A RANDOMIZED, DOUBLE-BLIND, PHASE 3 COMPARISON OF PLATINUM-BASED THERAPY WITH TSR 042 AND NIRAPARIB VERSUS STANDARD OF CARE PLATINUM-BASED THERAPY AS FIRST LINE TREATMENT OF STAGE III OR IV NONMUCINOUS EPITHELIAL OVARIAN CANCER

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This study has been transitioned to CTIS with ID 2024-510605-28-00 check the CTIS register for the current data. Primary Objective• To compare the progression free survival (PFS) of programmed death-ligand 1 (PD-L1) positive patients with Stage III...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ovarian and fallopian tube disorders
Study type	Interventional

Summary

ID

NL-OMON54558

Source
ToetsingOnline

Brief title
FIRST

Condition

- Ovarian and fallopian tube disorders

Synonym
adenocarcinoma; ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: TESARO, Inc.
Source(s) of monetary or material Support: TESARO;Inc.

Intervention

Keyword: Dostarlimab (TSR-042), Niraparib, ovarian cancer, Phase III

Outcome measures

Primary outcome

Efficacy Analysis

Primary Efficacy Endpoint

This study has dual primary efficacy endpoints: PFS in PD-L1 positive patients and PFS in all patients. The primary efficacy endpoint PFS is defined as the time from the date of treatment randomization to the date of first documentation of progression or death by any cause in the absence of progression, whichever occurs first, as determined by the Investigator. Progression will be assessed by RECIST v.1.1 criteria based on Investigator*s assessment.

Exploratory Efficacy Endpoint

The following exploratory efficacy endpoint will be evaluated:

• DpOR defined as the maximal amount of tumor shrinkage observed. DpOR will be assessed per RECIST v1.1 and irRECIST criteria in patients with measurable

disease.

• PFS in Arm 1 and Arm 2 BRCAwt patients who receive bevacizumab will be assessed per RECIST v1.1.

• PFS per Investigator-assessed RECIST v.1.1 criteria in patients with HRR/HRD status

Interim Analysis

Planned periodic safety analyses will be conducted by the Independent Data Monitoring Committee (IDMC) after 24 randomized patients have completed at least 2 cycles of treatment. Details of safety analyses are placed in the IDMC charter.

A second safety analysis will occur when approximately 60 patients in Arm 3 have completed at least 2 cycles of the maintenance treatment. After that, periodic safety review will be conducted every 6 months as determined by the IDMC.

Biomarker Analysis

Biomarkers related to ovarian cancer, PARP inhibition, and PD 1 therapy may be evaluated (eg, DNA repair deficiency, PD-L1 expression, and immune biomarkers).

Immunogenicity Analysis

Blood samples for the determination of dostarlimab ADAs will be part of the same blood collections as those taken for the PK assessments. ADAs will be analyzed in a tiered approach using electro chemiluminescence (ie, Screening,

confirmation, titer, and neutralizing antibody assay), if appropriate.

PK Analysis

Blood samples for PK will be collected at the time points specified in the sampling schedule.

Parameters of interest are minimum observed concentration (Cmin) and maximum observed concentration (Cmax) for niraparib and dostarlimab.

Secondary outcome

Secondary Efficacy Endpoints

For both PD-L1 positive and all patients, the following secondary efficacy endpoints will be evaluated:

• BICR determined PFS per RECIST v1.1

• PFS, per irRECIST criteria based on Investigator*s assessment

• OS, as measured from the date of randomization to the date of death by any cause

• The observed change from baseline and time to symptom worsening in the EQ 5D 5L, EORTC QLQ C30, and EORTC QLQ OV28 HRQoL assessments

• TFST, defined as the date of randomization in the current study to the start date of the first subsequent anticancer therapy or death

• TSST, defined as the date of randomization in the current study to the start date of the second subsequent anticancer therapy or death

• PFS2, defined as the time from randomization to the earlier date of assessment of progression on the next anticancer therapy following study treatment or death by any cause as assessed by the Investigator

• ORR, defined as the percentage of patients with complete response (CR) or partial response (PR) on study treatment as assessed by RECIST v.1.1 criteria for patients with measurable disease. ORR will also be assessed per irRECIST criteria.

