ISRCTN10996604 https://doi.org/10.1186/ISRCTN10996604

Second-line therapy for patients with progressive poorly differentiated extrapulmonary neuroendocrine carcinoma

Submission date
06/08/2018

Recruitment status
No longer recruiting

Registration date
07/09/2018

Overall study status
Completed

Last Edited
17/01/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-chemotherapy-for-neuroendrocrine-carcinoma-cancer-that-started-in-any-part-of-the-body (added 09/06/2021)

Background and study aims
There is currently no standard treatment beyond etoposide/platinum-based chemotherapy for patients with progressive poorly differentiated extra-pulmonary neuroendocrine carcinoma (NEC). Therefore the treatment of patients whose disease progresses on or after this treatment is an area of unmet need. Combination treatments such as irinotecan/5-fluorouracil/folinic acid are a second-line treatment option currently used in Europe and worldwide for these patients. However, there is currently no evidence supporting this treatment in these patients. The aim of this study is to test a new drug combination that has been reported to improve survival in patients with pancreas cancer (that has spread and cannot be cured), called nanoliposomal irinotecan and 5-fluorouracil, together with a vitamin-like substance called folinic acid or docetaxel (which is a treatment option currently available for patients with a diagnosis of NEC, and is used in other cancers such as breast cancer and lung cancer).

Who can participate?
Patients aged 18 and over with progressive poorly differentiated extra-pulmonary NEC who have been treated with etoposide/platinum-based chemotherapy

What does the study involve?
Participants are randomly allocated to receive either liposomal irinotecan/5-fluorouracil/folinic acid given every 14 days, or docetaxel given every 21 days. Participants are treated for a minimum of 6 months or until discontinuation of treatment as per protocol. Progression-free survival rate, defined as the time until disease progression or death from any cause, is measured at 6 months.

What are the possible benefits and risks of participating?
The results will show whether one of the treatment options delays growth (progression) of the disease more than the other.

Where is the study run from?
1. The Christie
2. Clatterbridge Cancer Centre
3. Weston Park Hospital
4. Southampton General Hospital
5. Hammersmith Hospital
6. Royal Free Hospital
7. Guy's Hospital
8. Beatson Oncology Centre
9. Velindre Cancer Centre
10. Western General Hospital
11. Northern Centre for Cancer Care
12. The Royal Marsden Hospital
13. St James's University Hospital

When is the study starting and how long is it expected to run for?
January 2017 to October 2023

Who is funding the study?
Shire Development Inc.

Who is the main contact?
Dr Jayne Swain
j.swain@leeds.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Jayne Swain

Contact details
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds
United Kingdom
LS2 9JT
+44 (0)113 343 4108
j.swain@leeds.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2017-002453-11

Integrated Research Application System (IRAS)
Nil known

ClinicalTrials.gov (NCT)
NCT03837977

Protocol serial number
CPMS 37246

Study information

Scientific Title
A multi-centre, randomised, parallel group, open-label, phase II, single-stage selection trial of nanoliposomal irinotecan (nal-IRI) and 5-fluorouracil (5-FU)/folinic acid or docetaxel as second-line therapy in patients with progressive poorly differentiated extra-pulmonary neuroendocrine carcinoma (NEC)

Acronym
NET-02

Study objectives
There is currently no standard treatment beyond first-line etoposide/platinum-based chemotherapy in patients with progressive poorly differentiated extra-pulmonary neuroendocrine carcinoma. Therefore the treatment of patients whose disease progresses on or after this first-line treatment is an area of unmet need.

Combination regimens such as irinotecan/5-fluorouracil/folinic acid are a second-line treatment option currently used in Europe and world-wide for this subset of patients. However, there is currently no trial evidence supporting this treatment regimen in these patients.

