ISRCTN16171129 https://doi.org/10.1186/ISRCTN16171129

A randomised Phase II trial to assess whether niraparib is beneficial in patients with mesothelioma that has progressed and been previously treated when compared to the standard of care treatment, termed active symptom control

Submission date	**Recruitment status**	[X] Prospectively registered
23/03/2022	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
11/05/2022	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
10/01/2024	Cancer	[_] Record updated in last year

Plain English summary of protocol

Background and study aims

Mesothelioma is a cancer that is caused by exposure to asbestos, an environmental contaminant. This cancer is incurable and lacks an effective treatment, particularly after initial chemotherapy. There has not been a licenced therapy for mesothelioma since 2003, and no treatment has yet demonstrated an improvement in survival following initial chemotherapy. There is an urgent need to explore more effective approaches to therapy. Targeted treatments offer potential hope for the treatment of mesothelioma. A class of drugs called PARP (poly adenosine diphosphate-ribose polymerase) inhibitors have already been proven to improve the survival of patients with breast and ovarian cancers that carry specific mutations. Mesothelioma has been shown in a recent trial to respond to this class of drug. Further investigation is warranted to test whether PARP inhibitors could be a new treatment option for patients. As with ovarian cancer studies of the past, this study will test a PARP inhibitor (niraparib) after successful treatment with chemotherapy. Patients whose tumours shrink or stabilise following chemotherapy are expected to have a greater chance of benefit from niraparib. It is not known whether niraparib will be able to improve the survival of patients with mesothelioma, or indeed whether or not toxicity could occur without benefit.

Who can participate?

Patients aged 18 years and over with unresectable mesothelioma (previously treated cancer that develops in the lining that covers the outer surface of some of the body's organs, and that cannot be surgically removed).

What does the study involve?

When the patient provides consent for the trial, they will undergo some tests to assess their

eligibility for the trial. If the patient is deemed eligible, they will be randomly allocated with a 2:1 chance of receiving a daily dose of 200 mg or 300 mg of niraparib for up to 24 weeks. Those patients who do not receive niraparib will be closely monitored for signs of early tumour growth so that they can go on to receive an alternative treatment if necessary.
During the treatment period of the trial, patients will visit the hospital every 3 weeks to undergo a physical examination and blood tests to ensure the patient is well enough to continue receiving the treatment.
In addition to this, before the first dose of treatment, patients will be asked for an additional blood sample and for an archival tissue sample of their tumour to be sent to a central laboratory.
During treatment patients will undergo a CT scan of their chest and abdomen every 6 weeks from randomisation. If randomised to niraparib it is advised that patients have an extra blood test during the second or third week of treatment. Their blood pressure and heart rate will also be monitored weekly for the first 8 weeks of treatment.
Patients will receive niraparib and/or standard care for a maximum of 24 weeks. They may stop treatment earlier than this if their disease gets worse, they experience severe side effects or they decide to withdraw from treatment. For patients who obtain a benefit from being on niraparib, there will be the opportunity to remain on this medication longer than the 24 weeks.
Following treatment, patients will move to the follow-up period of the study, which will last a minimum of 6 months to check for any side effects following treatment and for overall survival.

What are the possible benefits and risks of participating?
Participants may benefit from better disease control by having niraparib compared to the standard treatment. However, this cannot be guaranteed and there may be no additional benefit in relation to how long the cancer is controlled. If the results are positive, this study will lead to the approval of new medicine for use around the world, one that would extend the life expectancy of patients for the first time following initial chemotherapy.
The information from this study may help to treat future patients with the same condition in a more effective way. Participants will be helping to further knowledge of how to treat cancer and this will also benefit society as a whole.
The main risks are the potential side effects from niraparib and the patient will be monitored regularly to assess any side effects of the treatment.
During the trial, additional blood will be collected from a vein, which may cause pain where the needle is inserted. There is a small risk of bruising or infection at the site of insertion. Some people may experience dizziness, an upset stomach or fainting when blood is taken, but every effort will be made by hospital staff to minimise this.
During the trial, participants will have contrast-enhanced CT scans to assess their cancer. Some of these will be extra to those that would be completed as part of standard care. CT scans use ionising radiation to form images of the body. Ionising radiation may cause cancer many years or decades after exposure. In patients with the clinical condition under investigation in this trial, the chance of this happening is extremely small.