• pCR rate, per Investigator assessment, defined as the rate of pathologic complete response as assessed by the evaluation of residual microscopic disease at the time of surgery in neoadjuvant patients

• DOR, defined as the time from first documentation of CR or PR until the time of first documentation of PD as assessed by RECIST v.1.1, or death by any cause in the absence of progression, whichever occurs first. DOR will also be assessed per irRECIST criteria.

• DCR, defined as the proportion of patients with a best overall response of CR, PR, or stable disease, as assessed by RECIST v.1.1 criteria. DCR will also be assessed per irRECIST criteria.

• MPFS, defined as the time from the date of the first maintenance period dose to the date of first documentation of progression or death by any cause in the absence of progression, whichever occurs first, as determined by the Investigator. Progression will be assessed by RECIST v.1.1 criteria. MPFS will also be assessed per irRECIST criteria.

Safety Analysis (Secondary Endpoint)

The core safety analyses will be based on the Arm 2 and Arm 3 safety populations. In addition, a safety analysis will also be performed on the Arm 1 safety population for supportive analysis.

Safety will be evaluated based on the incidence of TEAEs, SAEs, treatment discontinuations or dose delays or dose reductions due to AEs, irAEIs, changes in ECOG performance status, changes in clinical laboratory results (hematology and chemistry), vital sign measurements, observations during physical examination, and use of concomitant medications. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities coding system.

Study description

Background summary

Please see the protocol, section 1. Introduction.

Study objective

This study has been transitioned to CTIS with ID 2024-510605-28-00 check the CTIS register for the current data.

Primary Objective
• To compare the progression free survival (PFS) of programmed death-ligand 1 (PD-L1) positive patients with Stage III or IV high-grade nonmucinous epithelial ovarian cancer treated with platinum-based combination therapy, dostarlimab, and niraparib to standard-of-care (SOC) platinum-based combination therapy.
• To compare the PFS of all patients with Stage III or IV high-grade nonmucinous epithelial ovarian cancer treated with platinum-based combination therapy, dostarlimab, and niraparib to SOC platinum-based combination therapy
The primary PFS analysis will be based upon the Investigator*s assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 criteria.

Secondary Objectives
For PD-L1 positive patients and all patients, secondary objectives will evaluate:
• Overall survival (OS)
• Blinded Independent Central Review (BICR)-determined PFS per RECIST v1.1
• Safety and tolerability of all treatments
• Health related quality of life (HRQoL)

• Time to first subsequent therapy (TFST)
• Time to second subsequent therapy (TSST)
• Time from treatment randomization to the earliest date of assessment of progression on the next anticancer therapy following study treatment or death by any cause (PFS2)
• Objective response rate (ORR) per RECIST v.1.1 for patients with measurable disease at baseline scan
• Disease control rate (DCR) per RECIST v.1.1
• Maintenance progression free survival (MPFS) per RECIST v.1.1
• pharmacokinetics (PK) and immunogenicity of dostarlimab
• PK of niraparib

Exploratory Objectives
• To measure biomarkers related to ovarian cancer, poly (adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibition, and anti programmed death 1 (anti PD 1) therapy, including deoxyribonucleic acid (DNA) repair pathways and immune checkpoint pathways
• To compare the PFS, per Investigator-assessed RECIST v.1.1 criteria, of all Arm 1 versus Arm 2 patients with wild-type breast cancer susceptibility gene (BRCAwt) who receive bevacizumab
• To evaluate PFS per Investigator-assessed RECIST v.1.1 criteria in patients with homologous recombinant repair (HRR)/ homologous recombinant deficiency (HRD) status

Study design

This is a global, multicenter, randomized, double-blind, controlled Phase 3 study in patients with newly diagnosed, Stage III or IV high-grade nonmucinous epithelial ovarian, fallopian tube, or peritoneal cancer (collectively referred to as *ovarian cancer*). The currently recommended SOC chemotherapy therapy for the first line treatment of Stage III or IV ovarian cancer is a combination of paclitaxel carboplatin, with or without concurrent and maintenance bevacizumab. Throughout this document *SOC* should be understood to mean paclitaxel-carboplatin ± bevacizumab. The use of bevacizumab must be determined prior to randomization.

