Essai Clinique

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Titre	A Phase 1B/2 Multicohort Umbrella Study to Evaluate the Safety and Efficacy of Novel Treatments And/Or Combinations of Treatments in Participants With Ovarian Cancer
Protocole ID	OPAL
ClinicalTrials.gov ID	NCT03574779
Type(s) de cancer	Ovaire
Phase	Phase I-II
Type étude	Clinique
Médicament	Niraparib, TSR-042, bévacizumab, carboplatine et paclitaxel
Institution	CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL
Ville	
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Statut	Fermé
But étude	This study will evaluate the efficacy and safety of niraparib and novel treatment combinations of niraparib as described within each cohort-specific supplement in participants with ovarian, fallopian tube, or primary peritoneal cancer. Cohort A (single arm) includes participants with recurrent ovarian cancer. Cohort B will not be initiated. Cohort C (randomized-2 arms) includes participants with newly diagnosed ovarian cancer.
Critères d'éligibilité	Participant must be female greater than or equal to (>=)18 years of age, able to understand the study procedures, and agree to participate in the study by providing written informed consent. • Participants must have the following histologic diagnosis unless otherwise specified in a cohort-specific supplement: 1. Phase 2 cohorts: Participant has histologically diagnosed high-grade recurrent epithelial (that is [i.e.], serous, endometrioid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer or carcinosarcoma of the ovary. Participant with high-grade mixed histology is also eligible. 2. For the Phase 1B components: Participant has histologically diagnosed gynecologic malignancy (i.e., any cancer that started in a woman's reproductive system). Gynecologic malignancies include cervical cancer; endometrial cancer; vaginal cancer; vulvar cancer; high-grade recurrent epithelial (i.e., serous, endometrioid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer; or advanced carcinosarcoma of the ovary. Participant with high-grade mixed histology is also eligible. • The allowed number of prior lines of anticancer therapy for primary cancer will be specified in each cohort-specific supplement. Treatment with hormonal agents alone are not counted in the number of lines of therapy. Treatment with single-agent bevacizumab or PARP inhibitors given as maintenance is not counted as a separate line of therapy. If a therapeutic regimen is modified or changed for a reason other than lack of response or PD (such as allergic reaction, toxicity, or drug availability), this is not counted as a separate line of therapy. • Phase 2 cohorts: Participant must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1. • Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. • Participant has adequate organ function, defined as follows: 1. Absolute neutrophil count >=1500 per microliter (/mcL), without growth factor support (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor administration is not permitted within 2 weeks prior to screening). 2. Platelets >=100,000/mcL without platelet transfusion support within 2 weeks prior to

screening.
3. Hemoglobin >=9 grams/deciliter (g/dL) without transfusion or growth factor (recombinant erythropoietin) within 2 weeks of screening.
4. Serum creatinine less than or equal to (<=)1.5 times (*) upper limit of normal (ULN) or calculated creatinine clearance >=50 milliliter per minute (mL/min) using Cockcroft-Gault equation.
5. Total bilirubin <=1.5* ULN, except in participants with Gilbert's syndrome. Participants with Gilbert's syndrome may enroll if direct bilirubin is <=1.5* ULN.
6. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <=2.5* ULN, unless liver metastases are present, in which case they must be <=5* ULN.
7. International normalized ratio or prothrombin time (PT) <=1.5* ULN unless participant is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants.
8. Activated partial thromboplastin time (aPTT) <=1.5* ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants. Participant with known lupus anticoagulant and elevated PTT may be eligible on a case-by-case basis after discussion with the Sponsor's Medical Monitor.

- Participant is not pregnant or breastfeeding, and at least 1 of the following conditions apply:
  1. Is not a woman of childbearing potential (WOCBP), or
  2. Is a WOCBP using a contraceptive method that is highly effective (with a failure rate of less than [<]1 percent [%] per year), with low user dependency, during the treatment period and for at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relation to the first dose of study treatment.
     - A WOCBP must have a negative pregnancy test (highly sensitive urine test or serum test as required by local regulations) within 72 hours before the first dose of study treatment. If a urine test cannot be confirmed as negative (for example [e.g.], an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
     - Additional requirements for pregnancy testing during and after study treatment as per protocol.
- Participant must provide sufficient tumor tissue samples based on requirements defined in each cohort-specific supplement.

