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Evaluating niraparib versus active symptom control in patients with previously treated mesothelioma (NERO): a study protocol for a multicentre, randomised, two-arm, open-label phase II trial in UK secondary care centres

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ABSTRACT

Background Malignant mesothelioma is a rapidly lethal cancer that has been increasing at an epidemic rate over the last three decades. Targeted therapies for mesothelioma have been lacking. A previous study called MiST1 (NCT03654833), evaluated the efficacy of Poly (ADP-ribose) polymerase (PARP) inhibition in mesothelioma. This study met its primary endpoint with 15% of patients having durable responses exceeding 1 year. Therefore, there is a need to evaluate PARP inhibitors in relapsed mesothelioma patients, where options are limited. Niraparib is the PARP inhibitor used in NERO.

Methods NERO is a multicentre, two-arm, open-label UK randomised phase II trial designed to evaluate the efficacy of PARP inhibition in relapsed mesothelioma. 84 patients are being recruited. NERO is not restricted by line of therapy; however, eligible participants must have been treated with an approved platinum based systemic therapy. Participants will be randomised 2:1, stratified according to histology and response to prior platinum-based chemotherapy, to receive either active symptom control (ASC) and niraparib or ASC alone, for up to 24 weeks. Participants will be treated until disease progression, withdrawal, death or development of significant treatment limiting toxicity. Participants randomised to niraparib will receive 200 or 300 mg daily in a 3-weekly cycle. The primary endpoint is progression-free survival, where progression is determined by modified Response Evaluation Criteria in Solid Tumors (mRECIST) or RECIST 1.1; investigator reported progression; or death from any cause, whichever comes first. Secondary endpoints include overall survival, best overall response, 12-week and 24 week disease control, duration of response, treatment compliance and safety/tolerability. If NERO shows niraparib to be safe and biologically effective, it may lead to future late phase randomised controlled trials in relapsed mesothelioma.

Ethics and dissemination The study received ethical approval from London-Hampstead Research Ethics Committee on 06-May-2022 (22/LO/0281). Data from all centres will be analysed together and published as soon as possible.

Trial registration number ISCRTN16171129; NCT05455424.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ There is no central review of CT scans, which could lead to a lack of consistency of RECIST reporting across sites.
⇒ We used knowledge from previous trials run by the Southampton Clinical Trials Unit, that had RECIST reporting, to make sure our progression-free survival endpoint was robust.
⇒ Recruitment of patients with any histological subtype and any site at multiple sites across all four nations of the UK, to be representative of the entire mesothelioma patient population.
⇒ Not placebo controlled and patients may come with preconceived perception that the treatment group will be more beneficial.

BACKGROUND

Malignant mesothelioma is a rapidly lethal cancer that has been increasing at an epidemic rate over the last three decades. The cancer is unusual in that it remains predominantly localised with distant metastasis occurring rarely. Mesotheliomas may exhibit three general histopathological variants—the more indolent epithelioid subtype, an aggressive

sarcomatoid subtype and a hybrid or biphasic subtype with representation of both sarcomatoid and epithelioid components. Progress with the development of new treatments has been very slow, with only two new licences for front line therapy having been approved since 2004 with pemetrexed and cisplatin, and ipilimumab and nivolumab, as of August 2022.[1 2] Although bevacizumab improves overall survival (OS) in the front-line setting, this is not a licensed schedule of treatment and is, therefore, widely unavailable throughout the world.[3] Maintenance therapy is not licensed for mesothelioma despite recent randomised trials. Evidence suggests that gemcitabine can confer meaningful clinical benefit in a switch maintenance phase II randomised study (NVALT19),[4] however, this schedule is not licensed.

Presently, no treatment has been licensed for patients with relapsed mesothelioma. A phase III trial has recently been the first to report that nivolumab shows improved overall and progression-free survival (PFS) in the relapsed setting.[5] Therefore, there is an unmet need for new, effective later line therapies. Stratified therapy for mesothelioma is in its infancy.[6] Studies exploring targeted therapy in molecularly preselected patients is feasible as evidenced from recent phase II trials.[7–9]

Poly (ADP-ribose) polymerase (PARP) inhibition is now standard therapy in ovarian, breast and prostate cancers harbouring BRCA1/2 mutations.[10–14] The homologous recombination (HR) pathway comprising BRCA1/2, regulates double-strand DNA breaks. When inactivated by mutation of BRCA1/2, cells rely on an alternative DNA repair pathway (PARP dependent single strand repair) exposing a vulnerability to PARP inhibition, which can induce synthetic lethality.[15] Niraparib is an inhibitor of PARP. This class of agents has demonstrated a high degree of efficacy in tumours harbouring inactivation of the BRCA1/BRCA2 tumour suppressors that leads to defective double-strand DNA repair.