The study is open to patients with inoperable ovarian cancer, patients who have macroscopic residual disease at the end of the primary debulking surgery (PDS) and have recovered from PDS and patients for whom platinum based combination neoadjuvant chemotherapy (NACT) is planned. Patients with Stage IIIC disease that has been completely resected (also known as complete cytoreduction score of 0 [CC0] are eligible if the following criteria is present: aggregate >5 cm extra-pelvic disease during PDS as assessed by the Investigator. The use of bevacizumab is optional and permitted if considered SOC per local treatment guidelines and/or practices.

All eligible enrolled patients will receive SOC during the Cycle 1 Chemotherapy

Run-In Period before randomization to study treatment at Cycle 2. Treatment Arm 1 consists of SOC and intravenous (IV) dostarlimab-placebo followed by oral niraparib-placebo and IV dostarlimab-placebo in the maintenance phase of treatment. Arm 2 consists of SOC and IV dostarlimab-placebo followed by oral niraparib and IV dostarlimab-placebo maintenance therapy. Arm 3 consists of SOC and IV dostarlimab followed by oral niraparib and IV dostarlimab maintenance therapy.

Randomization will be stratified by concurrent bevacizumab use, homologous recombinant repair (HRR) mutation status (ie, BRCA-mutated [BRCAmut], BRCA wild type HRR positive [BRCAwt HRRpos], and BRCA wild type HRR negative or not determined [BRCAwt HRRneg/not determined]), and disease burden as defined by Stage III cancer with residual disease <1 cm (ie, yes or no). To minimize bias, patients, Investigators, and the site investigative staff will be blinded to HRR status and treatment assignment.

This study is designed to enable rapid adaptation to evolving treatment paradigms and provide Investigators with the current SOC for patients with advanced ovarian cancer This ensures that study participants will have access to contemporaneous SOC with or without investigational treatment while maintaining the integrity of the study. Full details on adaptations to the study design are located in the protocol.

In Amendment 3, dated 17 July 2019, subsequent to data made available from the SOLO-1 study (a randomized Phase 3 study of olaparib maintenance treatment versus placebo following first-line SOC therapy in patients with BRCA-mutated Stage III/IV ovarian cancer), where it was reported that PARP inhibitor maintenance provided significant clinical benefit in this population, newly enrolled patients with BRCAmut in this study were randomized to Arm 2 or Arm 3 only. There was no change to patients with BRCAwt status; they continued to be randomized to Arm 1, Arm 2, or Arm 3. Arm 1 BRCAmut patients who were in the Chemotherapy Treatment Period when the amendment was implemented completed the 6 cycles of chemotherapy. Following completion of the Chemotherapy Treatment Period and confirmation of adequate hematologic parameters, these patients were allowed to start niraparib maintenance therapy as *post-study anticancer treatment* at the Investigator*s discretion. Arm 1 BRCAmut patients who were in the Maintenance Treatment Period when the amendment was implemented were allowed to start niraparib maintenance therapy as "post-study anticancer treatment" if the time after Cycle 6 Day 1 of the Chemotherapy Treatment Period was <=12 weeks. In order to facilitate this adaptation, Investigators were unblinded for Arm 1 BRCAmut patients enrolled prior to implementation of this amendment.

Recently, results from PRIMA, a randomized Phase 3 study of niraparib maintenance therapy or placebo following first-line platinum therapy for Stage III/IV ovarian cancer, and PAOLA-1, a randomized Phase 3 study of olaparib maintenance therapy or placebo added to bevacizumab maintenance treatment

following first-line platinum therapy for Stage III/IV ovarian cancer became available. The hazard ratio (HR) of 0.62 and 0.59, respectively, demonstrated that a PARP inhibitor with or without bevacizumab prolonged PFS in all patients with advanced ovarian cancer after response to first-line platinum-based chemotherapy. Therefore, the currently recommended SOC therapy for the maintenance treatment of Stage III or IV ovarian cancer is a combination of paclitaxel carboplatin with or without bevacizumab, and a PARP inhibitor.

