BMJ Open

Maintenance with niraparib in patients with stage III, stage IV, chemo-naïve recurrent or platinum-sensitive recurrent uterine serous carcinoma: study protocol for a phase II clinical trial

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To cite: Frimer M, Katcher A, Blustein P, *et al*. Maintenance with niraparib in patients with stage III, stage IV, chemo-naïve recurrent or platinum-sensitive recurrent uterine serous carcinoma: study protocol for a phase II clinical trial. *BMJ Open* 2025;**15**:e087115. doi:10.1136/bmjopen-2024-087115

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-087115).

Received 01 April 2024
Accepted 25 April 2025

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ABSTRACT

Introduction Uterine serous carcinoma (USC) accounts for 40% of endometrial cancer-related deaths. The standard of care for stages III and IV USC yields a 20%–30% survival at 2 years and a 10%–20% survival at 3–5 years. Recent advances in the second-line treatment of advanced or recurrent USC are rapidly evolving. Targeted therapeutic approaches with the use of lenvatinib plus pembrolizumab, as well as the use of trastuzumab deruxtecan, offer new hope for successful second-line therapies for patients. However, further investigation into novel targeted therapeutic approaches is warranted, given the high burden of disease associated with this aggressive histological subtype. USC shares clinical and genomic similarities with epithelial ovarian cancer, suggesting a correlation with 'BRCAness'. Niraparib, a potent PARP1 and PARP2 inhibitor, was shown to have a positive impact on platinum-sensitive recurrent ovarian cancer, regardless of the presence or absence of BRCA status. Our hypothesis is that patients with stage III, stage IV and platinum-sensitive recurrent USC receiving niraparib maintenance in addition to standard therapy for USC may have an improved progression-free survival.

Methods and analysis Participating sites include the primary site, Northwell Health Zucker Cancer Centre, and secondary site, Rutgers Cancer Institute of NJ. Females over the age of 18 with stage III, stage IV or platinum-sensitive recurrent USC will be recruited and enrolled based on inclusion/exclusion criteria. 24 subjects will be enrolled during phase 1 and 21 subjects will be enrolled during phase 2, over a total of 3 years. Patients will receive an individualised dose of niraparib daily every 28 days per cycle for 1 year or until progression of disease. Follow-up of disease status will continue for 5 years poststudy treatment. This phase II clinical trial will employ a Simon two-stage minimax design to test the null hypothesis that the 1 year response rate is <20% versus the alternative hypothesis that the 1 year response rate is ≥40%, with alpha=0.05 and power=0.90.

Ethics and dissemination Ethical approval was granted by Northwell Health Cancer Institute institutional review board (reference number: 19–0380) and PRMS. Alongside journal publications, results will be available publicly on completion of the study as approved by the sponsor investigator.

Trial registration number NCTN04080284

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol actively recruits from four large, academic hospital sites across two states focused on the recruitment of patients from racially and ethnically diverse backgrounds, supporting future applicability of study findings.
⇒ This trial actively recruits participants with uterine serous carcinoma, a tumour that is rare and underrepresented in clinical trials.
⇒ There are no differences in the allocation of interventions resulting in all participants receiving the same treatment and limiting potential bias.
⇒ Analysis of progression-free and overall survival of subjects is potentially limited by patients who might be lost to follow-up over 5 years.
⇒ Length of time required to reach adequate sample size is extensive due to the rareness of the cancer type.

INTRODUCTION

Background and rationale

Study rationale

The rationale for this trial is based on significant clinical and genomic similarities of uterine serous carcinoma (USC) and epithelial

ovarian carcinomas.[1–3] Currently, the treatment for stages III and IV USC yields approximately a 20%–30% survival at 2 years and a 10%–20% survival at 3–5 years postdiagnosis using current standard of care therapy of chemotherapy with or without radiation. There continue to be rapid advances in targeted therapy of advanced and recurrent USC. Keynote 775 demonstrated significantly longer progression-free survival (PFS) and overall survival (OS) in patients receiving lenvatinib plus pembrolizumab (PD-1 inhibitor) than chemotherapy.[4] The benefits were seen across all evaluated subgroups, including the pMMR population and those with less-common yet aggressive histological features (including serous).[4] Fader *et al* noted increased PFS and OS with the addition of trastuzumab to carboplatin/paclitaxel for advanced/recurrent HER2/Neu-positive USC. However, this demonstrated only modest improvement in progression–free survival and no significant OS benefit for patients with recurrent USC.[5] Additionally, dostarlimab plus carboplatin-paclitaxel showed significantly increased PFS in the RUBY trial among patients with advanced or recurrent endometrial cancer. However, only a minority of the study participants had a diagnosis of serous adenocarcinoma, and the observed benefit was smaller in magnitude for those in the pMMR-MSS population.[6] Most recently, results from the DESTINY-PanTumor01 trial demonstrated durable antitumour response in multiple tumour types, including a small number of advanced, recurrent uterine cancer with activating HER2 mutations with use of trastuzumab deruxtecan.[7]

Given the need for additional targeted treatment options in the specific population of women with USC, the current protocol was written based on prior NOVA trial results.[8] In the multi-national, Phase 3 NOVA trial in women with platinum-sensitive, recurrent ovarian cancer, niraparib significantly prolonged the median PFS, irrespective of the presence or absence of a germline BRCA mutation or the presence or absence of a homologous recombinant deficiency.[8]