Results of the NAPOLI-1 phase III trial of liposomal irinotecan in the treatment of patients with metastatic pancreatic adenocarcinoma after gemcitabine-based therapy reported improved survival for those patients who received a combination of liposomal irinotecan with 5-FU/folinic acid compared to those patients who received 5-FU/folinic acid alone. Liposomal irinotecan has been found to show an improved distribution into tumour tissue in comparison to irinotecan, and this may have clinical benefit in patients with extra-pulmonary neuroendocrine carcinoma.

Docetaxel is standardly used as a second-line treatment option in patients with small cell lung cancer who have progressed on primary etoposide-platinum combination therapy. Therefore this drug could also have clinical benefit in patients with extra-pulmonary neuroendocrine carcinoma as the biology of the disease is similar to small cell lung cancer.

The overall aim of the NET-02 trial is to select a treatment for continuation to a Phase III trial. The intention of the trial is to determine whether liposomal irinotecan/5-fluorouracil/folinic acid and docetaxel are sufficiently active in this population of patients. If both treatments are found to be efficacious, selection criteria will be applied to select a treatment to take forward.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The Greater Manchester Central Research Ethics Committee, 06/02/2018, ref: 18/NW/0031

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Neuroendocrine carcinoma

Interventions
NET-02 is a multi-centre, randomised, parallel group, open-label, phase II, single-stage selection trial of nal-IRI/5-fluorouracil/folinic acid or docetaxel as second-line therapy in patients with progressive poorly differentiated extra-pulmonary neuroendocrine carcinoma, with the aim of selecting a treatment for continuation to a phase III trial.

The design is an adaptation of a one-stage treatment design proposed by Simon, Wittes and Ellenberg where the A'Hern design is first implemented to assess efficacy of each treatment separately, to ensure a pre-specified minimum level of activity prior to selection. Selection criteria are then applied following the design of Simon, Wittes and Ellenberg, should both treatments be deemed sufficiently efficacious, to establish which treatment to take forward into a phase III trial. The intention of the trial is to show that the regimens are sufficiently active in this population of patients, but not to show that one regimen is significantly superior to the other.

The A'Hern method is advantageous over other single-stage designs, since it uses the exact binomial distribution as opposed to a normal approximation to the binomial distribution which can give a substantial margin of error in small trial sizes. Additionally, cut-off points are created which, if reached, could enable earlier planning for a phase III follow-on trial.

One hundred and two eligible participants will be randomised (1:1) to receive either nal-IRI, 5-FU and racemic folinic acid [nal-IRI (80mg/m*2 intravenously over 90 minutes (± 10 minutes)) prior to 5-FU (5-FU 2400 mg /m*2 BSA infusor over 46 hours) and racemic folinic acid (as per local standard practice) every 14 days] or docetaxel [75mg/m*2 intravenously over 60 minutes) every 21 days].

Participants will be treated for a minimum of 6 months or until discontinuation of treatment as per protocol. Trial treatment will continue until progressive disease or intolerable toxicity, delay of treatment for more than 28 days, development of any condition or occurrence of any event, which, in the opinion of the local investigator, justifies discontinuation of treatment, patient request or until 6 months after the last participant is randomised, whichever comes first.

Participants will attend the following visits:
- Screening visit/tests: including eligibility assessment, routine blood tests, consent, registration, electrocardiogram (ECG) for all participants, a routine pregnancy test will be carried out for those women of childbearing potential.
- Clinic visit at baseline: Once eligibility has been confirmed participant will be randomised. Participants will be asked to complete 2 quality of life questionnaires prior to randomisation. Participants randomised to nal-IRI/5-FU/folinic acid treatment will have a central line fitted. A