Tumours harbouring inactivation of BRCA1/BRCA2 exhibit a mutational landscape characterised by a large burden of indels and microhomology at breakpoints. These features confer a signature (mutation signature 3 or sig3) that signifies underlying homologous repair deficiency (HRD).[16 17] An Asthma and Lung UK-funded study called Mesothelioma Evolution: DrUgging Somatic Alterations (MEDUSA) identified significant clonal enrichment of mutations and copy number alterations predicted to cause HR deficiency. It utilised a state of the art AI-based algorithm, SIGMA to extract sig3.[18] Cell lines generated from sig3+cells (from MEDUSA patients) exhibited sensitivity to PARP inhibition, compared with sig3-patients. Interrogation of the mutational landscape of mesothelioma reveals extensive loss of heterozygosity at the 13q12-14 (BRCA2) and 15q11-15 (RAD51) loci,[19] MEDUSA has identified copy number and deleterious mutation of CHEK2, BRCA2, BRCA1, RAD51 and Fanconi anaemia genes FANCG, and FANCM. In the tumour genome atlas, somatic alterations predicted to cause HRD are found in more than 60% of patients.

The Asthma and Lung UK funded single arm, signal finding MiST1 trial (NCT03654833) has evaluated the efficacy of PARP inhibition in mesothelioma.[20] This study met its primary endpoint with 15% of patients maintaining disease control over 1 year. Based on this, we hypothesise that PARP inhibition in the relapsed setting will be tolerable and exhibit superior efficacy compared with active symptom control (ASC) and so will undertake this evaluation in the NERO (Evaluating niraparib versus active symptom control in patients with previoulsy treated mesothelioma) multicentre randomised phase II trial.

METHODS/DESIGN

NERO is a UK phase II trial evaluating the efficacy of ASC and niraparib versus ASC alone in mesothelioma patients who have relapsed after previously receiving an approved platinum-based systemic therapy.

Objectives

The primary objective is to determine whether niraparib and ASC improves PFS versus ASC alone in patients who have relapsed after previously receiving platinum-based systemic therapy. The primary endpoint will be PFS (time from randomisation to progression/death).

Secondary objectives include determining whether niraparib and ASC (over ASC alone) increases OS, improves best objective response, improves 12-week and 24-week disease control rate (DCR), exhibits durable response, has acceptable safety/tolerability and shows compliance to treatment. The secondary endpoints that will be used to evaluate these objectives include OS (time from randomisation to death), modified Response Evaluation Criteria in Solid Tumors (mRECIST) or Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 (from randomisation to progression), Common Terminology Criteria for Adverse Events (CTCAE) V.5.0 and drug exposure.

The translational research objectives for the study include correlating HR gene alterations and clinical outcome. We also aim to identify the causes of acquired resistance to niraparib in a subset of patients undergoing optional rebiopsy at disease progression.

Study design

NERO is a multicentre, two-arm, open-label UK randomised phase II trial comparing niraparib and ASC versus ASC alone in mesothelioma patients with any histological subtype (epithelioid or non-epithelioid) and any site (pleural or peritoneal) who have previously received an approved platinum-based systemic therapy. The treatment allocation ratio will be 2:1 (niraparib+ASC:ASC). The trial opened to recruitment on 11 July 2022 and recruitment will end on 31 December 2023. Eighty-four patients will be recruited at approximately 10 secondary care sites in the UK. Randomisation will be stratified by histology (epithelioid vs non-epithelioid) and length of response to prior platinum based therapy (≤6 months vs