Inclusion criteria specific to Cohort A:

- Participants must be resistant to the most recent platinum-based therapy, defined for the purpose of this protocol as progression within 6 months from completion of a minimum of 4 cycles of platinum-containing therapy. This should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing disease progression. Participants with primary platinum-refractory disease as defined by those who progressed during or within 4 weeks of completion of first platinum-based chemotherapy are not eligible.
- Participant must not have received any prior therapy for ovarian cancer with a PARP inhibitor
- Participant has had 1 to 2 prior lines of anticancer therapy for ovarian cancer
- Participant is able to take oral medications.

Inclusion criteria specific to Cohort C:

- Participant has newly diagnosed Stage III or IV ovarian, fallopian tube, or primary peritoneal cancer according to the International Federation of Gynecology and Obstetrics staging criteria.
- Participant must provide sufficient tumor tissue at Prescreening and agree to undergo a central HRD tumor testing using a fully validated assay. The tumor must be HRd as per central HRD tumor testing. If central testing does not confirm tumor HRd, the participant will not be eligible for the study.
  1. Participants with documented germline breast cancer gene (BRCA)1/2 deleterious or suspected deleterious mutations by approved test (e.g., BRAC Analysis companion diagnostic [CDx]) will be eligible but will require central HRD testing. Participants with local, academic, or university-based germline BRCA1/2 testing will not be allowed to enroll without results of central HRD test.
  2. All participants must agree to provide tumor tissue collected from IDS.
  3. Participant must provide 2 formalin-fixed paraffin-embedded tissue blocks (or slides if blocks are not available) with sufficient tumor content (as confirmed by the sponsor's designated central and/or testing laboratory) for central HRD testing at Prescreening and for exploratory biomarker testing at Prescreening or Screening. If sufficient tumor tissue is provided at Prescreening, participants do not need to provide additional tissue at Screening.
- Participant must have completed 1 run-in cycle of carboplatin-paclitaxel and not experienced disease progression after this treatment. Completion is defined as receiving >=50% of the prescribed dose of therapy within 5 weeks.
- Participant must not have known contraindication or uncontrolled hypersensitivity to carboplatin and paclitaxel and their excipients and no known pre-existing conditions that would preclude treatment with these agents.
- Participant must not have known contraindication or uncontrolled hypersensitivity to niraparib and its excipients.

- Participant must not have symptomatic ascites or pleural effusions as defined by the following criterion: presence of fluid in the abdominal or pleural cavities requiring removal within 1 week prior to signing the informed consent.
- Participant must agree to complete patient-reported outcomes (PRO) and work productivity questionnaires throughout the study.

Critères d'exclusion

- Participant has not recovered (i.e., to Grade <=1 or to Baseline) from prior chemotherapy-induced adverse events (AEs).
- Participant has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy exceeding an equivalent of prednisone 10 mg daily or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
- Participant is currently participating in a treatment study or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment.
- Participant has received prior systemic anticancer therapy including cytotoxic chemotherapy, PARP inhibitor, immune checkpoint inhibitors, hormonal therapy given with the intention to treat cancer, or biological therapy within 3 weeks of the first dose of study treatment. This washout period is required to ensure prior therapy is not confounding the toxicity profile of the investigational study drug or study drug combinations in cohorts.
- Participant has received live vaccine within 14 days of planned start of study therapy.
- Participant has symptomatic uncontrolled brain or leptomeningeal metastases. Participant who has untreated brain metastases and who is not symptomatic may enroll if the Investigator feels that treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Participant with spinal cord compression may be considered if she has received definitive treatment for this and evidence of clinically stable disease (SD) for 28 days prior to the first dose of study treatment.
- Participant had major surgery within 4 weeks of starting the study or participant has not recovered from any effects of any major surgery.
- Participant has a known additional malignancy that progressed or required active treatment within the last 2 years because reoccurrence of another malignancy would confound interpretation of ORR by RECIST v1.1 criteria. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cancer that is considered to be low risk for progression by the investigator.
- Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. These include, but are not limited to, Coronavirus disease 2019 (COVID-19), significant cardiovascular disease, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, and any psychiatric disorder that prohibits obtaining informed consent.
- Participant has a history or current evidence of any condition, therapy or laboratory abnormality that might confound the results of the study, might interfere with the participant's participation for the full duration of the study treatment, or is not in the best interest of the participant to participate.
- Participant has known active hepatitis B (hepatitis B surface antigen reactive) or hepatitis C (hepatitis C virus ribonucleic acid [qualitative] is detected).