Where is the study run from?
Southampton Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
March 2022 to June 2024

Who is funding the study?
Asthma and Lung UK

Who is the main contact?
Prof. Dean Fennell
df132@leicester.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Dean Fennell

ORCID ID
https://orcid.org/0000-0001-7373-1312

Contact details
Room 539, 5th Floor
Robert Kilpatrick Building
Leicester
United Kingdom
LE2 7LX
+44 (0)116 252 3170
df132@le.ac.uk

Type(s)
Public

Contact name
Dr Daniel Griffiths

Contact details
MP131, Southampton General Hospital
Southampton
United Kingdom
SO16 6YD
+44 (0)238 120 5154
NERO@soton.ac.uk

Type(s)
Principal investigator

Contact name
Dr Dean Fennell

ORCID ID
https://orcid.org/0000-0001-7373-1312

Contact details

Room 539, 5th Floor
Robert Kilpatrick Building
Leicester
United Kingdom
LE2 7LX
+44 (0)116 252 3170
df132@le.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2022-000198-26

Integrated Research Application System (IRAS)
1005002

ClinicalTrials.gov (NCT)
NCT05455424

Protocol serial number
RHMCAN1682, IRAS 1005002, CPMS 52250

Study information

Scientific Title
Niraparib efficacy in patients with unresectable mesothelioma: a randomised Phase II trial of niraparib versus active symptom control in patients with previously treated mesothelioma

Acronym
NERO

Study objectives
1. To determine the efficacy of active symptom control + niraparib versus active symptom control (ASC).
2. To determine whether niraparib (over ASC):
2.1. Increases overall survival
2.2. Improves best objective response overall response rate (ORR)
2.3. Improves 12- and 24-week disease control rate (DCR)
2.4. Exhibits durable response
2.5. Has acceptable safety/tolerability
2.6. Shows compliance to treatment

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/05/2022, London - Hampstead Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, BS1 6PN, UK; +44 (0)2071048345, +44 (0)2071048189; hampstead.rec@hra.nhs.uk), ref: 22/LO/0281

Study design
Open randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Unresectable mesothelioma

Interventions
Mesothelioma patients with any histological subtype (epithelioid or non-epithelioid) and any site (pleural or peritoneal) who have previously received an approved systemic therapy containing platinum, will be recruited from a secondary care setting. NERO is not restricted by line of therapy.

Once all screening procedures have been completed and the patient is confirmed eligible, they will be randomised in a 2:1 ratio between the experimental arm and the control arm. Randomisation will be completed using an online randomisation system called ALEA. Patients will be treated for up to 24 weeks, or until disease progression, withdrawal, death or development of significant treatment-limiting toxicity. Patients in the experimental arm will receive Active Symptom Control (ASC) and niraparib 200/300 mg orally once a day in a 3-weekly cycle. Patients randomised to the control arm will receive ASC, patients in this arm of the trial will be managed symptomatically.

During treatment, patients will be seen in clinic every 3 weeks for physical exams and blood tests to monitor safety. Patients will have a CT scan every 6 weeks from baseline, during treatment to assess their disease.

Patients will have to provide a mandatory biopsy sample for research purposes and they will be asked to have an optional one (for research) at progression, if they were randomised to the experimental arm.

Following disease progression patients will be monitored for overall survival.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)

Progression-free survival determined by modified Response Evaluation Criteria in Solid Tumours (RECIST) (pleural disease), RECIST 1.1 (for non-pleural disease) or investigator reported progression. RECIST will be assessed every 6 weeks from randomisation until disease progression or end of treatment.