As a result, following Sponsor and Steering Committee discussions, patients will not be enrolled into Arm 1 after Amendment 4 is approved at each site. Patients in Arm 1, Chemotherapy Treatment Period who are receiving bevacizumab when Amendment 4 is implemented, may continue the 6 cycles of chemotherapy. Following completion of the Chemotherapy Treatment Period and confirmation of adequate hematologic parameters, those patients may start bevacizumab maintenance therapy at the Investigator*s discretion. Patients in Arm 1, Maintenance Treatment Period who are receiving bevacizumab when Amendment 4 is implemented may continue bevacizumab maintenance therapy at the Investigator*s discretion. Investigators will remain blinded for those patients enrolled in Arm 1 and receiving bevacizumab at the time of implementation of Amendment 4. Patients in Arm 1, Chemotherapy Treatment Period not receiving bevacizumab when Amendment 4 is implemented, may continue the 6 cycles of chemotherapy. Following completion of the Chemotherapy Treatment Period and confirmation of adequate hematologic parameters, those patients may start niraparib maintenance therapy as *post-study anticancer treatment* at the Investigator*s discretion. Patients in Arm 1, Maintenance Treatment Period not receiving bevacizumab when Amendment 4 is implemented may start niraparib maintenance therapy as "post-study anticancer treatment" if the time after Cycle 6 Day1 of the Chemotherapy Treatment Period is <=12 weeks. Patients will be permitted to remain on study until disease progression, toxicity, or withdrawal from study. Patients who do not elect to receive niraparib or bevacizumab maintenance will be discontinued from the study treatment and given the option to stay in the study for follow up. Investigators will be unblinded for those patients enrolled in Arm 1 and not receiving bevacizumab at the time of implementation of Amendment 4.

In total, approximately 1333 patients will be randomized. The study started with a 1:1:2 randomization ratio. Arm 1 BRCAmut patient enrollment was stopped after Amendment 2. Arm 1 BCRAwt patient enrollment will stop after implementation of Amendment 4. It is estimated that approximately 193 patients will have been randomized to Arm 1. At the end of study enrollment, approximately 1140 patients will be randomized in a 1:2 ratio to Arm 2 or Arm 3 of the study.

Intervention

Pre-Screening Period
During the Pre-Screening Period, patients may sign a pre-screening informed

consent form consenting to collection of the required tumor tissue sample (a minimum of 1 formalin fixed paraffin embedded [FFPE] block or slides) and the circulating tumor deoxyribonucleic acid (ctDNA) HRR blood sample required for randomization. The blood sample for central gBRCA is required. The Pre-Screening Period can take place within the 14 days prior to the Screening Period, defined as the date of signing the main informed consent, but does not have to encompass the full period. A patient can move to the Screening Period once deemed able.

Screening Period
During the Screening Period, patients will sign the main consent form and complete all assessments required to determine eligibility into the study. The Screening Period is within 28 days prior to Cycle 1 Day 1 (C1D1) of the Chemotherapy Run-In Period.

Chemotherapy Run-In Period (Cycle 1)
Prior to randomization, all patients will receive 1 cycle of paclitaxel-carboplatin during a Chemotherapy Run-In Period. Patients may also receive bevacizumab with paclitaxel-carboplatin as part of SOC per local practice. However, bevacizumab must not be administered less than 28 days before or 28 days following major surgery, and post operative incisions must be fully healed. The determination to use bevacizumab must be made prior to randomization. Patients will be randomized following Cycle 1, prior to treatment in Cycle 2 during the Chemotherapy Treatment Period. Randomization may occur up to one week prior to Cycle 2 Day 1.
Intraperitoneal (IP) chemotherapy and weekly paclitaxel will not be allowed.

Chemotherapy Treatment Period (Cycles 2 to 6)
Prior to chemotherapy administration of Cycle 2, all of the following criteria must be met:
• Absolute neutrophil count (ANC) >=1,500 cells/µL, or >=1000 cells µL if granulocyte-colony stimulating factor (G-CSF) is to be administered
• Platelet count >=100,000 cells/µL
• Hemoglobin >= 8 g/dL
Thereafter, retreatment criteria for remaining chemotherapy Cycles 3 to 6 should be in accordance to SOC per local practice.
Following randomization, patients who have inoperable disease or who have undergone PDS will receive cycles 2 to 6 of paclitaxel carboplatin, for a total of 6 cycles of chemotherapy inclusive of Cycle 1. Patients will also receive dostarlimab/placebo in combination with paclitaxel-carboplatin started with Cycle 2 of chemotherapy, for a total 5 cycles. Bevacizumab may continue per local practice.
Patients for whom NACT is planned will receive 3 to 4 cycles of paclitaxel carboplatin prior to interval debulking surgery (inclusive of Cycle 1) and 2 to 3 additional cycles of paclitaxel carboplatin following surgery for a maximum of 6 cycles of chemotherapy that cannot be extended. Interval debulking surgery cannot occur after 6 cycles of chemotherapy without prior discussion with the