Background

USC accounts for up to 40% of endometrial cancer-related deaths. In contrast to the more common endometrioid histology, USC is more likely to present at an advanced stage and carries a worse prognosis. USC biologically mimics serous carcinoma of the ovary and has a high probability for nodal and intra-peritoneal spread. Furthermore, studies have indicated that USC harbours a high frequency of somatic TP53 mutations, germline BRCA1 mutations and mutations within the Fanconi Anemia-BRCA pathway. Data is supportive of an association of USC with hereditary breast and ovarian cancer, harbouring mutations in DNA repair genes. Approximately 5% of women with USC have germline mutations in three different tumour suppressor genes including BRCA1, CHEK2 and TP53.[1 2] Mutations in the DNA damage response (DDR) pathway present a novel therapeutic target for USC. Given the high association with TP53 mutations in USC, these tumours may be more vulnerable to inhibition of WEE1.[9] A recent Phase II study investigated the use of Adavosertib, a potent WEE1 inhibitor, and showed an improvement in PFS and OS, demonstrating just one association between the DDR and tumour direct therapy.[9]

The Cancer Genome Atlas (TCGA) Research Network reported four groups of endometrial tumours based on integrated genomic data including a novel POLE subtype in 10% of endometrial tumours. Patients with USC shared many similar characteristics with basal-like breast and high-grade serous ovarian cancers, suggesting a correlation with 'BRCAness'.[10] Given the 'BRCAness' of USC, a recent multicentre prospective cohort study of 1083 women with BRCA1 and BRCA2 mutations who underwent risk-reducing salpingo-oophorectomies (RRSO) without hysterectomy were noted to have increased serous/serous-like endometrial carcinoma if they harboured BRCA1 mutations.[11] The study recommended considering this risk of uterine cancer when discussing the advantages and risks of hysterectomy at the time of RRSO in women with BRCA1 mutations. Other studies support the view that USC is a component of BRCA 1/2-associated tumours and suggest that women with USC should be offered screening for germline mutations when there is a positive family history of malignancies associated with hereditary breast and ovarian cancer syndrome.[12]

Poly(ADP-ribose) polymerases (PARP1 and PARP2) play an important role in DNA repair. On formation of DNA breaks, PARP binds the ends of broken DNA strands, helping in DNA damage repair. Treatment with PARP inhibitors allows the killing of a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumour harbouring a BRCA or homologous recombination gene mutation will have selective blockage by PARP inhibitors to maintain genomic integrity. Data from studies in serous ovarian cancer has indicated that tumours arising in a non-BRCA patient who still has a homologous recombination deficiency could also exhibit tumour cell sensitivity to PARP inhibitors. PARP inhibitors (PARPi) are synthetically lethal to tumour cells with homologous recombination deficiency (HRD). HRD leads to genome-wide loss of heterozygosity (LOH). Analysis of the ARIEL2 study in platinum-sensitive ovarian cancer trial found that patients with germline or somatic BRCA mutation or wild-type BRCA with high LOH had longer PFS and improved responses with rucaparib, a PARPi, treatment than did patients with wild-type BRCA and low LOH.[13]

Niraparib is a potent, orally active PARP1 and PARP2 inhibitor developed as a treatment for patients with tumours that harbour defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors. In non-clinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic

lethality when administered to cells with homologous recombination defects. In a BRCA1-mutant xenograft study, niraparib dosed orally caused tumour regression, which was mirrored by a >90% reduction in tumour weight compared with the control. In a BRCA2-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumour volume and weight. In the randomised, double-blind, Phase 3 Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer (NOVA trial), a total of 553 patients were randomised at 107 centres worldwide.[8] Patients were categorised according to the presence or absence of a gBRCAmut within their tumours and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily. The primary endpoint was PFS. The study enrolled 203 patients in the gBRCAmut cohort and 350 patients in the non-gBRCAmut cohort. Among the 350 patients in the non-gBRCAmut cohort, 162 had tumours that were identified as HRD positive (HRDpos) and 134 had tumours that were HRD negative (HRDneg). Median PFS in patients with HRDneg tumours was 6.9 months (95% CI (CI): 5.6, 9.6) in the niraparib arm versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a HR of 0.58 (95% CI: 0.361, 0.922) (p=0.0226).

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least one treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. The incidences of Grade three or four TEAEs (74% vs 23%), serious adverse events (SAEs) (30% vs 15%), TEAEs leading to treatment interruption (67% vs 15%), TEAEs leading to dose reduction (69% vs 5%) and TEAEs leading to treatment discontinuation (15% vs 2%) were higher for niraparib than for placebo.

More recently emerging data has explored the use of PARP inhibitors in endometrial cancer, exploiting the 'BRCAness' of a subset of these tumours. In a recent abstract presentation of the UTOLA trial, olaparib was investigated as a maintenance therapy following platinum-based chemotherapy in advanced or metastatic endometrial cancer. The cohort was substratified by p53 and MMR status during analysis. The group showed a PFS benefit in HRDpos advanced and metastatic carcinoma. However, in this study, there was no demonstrated benefit of olaparib noted with p53 mutant tumours.[14]

Objectives

Hypothesis

Our hypothesis is that patients receiving niraparib maintenance in addition to standard therapy for USC may lead to improved PFS in women with stage III, stage IV and chemo-naïve recurrent or platinum-sensitive recurrent USC. We hypothesise that this treatment will be well tolerated in this group of patients.

Primary Objective:

To determine the PFS at 1 year in the proposed niraparib regimen in the population of patients with stage III, stage IV or recurrent uterine serous carcinoma (USC).