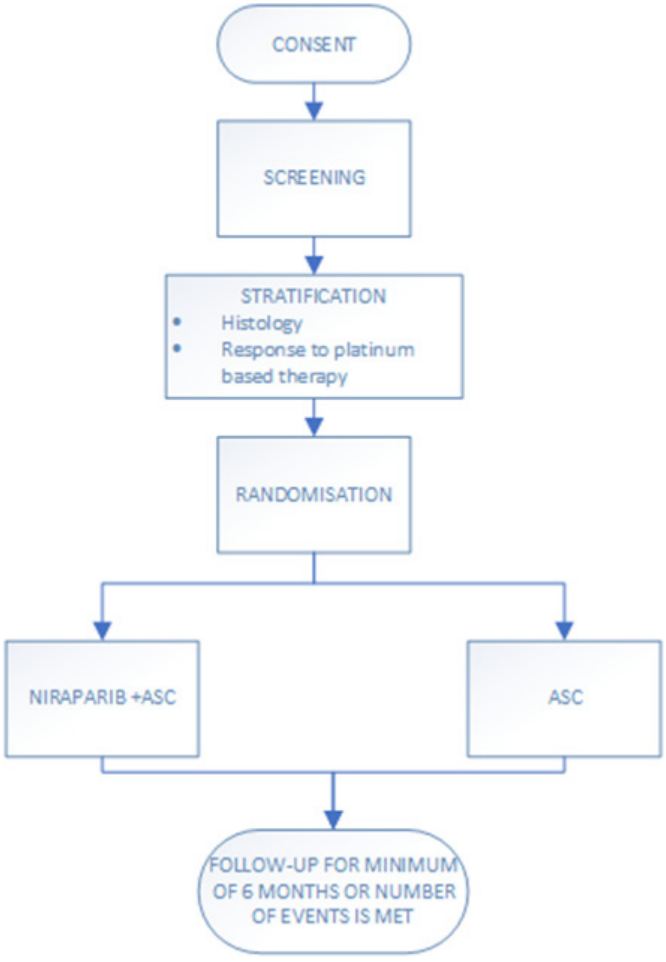

Figure 1 NERO trial schema. ASC, active symptom control; NERO, Evaluating niraparib versus active symptom control in patietns with previoulsy treated mesothelioma.

>6 months). Figure 1 provides an overview of the design and the patients pathway through trial.

Setting

NERO will be run in approximately 10 secondary care hospitals in the UK with the aim of recruiting a total of 84 evaluable patients.

The sites were selected based on patient availability and their performance on a previous mesothelioma study in the Southampton Clinical Trials Unit (SCTU).

Sample size and recruitment

Sample size calculations were carried out using the artsurv command[21] in Stata[22] to perform a log rank test: Based on an HR of 0.6 for PFS (equivalent to an improvement in median PFS from 6 weeks to 10 weeks) 80% power; recruitment period of 18 months, 6 months follow-up period and one-sided significance level of 10%. The required sample size is 84 evaluable patients, based on a total of 79 events (progression/deaths). Patients will be randomly assigned (2:1) to receive niraparib+ASC or ASC alone, aiming for 56 patients in the niraparib+ASC arm and 28 patients in the ASC arm.

Randomisation

Patients will be randomised to either niraparib or ASC alone on a 2:1 allocation using permuted block randomisation. The block sizes will not be disclosed, to ensure concealment. Stratification factors are histology (epithelioid and non-epithelioid) and response to prior platinum based chemotherapy (≤6 months vs >6 months). Participants will be randomised using a web based system, ALEA, after all screening procedures have been completed and the patient is confirmed to be eligible.

Ethical and regulatory aspects

The study received ethical approval from London-Hampstead Research Ethics Committee (REC) on 6 May 2022 (ref: 22/LO/0281) and has Health Research Authority (IRAS 1005002) and UK Medicines and Health Care Product Regulatory Agency (MHRA) approvals. SCTU, a Cancer Research UK core funded and UK Clinical Research Collaboration registered Clinical Trials Unit (CTU), is coordinating the trial. A list of recruiting sites can be obtained from the SCTU. The University Hospital Southampton National Health Service (NHS) Foundation Trust is the sponsor for the trial and is responsible for all legal requirements of conducting a non-commercial clinical trial of an investigational product. The trial is funded by Asthma and Lung UK with support from Cancer Research UK core funding at SCTU and staff within the NIHR Southampton Biomedical Research Centre (BRC) and NIHR Leicester BRC, with translational research funded by GSK. The drug for this trial is provided by GSK who are responsible for the Good Manufacturing Practice quality drug.

The NERO Trial Management Group (TMG) is responsible for overseeing the progress of the trial, including both the clinical and practical aspects. The chair of the TMG will be the co-chief investigator of the trial. The TMG includes representatives with expertise in oncology, radiology, translational science and medical statistics; as well as being supported by a patient and public involvement contributor and SCTU staff involved in the day-to-day running of the trial. An independent trial steering committee has also been established, and an independent data monitoring and ethics committee (DMEC) comprising two clinicians and a statistician experienced in this research area (but not directly involved in this trial apart from DMEC membership) has been set up. The aim of the independent DMEC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial. Charters for these groups are available via NERO@soton.ac.uk.

The SCTU has undertaken a risk assessment for the NERO trial, which includes the requirements for monitoring (both centrally and at site). The SCTU undertakes several internal audits of its own systems and processes annually and has routine audits from both its sponsor and the independent MHRA.

Study participants

The NERO trial is currently recruiting mesothelioma patients with any histological subtype (epithelioid or non-epithelioid) and any site (pleural or peritoneal). NERO is not restricted by line of therapy; however, eligible participants must have been treated with an approved platinum-based systemic therapy. The full inclusion criteria are located in box 1 and the full exclusion criteria are located in box 2. No other investigational medicinal products should be received while on study. The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressive agents, or with other cytotoxic medicinal products. Systemic anticancer or biological treatment and cytotoxic medicinal products not specified in the protocol are prohibited during the study. Prophylactic cytokines (eg, GCSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to local guidelines. Live vaccines within 30 days prior to the first dose of study treatment and during the study are prohibited. Prolonged systemic glucocorticoid therapy (>7 days) is also prohibited.