Sponsor. These patients will also receive dostarlimab/placebo, which will be started with Cycle 2 of chemotherapy, for a total of 5 cycles. Chemotherapy and dostarlimab/placebo will resume upon recovery of surgery. Patients for whom NACT is planned may receive bevacizumab with paclitaxel-carboplatin per local practice as SOC; however, bevacizumab must not be administered less than 28 days before or 28 days following major surgery, and post operative incisions must be fully healed.
IP chemotherapy and weekly paclitaxel will not be allowed.

Maintenance Treatment Period
Patients who complete the Chemotherapy Treatment Period without progressive disease (PD) will start the Maintenance Treatment Period after Cycle 6 Day 1. Dostarlimab/placebo ± bevacizumab will also continue in the Maintenance Treatment Period in combination with oral maintenance treatment, per study schedule. However, the start of niraparib will be delayed at least 6 weeks after Cycle 6 Day 1 and up to 9 weeks after to allow for adequate recovery of hematologic toxicity.
Prior to starting the first dose of oral niraparib maintenance treatment, patients must have a complete blood count (CBC) that demonstrate adequate recovery from hematologic toxicity from chemotherapy:
• Absolute neutrophil count >=1,500 cells/µL
• Platelet count >=100,000/µL
• Hemoglobin >=9 g/dL
• Blood pressure <150/100 mmHg
Weekly CBC is to be performed for the first 4 weeks from the start of niraparib in the Maintenance Treatment Period.
The recommended SOC order is provided below, unless local clinical practice or institutional policies differ:
• During the Chemotherapy Treatment Period, dostarlimab/placebo will be administered first, followed by bevacizumab, then paclitaxel, and lastly carboplatin.
• During the Maintenance Treatment Period, dostarlimab/placebo will be administered first, followed by bevacizumab, and then niraparib.

Study burden and risks

NIRAPARIB
Niraparib side effects experienced by patients taking niraparib as a single drug therapy:
These side effects are common (occur in 1 in 10 people or more)
Decrease in a type of blood cells called platelets that help stop bleeding; this may increase the risk of bleeding (thrombocytopenia)
Pain or burning when urinating which may indicate an infection (urinary tract infection)
Decrease in red blood cells that carry oxygen; this may make patients feel tired or short of breath (anemia)
Feeling tired, lack of energy (asthenia/fatigue)

Decrease in a type of white blood cells called neutrophils that fight infection; this may decrease the ability to fight infections and may also be associated with fever, and may lead to a potentially life-threatening condition caused by the body's response to an infection, triggering changes that can damage multiple organ systems (neutropenia, neutropenic infection, febrile neutropenia, neutropenic sepsis)
Headache
Difficulty with emptying the bowels, often because of hard stools (constipation)
Back pain
Feeling sick to the stomach (nausea)
Joint pain (arthralgia)
Vomiting
Breathlessness or difficulty breathing (dyspnea)
Reduced desire to eat (decreased appetite)
Common cold (nasopharyngitis)
Pain in belly (abdominal pain)
Increased blood pressure (hypertension)
Frequent watery stools (diarrhea)
Feeling lightheaded or like patient is about to faint (dizziness)
Indigestion (dyspepsia)
Cough
Sleeplessness, trouble sleeping (insomnia)
Noticeably rapid, strong, or irregular heartbeat (palpitations)

These side effects occur, but not that often (occur in 1 in 100 people or more)
Altered sense of taste: this means that food might taste differently than patients are used to (dysgeusia)
Rash
Reduced potassium in the blood (hypokalemia)
Muscle pain (myalgia)
An abnormally rapid heart rate (tachycardia)
An accumulation of fluid that causes swelling in the extremities such as lower legs, hands and feet (peripheral edema)
Dry mouth
Swelling or irritation of the lining of the mouth, throat, esophagus, stomach, or intestines (mucosal inflammation/mucositis/stomatitis)
Feeling anxious (anxiety)
Increased liver enzyme in the blood; aspartate transaminase (*AST*), alanine aminotransferase (*ALT*), gamma glutamyl transferase increased (*GGT*), or alkaline phosphatase (ALP); this may be a sign of damage to liver cells
Mood change to feeling sad/discouraged, listless (depression)
Increased level of creatinine in the blood; this may be a sign of kidney damage (blood creatinine increase)
Nose bleed (epistaxis)
Decrease in weight
Inflammation of the lining of the airways (bronchitis)

Infection of the white area of the eye (conjunctivitis)
Increased sensitivity of the skin to sunlight (photosensitivity)

These side effects are considered uncommon (may affect up to 1 in 100 people):
Decrease in number of all types of blood cells (pancytopenia)

These side effects are considered rare (may affect 1 or more, but less than 10 out of every 10,000 patients):
A brain condition with symptoms including seizures, headache, confusion and changes in vision (posterior reversible encephalopathy syndrome [PRES])
Severe increase in blood pressure (hypertensive crisis)

In addition to the above, the side effects below were reported by patients who were prescribed niraparib by their doctors:
• Allergic reaction (hypersensitivity*, including anaphylaxis**).
• Life-threatening allergic reaction (such as difficulty breathing, rash, localized swelling, such as tongue, throat or lips) (anaphylaxis*)
• Confusion (confusional state*: symptom that makes you feel as if you can't think clearly. You might feel disoriented and have a hard time focusing or making decisions)
• Seeing or hearing things that are not really there (hallucination*)
• Impaired concentration, understanding, memory* and thinking (cognitive impairment*)

• Inflammation of the lungs which can cause shortness of breath and difficulty breathing (non-infectious pneumonitis*)
*Observed frequency in clinical trials uncommon (may affect up to 1 in 100 people).
**No events reported in monotherapy clinical trials.

Potential for a new blood cancer, myelodysplastic syndrome and/or acute myeloid leukemia (MDS/AML), a new primary cancer, embolic and/or thrombotic events (blood clots):
Niraparib belongs to a group of drugs called PARP inhibitors. This group of drugs are suspected of causing new blood cancers known as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Because niraparib is a PARP inhibitor there is a potential risk of developing a new blood cancer leading to leukemia.
If patients have had MDS or leukemia before entering this study, they are at increased risk for developing leukemia again.
Although rare, patients in niraparib clinical trials have had MDS/AML. In another study in recurrent ovarian cancer patients, MDS/AML was not more common in patients receiving niraparib than in patients receiving placebo.
PARP inhibitors may also cause a new primary cancer.
Blood clotting (venous thrombosis) has been noted in ovarian cancer patients with and without use of niraparib. This may cause symptoms such as swelling, pain, warmth and redness in your legs or elsewhere. Clotting in the lungs may

cause trouble breathing, cough and rapid heartbeat.
Niraparib capsules contain tartrazine which may cause allergic-type reactions.

DOSTARLIMAB
Dostarlimab side effects experienced by patients taking Dostarlimab as a single drug therapy:
These side effects are very common (occur in 1 in 10 people or more)
Decrease in the number of red blood cells that carry oxygen. Low red blood cells count may make you feel tired or short of breath and symptoms may require a blood transfusion (anaemia)
Feeling sick to the stomach (nausea)
Vomiting
Loose/liquid stools (diarrhoea)
Itchy skin (pruritus)
Rash
Increased levels of substances in the blood produced by the liver which may be a sign of liver injury (AST increased, ALT increased) (transaminases increased)

These side effects are common (occur in more than 1 people in 100, but less than 10 people in 100)
Decreased production of adrenal hormones resulting in possible weakness and/or low blood pressure (adrenal insufficiency)
Underactive thyroid gland (hypothyroidism)
Overactive thyroid gland (hyperthyroidism)
Inflammation of the lungs which can cause shortness of breath and difficulty breathing (pneumonitis)
Inflammation of the colon that can cause stomach pain or diarrhea (colitis)
Muscle pain (myalgia)
Chills
Fever (pyrexia)
Infusion-related reaction which can occur within 24 hours after receiving an intravenous infusion, or which can be delayed for up to about 2 weeks. Infusion-related reactions may include dizziness or fainting, flushing, rash, fever, chills, shortness of breath, increased or decreased blood pressure, increased heart rate, swelling of the lips, tongue or face, feeling sick to your stomach, back pain or pain at the site of infusion. Although infusion-related reactions are usually reversible, they can be severe or life threatening. (infusion related reactions)

