An Open-Label, Non-randomised, Parallel Group, Multicentre, Phase I Study to Assess the Safety and the Effect of Olaparib at Steady State on the Pharmacokinetics of the Anti-hormonal Agents Anastrozole, Letrozole and Tamoxifen at Steady State, and the Effect of the Anti-hormonal Agents on Olaparib, Following Administration in Patients With Advanced Solid Cancer

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• To evaluate the effect of olaparib on exposure to anastrozole by determination of steady-state exposure to anastrozole in the presence and absence of steady-state exposure to olaparib• To evaluate the effect of anastrozole on exposure to olaparib...

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

Summary

ID

NL-OMON40826

Source
ToetsingOnline

Brief title
D081CC00001 - Olaparib and Anti-Hormonal Treatment

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Solid Tumors

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Anti-Hormonal treatment, Olaparib, Pharmacokinetics, Phase I

Outcome measures

Primary outcome

Pharmacokinetics

In Part A, the following variables will be calculated for olaparib,

anastrozole, letrozole, tamoxifen, and the tamoxifen metabolites N-desmethyl

tamoxifen (N-DMT) and 4-hydroxy- N-desmethyl tamoxifen (endoxifen) where the

data allow:

* maximum plasma concentration at steady state (Cmax ss)

* area under the plasma concentration-time curve over the dosing interval at

steady state (AUC 0-*)

* minimum plasma concentration at steady state (Cmin ss).

These variables will be calculated for each of the following treatment periods:

* olaparib when dosed alone

* anastrozole/letrozole/tamoxifen [and metabolites] when dosed alone

* anastrozole/letrozole/tamoxifen [and metabolites] when dosed in combination with olaparib.

Pharmacokinetics will not be measured in Part B.

Secondary outcome

• Safety

Assessment of adverse events (AEs) graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.0, physical examination, vital signs (including blood pressure, pulse), standard 12-lead electrocardiogram (ECG), and evaluation of laboratory parameters (clinical chemistry, haematology and urinalysis).

Study description

Background summary

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. PARP inhibition is a novel approach to targeting tumours with deficiencies in deoxyribonucleic acid (DNA) repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair. Tumours with homologous recombination (HR) deficiencies (HRD), such as ovarian or breast cancers in patients with breast cancer gene (BRCA) 1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as they accumulate. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Study objective

• To evaluate the effect of olaparib on exposure to anastrozole by determination of steady-state exposure to anastrozole in the presence and

absence of steady-state exposure to olaparib
• To evaluate the effect of anastrozole on exposure to olaparib by determination of steady-state exposure to olaparib in the presence and absence of steady-state exposure to anastrozole
• To evaluate the effect of olaparib on exposure to letrozole by determination of steady-state exposure to letrozole in the presence and absence of steady-state exposure to olaparib
• To evaluate the effect of letrozole on exposure to olaparib by determination of steady-state exposure to olaparib in the presence and absence of steady-state exposure to letrozole
• To evaluate the effect of olaparib on exposure to tamoxifen, N-desmethyl tamoxifen (N-DMT) and 4-hydroxy-N-desmethyl tamoxifen (endoxifen) by determination of steady-state exposure to tamoxifen in the presence and absence of steady-state exposure to olaparib
• To evaluate the effect of tamoxifen on exposure to olaparib by determination of steady-state exposure to olaparib in the presence and absence of steady-state exposure to tamoxifen
• To evaluate the safety and tolerability of olaparib alone and in combination with anastrozole/letrozole/tamoxifen.

Study design

This is a non-randomised, open-label 2-part Phase I study in patients with advanced solid tumours. Part A of the study (mandatory) will assess the effect of olaparib on the Pharacokinetics (PK) of anastrozole, letrozole and tamoxifen and vice versa; Part B will allow patients (if eligible) continued access to olaparib after the PK phase and will provide additional safety data.

Intervention

Part A
Treatment Period 1
On Day 1, patients will attend the clinic as an outpatient and commence oral doses of olaparib 300 mg (administered as 2 x 150 mg tablets) twice daily (bid). On Day 5, patients will return to the clinic for their last dose of olaparib in Treatment Period 1 (morning dose only). Blood sampling and safety assessments will be conducted. Treatment Period 1 will be followed by a 4-day washout period.
Treatment Period 2
On Day 10, patients will attend the clinic as an outpatient and commence once daily doses of tamoxifen 60 mg (Cohort 1), anastrozole 1 mg (Cohort 2) or letrozole 2.5 mg (Cohort 3). Patients in Cohort 1 will return to the clinic as an outpatient on Day 14 and change to a maintenance dose of 20 mg tamoxifen once daily. All patients will return to the clinic again on the morning of Day 26 (Cohort 1), Day 19 (Cohort 2) or Day 38 (Cohort 3) and remain resident until 24 hours post-dose, during which time blood sampling and safety assessments

will be conducted.
Treatment Period 3
Patients will continue to receive the same treatment as in Treatment Period 2, concomitantly with olaparib 300 mg bid for 5 days, starting on Day 27 (Cohort 1), Day 20 (Cohort 2) or Day 39 (Cohort 3). Patients will return to the clinic on Day 31 (Cohort 1), Day 24 (Cohort 2) or Day 43 (Cohort 3) and remain resident until 24 hours post-dose, during which time blood sampling and safety assessments will be conducted.
Optional Part B
On completion of Part A, patients have the option to enter into Part B and continue to take olaparib tablets (300 mg bid), if they and the Investigator agree that this is appropriate and the baseline safety assessments for Part B are in accordance with the study inclusion and exclusion criteria. In Part B, olaparib will be given as monotherapy unless the Investigator considers a combination of olaparib and endocrine agent (anastrozole, letrozole or tamoxifen) to be appropriate; in this case the endocrine agent will be given according to routine clinical practice.
In Part B, patients will have weekly clinic visits for the first 4 weeks; thereafter, visits will be every 4 weeks. Part B will be of 12 months* duration from the date the last patient enters this part of the study; at this point the database will be closed.
During and after Part B (ie, after closure of the database), patients may continue to take olaparib until such time as their disease progresses, the Investigator believes they are no longer deriving clinical benefit, or they stop taking olaparib for any other reason. After the end of Part B, patients will be seen as per their normal routine clinical schedule and no clinical data will be collected, other than serious adverse events (SAEs).

