OPINION - A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

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This research study is designed to check whether olaparib is also effective in treating ovarian cancer which does not have a germline deleterious BRCA mutation, and whether olaparib causes any side effects.A tablet formulation of olaparib is being...

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

Summary

ID

NL-OMON48759

Source
ToetsingOnline

Brief title
OPINION

Condition

- Ovarian and fallopian tube disorders

Synonym
high-grade serous ovarian cancer or high grade endometrioid cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: efficacy, Olaparib, Ovarian cancer, safety

Outcome measures

Primary outcome

Primairy objective:

To determine the efficacy by progressionfree survival (PFS)

(investigator-recorded assessments according to modified Response Evaluation

Criteria In Solid Tumors [RECIST v1.1]) of olaparib maintenance monotherapy in

nongBRCAm platinum sensitive relapsed (PSR) ovarian cancer

Outcome measure:

PFS: Time from date of first dose until the date of objective radiological

disease progression according to modified RECIST 1.1 or death (by any cause in

the absence of progression)

Secondary outcome

Secundairy objective:

To determine the efficacy of olaparib maintenance monotherapy in nongBRCAm PSR

ovarian cancer by assessment of time to first subsequent therapy or death (TFST)

To determine the efficacy of olaparib maintenance monotherapy in nongBRCAm PSR

ovarian cancer by assessment of time to treatment discontinuation or death (TDT)

To determine the efficacy by PFS (investigator-recorded assessments according to modified RECIST v1.1) of olaparib maintenance in non-gBRCAm PSR ovarian cancer according to tumour homologous recombination deficiency (HRD) status using the Myriad myChoice HRD plus test

To determine the efficacy of olaparib maintenance monotherapy in nongBRCAm PSR ovarian cancer by assessment of chemotherapy-free interval (CT-FI)

To determine the overall survival (OS) of non-gBRCAm PSR ovarian cancer patients treated with olaparib maintenance monotherapy

To investigate the Health-related Quality of Life (HRQoL) of non-gBRCAm PSR ovarian cancer patients treated with olaparib maintenance monotherapy as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy * Ovarian (FACT-O)

To assess the safety and tolerability of olaparib maintenance monotherapy in patients with non-gBRCAm PSR ovarian cancer

Outcome meassure :

TFST: Time from date of first dose to date of first subsequent treatment commencement or death due to any cause if this occurs before commencement of

first subsequent treatment

TDT: Time from date of first dose to date of study drug discontinuation or death due to any cause if this occurs before study drug discontinuation

PFS in the following subgroups: -

1. Somatic BRCA mutated and HRD scar positive;

2. HRD scar positive, non-BRCA mutated;

3. HRD scar negative, non-BRCA mutated

CT-FI: Time from the date of the last dose of platinum chemotherapy prior to olaparib maintenance therapy until the date of initiation of the next anticancer therapy

OS: Time from the date of first dose of olaparib to the date of death from any cause.

Proportion of patients with any improvement from baseline in TOI score at any point during the treatment period

Proportion of patients with a 10 point deterioration from baseline in TOI score at any point during the treatment period

Adverse events/serious adverse events

Collection of clinical chemistry/haematology

parameters

Study description

Background summary

A capsule formulation of olaparib (tradename Lynparza*) is approved by the European Commission (EC), US Food and Drug Administration (FDA) and other countries for the treatment of women with advanced BRCA-mutated ovarian cancer. In this type of ovarian cancer certain genes (called BRCA1 and 2) show a mutation that alters the function of these genes (this is called *deleterious*). Mutations can either be inherited (*germline*) or they can occur spontaneously in ovarian tissue (*somatic*). Some mutations do not affect the gene function, they are called *variants*.

Study objective

This research study is designed to check whether olaparib is also effective in treating ovarian cancer which does not have a germline deleterious BRCA mutation, and whether olaparib causes any side effects.
A tablet formulation of olaparib is being tested in this study. It is a new formulation which is more convenient for patients than the approved capsule formulation because fewer tablets of olaparib need to be taken daily than with capsules.

Study design

This is a Phase IIIb, single-arm, open-label, multicentre study to assess the efficacy and safety of single-agent olaparib as a maintenance treatment in patients with relapsed HGSOC (including patients with primary peritoneal and/or fallopian tube cancer) or high grade endometrioid cancer who do not have known deleterious or suspected deleterious germline BRCA mutations (non-gBRCAm) and who had responded following platinum based chemotherapy. Tumour assessments will be conducted every 8 weeks for the first 12 months, and thereafter every 12 weeks up to disease progression.*

Intervention

Patients must have an existing known and documented gBRCA test result. Patients with known deleterious or suspected deleterious gBRCA mutations will be excluded. The gBRCA status of enrolled patients will be confirmed retrospectively using a central laboratory gBRCA test. All patients should

additionally have tumour sample available for the Myriad myChoice® HRD test plus other molecular tests that measure homologous recombination repair competency and genomic instability
Following screening assessments, all patients should have radiological (CT or MRI) tumour assessments at baseline (within 28 days of starting treatment), then every 8 weeks (±7 days) for the first 12 months, and every 12 weeks (± 7 days) until documented evidence of objective radiological disease progression in accordance with modified RECIST 1.1, irrespective of treatment decisions (i.e. RECIST follow up until progression even if a patient discontinues study treatment prior to progression and/or receives subsequent therapy prior to progression). At
baseline, eligible patients can have measurable disease (target lesions) or non-measurable disease (non-target lesions or no evidence of disease).
Once a patient has progressed, the patient will be treated as per local clinical practice and will be followed to first subsequent treatment, and then approximately every 12 weeks for survival.

Study burden and risks

Very common side effects (affects more than 1 in 10 patients):
Feeling sick (nausea)
Being sick (vomiting)
Tiredness/weakness
Indigestion/heartburn (dyspepsia)
Loss of appetite
Headache
Change in taste of foods (dysgeusia)
Dizziness
Diarrhoea. Your doctor may prescribe a medicine to treat this. If it gets severe, tell your doctor straight away.

Common side effects (affects 1 to 10 in 100 patients):
Sore mouth (stomatitis)
Pain in the stomach area under the ribs (upper abdominal pain)
Rash

The following side effects are very commonly shown in tests (Affects more than 1 in 10 patients):
Decrease in the number of red blood cells (anaemia) which can be associated with symptoms of shortness of breath, fatigue, pale skin or fast heart beat
Decrease in the number of white blood cells that support the immune system (lymphopenia) which can be associated with increased susceptibility to infection
Increase in blood creatinine seen from a laboratory test showing how your kidneys are working.
Mean cell volume elevation (an increase in size of red blood cells): This will be monitored by the laboratory safety tests that will be done in this study because this doesn*t normally have any symptoms.

The following side effect is commonly shown in tests (Affects 1 to 10 in 100 patients):
Decrease in the number of platelets in blood (thrombocytopenia) which can be associated with symptoms of bruising or bleeding for longer if injured
Decrease in the total number of white blood cells (leukopenia) and in certain white blood cells (neutropenia) that protect from infection, which can be associated with symptoms of fever

Uncommon (affects up to 1 in 100 patients) side effects that may occur are:
* Allergic reactions
* Itchy rash on swollen, reddened skin (dermatitis)

Driving and using machines
The study drug may affect your ability to drive or use machines. If you feel dizzy, weak, or tired while taking your study treatment, take special care when driving or using tools or machines.
Other potential risks
Other side effects have been seen in previous studies, but it is not yet known if these were related to olaparib, or if they were unrelated events possibly due to the patient*s cancer or other cause. Assessing the full range of side effects of olaparib is an important part of this study.
Pneumonitis (lung inflammation) has been reported in a small number of patients treated with olaparib in previous studies, and some reports have been fatal. It is not known if olaparib caused the pneumonitis in these patients as they had other possible causes such as lung cancer and/or metastases in the lungs, pre-existing lung disease, were smokers, or had been treated previously with chemotherapy or radiotherapy. If you experience any new or worsening symptoms of shortness of breath, cough and fever, you should contact your Study Doctor as soon as you can.
Myelodysplastic syndrome and acute myeloid leukaemia: These side effects have been reported in a small number of patients treated with olaparib in previous studies and the majority of cases have been fatal. It is not known if olaparib caused myelodysplastic syndrome and/or acute myeloid leukaemia in these patients as they had other possible causes, in particular they had received extensive previous chemotherapy. Your Study Doctor will monitor your blood cell levels during the study and may decide you need to have further tests, which may include a bone marrow sample or a blood sample.
* Myelodysplastic syndrome is a pre-cancerous condition where the bone marrow isn*t as good at producing blood cells as it was before (red blood cells and/or white blood cells and/or platelets). This condition has the potential to transform into acute myeloid leukaemia
* Acute myeloid leukaemia is a cancer of the bone marrow where many abnormal and immature white blood cells (blast cells) are made while normal functioning blood cells are not made.

The Study Doctor may decide to interrupt and/or reduce your olaparib dose if you experience certain side effects. If your dose is reduced you will be given

a new bottle of tablets.
There may be risks involved in taking this drug that have not yet been discovered. There is always a risk involved in taking an experimental drug but every precaution will be taken. If you suffer any side effects or injuries, or your condition gets worse, tell your study doctor immediately so you can receive appropriate care.

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

For inclusion in the study patients should fulfill all of the following criteria:
1. Provision of informed consent prior to any study specific procedures
2. Patients must be *18 years of age
3. Female patients with histologically diagnosed relapsed HGSOC (including primary

peritoneal and / or fallopian tube cancer) or high grade endometrioid ovarian cancer
4. Documented gBRCA1/2 mutation status
Evidence that the patients do not have a gBRCA mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental / lead to loss of function). gBRCA1 and/or gBRCA2 variants that are classified as *Variants of uncertain clinical significance* or *Variant of unknown significance (VUS)* are eligible, as well as *Variant, favor polymorphism* or *benign polymorphism*. ;Evidence of the absence of a somatic BRCA mutation is not required. Patients with a tumour BRCA test result only must undergo a gBRCA test to determine whether the BRCA aberration is germline or somatic in origin. If this analysis identifies the aberration as germline the patient is not eligible ;5. Patients must have completed at least 2 previous courses of platinum containing therapy:
(a) For the penultimate chemotherapy course prior to enrolment on the study:;* Treatment must have contained a platinum agent (e.g. carboplatin, cisplatin or oxaliplatin per standard clinical practice; there are no other specific requirements);* Patient was platinum sensitive after this treatment; defined as disease progression greater than 6 months after completion of their last dose of platinum chemotherapy;* Maintenance treatment is allowed at the end of the penultimate platinum regimen, including bevacizumab;(b) For the last chemotherapy course immediately prior to enrolment on the study;* Patients must be, in the opinion of the investigator, in response (partial or complete radiological response), or may have no evidence of disease (if optimal cytoreductive surgery was conducted prior to chemotherapy), and no evidence of a rising CA-125, as defined below, following completion of this chemotherapy course;* Patient must have received a platinum based chemotherapy regimen (e.g. carboplatin, cisplatin or oxaliplatin) and have received at least 4 cycles of treatment;* Patients must not have received bevacizumab during this course of treatment;* Patients must not have received any investigational agent during this course of treatment;* Patients must initiate treatment within 8 weeks of their last dose of chemotherapy (last dose is the day of the last infusion);6. Pre-treatment CA-125 measurements must meet criterion specified below:;* If the first value is within upper limit of normal (ULN) the patient is eligible to be enrolled and a second sample is not required;* If the first value is greater than ULN a second assessment must be performed at least 7 days after the 1st. If the second assessment is * 15% more than the first, the patient is not eligible;7. Patients must have normal organ and bone marrow function measured within 28 days of starting study treatment, as defined below. In the event of minor deviations from these values which would lead to screen failure, repeat testing within the 28-day screening period (limited to the tests listed below) is allowed before the patient is declared a screen failure.
* Haemoglobin *10.0 g/dL with no blood transfusion in the past 28 days
* Absolute neutrophil count (ANC) *1.5 X 109/L
* Platelet count *100 X 109/L
* Total bilirubin (TBL) *1.5 X ULN
* Aspartate aminotransferase (AST), serum glutamic oxaloacetic transaminase (SGOT)/alanine aminotransferase (ALT), serum glutamic pyruvate transaminase (SGPT) *2.5 X institutional ULN, unless liver metastases are present in which case they must be *5 X ULN
* Patients must have creatinine clearance, estimated (below), or based on a 24 hour urine test, using the Cockcroft-Gault equation of *51 mL/min:
Estimated creatinine clearance (females) <= (140-age [years]) x weight (kg) x 0.85
serum creatinine (mg/dL) x 72

8. ECOG performance status 0-1
9. Patients must have a life expectancy *16 weeks
10. Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1
Postmenopausal is defined as any of the following:
* Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments
* For women under 50 years old, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range
* Radiation-induced oophorectomy with interval of 1 year or more since last menses
* Chemotherapy-induced menopause with >1 year interval since last menses
* Surgical sterilisation (bilateral oophorectomy or hysterectomy).
11. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations
12. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline with computed tomography (CT) or magnetic resonance imaging (MRI) and is suitable for repeated assessment
OR
No evidence of disease following a complete response to chemotherapy (with or without cytoreductive surgery)
13. An appropriately prepared tumour sample from the cancer, of sufficient quantity and quality (as specified in the Central Laboratory Services Manual) must be available for future central testing of tumour genetic status. If a recent biopsied sample is provided, the biopsied tumour should not be assessed as target lesions as part of the RECIST assessments if there are other lesions available, and the biopsy should be taken after the baseline scan has been performed. Archival tissue samples may be from the primary tumour or metastatic tumour deposits. Archival bone metastases are not acceptable. Provision of blocks is usually preferred. Any exceptions to these conditions should be discussed with the Sponsor before enrollment of the patient.

Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled.
1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site*
2. Previous enrolment in the present study*
3. Participation in another clinical study with an investigational product (IP) during the most recent chemotherapy course*
4. Patients receiving any systemic hormonal therapy, chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to start of study treatment
5. Any previous treatment with PARP inhibitor, including olaparib*
6. Patients with a germline BRCA mutation that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental / lead to loss of function).
7. Other malignancy unless curatively treated with no evidence of disease for > 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of

the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma
8. Concomitant use of known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks*.
9. Concomitant use of known strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John*s Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for phenobarbital and 3 weeks for other agents*
10. Persistent toxicities (* Grade 2 Common Terminology Criteria for Adverse Event (CTCAE) adverse event) caused by previous cancer therapy, excluding alopecia
11. Patients with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML*
12. Patients with symptomatic uncontrolled brain metastases. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease (SD) for 28 days*
13. Major surgery within 3 weeks of starting study treatment and patients must have recovered from any effects of any major surgery
14. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection.
15. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication*
16. Currently pregnant (confirmed with a positive pregnancy test) or breastfeeding women*
17. Immuno-compromised patients e.g., Human Immunodeficiency Virus (HIV) requiring treatment or active Hepatitis B or C*
18. Patients with a known hypersensitivity to olaparib or any of the excipients of the product*
19. Patients with known active hepatitis (i.e., hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids*
20. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)*
21. Patients having gBRCA testing should not have had whole blood transfusions in the last 30 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable)
22. Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely or unable to comply with study procedures, restrictions and requirements.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-06-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lynparza
Generic name:	Olaparib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-12-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	21-12-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	18-06-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	03-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-10-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-06-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
EudraCT	EUCTR2017-002767-17-NL
CCMO	NL63293.028.17