There are rare but serious immune-related adverse events which have been seen when dostarlimab was used in combination with other medicines:
Inflammation of the muscle which can cause weakness, swelling and pain (myositis)
Inflammation throughout the whole body leading to high or low temperatures, low blood pressure, increased heart rate, increased rate of breathing and low or high white blood cell count (systemic inflammatory response syndrome)

Overactive immune-system cells which can damage body tissues and organs leading to signs of uncontrolled fever, enlarged spleen, low blood count and liver test abnormalities. This disease can be fatal. (hemophagocytic lymphohistiocytosis)

UNFORESEEABLE RISKS
When Study Drugs are taken alone or in combination with other medic

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be considered eligible to participate in this study, all of the following requirements must be met:
1. Patients must be female, >=18 years of age, able to understand the study procedures, and agree to participate in the study by providing written informed

consent.
2. Patients with a histologically confirmed diagnosis of high-grade nonmucinous epithelial ovarian (serous, endometrioid, clear cell, carcinosarcoma, and mixed pathologies), fallopian tube, or primary peritoneal cancer that is Stage III or IV according to the International Federation of Gynecology and Obstetrics or tumor, node and metastasis staging criteria [ie, American Joint Committee on Cancer].
3. All patients with Stage IV disease are eligible. This includes those with inoperable disease, those who undergo PDS (CC0 or macroscopic disease), or those for whom NACT is planned.
4. Patients with Stage III are eligible if they meet one or more of the following criteria:
a. Stage IIIC patients with CC0 resection if they meet the following criteria: aggregate >=5 cm extra-pelvic disease during PDS as assessed by the Investigator
b. All patients with inoperable Stage III disease
c. All Stage III patients with macroscopic residual tumor (per Investigator judgment) following PDS
d. All Stage III patients for whom NACT is planned.
5. Patient must provide a blood sample for ctDNA HRR testing at Pre-Screening or Screening.
6. Patient must provide sufficient tumor tissue sample (a minimum of 1 FFPE block or slide at Pre-Screening or Screening for PD-L1, homologous recombination deficiency HRD testing.
7. Patients of childbearing potential must have a negative serum or urine pregnancy test (beta human chorionic gonadotropin) within 3 days prior to receiving the first dose of study treatment.
8. Patients must be postmenopausal, free from menses for >1 year, surgically sterilized, or willing to use highly effective contraception to prevent pregnancy or must agree to abstain from activities that could result in pregnancy throughout the study, starting with enrollment through 180 days after the last dose of study treatment.
9. Patients must have adequate organ function, defined as follows (Note: CBC test should be obtained without transfusion or receipt of stimulating factors within 2 weeks before obtaining Screening blood sample):
a. Absolute neutrophil count >=1,500/µL
b. Platelet count >=100,000/µL
c. Hemoglobin >=9 g/dL
d. Serum creatinine <=1.5 × upper limit of normal (ULN) or calculated creatinine clearance >=60 mL/min using the Cockcroft-Gault equation
e. Total bilirubin <=1.5 × ULN or direct bilirubin <=1.5 × ULN
f. Aspartate aminotransferase and alanine aminotransferase (ALT) <=2.5 × ULN unless liver metastases are present, in which case they must be <=5 × ULN
10. Patients must have an ECOG score of 0 or 1.
11. Patients must have normal blood pressure (BP) or adequately treated and controlled hypertension (systolic BP <=140 mmHg and/or diastolic BP <=90 mmHg).
12. Patients must agree to complete HRQoL questionnaires throughout the study.