Key secondary outcome(s))

Measured until disease progression or death (unless otherwise specified):
1. Overall survival defined as the time from randomisation to death from any cause
2. Best overall response (progressive disease, stable disease, partial or complete response) assessed by modified RECIST or RECIST 1.1. The best overall response is the best response recorded from the start of treatment until disease progression or death.
3. ORR (assessed by modified RECIST or RECIST 1.1), the percentage of patients whose best overall response is partial or complete response
4. Disease control at 12 and 24 weeks (stable disease, partial or complete response) assessed by modified RECIST or RECIST 1.1 at 12 and 24 weeks
5. Duration of response, defined as the time from complete or partial response (where this occurs) until progression or death
6. Treatment compliance assessed by summarising the percentage of the received dose relative to the intended dose at each cycle
7. Toxicity assessed through evaluation of adverse events (graded using Common Terminology Criteria for Adverse Events [CTCAE] v5.0), laboratory results, vital signs and physical examination at baseline, after each treatment cycle, and for 100 days post treatment discontinuation and for ongoing drug-related AEs until resolved, return to baseline, or deemed irreversible

Completion date

31/12/2024

Eligibility

Key inclusion criteria

1. Patients must have signed and dated a REC-approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care
2. Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.
3. Histologically confirmed diagnosis of mesothelioma. Any histological subtype (epithelioid, biphasic or sarcomatoid) and any site (e.g. pleural or peritoneal) with an available tissue block. Tissue blocks will be requested at the time of screening
4. Patients must have received prior systemic therapy (any number of lines) for pleural or peritoneal mesothelioma
5. Disease progression must be confirmed per Investigator's assessment prior to screening
6. Any prior treatment must be completed at least 14 days prior to receiving study treatment, with no ongoing toxicity of CTCAE Grade 3 or above.
7. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 (see appendix 1)
8. Radiologically assessable disease by modified RECIST (pleural mesothelioma) or RECIST 1.1 (non-pleural mesothelioma or where measurements for modified RECIST cannot be obtained)
9. Age ≥18 years old
10. Consent to provide mandatory diagnostic tissue blocks and blood samples for translational research, including an optional rebiopsy at progression
11. Adequate organ function, including suitable bone marrow reserve and creatinine clearance

12. Screening laboratory values must meet the following criteria within 48 hours prior to commencement of treatment:
12.1. White blood cells ≥2 x 10e9/l
12.2. Neutrophils ≥1.5 x 10e9/l
12.3. Platelets ≥100 x 10e9/l
12.4. Haemoglobin ≥90 g/l
12.5. Serum creatinine of ≤1.5 X ULN or creatinine clearance (CrCl) >50 ml/minute (using Cockcroft/Gault formula)
12.5.1. Female CrCl= [(140 - age in years) x weight in kg x 0.85) ÷ (72 x serum creatinine in µmol/l)]
12.5.2. Male CrCl= [(140 - age in years) x weight in kg x 1.00) ÷ (72 x serum creatinine in µmol/l)]
12.6. AST ≤3 x ULN OR ALT ≤3 x ULN (if both are assessed, both need to be ≤3 x ULN)
12.7. Total bilirubin ≤1.5 x ULN (except patients with Gilbert Syndrome, who must have total bilirubin <51.3 µmol/l)
13. Reproductive status (refer to section 4.6)
13.1. Women of childbearing potential (WOCBP, as defined in section 4.6) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) at enrolment and within 24 hours prior to the start of study treatment. An extension up to 3 days prior to the start of study treatment may be permissible in situations where results cannot be obtained within a 24-hour window.
13.2. Women must not be breastfeeding
13.3. WOCBP must agree to use a highly effective method of contraception (as outlined in section 4.6) for the duration of treatment and 180 days after the last dose of ASC+ niraparib
13.4. Men who are sexually active with WOCBP must use the contraceptive methods as outlined in section 4.6 for the duration of treatment and for 90 days after the last dose of ASC+ niraparib
14. Expected survival of at least 12 weeks per Investigator's assessment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
88