Secondary Objective:

1. Progression-free survival, Overall Survival and overall response rate at 2 and 3 years intervals from the start of the treatment protocol.
2. To further describe safety and assess toxicities encountered with the use of the proposed treatment regimen in patients with stage III, stage IV or recurrent USC.
3. To identify the prevalence of somatic mutations, homologous recombination deficiency mutations and overall mutational burden in patients with USC and classify tumor into loss of heterozygosity high and low phenotypes.
4. To evaluate quality of life (QoL) for the subjects undergoing this treatment, using validated tools. QoL will be assessed every 3 months during treatment course.

Trial design

Overall design

This is a multi-centre Phase II, open label, clinical trial with ~5 years patient accrual, and the end of the study is defined as the last patient's last follow-up visit or 5 years from the patient's end of therapy, whichever occurs first. The PFS and OS of subjects in this trial is compared with a historical control.

METHODS AND ANALYSIS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

Sites enrolling participants will be Northwell Health with four actively recruiting sites: Zuckerberg Cancer Centre, Imbert Cancer Centre, Greenlawn Cancer Centre, Lenox Hill Hospital and Rutgers Cancer Institute of New Jersey. Northwell Health is the largest health system located in New York, NY, USA. Rutgers Cancer Institute of New Jersey is an academic hospital located in New Brunswick, New Jersey, USA.

Patient and public involvement statement

Patient involvement and/or feedback was not pursued in the development of this protocol. Multiple physician experts in this field were involved in the study design phase.

Eligibility criteria

Inclusion criteria

1. Female sex assigned at birth, age at least 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance status of <2.
3. Written voluntary informed consent.
4. Histologically diagnosed USC.

5. Patient must agree to undergo molecular tumour testing, if not previously performed.
6. Patient diagnosed with advanced stage USC including stage III, stage IV (based on FIGO 2019 Staging Criteria) platinum-sensitive recurrent USC and chemo-naïve recurrent USC.
7. If recurrent USC, the patient must have platinum-sensitive disease after initial treatment; defined as achieving a response (complete response (CR) or partial response (PR)) and disease progression >6 months after completion of their last dose of platinum chemotherapy.
8. If chemo-naïve, patients with recurrent disease are eligible to enter the study with standard platinum-based treatment followed by niraparib maintenance.
9. Patients eligible if receiving first- or second-line chemotherapy for recurrence.
10. The patient must have achieved a partial, stable or complete tumour response following the last chemotherapy (minimum of three cycles) regimen of physician choice chemotherapy indicating partial, stable or complete tumour response.
11. Patients must receive niraparib maintenance within 12 weeks after completion of their final dose of chemotherapy regimen or within 20 weeks if the patient also received adjuvant radiation therapy. CT chest/abdomen/pelvis will be performed within 28 days of starting niraparib.
12. Lesions can be non-measurable or measurable by RECIST 1.1 criteria.
13. Adequate organ function, defined as:
    a. Absolute neutrophil count ≥1500/µL.
    b. Platelets ≥1 00 000/µL.
    c. Haemoglobin ≥9 g/dL.
    d. Serum creatinine ≤1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥30 mL/min using the Cockcroft–Gault equation.
    e. Total bilirubin ≤1.5× ULN (≤2.0 in patients with known Gilberts syndrome) OR direct bilirubin ≤1× ULN.
    f. Aspartate aminotransferase and alanine aminotransferase ≤2.5× ULN unless liver metastases are present, in which case they must be ≤5× ULN.
14. Participants receiving corticosteroids may continue as long as their dose is stable for at least 4 weeks prior to initiating protocol therapy.
15. Participants must agree not to donate blood during the study or for 90 days after the last dose of study treatment.
16. Female participants have a negative urine or serum pregnancy test within 7 days prior to taking study treatment if of childbearing potential and agree to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment or are of non-childbearing potential. Non-childbearing potential is defined as follows (by other than medical reasons):
    a. ≥45 years of age and has not had menses for >1 year.
    b. Patients who have been amenorrhoeic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range on screening evaluation post-hysterectomy, post-bilateral oophorectomy or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. Information must be captured appropriately within the site's source documents. Note: abstinence is acceptable if this is the established and preferred contraception for the patient.
17. Participants must agree to not breastfeed during the study or for 180 days after the last dose of study treatment.
18. Able to take oral medications.

Exclusion criteria

1. Participant must not be simultaneously enrolled in any interventional clinical trial.
2. Drainage of ascites during the last two cycles of last chemotherapy.
3. Radiotherapy was given within 2 weeks encompassing >20% of the bone marrow or any radiation therapy within 1 week prior to Day 1 of protocol therapy. Participants must not have received investigational therapy ≤4 weeks or within a time interval less than at least five half-lives of the investigational agent, whichever is shorter, prior to initiating protocol therapy.
4. Persistent >Grade two anaemia, neutropaenia or thrombocytopaenia from prior cancer therapy that has persisted >4 weeks and was related to the most recent treatment.
5. Symptomatic uncontrolled brain or leptomeningeal metastases.
6. Known hypersensitivity to the components of niraparib.
7. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
8. Diagnosis, detection or treatment of invasive cancer other than uterine cancer ≤2 years prior to study enrollment (except basal or squamous cell carcinoma of the skin that has been definitively treated).
9. Patient considered a poor medical risk due to serious, uncontrolled medical disorder, non-malignant systemic disease or active uncontrolled infection.
10. Patients must not have received a transfusion within 4 weeks of the first dose of study treatment.
11. Participants must not have received colony-stimulating factors (eg, granulocyte colony-stimulating factor (GCSF), granulocyte macrophage colony-stimulating

factor or recombinant erythropoietin) within 4 weeks prior to initiating protocol therapy.
12. Participants must not have any known history of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML).
13. Immunocompromised patients (splenectomy patients are allowed).
14. Patients with known active hepatitis disease.
15. Prior treatment with a known PARP inhibitor.
16. Patients noted to have MSI-H mutational burden.