Informed consent

Consent to enter the trial will be sought from each participant only after a full explanation has been given, a patient information sheet (PIS) offered (online supplemental additional file 1) and time allowed for consideration and discussion with family and friends. Signed participant consent will be obtained using the trials informed consent form (ICF) (online supplemental additional file 2). The process will be documented in the patient's medical records. Only site staff named on the Delegation Log and authorised to do so may obtain consent. Patients may refuse to participate without giving reasons and this will not prejudice their future treatment.

The trial's PIS and ICF detail the consent provisions for collection and use of participant data and biological specimens in future research (online supplemental additional files 1 and 2).

Withdrawal criteria

Participants are free to withdraw consent from the study at any time without providing a reason. Participants may withdraw or be withdrawn from study visits and/or other data collection procedures, but routinely collected data (ie, survival and progression status) will continue to be collected unless a participant withdraws from the study completely.

If a participant wishes to withdraw from trial treatment, participating sites should explain the importance of remaining on trial follow-up for the purposes of data capture. Where possible, patients who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If patients additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would

Box 1 Inclusion criteria for the NERO trial

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 (eg, pleural or peritoneal) with an available tissue block.
4. Patients must have received prior systemic therapy containing platinum for pleural or peritoneal mesothelioma (patients are not restricted by line of therapy).
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, where all toxicities have recovered or returned to grade 1, with the exception of alopecia and neuropathy due to chemotherapy which should have returned to grade 2.
7. Eastern Cooperative Oncology Group Performance Status 0–1.
8. Radiologically evaluable (assessable) disease by modified RECIST (pleural mesothelioma) or RECIST V.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 3 working days prior to commencement of treatment:
    a. White cell count≥2×10^9/L.
    b. Neutrophils≥1.5×10^9/L.
    c. Platelets≥100×10^9/L.
    d. Haemoglobin≥90 g/L.
    e. Creatinine clearance (CrCl)>30 mL/minute (using Cockcroft/Gault formula [(140−age)×mass (kg)×(1.04 (for women) or 1.23 (for men))/serum creatinine (µmol/L)]).
    f. AST≤3×upper limit of normal (ULN) OR ALT≤3×ULN (if both are assessed, both need to be ≤3×ULN).
    g. Total bilirubin≤1.5×ULN (except patients with Gilbert syndrome, who must have total bilirubin<51.3 µmol/L).
13. Reproductive status:
    a. Women of childbearing potential (WOCBP, as defined in the Contraception section) 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 days prior to start of study treatment may be permissible in situations where results cannot be obtained within a 24-hour window.
    b. Women must not be breast feeding.
    c. WOCBP must agree to use a highly effective method of contraception (as outlined in the Contraception section) for the duration of treatment and 180 days after the last dose of ASC+niraparib.
    d. Men who are sexually active with WOCBP must use the contraceptive methods as outlined in the Contraception section 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.

Box 2 Exclusion criteria for the NERO trial

Exclusion criteria

1. Patients with untreated, symptomatic central nervous system (CNS) metastases, 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. Once drained the patient may enter the trial.
3. Second malignancy within 5 years except cancers 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 poly (ADP-ribose) polymerase inhibitor or known hypersensitivity to the components of niraparib.
8. New York Heart associated class II or greater heart failure.
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. Patients with known history or current diagnosis of myelodysplastic syndrome or acute myeloid leukaemia.
14. Patient with known history of active tuberculosis.
15. Patients with uncontrolled hypertension.
16. Participants have confirmed active pneumonitis within 90 days of planned start of the study.
17. Patients that have received colony-stimulating factors (eg, 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 while participating in this clinical study.
19. Known history of testing positive for HIV or known AIDS.
20. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

remain useful for the trial team to continue to collect routinely collected data and, unless the patient explicitly states otherwise, these data will continue to be collected. Patients who withdraw from treatment only will continue to have assessments until disease progression.

Data and samples collected prior to participant withdrawal will be used for trial analysis by the SCTU.

Treatment

Patients will be randomised to receive ASC+niraparib or ASC alone for a study period of up to 24 weeks. Patients will be treated until disease progression, withdrawal, death or development of significant treatment limiting toxicity. If randomised to ASC alone, patients will be managed symptomatically and will be treated as per standard practice at site. ASC could involve regular specialist follow-up; structured assessment of physical, psychological and social problems; and appropriate treatment, including palliative radiotherapy and steroids.

If randomised to niraparib patients will receive drug at a starting dose of 200 mg, taken once daily, in three weekly cycles, up to 24 weeks. Patients will be treated until disease progression, withdrawal, death or development of significant treatment limiting toxicity. For patients who weigh ≥77 kg and have a baseline platelet count ≥150×10^9/L, the recommended starting dose is 300 mg, taken once daily. Niraparib will be supplied to patients in oral formulation as 100 mg capsules. The capsules should be swallowed whole with water and should not be chewed or crushed. Niraparib can be taken without regard to meals. Patients should be encouraged to take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea. If a patient vomits or misses a dose of niraparib, an additional dose should not be taken. The next dose should be taken at the regularly scheduled time. Patients will be provided with a drug diary to complete to monitor compliance to treatment. The schedule of events (table 1) details the trial treatment schedule.