Study burden and risks

Although patients may not initially gain any benefit from participation in Part A of the study due to the short dosing period, eligible patients may potentially gain some benefit in Part B. If the Investigator believes it is in the patient*s interest, the patient may continue treatment with olaparib until such time as their disease progresses, the Investigator believes they are no longer deriving clinical benefit, or they stop taking olaparib for any other reason.
Like all medicines, olaparib can cause adverse effects, although not everybody gets them. Very common side effect due to olaparib are: nausea or vomiting, diarrhoea, upper abdominal pain, decreased appetite, fatigue, dyspepsia dizziness, headache, dysgeusia, anaemia, neutropenia and lymphopenia, mean cell volume elevation , increase in creatinine.

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

1. Provision of written informed consent prior to any study specific procedures
2. Male or female aged >=18 years
3. Histological or cytological confirmation of any malignant solid tumour in an advanced or metastatic setting who meet one of the criteria below:
o Patients should be resistant or refractory to standard treatment if such treatment exists OR
o Patients for which no suitable effective standard therapy exists OR
o Patients with advanced breast cancer for whom anastrozole, letrozole or tamoxifen are indicated may also enter the study (postmenopausal breast cancer patients will be eligible for any of the cohorts; however, premenopausal breast cancer patients will be eligible for the tamoxifen cohort only).
4. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

o Haemoglobin (Hb) >=10.0 g/dL with no blood transfusions in the past 28 days
o Absolute neutrophil count (ANC) >=1.5 x 109/L
o Platelet count >=100 x 109/L
o Total bilirubin <=1.5 x institutional upper limit of normal (ULN) (except in the case of Gilbert's disease)
o Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <=2.5 x institutional ULN unless liver metastases are present, in which case they must be <=5x ULN
o Serum creatinine <=1.5 x institutional ULN
5. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2
6. Patients must have a life expectancy >=16 weeks
7. Evidence of non-childbearing status for women of childbearing potential, or postmenopausal status: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Day 1 of Part A.
Postmenopausal is defined as:
o Age >= 60 years
o Age <60 years and amenorrheic for 1 year or more in the absence of chemotherapy and/or hormonal treatment
o Luteinising hormone (LH), follicle stimulating hormone (FSH) and plasma oestradiol levels in the postmenopausal range for women under 60 years
o Radiation-induced oophorectomy with last menses >1 year ago
o Or surgical sterilisation (bilateral oophorectomy or hysterectomy)
8. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment, and scheduled visits and examinations
9. Patients must be on stable concomitant medication regimen (with the exception of electrolyte supplements), defined as no change in medication or dose within 2 weeks prior to start of study treatment.

Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff, its agents, and/or staff at the study site)
2. Previous enrolment in the present study
3. Exposure to an investigational product (IP) (including PARP inhibitor) within 30 days or 5 half lives (whichever is the longer) prior to enrolment
4. Prior chemotherapy within 3 weeks of study entry
5. Prior radiotherapy within 2 weeks of study entry
6. If prior endocrine treatment is given, adequate washout period is required: at least 2 weeks for anastrozole, at least 4 weeks for letrozole and at least 10 weeks for tamoxifen
7. Resting ECG with QTc >470 msec detected on 2 or more time points within a 24 hour period, or family history of long QT syndrome. If ECG demonstrates QTc >470 msec, patient will be eligible only if repeat ECG demonstrates QTc <470 msec.
8. Patients who are receiving inhibitors or inducers of CYP3A4 unless washed out prior to start of study treatment.
9. Persistent toxicities (Common Toxicity Criteria for Adverse Events [CTCAE] grade >=2) caused by previous cancer therapy, excluding alopecia and/or CTCAE grade 2 peripheral

neuropathy
10. Patients with myelodysplastic syndrome/acute myeloid leukaemia
11. Major surgery within 2 weeks of starting study treatment: patients must have recovered from any effects of any major surgery
12. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled seizures or active uncontrolled infection.
13. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders or significant gastrointestinal resection likely to interfere with absorption of the study medication
14. Patients who have gastric, gastro-oesophageal, or oesophageal cancer
15. Pregnant or breastfeeding women
16. Patients with known active Hepatitis B or C, or human immunodeficiency virus (HIV).
17. Patients with a known hypersensitivity to olaparib (all cohorts), tamoxifen (Cohort 1) anastrozole (Cohort 2), letrozole (Cohort 3), or any of the excipients of these products.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-10-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Brand name:	Femara
Generic name:	Letrozole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Not Applicable
Generic name:	Olaparib
Product type:	Medicine
Brand name:	Tamoxifen
Generic name:	Tamoxifen
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-07-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2014-000542-29-NL
ClinicalTrials.gov	NCT02093351
CCMO	NL49401.029.14