Key exclusion criteria
1. Patients with untreated, symptomatic central nervous system (CNS) metastases are excluded, including carcinomatous meningitis, leptomeningeal disease, and radiographic signs of CNS haemorrhage are excluded
2. Patients with untreated third space fluid collection requiring therapeutic drainage are excluded
3. Second malignancy within 5 years except cancers with definitely treated with curative intent

(eg. basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ bladder or in situ cervical cancer)
4. Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the patient to receive protocol therapy
5. Difficulty swallowing or previous significant resection of the stomach or small bowel
6. Patients who have not recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment
7. Prior exposure to PARP Inhibitor or known hypersensitivity to the components of niraparib
8. New York Heart associated class II or greater heart failure, hepatic [AST > 3 x ULN, ALT >3 x ULN Total bilirubin >1.5 x ULN] or renal impairment [serum creatinine of >1.5 x ULN or creatinine clearance (CrCl) ≤50 ml/minute (using Cockcroft/Gault formula)]
9. Known alcohol or drug abuse
10. Patients are not permitted to enter any other interventional studies
11. Any patient not able to give consent
12. Any pregnant or breastfeeding patient
13. Patient with known history or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)
14. Patient with known history of active tuberculosis
15. Patients with uncontrolled hypertension
16. Participants have current pneumonitis within 90 days of the planned start of the study or a known history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis requiring steroid treatment
17. Patients that have received colony-stimulating factors (e.g., granulocyte-macrophage colony-stimulating factor or recombinant erythropoietin) within 2 weeks prior to the first dose of study treatment
18. Live vaccines within 30 days prior to the first dose of study treatment and while participating in this clinical study
19. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
20. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

Date of first enrolment
11/07/2022

Date of final enrolment
21/12/2023

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

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

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
The Princess Alexandra Hospital
Hamstel Road
Harlow
United Kingdom
CM20 1QX

Study participating centre
Musgrove Park Hospital
Parkfield Drive
Taunton
United Kingdom
TA1 5DA

Study participating centre
Velindre Hospital
Velindre Road

Cardiff
United Kingdom
CF14 2TL

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

Study participating centre
Weston Park Hospital
Whitham Road
Sheffield
United Kingdom
S10 2SJ

Study participating centre
Belfast Health and Social Care Trust
Trust Headquarters
A Floor - Belfast City Hospital
Lisburn Road
Belfast
United Kingdom
BT9 7AB

Study participating centre
Hull University Teaching Hospitals NHS Trust
Castle Hill Hospital
Castle Road
Cottingham
United Kingdom
HU16 5JQ

Study participating centre
Medway Maritime Hospital
Windmill Road
Gillingham
United Kingdom
ME7 5NY

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Charity

Funder Name
Asthma and Lung UK

Results and Publications

Individual participant data (IPD) sharing plan
Individual participant data will be made available, including data dictionaries, for approved data sharing requests. Individual participant data will be shared that underlie the results after de-identification and normalisation of information (text, tables, figures, and appendices). The study protocol and statistical analysis plan will also be available. Anonymous data will be available for request from 3 months after the publication of the results to researchers who provide a completed data sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate, signed a data-sharing agreement. Pseudonymised participant data within the clinical trial dataset will be available for sharing via controlled access by authorised Southampton Clinical Trials Unit (SCTU) staff. The request for data access will need to detail the specific requirements and the proposed research, statistical analysis, publication plan and evidence of research group qualifications. Data access requests will be reviewed against specific eligibility criteria by the SCTU data custodian and key members of the trial team. Data will be shared once all parties have signed relevant data sharing documentation covering SCTU conditions for sharing and if required, an additional data sharing agreement from the sponsor. Proposals should be directed to ctu@soton.ac.uk.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		22/11/2023	18/12/2023	Yes	No

HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes