A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Published: 25-09-2014
Last updated: 22-04-2024

Protocol v1.0 31-Mar-2014, paragraph 2.1-2.4, pages 37-39:The primary objective of this study is: - To determine the efficacy of Olaparib maintenance monotherapy compared to placebo by progression free survival (PFS).The secundary objectives of this...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON55810

Source
ToetsingOnline

Brief title
POLO

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Pancreatic adenocarcinoma, Pancreatic cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BRCA, Olaparib, Pancreatic Cancer

Outcome measures

Primary outcome

Protocol v1.0 31-Mar-2014, paragraph 2.1, page 37:

The primary outcome measure of this study is:

- Progression Free Survival (PFS) by BICR using modified RECIST 1.1.

Secondary outcome

Protocol v1.0 31-Mar-2014, paragraph 2.1-2.4, pages 37-39:

The secundary outcome measures of this study are:

- Overall Survival (observed and predicted using observed PFS and OS data).

- Time from randomisation to second progression (PFS2).

- Time from randomisation to first subsequent therapy or death (TFST).

- Time from randomisation to second subsequent therapy or death (TSST).

- Time from randomisation to study treatment discontinuation or death (TDT).

- Objective Response Rate by BICR using modified RECIST 1.1 criteria for

evaluable patients.

- Disease Control Rate at 16 weeks by BICR using modified RECIST 1.1 criteria.

- Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire.

The safety outcome measure of this study is:

- Adverse event (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology.

The exploratory outcome measures of this study are:

- Adjusted mean change from baseline on EORTC-QLQ-C30 functioning domains (physical, role, cognitive, emotional, social), on EORTC-QLQ-C30 + PAN26 symptom scales and items (pain, fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice and on performance status measured by the ECOG Performance Status scale.
- Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay.
- Health state utility derived from the HRQL instrument, the EuroQoL EQ5D.
- Overall survival adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement appraisals).
- BRCA1 and/or BRCA2 mutation status in tumour.
- Potential tissue biomarkers identified.

Study description

Background summary

Protocol v1.0 31-Mar-2014, paragraph 1.1, pages 24 and 28:

[...] Despite the development of more *active* regimens for first treatment of metastatic pancreatic cancer in the last decade, their limited absolute benefit and significant toxicity strongly suggest that improving the results of initial therapy of metastatic pancreas cancer constitutes an unmet medical need. Furthermore to date there has been no marker, clinical or molecular that would predict for increased likelihood of benefit from systemic therapies for pancreas cancer.
[...]
Phase I and proof-of-concept phase II studies have shown that PARP inhibitors have significant activity with limited toxicity when used as single agents in the treatment of gBRCA1/2 mutation-associated breast and ovarian cancer and pancreas cancer. The present trial is an important step in defining the role of Olaparib as a PARP inhibitor in patients with deleterious germline BRCA1/2 mutations and metastatic pancreas cancer and the strategy of switch maintenance to prolong disease control after beneficial effect of a platinum regimen as has been suggested for gBRCA-mutated ovarian cancer.
[...]
If the trial is successful it will give patients a relatively non-toxic oral therapeutic which will delay progression after stopping first line platinum based chemotherapy.

Study objective

Protocol v1.0 31-Mar-2014, paragraph 2.1-2.4, pages 37-39:

The primary objective of this study is:
- To determine the efficacy of Olaparib maintenance monotherapy compared to placebo by progression free survival (PFS).

The secundary objectives of this study are:
- To determine the efficacy of Olaparib maintenance monotherapy compared to placebo.
- To assess the effect of Olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale.

The safety objective of this study is:
- To assess the safety and tolerability of Olaparib maintenance monotherapy.

The exploratory objectives of this study are:
- To assess the effect of Olaparib on functioning as measured by the EORTC

QLQ-C30 functioning domains (physical, role, cognitive, emotional and social).
- To assess the effect of Olaparib on pancreas cancer symptoms as measured by the EORTC QLQ-PAN26 items and scales.
- To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), jaundice.
- To assess change in performance status as measured by the ECOG Performance Status scale.
- To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility.
- To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5*diphosphoribose [poly (ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.
- To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status.
- To identify tumour tissue based biomarkers (including but not limited to somatic BRCA1/2 mutations, BRCA methylation and/or other HRD biomarkers) that could be used to guide future patient segmentation approaches for development
- Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at day 1 and on disease progression or on residual tissue material collected as part of the study.