Dose delays and reductions for toxicity will be allowed within NERO; however, no dose escalations will be allowed. Tumour assessments for all patients should continue as per protocol even if dosing is delayed.

No dose adjustment is necessary for elderly patients (≥65 years). There are limited clinical data in patients aged 75 years or over.

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end-stage renal disease undergoing haemodialysis. Niraparib should be used with caution in these patients.

No dose adjustment is needed in patients with mild hepatic impairment (either aspartate aminostransferase (AST)>upper limit of normal (ULN) and total bilirubin (TB)≤ULN or any AST and TB >1.0×ULN–1.5×ULN). For patients with moderate hepatic impairment (any AST and TB>1.5×ULN–3×ULN) the recommended starting dose of niraparib is 200 mg once daily. There are no data in patients with severe hepatic impairment (any AST and TB >3×ULN); use with caution in these patients.

IMP administration should be delayed for the following:

- Any grade 2 non-skin, drug-related adverse event (AE), except for fatigue and laboratory abnormalities.
- Any grade 3 skin drug-related AE.
- Any AE, laboratory abnormality or intercurrent illness, which in the judgement of the investigator, warrants delaying the dose of study medication.
- Any grade 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, alanine aminotransferase (ALT), or TB or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia does not require a dose delay.

Table 1 Schedule of observations and procedures

Visit	Screening: ≤28 days prior to day 1 cycle 1	Baseline: day 1 cycle 1 Assessments ≤3 working days prior to administration	From cycle 2 niraparib until disease progression: day 1 of cycle	28±7 days post-treatment discontinuation	Follow-up
Informed consent	X				
Eligibility evaluation	X				
Medical history	X				
Physical exam (height and weight), vital signs (temperature, BP, HR, respiratory rate, oxygen saturation), ECOG performance status	X	X*†	X*†	X*	
Concomitant medication record	X‡	X	X	X	
Pregnancy test in WOCBP§	X	X¶	X¶	X¶	X¶**
CT†† with modified RECIST (or RECIST V.1.1)‡‡	X		X§§		
Serum chemistry (Blood urea nitrogen (BUN) or serum urea, serum creatinine, Na, K, Ca and phosphate)	X	X¶¶	X***	X	
FBC (WCC, lymphocyte count, ANC, haemoglobin, haematocrit and platelet count)	X	X¶¶†	X***	X	
Liver function tests (aspartate aminotransferase (AST) or alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin, albumin)	X	X¶¶	X***	X	
International normalised ratio test	X				
Urine dipstick†††	X				
Randomisation‡‡‡		X			
AEs	X§§§	X	X	X	X¶¶¶
Record details of next treatment				X	X
Treatments (niraparib±ASC)		X	X		
Archival/Fresh (Formalin-Fixed Paraffine-Embedded (FFPE)) translational tissue (screening and access to tissue for translational research is mandatory).	X****			X††††¶	
Translational blood sample‡‡‡‡		X		X¶	
Survival status assessed every 6 months				X	X§§§§

*Targeted physical exam as clinically required.
†For safety, it is advised that patients taking niraparib have a weekly FBC for the first cycle of treatment and have their BP and HR monitored weekly for the first 8 weeks. This information does not need to be recorded in the eCRF.
‡Baseline concomitant medication review within 14 days prior to first dose.
§Serum or urine pregnancy test is acceptable.
¶Not required for patients randomised to the ASC only arm.
**Pregnancy test must be performed every 4 weeks up to 180 days after the last dose of niraparib for WOCBP.
††Chest and abdomen for all participants; pelvis for patients with peritoneal mesothelioma only; and all other known sites of disease.
‡‡Modified RECIST should be used for pleural mesothelioma. For non-pleural mesothelioma, or where measurements for mRECIST cannot be obtained, RECIST V.1.1 should be used.
§§Every 6 weeks from randomisation (±3 days, although, ±5 days will be permitted with advanced permission from SCTU) to ascertain disease status, until disease progression or end of treatment. If the patient progresses no further CT scans should be performed per protocol. If the patient stops treatment and has not progressed CT scans should be performed every 12 weeks (from randomisation), until disease progression.
¶¶If screening is within three working days of first treatment, assessments do not need to be repeated.
***Samples can be taken ≤3 working days prior to dosing.
†††Urinary tract infection is an adverse drug reaction of niraparib. Therefore, following baseline test, urine dipstick should be done as clinical indicated.
‡‡‡Within three working days prior to treatment.
§§§AEs to be reported from consent, graded using Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.
¶¶¶All AEs to be reported for 100 days post-treatment discontinuation and for ongoing drug-related AEs until resolved, return to baseline or deemed irreversible.
****Retrieval of archival sample or re-biopsy if sample not available. Only to be performed following consent (mandatory sample).
††††Optional.
‡‡‡‡Whole blood to be collected which will be separated for DNA sequencing, see Lab Manual for further details.
§§§§Assess every 6 months.
AE, adverse event; ASC, active symptom control; BP, blood pressure; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FBC, full blood count; HR, heart rate; RECIST, Response Evaluation Criteria in Solid Tumors; SCTU, Southampton Clinical Trials Unit; WCC, white cell count; WOCBP, women of childbearing potential.