computed tomography (CT) or magnetic resonance imaging (MRI) scan may be required if treatment is more than 28 days after the most recent CT/MRI scan. Participants recruited from Christie may have a blood sample taken for mouse model development if they have given consent for the sample to be collected.
- Day 1 of treatment cycles (2-weekly cycles in nal-IRI/5-FU/folinic acid arm, 3-weekly in docetaxel arm): Routine blood tests, treatment infusion.
- CT or MRI scans every 8 weeks to monitor disease progression.
- Participants will be asked to provide a blood sample for translational analysis at baseline, 6 weeks after treatment has started and on diagnosis of disease progression.
- Participants will be asked to provide a blood sample for neuron-specific enolase measurement at 6-weekly intervals and on diagnosis of disease progression.
- Quality of life questionnaires will be completed at 6-weekly intervals until diagnosis of disease progression.
- Post-treatment clinic visit or phone call between 28 and 42 days after permanently stopping trial treatment.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Irinotecan, 5-fluorouracil, folinic acid, docetaxel

Primary outcome(s)
Progression-free survival rate, defined as the time from randomisation to progression or death from any cause; Timepoint(s): 6 months

Key secondary outcome(s))
1. Overall survival (OS), defined as the time from randomisation to death from any cause
2. Objective response rate (ORR) using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.11 Assessed by CT or MRI scan at baseline and then at 8-weekly intervals
3. Toxicity defined as the AE and SAEs reported on the trial according to CTCAE v5.0
4. Quality of life (QoL) using European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QLQ) validated questionnaires C30 and NET21 assessed according to the patient reported outcome measures; EORTC QLQC30 and EORTC QLQ-GI.NET21. Assessed at the point of randomisation, at 6-weekly intervals and at disease progression
5. Serum concentration of neuron-specific enolase (NSE) assessed at the point of randomisation, at 6-weekly intervals and at disease progression

Completion date
01/10/2023

Eligibility

Key inclusion criteria
1. Age ≥18 years and life expectancy >3 months
2. Diagnosed with poorly differentiated (as defined by the World Health Organisation in 2010, Ki 67 >20%) extra-pulmonary neuroendocrine carcinoma (NEC grade 3). (Carcinoma of unknown primary is allowed if lung primary has been excluded)

3. Prior treatment with first-line platinum-based chemotherapy for NEC in the advanced setting and ≥28 days from Day 1 of the previous treatment cycle
4. Documented radiological evidence of disease progression OR discontinuation of first-line platinum-based chemotherapy due to intolerance
5. Measurable disease according to RECIST 1.1 (Appendix 1)
6. Eastern Co-operative Oncology Group (ECOG) performance status ≤2 (see Appendix 2)
7. Adequate renal function with serum creatinine ≤1.5 times upper limit of normal (ULN) and creatinine clearance ≥50ml/min according to Cockroft-Gault or Wright formula (see Appendix 3)
8. Adequate haematological function: Hb ≥90g/L, WBC ≥3.0 x 109/L, ANC ≥1.5 x 109/L, platelet count ≥100 x 109/L
9. Adequate liver function: serum total bilirubin 1.5 x ULN (biliary drainage is allowed for biliary obstruction) and ALT and/or AST 2.5 x ULN in the absence of liver metastases, or 5 x ULN in the presence of liver metastases
10. A negative pregnancy test is required at registration in women of childbearing potential
11. Men* and women** of reproductive potential must agree to use a highly effective form of contraception*** during the study and for 6 months following the last dose of trial treatment. In addition, male participants should use a condom during study participation and for 6 months following the last dose of trial treatment
12. Patients must be able to provide written informed consent
13. Patients must be able and willing to comply with the terms of the protocol

* Women of reproductive potential are defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
** Men of reproductive potential are defined as post-pubescent and not permanently sterile by vasectomy or bilateral orchidectomy.
*** Highly effective contraception is defined as one of the following: combined (oestrogen and progesterone-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; practising true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
58