Study design

Protocol v1.0 31-Mar-2014, paragraph 1.5, page 34:

This is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of Olaparib maintenance monotherapy in metastatic pancreatic cancer patients with gBRCA mutations [documented mutation in gBRCA1 or gBRCA2] that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and whose tumours have not progressed on at least 16 weeks of first line platinum based chemotherapy.

Intervention

Protocol v1.0 31-Mar-2014, page 8-9:

Patients will be randomised (using an IVRS) in a 3:2 ratio (Olaparib:placebo) to the treatments as specified below:
* Olaparib tablets po. 300 mg twice daily
* Placebo tablets twice daily

Investigational product, dosage and mode of administration Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg of Olaparib. Patients will be administered study treatment orally at a dose of 300 mg twice daily (bid). The planned dose of 300 mg bid will be made up of two x 150 mg tablets bid with 100 mg tablets used to manage dose reductions.

Placebo will be available as green film-coated tablets matching the Olaparib tablets. These should be taken as per instructions for Olaparib tablets.

Study burden and risks

Protocol v1.0 31-Mar-2014, paragraph 1.4

As of 2 October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreas, and a variety of other solid tumours are estimated to have received treatment with Olaparib across the dose range 10 mg qd to 600 mg bid in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anticancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing.

The majority of patients to date have received the capsule formulation of Olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the Olaparib development programme. An analysis of monotherapy data across 12 AstraZeneca sponsored monotherapy studies in 975 patients who have been given Olaparib capsule estimated that 16.1% (157/975) of patients had been exposed to Olaparib capsule for *12 months at the time of database closure for the 12 studies. Furthermore, 41/ 975 patients received treatment for >24 months (longest duration was 44 months).

From the available data to date, there is no evidence of any unexpected toxicity following long-term Olaparib (capsule) monotherapy exposure. Olaparib as monotherapy at doses up to 400 mg bid capsule is generally well tolerated, with the most common AEs nausea, fatigue, vomiting, diarrhoea, upper abdominal pain, dyspnoea, decreased appetite, dyspepsia, dizziness, headache, dysgeusia, cough, leukopenia, neutropenia, thrombocytopenia and anaemia mainly mild-to-moderate (CTCAE Grade * 2) in severity. In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

Contacts

Public
Astra Zeneca

Pepparedsleden 1
Sodertalje SE-15185
SE
Scientific
Astra Zeneca

Pepparedsleden 1
Sodertalje SE-15185
SE

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 fulfil the following criteria:, 1. *Provision of informed consent prior to any study specific procedures, 2. *Patients must be male or female *18 years of age, 3. *Histologically or cytologically confirmed pancreas adenocarcinoma receiving initial chemotherapy for metastatic disease and without evidence of disease progression on treatment, 4. Patients with measurable disease and/or non-measurable or no evidence of disease assessed at baseline by CT (or MRI where CT is contraindicated) will be entered in this study. , 5. Documented mutation in gBRCA1 or gBRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) , 6. Patients are on treatment with a first line platinum-based regimen for metastatic pancreas cancer, have received a minimum of 16 weeks of continuous platinum treatment and have no evidence of progression based on investigator*s opinion. , 7. Patients who have received platinum as potentially curative treatment for a prior cancer (eg ovarian cancer) or as adjuvant/neoadjuvant treatment for