Table 2 Niraparib dose reduction for adverse reactions

Dose level	Initial dose: 300 mg per day	Initial dose: 200 mg per day
Starting dose	300 mg/day (three 100 mg tablets)	200 mg/day (two 100 mg tablets)
First dose reduction	200 mg/day (two 100 mg tablets)	100 mg/day (one 100 mg tablet)
Second dose reduction	100 mg/day (one 100 mg tablet)	N/A or discontinuation of niraparib

N/A, not available.

- If a patient has a baseline AST, ALT or TB that is within normal limits, delay dosing for drug-related grade 2 toxicity.
- If a patient has baseline AST, ALT or TB within the grade 1 toxicity range, delay dosing for drug-related grade 3 toxicity.

Patients who require delay of IMP should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when retreatment criteria are met. Treatment can be delayed for up to 4 weeks from the last dose. Delays for longer than 4 weeks will be discussed with the chief investigator.

Following the occurrence of an AE leading to a dose delay for any reason stated above, and a return to grade 2 or complete resolution of symptoms, treatment can be restarted with a reduced dose of niraparib. Niraparib dose reduction can be reduced in 100 mg increments as per table 2. No more than two dose reductions are allowed.

Risk minimisation measures for non-haematological and haematological adverse reactions for patients administered niraparib can be found within online supplemental additional file 3.

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. Blood pressure and heart rate should be monitored at least weekly for the first 2 months, then at the start of each cycle.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose, if necessary. In the clinical development programme, most cases of hypertension were controlled adequately using standard hypertensive treatment with or without niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving niraparib. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. If PRES occurs as an adverse reaction, niraparib should be discontinued and symptoms should be treated.

Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), including cases with fatal outcome, have been reported with the use of niraparib. In clinical trials, the duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to >4 years. The cases were typical of secondary, cancer therapy related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA-damaging agents and radiotherapy. Some of the patients had a history of bone marrow suppression. For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS and/or AML is confirmed, then niraparib should be permanently discontinued and the patient should be treated appropriately.

Study procedure

Screening

Following informed consent for the main trial, assessments including a physical examination, full blood count (FBC), serum biochemistry, including liver function tests and International Normalised Ratio tests and a urine dipstick are completed within 28 days prior to niraparib treatment commencing. A CT scan is also undertaken to assess the disease according to modified RECIST or RECIST V.1.1. Concomitant medication and medical history will be recorded. In addition, women of childbearing potential (WOCBP) will undertake a pregnancy test. Archival/fresh tissue and blood samples for translational research will also be collected during screening.

Treatment and follow-up visits

Participants will be randomised to receive ASC+niraparib or ASC alone for a study period up to 24 weeks. Participants will be treated until disease progression, withdrawal, death or development of significant treatment limiting toxicity. There will be a provision for patients who are continuing to receive benefit from Niraparib to continue beyond the 24 weeks, however, this will be done off protocol.

Regardless of the arm the participant is randomised to, they will attend hospital appointments for treatment cycles with assessments similar to those performed during screening, plus reviews of AEs and treatment adherence. For safety, it is advised that patients taking niraparib have a weekly FBC for their first cycle of treatment and have their blood pressure and heart rate monitored weekly for the first 8 weeks. The time schedule of enrolment,

interventions, assessments and visits for participants are fully detailed in the schedule of events (table 1). Participants completing the trial, defined as progression on niraparib, according to modified RECIST or RECIST V.1.1, investigator reported progression, or death from any cause (whichever comes first) will continue to be followed up every 6 months for details of next treatment and survival until the required number of events (n=79 progression and/or death) have been achieved or every patient has 6 months follow-up.

Serious AE reporting occurs in real-time to the SCTU safety desk throughout the study. Serious AEs are assessed to determine whether they are related to drug treatment and unexpected or not, and subsequently reported to both GSK and the UK regulatory bodies.