Who will take informed consent?

Written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating institution. The investigator or co-investigators will provide the patient with a copy of the IRB/IEC-approved informed consent form (ICF) prior to the start of the study. As part of the informed consent process, the investigator will explain orally and in writing the nature, duration and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences or AEs that may occur.

Additional consent provisions for collection and use of participant data and biological specimens

Data collected for this study will be analysed and stored in a password-protected database. Permission to transmit data to the database will be included in the informed consent. No biological specimens will be stored for use in ancillary studies, so additional consent provisions are not applicable.

Interventions

Explanation for the choice of comparators

This is a Phase 2 Trial with a single treatment arm of patients receiving niraparib maintenance. The group receiving the treatment will be compared with survival curves of historical controls. (figure 1)

Intervention description

Study treatment will be administered daily and orally continuously. Niraparib capsules of 100 mg strength each will be taken with eight ounces of water daily, with or without food, preferably in the morning, at the same time. Up to three capsules of 100 mg strength will be taken at each dose administration (for a total of 300 mg). The initiation dose will be defined per current Food and Drug Administration (FDA) guidelines for niraparib treatment in ovarian cancer. Dose interruptions (no longer than 28 days) will be allowed. Dose reduction will be allowed based on treatment side effects. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions. Study treatment will be dispensed to patients on Cycle 1/Day one and every cycle (every 28 days) thereafter, until the patient discontinues study treatment. If the starting dose is 300 mg/day, the first dose reduction is 200 mg/day, and the second dose reduction is 100 mg/day. Patients on study will receive a treatment dose of 200 mg for those whose baseline weight is less than 77 kg or have a baseline platelet count of less than 1 50 000 µL. If the starting dose is 200 mg/day, only one dose reduction to 100 mg/day is allowed. Niraparib is discontinued if a dose reduction below 100 mg/day is required. This dosing regimen is based on the recent NOVA trial results (niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer).

If a participant misses a dose (greater than 12 hours from normal dosing time) of niraparib, they should skip that dose and take their next dose at its regularly scheduled time. Vomited doses should not be made up. If niraparib is dose reduced, participants should be instructed to continue using their current supply at their new dose. Participants must be instructed to return unused study drugs to the site at the end of each 28 day cycle. The site personnel must ensure that the appropriate dose of each study drug is administered and that the drug accountability is performed and documented.

Criteria for discontinuing or modifying allocated interventions

DOSE MODIFICATION

Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient. Treatment must be interrupted for any non-hematologic National Cancer Institute (NCI)-CTCAE

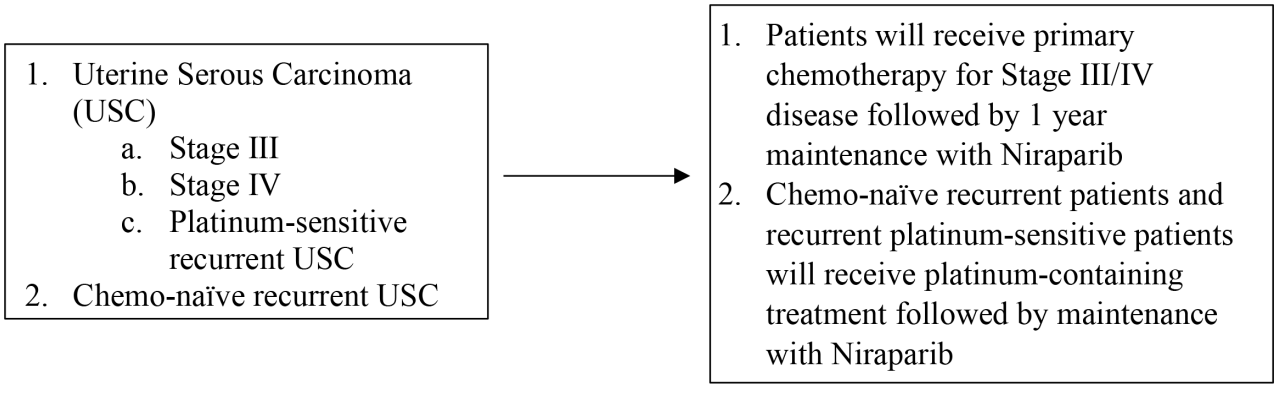

Figure 1 Study design schematic.

(v.5) Grade 3 or 4 AE which the investigator considers to be related to administration of niraparib. If toxicity is appropriately resolved to baseline or Grade 1 or less within 28 days, the patient may restart treatment with niraparib, but with a dose level reduction/modification per above criteria if prophylaxis is not considered feasible. If the event recurs at similar or worse grade, treatment should be interrupted again, and, on resolution, a further dose reduction must be made. No dose reductions below 100 mg once daily will be permitted.

Strategies to improve adherence to interventions

Study intervention compliance

The drug will be dispensed to the subject at the start of each cycle, and the subject will capture daily their intake in a diary that is provided by the research staff. Diaries will be collected at the time of visit along with the returned pill bottle. Pills should be counted and compared with the diaries for compliance.

