatinib-treated patients, the most frequently observed adverse events of grade 3 or higher were thrombocytopenia (25.4%), hypertension (17.7%), and peripheral edema (15.5%). In the phase III SELECT trial of thyroid cancer, the most common reasons for dose reduction were diarrhoea, hypertension, and proteinuria. In fact, most patients in daily clinical practice cannot continue lenvatinib at the starting dose of 24 mg. In addition, nephrotic syndrome, delayed wound healing, and cardiac dysfunction are also adverse effects of lenvatinib which must be carefully monitored. Lenvatinib must be used with careful monitoring of these adverse events and continued until its side effects are well controlled.

Lenvatinib may also result in reduced fertility in females of reproductive potential and may result in damage to male reproductive tissues leading to reduced fertility of unknown duration. Female participants of childbearing/reproductive potential must adhere to the contraception requirement from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days after the last dose of trial medication.

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

When is the study starting and how long is it expected to run for?
July 2023 to July 2026

Who is funding the study?
Merck Sharp & Dohme (USA)

Who is the main contact?
PELICAN study team, pelican-trial@imperial.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-chemotherapy-pembrolizumab-and-lenvatinib-for-neuroendocrine-tumours-pelican

Contact information

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Additional identifiers

EudraCT/CTIS number
2020-004105-30

IRAS number

1004397

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
DP-IC001, IRAS 1004397, CPMS 59994

Study information

Scientific Title
A phase II study of etoposide-carboplatin (EP) chemotherapy in combination with pembrolizumab and lenvatinib maintenance in advanced high-grade neuroendocrine tumours (HG-NETs)

Acronym
PELICAN

Study hypothesis
The principle research objective is to find out how effective carboplatin, etoposide and pembrolizumab is as primary treatment followed by pembrolizumab and lenvatinib as maintenance therapy, for patients with high grade neuroendocrine tumours with no previous therapy.

Secondary objectives of this study are to confirm the safety of carboplatin, etoposide and pembrolizumab followed by pembrolizumab and lenvatinib maintenance in treatment of HG-NETs (high grade neuroendocrine tumours) who have not received previous therapy.
Evaluate disease-modulating effects of carboplatin, etoposide and pembrolizumab followed by pembrolizumab and lenvatinib maintenance in treatment of HG-NETs who have not received previous therapy

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 15/11/2023, London - Westminster Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +4420 7972 2545; westminster.rec@hra.nhs.uk), ref: 23/LO/0648

Study design
Interventional single-arm open-label phase II study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
See study outputs table

Condition
High-grade neuroendocrine tumours

Interventions
Carboplatin + etoposide (SOC) + pembrolizumab induction treatment followed by pembrolizumab + lenvatinib maintenance treatment.
Induction: patients will receive 4 cycles of induction chemotherapy with carboplatin (AUC 5 mg /ml/min) administered IV alongside etoposide (120 mg/m2) and pembrolizumab (200 mg IV) on day 1 of a 21-day cycle, followed by oral etoposide (100 mg twice daily) on day 2-3 of each cycle.
Maintenance: in patients who achieve a complete, partial response or stable disease following induction, maintenance pembrolizumab (200 mg IV on day 1 every 21 days) and lenvatinib (20 mg PO daily) will start following completion of induction treatment and will continue until unacceptable toxicity, disease progression, withdrawal of consent or completion of 2 years of treatment. In days when lenvatinib is co-administered with pembrolizumab, lenvatinib should be administered prior to pembrolizumab, ideally in the morning of the study visit.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase II

Drug/device/biological/vaccine name(s)
Lenvatinib, pembrolizumab, carboplatin, etoposide

Primary outcome measure
1. To evaluate the preliminary efficacy of carboplatin, etoposide and pembrolizumab followed by pembrolizumab and lenvatinib maintenance in treatment naïve HG-NETs as measured by RECIST v1.1 criteria – Trial completion
2. To confirm the safety of carboplatin, etoposide and pembrolizumab followed by pembrolizumab and lenvatinib maintenance in treatment naïve HG-NETs measured by NCI CTC criteria v5.0 – Up to 120 days after treatment cessation for each patient
3. To evaluate disease-modulating effects of carboplatin, etoposide and pembrolizumab followed by pembrolizumab and lenvatinib maintenance in treatment naïve HG-NETs by characterisation of tumour infiltrating and peripheral lymphocyte responses – Trial completion and/or until the patient has disease progression, whichever is first