Key exclusion criteria

Current participant exclusion criteria as of 25/11/2021:
1. Known or suspected allergy or hypersensitivity reaction to any of the components of study treatment or their excipients
2. Use (including self-medication) within one week of randomisation and for the duration of the study of any of the following: St. John's wort, grapefruit, Seville oranges, medicines known to inhibit UGT1A1 and medicines known to inhibit or induce either CYP3A4 or CYP3A5 (see Appendix 8 of protocol for list*)
3. Previous treatment (for neuroendocrine carcinoma) with any of the components of combination chemotherapy regimens detailed in this study (nal-IRI or 5-FU or irinotecan or topoisomerase inhibitors or taxane-based therapy)
4. Incomplete recovery from previous therapy in the opinion of the investigator (surgery /adjuvant therapy/radiotherapy/chemotherapy in advanced setting), including ongoing peripheral neuropathy of > CTCAE grade 2 from previous platinum-based therapy
5. Concurrent palliative radiotherapy involving target lesions used for this study (< 28 days from discontinuation of radiotherapy). Radiotherapy for non-target lesions is allowed if other target lesions are available outside the involved field
6. Patients must not have a history of other malignant diseases (within the previous 3 years, and there must be no evidence of recurrence), other than:
6.1. Extra-pulmonary neuroendocrine carcinoma
6.2. Non-melanoma skin cancer where treatment consisted of resection only or radiotherapy
6.3. Ductal carcinoma in situ (DCIS) where treatment consisted of resection only
6.4. Cervical carcinoma in situ where treatment consisted of resection only
6.5. Superficial bladder carcinoma where treatment consisted of resection only
7. Documented brain metastases, unless adequately treated (surgery or radiotherapy only), with no evidence of progression and neurologically stable off anticonvulsants and steroids
8. Clinically significant gastrointestinal disorder (in the opinion of the treating clinician) including hepatic disorders, bleeding, inflammation, obstruction, or diarrhoea > CTCAE grade 1 (at time of study entry)
9. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion
10. New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure**
11. Severe bone marrow failure or bone marrow depression after radiotherapy or treatment with other antineoplastic agents (defined as haematological values of haemoglobin or white blood cells or neutrophils or platelets not meeting inclusion criteria)
12. Known active hepatitis B virus, hepatitis C virus or HIV infection. Infection status should be confirmed in cases of clinical suspicion.
13. Active chronic inflammatory bowel disease
14. Breastfeeding women
15. Evidence of severe or uncontrolled systemic diseases which, in the view of the treating clinician, makes it undesirable for the patient to participate in the trial
16. Evidence of significant clinical disorder or laboratory finding which, in the opinion of the treating clinician, makes it undesirable for the patient to participate in the trial
17. Medical or psychiatric conditions that impair the ability to give informed consent
18. Any other serious uncontrolled medical conditions (in the opinion of the treating clinician)
19. Use of warfarin or warfarin-type anti-coagulation therapies within one week of randomisation and for the duration of the study (the use of low ,olecular weight heparin is permitted as appropriate).

* For patients receiving any of these medications, use of an alternative agent is recommended.
** It is recommended that subjects should have a systolic blood pressure of either less than 150 mmHG, and/or a diastolic blood pressure of less than 100 mmHg at rest (average of 3 consecutive readings 3-5 minutes apart). Anti-hypertensive drugs may be used to achieve these values.