Acquisition and accountability

The investigator or designee is responsible for maintaining accurate dispensing records of the study drug throughout the clinical study and ensuring appropriate supply, handling, storage, distribution and usage of these materials in accordance with the protocol and any applicable laws and regulations. The drug accountability log includes information including the enrolment number, amount dispensed and amount returned to the pharmacy, if applicable. Product returned to the pharmacy will be stored under the same conditions as products not yet dispensed but will be marked as 'returned' and kept separate from the products not yet dispensed. Investigative sites should follow their local standard operating procedures (SOPs) for the protocol regarding IP accountability and final disposition.

Formula, appearance, packaging and labeling

Niraparib 100 mg capsules are packaged in high-density polyethylene bottles with child-resistant plastic closures. The label text of the study treatment will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. Detailed information on the product can be found in the Niraparib Storage and Handling Guidelines. Until dispensed to the patients, the study treatment will be stored in a securely locked area, accessible to authorised personnel only.

Product storage and stability

All investigational study drug supplies in the USA must be stored at 15° to 30°C (59° to 86°F). All dispensing and accountability records will be available for review. A study reviewer will assume the responsibility to reconcile the drug accountability log. The pharmacist will dispense the study drug for each patient according to the protocol, if applicable. Unused drugs should be destroyed at the investigational site if permitted by local regulations.

Relevant concomitant care permitted or prohibited during the trial

Previous and concomitant medications

Any medication the patient takes other than the study treatment, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in electronic Case Report Form (eCRF). The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF. At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

Niraparib safety profile includes thrombocytopaenia; therefore, use caution with anticoagulation and antiplatelet drugs.

The following medications are prohibited while receiving protocol therapy:

1. Systemic anticancer or biological therapy.
2. Immunotherapy not specified in this protocol.
3. Chemotherapy not specified in this protocol.
4. Investigational agents other than niraparib.
5. Radiation therapy encompassing >20% of the bone marrow is prohibited within 2 weeks prior to Day 1 and during study treatment. Note: palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may be allowed.
6. Any surgery that involves tumour lesions. Note: administration of radiation therapy or surgery done that involves tumour lesions will be considered as disease progression at the time the procedure is performed.
7. Niraparib has the potential to induce cytochrome P450 (CYP)1A2; therefore, use caution with drugs metabolised by CYP1A2. Niraparib is a substrate for P-glycoprotein; therefore, use caution with drugs that are inhibitors or substrates of P-glycoprotein (table 1).
8. Prophylactic cytokines (ie, GCSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to the current American Society of Clinical Oncology guidelines.

BIRTH CONTROL

Participants of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation beginning with time of consent, during the study treatment and for 180 days after last dose of study treatment(s):

1. Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation.
3. Intrauterine device.

Table 1 Drugs metabolised by cytochrome P450 1A2

Inhibitors of CYP1A2		
Strong ≥ fivefold increase in AUC or >80% decrease in CL	**Moderate** ≥ twofold but <5 fold increase in AUC or 50% to 80% decrease in CL	**Weak** ≥1.25 fold but <2 fold increase in AUC or 20% to 50% decrease in CL
Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, daidzein, disulfiram, echinacea, famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
Inducers of CYP1A2		
Strong 80% decrease in AUC	**Moderate** 50% to 80% decrease in AUC	**Weak** 20% to 50% decrease in AUC
	Montelukast, phenytoin, smokers vs non-smokers	Moricizine, omeprazole, phenobarbital
Substrates of CYP1A2		
Sensitive substrates		**Substrates with narrow therapeutic range**[2]
Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine		Theophylline, tizanidine, warfarin

AUC, area under the curve; CL, drug clearance.

4. Intrauterine hormone-releasing system.
5. Bilateral tubal occlusion.
6. Vasectomised partner.
7. Sexual abstinence, if the preferred and usual lifestyle of the subject.

Provisions for post-trial care

Not applicable.

Outcomes

Primary endpoint:

PFS at 1 year; the time from niraparib treatment start until the earlier date of assessment of progression of disease or death by any cause in the absence of progression. Progression will be assessed by RECIST v. 1.1 criteria.

Secondary endpoints:

1. Progression-free survival, overall survival and overall response rate at 2 and 3 years interval from start of treatment protocol.
2. Proportion of participants with toxicities/adverse events defined per Common Terminology Criteria for Adverse Events version 5.0.
3. Mutational burden in uterine serous carcinoma and loss of heterozygosity within the tumour tissue tested.
4. QoL measures using Functional Assessment of Cancer Therapy (FACT—endometrial cancer) and European Quality of Life Scale, 5-Dimensions (EQ-5D-5L) Euroqol.

Definitions of outcomes

Response to treatment at 1 year: a subject is considered responding to treatment if at the 1 year follow-up from start of niraparib treatment, the subject is known to be alive and has not progressed (ie, RECIST=SD/PR/CR). Subjects who die or are lost to follow-up prior to 1 year will be considered treatment failures at 1 year. Note that this is like the PFS without censoring. It is important to note that all patients will be evaluated for their 1 year response status only after at least 1 year has elapsed since treatment commencement.

PFS: PFS will be analysed by examining the time from start of niraparib treatment to progression of disease (or recurrence or death), using Kaplan–Meier curves. A subject who is alive and whose disease has not progressed as of the last follow-up time will be considered 'censored', and the number of months from start of niraparib treatment to the last follow-up will be used.