Secondary outcome measures
There are no secondary outcome measures

Overall study start date

03/07/2023

Overall study end date
31/07/2026

Eligibility

Participant inclusion criteria
In order to be eligible for participation in this trial, the participant must:
1. Be willing and able to provide written informed consent for the trial.
2. Be >18 years of age on the day of signing informed consent.
3. ECOG performance status of 0-2.
4. Have histologically or cytologically confirmed diagnosis of neuroendocrine carcinoma.
5. Have Ki-67 labelling index >20% and/or >20 mitoses/10 high-power fields.
6. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Have had no prior systemic treatment in the metastatic setting.
8. Demonstrate adequate organ function as shown below:
8.1. Haematological
8.1.1. Absolute neutrophil count (ANC): ≥1,500 cells/µl
8.1.2. Platelets: ≥100,000/µl
8.1.3. Haemoglobin: ≥9.0 g/dL
9. Patients may be transfused to meet this criterion:
9.1. Renal:
9.1.1. Serum creatinine OR Measured or calculated creatinine clearance (CrCl) calculated by Cockcroft Gault criteria [Glomerular Filtration Rate (GFR) can also be used in place of creatinine or CrCl]: ≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for subjects with creatinine levels > 1.5 X ULN
9.2. Hepatic
9.2.1. Serum total bilirubin: ≤1.25 X ULN
9.2.2. AST and ALT: ≤2.5 X ULN
9.2.3. Patients with documented liver metastases: AST and/or ALT <5 X ULN
10. Coagulation International Normalized Ratio (INR) or Prothrombin Time (PT):
10.1. Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN unless the participant is receiving anticoagulant therapy as long as PT or PTT is within the therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless the participant is receiving anticoagulant therapy as long as PT or PTT is within the therapeutic range of intended use of anticoagulants aCrCl should be calculated per institutional standard.
11. Female subjects of childbearing potential should have a negative urine or serum pregnancy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12. Women of childbearing potential must be willing to use a highly effective method of contraception for the course of the study through 120 days after the last dose of the Investigational Medicinal Product (IMP).
Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
13. Sexually active males must agree to use an adequate method of contraception starting with the first dose of IMP through 120 days after the last dose of study therapy.
Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Sex
Both

Target number of participants
20

Participant exclusion criteria
Participants are excluded from the study if any of the following criteria apply:
1. Has a diagnosis of large cell and small cell histology of lung origin or Merkel cell carcinoma.
2. Has a diagnosis of immunodeficiency or is 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.
3. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease and stereotactic radiotherapy to the CNS.
4. Has an active infection requiring systemic therapy.
5. Has a known history of Human Immunodeficiency Virus (HIV). Note: No HIV testing is required unless mandated by local health authority.
6. 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 detectable levels) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
7. Has a known history of active Bacillus Tuberculosis (TB).
8. Has a known history of or any evidence of active pneumonitis.
9. Has a known history of interstitial of lung disease.
10. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
11. Has 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.
12. Uncontrolled blood pressure (Systolic BP>140 mmHg or diastolic BP >90 mmHg) in spite of an optimized regimen of antihypertensive medication.
13. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug.
14. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis

following lenvatinib therapy.
15. Subjects having >1+ proteinuria on urine dipstick testing unless a 24-hour urine collection for quantitative assessment indicates that the urine protein is <1 g/24 hours.
16. Is currently participating and receiving therapy or has participated or is participating in a study of an IMP or used an investigational device within 4 weeks of the first dose of IMP.
17. Has had major surgery within 3 weeks prior to first dose of study treatment.
18. Has a history of hypersensitivity to pembrolizumab, lenvatinib, carboplatin, etoposide or any of their excipients.
19. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
20. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Principal Investigator (PI).
21. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
22. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through to 120 days after the last dose of IMP.
23. Has received prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent.
24. Has received a live vaccine within 30 days of first dose of IMP administration. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed. It is advised that as a precautionary measure 24 hours should elapse between a dose of vaccine and the next dose of study drug

Recruitment start date
19/09/2023

Recruitment end date
30/09/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Imperial College Healthcare NHS Trust
The Bays
St Marys Hospital
South Wharf Road
London
United Kingdom
W2 1BL

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
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Study participating centre
Royal Free London NHS Foundation Trust
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Sponsor type
University/education

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ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp and Dohme

Alternative Name(s)
MSD United Kingdom, Merck Sharp & Dohme, Merck Sharp & Dohme Corp., MSD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals. The results may be published or presented by the CI /delegate(s).
2. Submission to regulatory authorities
3. Patients will be given an anonymised ID and data will only be shared using that ID. No identifiable data will be shared.

Intention to publish date
31/07/2027

Individual participant data (IPD) sharing plan
Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The CI may use this information for the purposes of the study only. It is understood by the CI that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. To allow the use of the information derived from this clinical study, the CI 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 CI is completed.

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?
Participant information sheet	version 1.0	10/05/2023	06/07/2023	No	Yes