pancreas cancer are eligible provided at least 12 months have elapsed between the last dose of platinum-based treatment and initiation of the platinum-based chemotherapy for metastatic pancreas cancer., 8. Patients must have normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:, * Haemoglobin * 9.0 g/dL with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days, * Absolute neutrophil count (ANC) * 1.5 x 109/L, * White blood cells (WBC) >3 x 109/L, * No features suggestive of MDS/AML on peripheral blood smear, * Platelet count * 100 x 109/L, * Total bilirubin * 1.5 x institutional upper limit of normal, * AST (SGOT)/ALT (SGPT) * 2.5 x institutional upper limit of normal value unless liver metastases are present in which case they must be * 5x ULN, * Serum creatinine * 1.5 x institutional upper limit of normal (ULN), 9. *ECOG performance status 0-1 at date signing of informed consent, 10. *Postmenopausal or evidence of non-childbearing status for women of childbearing, potential: negative urine or serum pregnancy test. Postmenopausal is defined as:, * Amenorrheic for 1 year or more following cessation of exogenous hormonal, treatments, * Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in, the post menopausal range for women under 50, * Radiation-induced oophorectomy with last menses >1 year ago, * 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. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour or a metastatic site if available or 3 unstained cytology slides if available.

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 AstraZeneca staff and/or staff at the study site)., 2. gBRCA1 and/or gBRCA2 mutations that are considered to be non detrimental (eg, *Variants of uncertain clinical significance* or *Variant of unknown significance* or *Variant, favour polymorphism* or *benign polymorphism* etc.)., 3. Progression of tumour between start of first line platinum based chemotherapy for metastatic pancreas cancer and randomisation., 4. Cytotoxic chemotherapy or non-hormonal targeted therapy within 28 days of Cycle 1 Day 1 is not permitted. Palliative radiotherapy must have been completed 14 or more days before Cycle 1 Day 1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 2 weeks prior to study treatment., 5. *Previous randomisation in the present study., 6. Exposure to an investigational product within 30 days or 5 half lives (whichever is, longer) prior to randomisation, 7. *Any previous treatment with a PARP inhibitor,

including Olaparib., 8. *Patients with second primary cancer, EXCEPTIONS: adequately treated nonmelanoma skin cancer, curatively treated in-situ cancer of the cervix, Ductal Carcinoma in Situ (DCIS), stage 1 grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for * 5 years prior to study entry., 9. Resting ECG with QTc * 450 msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTc * 450 msec, patient will be eligible only if repeat ECG demonstrates QTc *450 msec., 10. Concomitant use of known potent CYP3A4/5 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir., 11. Persistent toxicities (*CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 3 peripheral neuropathy., 12. *Patients with myelodysplastic syndrome/acute myeloid leukaemia., 13. Major surgery within 2 weeks of starting study treatment: patients must have recovered from any effects of any major surgery., 14. *Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV)., 15. *Clinically significant uncontrolled medical conditions are not permitted (eg active infection requiring IV antibiotics, symptomatic congestive heart failure, unstable angina pectoris, recent (3 months) myocardial infarction, extensive bilateral interstitial lung disease, psychiatric illness that would limit ability to comply with study procedures, and any other medical condition that, in the opinion of the investigator, places the patient at unacceptable risk of toxicity. NB: Diabetes which, is controlled by medication does not exclude participation in the study, 16. *Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study. No history of intracranial haemorrhage or spinal cord haemorrhage. Minimum of 2 weeks between completion of radiotherapy and cycle 1 Day 1 and recovery from significant (Grade *3) acute toxicity with no ongoing, 17. *Patients unable to swallow orally administered medication and patients with, gastrointestinal disorders likely to interfere with absorption of the study medication., 18. *Pregnant or breast feeding women., 19. *Previous allogeneic bone marrow transplant., 20. *Patients with a known hypersensitivity to Olaparib or any of the excipients of the, product., 21. *Whole blood transfusions in the last 120 days prior to enrolment to the study, which may interfere with gBRCA testing (packed red blood cells and platelet

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:	Recruitment stopped
Start date (anticipated):	14-04-2016
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not available yet
Generic name:	Olaparib

Ethics review

Approved WMO Date:	25-09-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-12-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-01-2015
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-05-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-05-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-02-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-10-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-03-2021
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:	28-04-2021
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	EUCTR2014-001589-85-NL
ClinicalTrials.gov	NCT02184195
CCMO	NL50342.028.14