OS: OS is the time from start of niraparib treatment to death. A subject who is known to be alive as of the last follow-up time will be considered 'censored', and the number of months from the start of niraparib treatment to the last follow-up will be used.

Overall response rate (ORR): ORR at 1 year from the time of niraparib initiation will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. A subject who achieves SD/PR/CR based on RECIST criteria at 1 year from start of treatment will be considered a 'responder'; a subject who is determined to have progression of disease (RECIST=PD) will be considered a 'non-responder'.

Variables to be collected

1. Outcome Variables:
   a. PFS.
   b. OS.
   c. ORR at 1 year based on RECIST Criteria Classification and CA-125 levels.
2. Toxicities and AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE V 5.0).
3. Presence of somatic mutations, HRD status (HRDpos vs HRDneg), LOH.
4. Demographics and clinical characteristics:
   a. Age.
   b. ECOG performance status

c. Histology.
d. Tumour grade
e. Stage of disease.
f. Presence/absence of lymphovascular invasion.
g. Date of diagnosis, date of recurrence, date of death, date of last follow-up.
h. Type of first-line treatment, type of treatment at recurrence.
i. RECIST Criteria classification evaluated at 3 month intervals.
j. CA125 levels measured at 1 month intervals.

5. Quality of Life Measures based on validated questionnaires, namely:
   a. FACT—endometrial cancer.
   b. EQ-5D-5L.

Participant timeline

Niraparib maintenance treatment will be given to patients for 1 year on study or until disease progression. Patient follow-up for disease status will continue for 5 years post study treatment. Patients not tolerating the treatment will stop the niraparib treatment based on the criteria described above. Patients who are benefiting from treatment will have access to their assigned treatment as long as considered acceptable by their treating physician or until they are discontinued for one of the reasons below.

Sample size

The rationale for this type of study design is based on the determination of successes as the study recruitment continues. Therefore, the study design is split into two stages, recruiting 24 patients in stage 1 and an additional 21 patients in stage 2. This design will test the null hypothesis to determine a true objective response rate of 40% or greater, with alpha=0.05. Two-step design is necessary to prevent futility of the study.

For the required sample size, assuming the current PFS rate of 20% will increase by 20% to a PFS rate of 40%. Simon's two-stage design (minimax)[15] will be used. The null hypothesis that the true response rate is p_0=0.20 will be tested against a one-sided alternative. In the first stage, n_1=24 patients will be accrued. If there are r_1=5 or fewer responses in these n_1=24 patients, the study will be stopped. Otherwise, (n-n_1=45–24=21) 21 additional patients will be accrued for a total of n=45. The null hypothesis will be rejected if (r_2+1) 14 or more responses are observed in 45 patients. This design yields a type I error rate of alpha=0.05 and power of 0.90 when the true response rate is 0.40.

Populations for analyses

The intent-to-treat (ITT) population will be defined as all patients (female subjects over the age of 18) with stage III, stage IV, platinum-sensitive recurrent USC or chemonaïve recurrent USC who received niraparib maintenance for any time period on trial. The ITT population is the primary analysis population for the efficacy analysis.

Efficacy will also be analysed by using the following outcomes:

1. One-year PFS (primary outcome).
2. PFS at the 2 and 3 year intervals from the start of treatment protocol, OS and ORR at 1 year for measurable disease (secondary outcomes).

Recruitment

In order to achieve adequate recruitment, multiple sites were opened within a major healthcare network as well as an additional outside institution.

Assignment of interventions: allocation

Sequence generation

Not applicable. There is no allocation of interventions as all participants receive the same treatment.

Concealment mechanism

Not applicable. There is no allocation of interventions as all participants receive the same treatment. No placebo option available.

Implementation

Not applicable. There is no generation of allocation of interventions or anyone to assign participants to interventions; all participants receive the same treatment.

ETHICS AND DISSEMINATION

Assignment of interventions: blinding

Who will be blinded

Not applicable. There is no blinding of interventions, as all participants receive the same treatment.

Procedure for unblinding if needed

Not applicable. There is no blinding of interventions, as all participants receive the same treatment.

Data collection and management

Plans for assessment and collection of outcomes

All data will be collected and stored in a RedCap Database.[15–17] Data will be collected from recruitment to last follow-up as described in the protocol. Data quality will be ensured by regular checks by PI and a quarterly monitoring committee. Study instruments used are externally validated and include EQ-5D-5L and FACT-En Questionnaires.[18 19]

Plans to promote participant retention and complete follow-up

After screening and the consent process, patients will be seen during scheduled monthly visits. Patient retention will be ensured by regular visits with the research team and physicians/nurse. Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. Screen failures do not count towards enrolment. All slots are to be filled by complete enrolment on subjects who are enrolled.

The following actions are taken if a participant fails to return to the clinic for a required study visit:

The site will attempt to contact the participant and reschedule the missed visit as per protocol and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Data management

The REDCAP electronic data capture system will be used to manage data collection. Each participating investigator will ensure the accuracy, completeness and timeliness of the data reported to the principal investigator (PI). De-identified data will be collected at screening, eligibility, Cycle 1, Cycle 3, Cycle 6 and every three cycles thereafter to conduct remote monitoring during the study quarterly.

Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, staff and sponsor. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party without prior written approval of the sponsor, and all research activities will be conducted in as private a setting as possible. Study participant research data, which is used for the purpose of statistical analysis and scientific reporting, will be transmitted to and stored securely, and individual participants' research data will be identified by a unique study identification number.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Tumour genetic testing will be performed using the commercially available Foundation Medicine testing platform to identify the appropriate genetic mutations. Clinical specimens will not be stored following testing.

Statistical methods

Statistical methods for primary and secondary outcomes

This Phase II clinical trial will employ a Simon two-stage *minimax* design to test the null hypothesis that the 1 year response rate is <20% (which would not be clinically meaningful) versus the alternative hypothesis that the 1 year response rate is ≥40%. A treatment 'success'will be defined as the patient being alive and progression-free at 1 year post-treatment. The largest proportion of success where the proposed treatment regimen would be considered ineffective in this patient population is 20%, whereas the smallest proportion of success that would warrant subsequent (phase III) studies with the proposed regimen in this population is 40%.

The following two-stage *minimax* design (Simon, 1989) uses up to 45 patients to test the null hypothesis that the true success proportion in each patient population is at most 20%. In Stage 1, 24 patients will be enrolled into the study. If five or fewer successes are observed in the first 24 evaluable patients, we will consider the treatment strategy ineffective in this patient population and terminate the study for futility. Otherwise, if the number of successes in these 24 patients is at least six or more, we will proceed to Stage 2.

In the second stage, 21 additional patients will be enrolled, for a total of 45 subjects. If 13 or fewer successes are observed in the combined group of 45 evaluable patients, we will consider this treatment regimen ineffective in this patient population. If 14 or more successes are observed in the combined group of 45 evaluable patients, then the proposed treatment regimen will be considered effective and a candidate for further larger clinical trials.

This design corresponds to testing the null hypothesis that the true objective response rate is 20% or less versus the alternative hypothesis that the true response rate is 40% or greater, with alpha=0.05 and power=0.90.

The primary objective of this trial is to determine the efficacy of the proposed niraparib regimen in the population of patients with stage III, stage IV or recurrent USC. Efficacy will be evaluated using PFS at 1 year. The proportion of responders will be estimated by calculating the proportion of subjects who are known to be alive (and have not progressed) at 1 year from treatment commencement. Subjects who die or are lost to follow-up prior to 1 year will be considered treatment failures at 1 year. Exact 95% CIs for the proportion will be computed. PFS will be calculated at the one interval from the start of the treatment protocol using the Kaplan–Meier Product Limit Method.

PFS, OS and ORR at 2 and 3 years intervals from the start of treatment protocol. PFS at the 2 and 3 years intervals from the start of the treatment protocol will be calculated using the Kaplan–Meier Product Limit Method. Subjects who are known to have not progressed as of the last follow-up will be censored. OS will be analysed using the Kaplan–Meier Product Limit Method. ORR will be estimated, along with the corresponding exact 95% CIs. ORR will be measured in patients with measurable disease at the time of treatment initiation. ORR will evaluate for treatment response using CR and PR.

Safety and toxicities of treatment will be assessed in patients receiving the planned treatment. Toxicities will be tabulated and graded according to the NCI CTCAE V 5.0. Proportions of subjects experiencing specific toxicities will be estimated using standard methods for proportions; exact 95% CIs will be computed. The prevalence of somatic mutations, HRD mutations and LOH will be estimated in these patients with USC, and exact 95% CIs will be computed.

Repeated measures analysis of variance will be carried out to examine the patterns of change in QoL)measures FACT—endometrial cancer, EQ-5D-5L) over time, that is, to determine if QoL generally improves, worsens or remains the same. Tukey-adjusted pairwise comparisons between times will be carried out. Time-to-symptom worsening will be analysed using survival analysis techniques (Kaplan–Meier, Cox Regression).

Interim analyses

Interim analyses will be performed after Phase 1 patient recruitment of 24 patients. If five or fewer successes are observed in these first 24 evaluable patients, we will consider the treatment strategy ineffective in this patient population and terminate the study for futility. The sponsor investigator retains the final decision to terminate the trial. Otherwise, if the number of successes in these 24 patients is at least six (six or more), we will proceed to Phase 2 patient recruitment, which is an additional 21 patients.

Methods for additional analyses (eg, subgroup analyses)

There is no subgroup or adjusted analyses.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

All patients will be considered evaluable if they received any drug treatment for the ITT analysis.

Plans to give access to the full protocol, participant level data and statistical code

The protocol is accessible to the public on clinicaltrials.gov. The full protocol and statistical code will be made available upon request.

Oversight and monitoring

Composition of the coordinating center and trial steering committee

The trial steering committee is composed of research coordinators, research nurses and a study team. The PI provides full oversight and is available for all questions/concerns. The PI runs biweekly meetings to review all patients on study with the study team and reviews potential patients at a weekly tumor board. The data management team enters data with PI oversight.

Composition of the data monitoring committee, its role and reporting structure

A Data and Safety Monitoring Board (DSMB) is established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participating patients in the study. The DSMB is independent from the sponsor and competing interests. The composition of the DSMB consists of three independent and qualified individuals, including one biostatistician and two physicians. The DSMB is tasked with making a recommendation to the PI based on their review to continue or stop the trial based on their assessment of efficacy and safety information. Members will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimise perceived conflict of interest. The DSMB will meet every 6 months to review monitored data and to make a formal safety determination on whether the study may continue. The DSMB will issue a written and signed report describing what they reviewed, on what date, and the result of their review to the PI, the institutional monitor and the institutional PRMC/IRB committees.