13. Patients must be able to take oral medication.

Exclusion criteria

Patients will not be eligible for study entry if any of the following criteria are met:
1. Patient has mucinous, germ cell, transitional cell, or undifferentiated tumor.
2. Patient has low grade or Grade 1 epithelial ovarian cancer.
3. Stage III patient with R0 resection after PDS (ie, no macroscopic residual disease, unless inclusion criterion #4a is met).
4. Patient has not adequately recovered from prior major surgery.
5. Patient has a known condition, therapy, or laboratory abnormality that might confound the study results or interfere with the patient*s participation for the full duration of the study treatment in the opinion of the Investigator.
6. Patient is pregnant or is expecting to conceive children while receiving study drug or for up to 180 days after the last dose of study drug. Patient is breastfeeding or is expecting to breastfeed within 30 days of receiving the final dose of study drug (women should not breastfeed or store breastmilk for use, during niraparib treatment and for 30 days after receiving the final dose of study treatment).
7. Patient has known active central nervous system metastases, carcinomatous meningitis, or both.
8. Patient has clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, myocardial infarction, uncontrolled cardiac arrhythmia or unstable angina <6 months to enrollment, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, Grade 2 or greater peripheral vascular disease, and history of cerebrovascular accident within 6 months).
9. Patient has a bowel obstruction by clinical symptoms or CT scan, subocclusive mesenteric disease, abdominal or gastrointestinal fistula, gastrointestinal perforation, or intra abdominal abscess.
10. Patient initiating bevacizumab as SOC has proteinuria as demonstrated by urine protein:creatinine ratio >=1.0 at Screening or urine dipstick for proteinuria >=2 (patients discovered to have >=2 proteinuria on dipstick at baseline should undergo a 24 hour urine collection and must demonstrate <2 g of protein in 24 hours to be eligible).
11. Patient has any known history or current diagnosis of MDS or AML.
12. Patient has been diagnosed and/or treated with any therapy for invasive cancer <5 years from study enrollment, completed adjuvant chemotherapy and/or targeted therapy (eg, trastuzumab) less than 3 years from enrollment, or completed adjuvant hormonal therapy less than 4 weeks from enrollment. Patients with definitively treated noninvasive malignancies such as cervical carcinoma in situ, ductal carcinoma in situ, Grade 1 or 2, Stage I endometrial cancer, or

non -melanomatous skin cancer are allowed.
13. Patient is at increased bleeding risk due to concurrent conditions (eg, major injuries or major surgery within the past 28 days prior to start of study treatment and/or history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months).
14. Patient is immunocompromised. Patients with splenectomy are allowed. Patients with known human immunodeficiency virus (HIV) are allowed if they meet all of the following criteria:
a. Cluster of differentiation 4 >=350/µL and viral load <400 copies/mL
b. No history of acquired immunodeficiency syndrome-defining opportunistic infections within 12 months prior to enrollment
c. No history of HIV associated malignancy for the past 5 years
d. Concurrent antiretroviral therapy as per the most current National Institutes of Health (NIH) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV started >4 weeks prior to study enrollment
15. Patient has known active hepatitis B (eg, hepatitis B surface antigen reactive) or hepatitis C (eg, hepatitis C virus ribonucleic acid [qualitative] is detected).
16. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or uncontrolled infection. Specific examples include, but are not limited to, history of non-infectious pneumonitis that required steroids, current pneumonitis, uncontrolled autoimmune disease, uncontrolled ventricular arrhythmia, recent myocardial infarction within 90 days of consent, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).
17. Patient has had investigational therapy administered within 4 weeks or within a time interval less than at least 5 half lives of the investigational agent, whichever is longer, prior to the first scheduled day of dosing in this study.
18. Patient has received a live vaccine within 14 days of planned start of study therapy. Seasonal influenza vaccines that do not contain live viruses are allowed.
19. Patient has a known contraindication or uncontrolled hypersensitivity to the components of paclitaxel, carboplatin, niraparib, bevacizumab, dostarlimab, or their excipients.
20. Prior treatment for high-grade nonmucinous epithelial ovarian, fallopian tube, or peritoneal cancer (immunotherapy, anticancer therapy, radiation therapy).
21. Patient 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 (eg, thyroid hormone or insulin).
22. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of systemic immunosuppressive therapy within

7 days prior to the first dose of study treatment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-01-2020
Enrollment:	38
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Dostarlimab
Generic name:	TSR-042
Product type:	Medicine
Brand name:	Zejula
Generic name:	Niraparib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	02-10-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-10-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	06-04-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-510605-28-00
EudraCT	EUCTR2018-000413-20-NL
CCMO	NL66122.042.18