Translational research

Availability of a baseline tissue block (formalin fixed, paraffin embedded) prior to randomisation will be mandatory. Research bloods will be collected at baseline and disease progression, and then stored. Tissue and blood will be biobanked at Leicester for translational analysis. This will include whole exome sequencing (tissue and whole blood) of responders and refractory patients to enable:

- Correlation of HR deficiency signature 3 (present, absent) with response (partial response (PR) or progressive disease (PD)).
- Presence of known somatic aberrations involving the double strand DNA damage repair (dsDDR) pathway in mesothelioma, including BAP1, BRCA1, BRCA2, RAD51B, FANCD2, FANCG, FANCM, CHECK2, POLQ (single nucleotide variation, copy number alteration, translocation, fusions, promoter mutations, methylation). These events will be correlated with response to refine a biomarker of PARP inhibitor sensitivity.
- Biomarker cross-validation with PARP inhibitor treated patients in MIST1, and mesothelioma explants/cell lines treated with PARP inhibitor.

Patients who received niraparib, and exhibited clinical benefit, will have optional rebiopsies at disease progression to determine mechanisms of acquired drug resistance. The paired biopsies will be studied using whole exome sequencing to identify any acquired genomic alterations.

Contraception

Definitions of WOCBP and fertile men

A WOCBP is a sexually mature woman (ie, any female who has experienced menstrual bleeding) who has not:

- Undergone hysterectomy or bilateral oophorectomy/salpingectomy.
- Been postmenopausal for 12 consecutive months (ie, who has had menses at any time in the preceding 12 consecutive months without an alternative medical cause).
- Had premature ovarian failure confirmed by a specialist gynaecologist.

A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

Female patients

To be considered eligible for the trial, all female patients who are WOCBP must consent to use one of the following methods of highly effective contraception from the first administration of study treatment, throughout the trial and for 180 days after the last dose of study treatment:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral.
  - Injectable.
  - Implantable.[2]
- Intrauterine device.[2]
- Intrauterine hormone-releasing system.[2]
- Bilateral tubal occlusion.[2]
- Vasectomised partner.[2,3]
- Sexual abstinence.[4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2]Contraception methods that in the context of this guidance are considered to have low user dependency.

[3]Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4]In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

Male patients

To be considered eligible for the trial, male patients (including those with partners of childbearing potential) must consent to use the following methods of contraception from the first administration of the study treatment, throughout the trial and for 90 days after the last dose of niraparib/ASC:

- Condom.
- Female partner to use one of the highly effective methods of contraception detailed in the Female patients section above.

Male patients must also refrain from donating sperm during this period.

Data collection and management

Plans for assessment and collection of outcomes

Hospital research staff will enter participant data into the study electronic case report forms (eCRFs) via a remote data collection tool (Medidata Rave). Only trained personnel with specific roles in the study will be granted access to the eCRFs. SCTU trial staff will regularly check the data for missing or anomalous values. Data queries will either be automatically generated within the eCRF, or manually raised with site by the SCTU team. Site staff will respond to explain or resolve the discrepancies.

The PIS and ICF will outline the participant data to be collected and how it will be managed or might be shared, including handling of all patient identifiable data (PID) and sensitive PID adhering to relevant data protection law.

Data management

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. The principal investigator (PI) at each site is responsible for ensuring the accuracy, completeness and timeliness of the data entered.

The participant data are pseudoanonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant-specific correspondence between the SCTU and site. The site retains a participant identification code list, which is only available to site staff.

Only the investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the PI for future reference.

Data queries will either be automatically generated within the eCRF, or manually raised by the SCTU, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial, after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Oversight and monitoring

The trial may be subject to inspection and audit by University Hospital Southampton NHS Foundation Trust (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

On receipt of a request from SCTU, the sites will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to trial staff and departments (eg, pharmacy). Following a trial risk assessment a trial monitoring plan was developed which fully describes the monitoring procedures.

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, including representatives of the competent authority. Details will remain confidential and participants' names will not be recorded outside the trial site without informed consent.

Patient and public involvement

Mavis Nye, PPI representative coapplicant and founder and president of the Mavis Nye Foundation has been involved in the design of NERO. Mavis is supportive of the trial and was able to confirm that the trial, as described, would be attractive to patients, especially given the very poor prognosis and lack of treatment options for these patients.

During a previous mesothelioma trial run by SCTU, we had significant media coverage (regional and national TV, national newspapers) for which our PPI played a significant part in telling their stories and raising awareness of the trial. We would do the same with NERO.

While the trial is active the TMG and trial steering committee oversight groups will have PPI representation. There has been PPI contribution to the protocol, PIS and ICF.

The national charity Mesothelioma UK will be involved in promoting the study and disseminating lay results when the trial ends. This will include a lay summary on appropriate websites.

Southampton CTU is a cofounder of the Wessex Public Involvement Network which established the area as a beacon of best practice in PPI, impacting positively on the reach, relevance and refinement of applied health research. As a UKCRC-registered, NIHR and Cancer Research UK core funded CTU we have significant experience in involving PPI in everything we do.

Statistical analysis

A detailed statistical analysis plan will be developed prior to database lock, and all data and appropriate documentation will be stored for a minimum of 25 years after the completion of the trial.