Adverse event reporting and harms

All adverse events occurring from the time of signing the main ICF through study treatment discontinuation visit will be documented in the eCRF. Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the medical history or other appropriate page. SAEs will be collected from the time of signing the main ICF through treatment discontinuation. New SAEs (including deaths) will be collected for 30 days after treatment discontinuation. AEs will be assessed using CTCAE v.5.0. AEs of special interest for niraparib will be tracked, including MDS, AML, secondary cancers and pneumonitis. All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilised with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

Frequency and plans for auditing trial conduct

Regulatory and study oversight considerations

This investigator-initiated trial is being conducted according to Good Clinical Practice (GCP) guidelines. Northwell Cancer Institute staff conducted a study initiation visit to verify the qualifications of the investigator, inspect the facilities and inform the investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. PI meets weekly with each clinical site to ensure that the safety of the study is monitored adequately. The investigator makes all appropriate safety assessments on an ongoing basis. The DSMB reviews safety information as it becomes available throughout the study and meets every 6 months. All aspects of the study will be carefully monitored with respect to GCP and SOPs for compliance with applicable government regulations. The study monitor will have access to all records necessary to ensure the integrity of the data and will monitor the progress of the study with the investigator or designee every 3 months.

Clinical monitoring

Monitoring and auditing procedures will be followed, to comply with GCP guidelines. Remote monitoring of the CRFs for completeness and clarity, cross-checking with source documents and clarification of administrative matters will be performed. The study will be monitored by non-participant study research staff or their designee. Monitoring will be done remotely or onsite to review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent review of the data and by communications (letter, telephone and fax). All unused study treatment and other study materials will be returned to the sponsor after the clinical phase of the study has been completed.

Quality assurance and quality control

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualised quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The data monitors will verify that the clinical trial is conducted, and data are generated and biological specimens are collected, documented (recorded) and reported in compliance with the protocol, International Conference on Harmonisation (ICH) GCP and applicable regulatory requirements (eg, Good Laboratory Practices, Good Manufacturing Practices).

The investigational site will provide direct access to all trial-related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Plans for communicating important protocol amendments to relevant parties (eg, trial participants, ethical committees)

The trial will be carried out in accordance with ICH GCP and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312 and/or 21 CFR Part 812). The protocol, ICFs, recruitment materials and all participant materials were submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form was obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. Any amendment to the protocol will be communicated to all investigators and active research staff. All investigators and staff are trained on any changes. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Dissemination plans

Any information regarding publication of study results will be approved by the sponsor Iivestigator. There are no publication restrictions from the study sponsor. Results will be published and available publicly upon completion of the study.

DISCUSSION

USC is a rare subtype of endometrial cancer that accounts for up to 40% of endometrial cancer-related deaths. The literature reports that USC biologically mimics serous carcinoma of the ovary and has a high probability for nodal and intra-peritoneal spread. Given the published benefits of PARP inhibitors in patients with ovarian cancer, this trial was initiated.[13 14] There are currently several FDA approvals for the use of immunotherapy in endometrial cancer. However, despite these approvals, there remain gaps in the treatment of those patients who fall outside of the approval guidelines. Both the RUBY and GY018 studies investigated the use of immunotherapy in conjunction with standard chemotherapy in advanced or recurrent endometrial cancer. As previously mentioned, these studies did include serous histology; however, this group only represented a small portion of patients in the studies.[6 20] The DESTINY-PanTumor01 specifically investigated solid tumours with HER2 overexpression (IHC 2+and 3+).[7] Although histological subtypes were not explicitly reported, these results have been adapted in the treatment of serous endometrial cancers showing overexpression of HER2. The rate of HER2 overexpression in endometrial cancer is quoted widely in the literature, with some studies quoting between 4% and 70%, with a significant portion of these being serous subtype.[21] Our study includes all molecular subtypes of endometrial serous carcinoma with no restrictions based on HER2 or MMR/MSI status. This is in contrast with the above-mentioned studies and approvals allowing for a broader patient population. For those patients who fall out of the previously studied molecular subgroups, our study provides an option for treatment in a population with aggressive disease. Although the current literature has shifted its focus to patients specifically with HRD ovarian cancers, the uterine cancer literature is still lacking. This has driven the development of this investigator-initiated trial with a unique focus on a rare uterine cancer: USC. In the event of a positive study outcome, we will aim to further identify patients who most benefit from PARP inhibitors and the sequence of therapy in these patients. Our trial was initiated during the COVID-19 pandemic, and as a result, the trial recruitment was initially lagging. Currently, we

have had the opportunity to recruit additional sites to expand the cohort of patients receiving this trial. As with all rare tumours, trial recruitment is limited, and we will continue to champion recruitment efforts.

Trial status

Protocol Version 5.0, Date 10/13/2022. Until the date of submission of this protocol, we have recruited 20 patients. Recruitment began in January 2020, and we anticipate completion of recruitment by June 2026. Study recruitment was originally halted due to the COVID-19 pandemic. Once recruitment opened, we added additional sites within Northwell Health and an outside site at Rutgers Cancer Institute of New Jersey and are currently adding additional sites within the Rutgers system. Screening will occur at each site at multiple time points throughout each week.

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Funding This work was supported by funding from GlaxoSmithKline.

Competing interests MS and ND are employed at the Foundation Medicine Inc Stock/Ownership-Roche Ltd. Author Frimer received funding for the study by GlaxoSmithKline. Otherwise, no financial and non-financial competing interests to report for all other investigators.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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