Cohort A-specific Exclusion Criteria:

- Participant has known hypersensitivity to TSR-042, bevacizumab, niraparib, their components, or their excipients.
- Participant has a known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
- Participant has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
- Participant received prior treatment with an anti-PD-1 or anti-PD-L1 agent.
- Participant has received prior treatment with anti-angiogenic therapy with the exception of bevacizumab. (Participants who received prior bevacizumab are eligible only if they did not discontinue bevacizumab due to toxicity, as established by the Investigator).
- Participant has bowel obstruction, had bowel obstruction within the past 3 months, or is otherwise judged by the Investigator to be at high risk for bowel obstruction related to the underlying disease. Participant has any history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscesses. Evidence of recto-sigmoid involvement by pelvic examination or significant bowel involvement on computed tomography scan.
- Participant has proteinuria as demonstrated by urine protein:creatinine ratio >=1.0 at screening or urine dipstick for proteinuria >=2 (Participants discovered to have >=2 proteinuria on dipstick at Baseline should undergo 24-hour urine collection and must demonstrate <2 gram of protein in 24 hours to be eligible).
- Participant is at increased bleeding risk due to concurrent conditions (e.g., major injuries or surgery within the past 28 days prior to start of study treatment, history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).
- Participant has a history of recent major thromboembolic event defined as follows: Pulmonary embolism diagnosed within 3 months of enrollment; and Lower extremity deep venous thrombosis diagnosed within 3 months of enrollment.

Exclusion criteria specific to Cohort C:

- Participant has low-grade or Grade 1 epithelial ovarian cancer (OC) or mucinous, germ cell, transitional cell, carcinosarcoma, or undifferentiated tumor.
- Participant has contraindications to surgery.
- Participant has a bowel obstruction by clinical symptoms or computed tomography (CT) scan, subocclusive mesenteric disease, abdominal or gastrointestinal fistula, gastrointestinal perforation, or intra-abdominal abscess.
- Participant has any known history or current diagnosis of MDS or AML
- Participant is at increased bleeding risk due to concurrent conditions (e.g., major injuries or major surgery within the past 28 days prior to the start of study treatment and/or history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).
- Participant is immunocompromised. Participants with splenectomy are allowed. Participants with known human immunodeficiency virus (HIV) are allowed if they meet all of the following criteria: i) Cluster of differentiation 4-positive T cell count >=350/microliters and viral load <400 copies/mL ii) No history of acute immunodeficiency syndrome (AIDS)-defining opportunistic infections within 12 months prior to enrollment iii) No history of HIV-associated malignancy for the past 5 years iv) Concurrent antiretroviral therapy as per the most current National Institutes of Health Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV started greater than (>)4 weeks prior to study enrollment
- Participant received prior treatment for high-grade non-mucinous epithelial ovarian, fallopian tube, or peritoneal cancer (e.g., prior surgery, immunotherapy, anticancer therapy [with the exception of 1 run-in cycle of carboplatin-paclitaxel], or radiation therapy).
- Participant has an active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy is not considered a form of systemic therapy (e.g., thyroid hormone or insulin).
- Participant is unable to swallow orally administered medication or has a gastrointestinal disorder likely to interfere with absorption of the study medication.
- Participant received whole blood transfusions in the 2 weeks prior to entry to the study (packed red blood cells and platelet transfusions are acceptable outside of 2 weeks prior to treatment.