Study populations:

- Intention-to-treat (ITT) population—consists of all patients who have consented and been randomised to a treatment arm.
- Safety population—consists of the ITT population who have received at least one dose of treatment.

The primary analysis population is the ITT population.

Time-to-event data (PFS and OS) will be analysed and presented using Kaplan-Meier curves according to the ITT principle. Based on the estimands framework,[23] treatment-related intercurrent events (non-initiation,

missed doses, early withdrawal) will be handled using the treatment strategy policy, and study withdrawal following the 'while on study' strategy. For PFS, progression is defined according to modified RECIST or RECIST V.1.1, investigator reported progression, or death from any cause, and hence represents a composite endpoint of progression or death. We will use a Cox proportional hazards model to calculate the HR, 95% CIs and p value adjusted for stratification factors (as above). The Cox regression models for PFS will form the primary endpoint analysis model. Median PFS (with 95% CIs) and 6-month and 12-month PFS and OS will also be reported. Best objective response will be reported (as frequency and percentage) for the ITT population, and duration of response as median and quartiles. As it is expected that complete duration will be observed for the vast majority of those with complete or PR (ie, no censoring for end of duration), median and quartiles will be reported from direct observation rather than Kaplan-Meier estimates.

Summary statistics will be reported for best overall response (PD, stable disease, PR or complete response) assessed by modified RECIST or RECIST V.1.1. Overall response rate will subsequently be presented as a percentage of patients whose best overall response is either PR or complete response. DCR will also be reported at both 12 and 24 weeks, as a percentage of patients who had stable disease, PR or complete response at these respective time points. We will assess treatment compliance by summarising the percentage of received dose relative to intended dose.

In addition, summary statistics and listings will be reported for patients in the safety population and will be summarised by treatment arm with classification by the latest version of MedDRA. Grade will be reported on the CTCAE toxicity scale (V.5.0). Both all cause and treatment related or emergent AEs will be included in the analysis.

All analyses will be carried out using R, STATA V.16 or higher and/or SAS V.9.4 or higher licensed to University of Southampton.

There are no plans for an interim analysis to be conducted during the NERO trial.

Translational analysis

Formalin-fixed paraffin-embedded tissue blocks will be subjected pathology review, and DNA extraction using a robotic platform (Thermofisher, Kingfisher). In parallel, germline DNA will be extracted from buffy coat.

DNA will be whole exome sequenced (Novogene) to enable analysis of single nucleotide and copy number variants. As part of the translational research, whole exome sequencing analysis will account for interactions between germline and somatic mutations. Germline and somatic, biallelic DNA repair gene alterations will be curated. HR deficiency mutation signature (sig3) will be interrogated. If a germline bap1 mutation is identified (expected rate is 8%) centres will be notified and patients managed as per local standard of care.

Machine learning of normalised response data and exome derived decipher DDR somatic alterations, HRDmeso will be inferred and correlated with clinicopathological, genomic features and clinical outcome in NERO.

AE reporting and harms

Data on AEs will be collected at treatment and follow-up visits. Real-time SAEs will be reported up to 100 days post treatment discontinuation to the SCTU safety desk. The trial also has a UK regulatory compliant real-time SAE reporting process to identify serious AEs and suspected unexpected SAEs that could suspend or stop the trial if warranted.

End of the trial

The primary endpoint analysis will occur once the required number of events (n=79 progression and/or death) has been reached. This is anticipated to be 6 months after the end of the recruitment period. The end of trial will occur when 79 events have been achieved or every patient has 6 months follow-up and when all data has been cleaned.

Trial status

The trial opened to recruitment on 11 July 2022. Eighty-four patients will be recruited over an 18-month period at approximately 10 sites in the UK.

This clinical trial was registered on ISRCTN and ClinicalTrials.gov on 11 May 2022 and 12 July 2022, respectively (ISRCTN 16171129; ClinicalTrials.gov reference: NCT05455424). The current protocol is version 6 dated 27 July 2023. REC/MHRA approved protocol amendments will be communicated to sites via email and updated trial documentation provided centrally via the trial website. Trial registries will be amended where relevant with explanations for these changes.

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Contributors DF is the chief investigator and medical expert and conceived the idea of the study. GG is the methodological chief investigator and contributed to study design and protocol and was involved in developing the funding application. JC, SD and PT are involved in patient recruitment and data collection. DG, ZE and AM-F are responsible for the management of the trial and its conduct. KH and SE contributed statistical advice and developed the statistical analysis plan. CS, LJ and KM are responsible for the trial data management. LD is the Mesothelioma UK CEO and contributed to the study design and protocol and were involved in the

funding application. CP, AB, JS and JL-L contributed to the translational protocol. MN is the patient representative, contributing to the design and conduct of the trial. All authors contributed to the manuscript drafting and have read and approved the final manuscript.

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