Previous participant exclusion criteria:
1. Known or suspected allergy or hypersensitivity reaction to any of the components of study treatment or their excipients
2. Use (including self-medication) within one week of randomisation and for the duration of the study of any of the following: St. John's wort, grapefruit, Seville oranges, medicines known to inhibit UGT1A1 and medicines known to inhibit or induce either CYP3A4 or CYP3A5 (see Appendix 8 of protocol for list*)
3. Previous treatment (for neuroendocrine carcinoma) with any of the components of combination chemotherapy regimens detailed in this study (nal-IRI or 5-FU or irinotecan or topoisomerase inhibitors or taxane-based therapy)
4. Incomplete recovery from previous therapy in the opinion of the investigator (surgery /adjuvant therapy/radiotherapy/chemotherapy in advanced setting), including ongoing peripheral neuropathy of > CTCAE grade 2 from previous platinum-based therapy
5. First line treatment administered within 4 weeks, or within a time interval less than at least 5 half-lives of the agent, whichever is longer, prior to treatment start in this study
6. Concurrent palliative radiotherapy involving target lesions used for this study (< 28 days from discontinuation of radiotherapy). Radiotherapy for non-target lesions is allowed if other target lesions are available outside the involved field
7. Patients must not have a history of other malignant diseases (within the previous 3 years, and there must be no evidence of recurrence), other than:
7.1. Extra-pulmonary neuroendocrine carcinoma
7.2. Non-melanoma skin cancer where treatment consisted of resection only or radiotherapy
7.3. Ductal carcinoma in situ (DCIS) where treatment consisted of resection only
7.4. Cervical carcinoma in situ where treatment consisted of resection only
7.5. Superficial bladder carcinoma where treatment consisted of resection only
8. Documented brain metastases, unless adequately treated (surgery or radiotherapy only), with no evidence of progression and neurologically stable off anticonvulsants and steroids
9. Clinically significant gastrointestinal disorder (in the opinion of the treating clinician) including hepatic disorders, bleeding, inflammation, obstruction, or diarrhoea > CTCAE grade 1 (at time of study entry)
10. Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion
11. New York Heart Association (NYHA) Class III or IV congestive heart failure, ventricular arrhythmias or uncontrolled blood pressure**
12. Severe bone marrow failure or bone marrow depression after radiotherapy or treatment with other antineoplastic agents (defined as haematological values of haemoglobin or white blood cells or neutrophils or platelets not meeting inclusion criteria)
13. Known active hepatitis B virus, hepatitis C virus or HIV infection
14. Active chronic inflammatory bowel disease
15. Breastfeeding women
16. Evidence of severe or uncontrolled systemic diseases which, in the view of the treating clinician, makes it undesirable for the patient to participate in the trial
17. Evidence of significant clinical disorder or laboratory finding which, in the opinion of the treating clinician, makes it undesirable for the patient to participate in the trial
18. Medical or psychiatric conditions that impair the ability to give informed consent
19. Any other serious uncontrolled medical conditions (in the opinion of the treating clinician)

* For patients receiving any of these medications, use of an alternative agent is recommended.
** It is recommended that subjects should have a systolic blood pressure of either less than 150 mmHG, and/or a diastolic blood pressure of less than 100 mmHg at rest (average of 3 consecutive readings 3-5 minutes apart). Anti-hypertensive drugs may be used to achieve these values.

Date of first enrolment
01/10/2018

Date of final enrolment
21/12/2021

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
The Christie
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
Clatterbridge Cancer Centre
Clatterbridge Road
Bebington
Wirral
United Kingdom
CH63 4JY

Study participating centre
Weston Park Hospital
Whitham Road

Sheffield
United Kingdom
S10 2SJ

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Hammersmith Hospital
Du Crane Road
Garry Weston Centre
London
United Kingdom
W12 0HS

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Beatson Oncology Centre
Gartnavel General Hospital
1089 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Velindre Cancer Centre
Velindre Road
Whitchurch
Cardiff
United Kingdom
CF14 2TL

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
United Kingdom
EH4 2XU

Study participating centre
Northern Centre for Cancer Care
Freeman Hospital
Freeman Road
High Heaton
Newcastle
United Kingdom
NE7 7DN

Study participating centre
The Royal Marsden Hospital
Downs Road
Sutton
United Kingdom
SM2 5PT

Study participating centre
St James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre

Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
University Hospital Coventry
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Sponsor information

Organisation
The Christie NHS Foundation Trust

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type
Industry

Funder Name
Shire Development Inc.; Grant Codes: O16-34263

Results and Publications

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security) and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree on suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		02/06/2023	17/01/2025	Yes	No
Protocol article	protocol	05/02/2020	10/02/2020	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results			08/03/2024	No	Yes