An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study of the Pharmacokinetics, Safety and Tolerability of Olaparib Following a Single Oral 300 mg Dose to Patients with Advanced Solid Tumours and Normal Renal Function or Renal Impairment.

Published: 27-08-2013
Last updated: 22-04-2024

-The primary objective of this study is to investigate the pharmacokinetics of olaparib after a single oral dose of 300 mg to patients with advanced solid tumours and mild or moderate renal impairment compared to those with normal renal function.-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON40271

Source
ToetsingOnline

Brief title
Phase 1-Olaparib/Renal

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym

1 - An Open-label, Non-randomised, Multicentre, Comparative, Phase I Study of the Ph ... 22-06-2025

Cancer, Solid tumour

Health condition

Cancer: Solid tumour (Malignant solid tumour)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Olaparib, Oncology, pharmacokinetics, Renal function

Outcome measures

Primary outcome

Pharmacokinetics (primary variables)

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

data allow: maximum plasma concentration (Cmax), time to reach maximum plasma

concentration (tmax), area under the plasma concentration-time curve from zero

to the last measurable time point (AUC0-t), area under the plasma

concentration-time curve from zero to infinity (AUC), apparent plasma clearance

following oral administration (CL/F), terminal half-life (t*), apparent volume

of distribution (Vz/F), terminal rate constant (*z) and renal clearance (CLR).

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, standard 12 lead electrocardiograms (ECGs),

physical examination, vital signs (including blood pressure, pulse), and

evaluation of laboratory parameters (clinical chemistry, haematology, and

urinalysis).

Exploratory

In Part A, plasma protein binding at 1 hour after dosing, used to calculate

free Cmax (Cmax of unbound olaparib), free AUC (AUC of unbound olaparib) and

unbound CL/F (CL/F of unbound olaparib).

Study description

Background summary

Olaparib (AZD2281, KU-0059436) is a potent polyadenosine 5*diphosphoribose [poly ADP ribose] polymerisation (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 repair deficiencies (HRD), such as ovarian cancers in patients with breast cancer gene (BRCA)1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

Study objective

-The primary objective of this study is to investigate the pharmacokinetics of olaparib after a single oral dose of 300 mg to patients with advanced solid

tumours and mild or moderate renal impairment compared to those with normal renal function.
-The secondary objective is to assess the safety and tolerability of single and multiple oral doses of olaparib in advanced solid tumour patients with mild or moderate renal impairment and in those with normal renal function.
-The exploratory objective of this study is to explore changes in protein binding of olaparib and the subsequent effects on its pharmacokinetics in patients with varying degrees of renal function.

Study design

This is a 2-part study: Part A will investigate the pharmacokinetics (PK) of olaparib in patients with mild or moderate renal impairment compared to patients with normal renal function; Part B will allow patients with mild or moderate renal impairment or normal renal function continued access to olaparib after the PK phase and will provide additional safety data. Patients with normal renal function and mild renal impairment will be recruited before those with moderate renal impairment. Pharmacokinetic data and at least 3 months of safety data from at least 3 patients with mild renal impairment will be reviewed before recruiting patients with moderate renal impairment into the study, first in Part A and then in Part B. If the safety, tolerability and PK data from the 3 patients with mild renal impairment dosed continuously with olaparib for 3 months raises safety concerns for the continuous dosing of patients with moderate renal impairment, then patients with moderate impairment will not enter the study.
Approximately 42 patients aged 18 to 75 years with advanced solid tumours are planned to be enrolled, with at least 36 evaluable patients required to complete Part A (12 patients with moderate renal impairment, 12 with mild renal impairment and 12 with normal renal function).
Part A is an open-label, parallel group, PK study. Each patient will receive a single oral dose of olaparib 300 mg (given via the tablet formulation). Patients will check into the clinic on Day 1, the evening prior to dosing (Day 1), remain resident until 24 hours after the dose of olaparib (Day 2), and then return to the clinic for assessments on Day 3 (48 hours), Day 4 (72 hours) and Day 5 (96 hours). Blood and urine samples will be collected for the determination of olaparib.
On completion of Part A, patients may be entered into Part B and continue to take olaparib tablets (300 mg twice daily [bd]) if they and the investigator agree that this is appropriate, providing the baseline safety assessments for Part B are in accordance with the study inclusion and exclusion criteria. Patients must start Part B within 2 weeks (minimum 5 days, maximum 14 days) of dosing in Part A. 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.
During and after Part B, patients may continue to take olaparib, if they and the investigator deem it appropriate, 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). Patients will return to the clinic for follow-up assessments either 30 days (±7 days) after dosing in Part A or 30 days (±7 days) after discontinuation of olaparib in Part B. If a patient discontinues olaparib during Part B, they will also attend a study treatment discontinuation visit.

Intervention

In Part A, each patient will receive a single 300 mg oral dose of olaparib (administered as 2 x 150 mg tablets).
In Part B, patients will receive 300 mg oral olaparib (administered as 2 x 150 mg tablets) twice daily for the duration of their participation.

Study burden and risks

Pre clinical and emerging clinical tolerability data from patients indicate that olaparib is generally well tolerated by patients with advanced cancer (please refer to the IB for details). Although patients may not initially gain any benefit from participation in Part A of the study due to the short dosing period, some benefit may be gained in Part B. The data generated from this study will support further development of olaparib for the treatment of cancer. The benefit/risk assessment for the conduct of this study of olaparib in patients is acceptable.

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 as a patient with renal impairment, the following criterion must be met:
1. Patients must have stable renal impairment (moderate or mild), depending on creatinine clearance estimated using the Cockcroft-Gault equation (moderate 31 to 50 mL/min; mild 51 to 80 mL/min), for at least 2 months prior to the start of the study.
For inclusion in the study as a patient with normal renal function, the following criterion must be met:
2. Calculated serum creatinine clearance *81 mL/min (using Cockcroft-Gault equation).
All patients must fulfil the following criteria:
3. Provision of written informed consent prior to any study specific procedures.
4. Patients must be *18 and *75 years of age.
5. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory or resistant to standard therapy or for which no suitable effective standard therapy exists.
6. BMI between 18-30 kg/m2
7. Normal liver and bone marrow function measured within 28 days prior to administration of IP as defined below:
* Haemoglobin (Hb) *10.0 g/dL, with no blood transfusions in the previous 28 days
* Absolute neutrophil count (ANC) *1.5 x 109/L
* White blood cells (WBC) >3 x 109/L
* Platelet count *100 x 109/L
* Total bilirubin *1.5 x institutional upper limit of normal (ULN) (except in the case of Gilbert*s disease)
* Aspartate aminotransferase or serum glutamic oxaloacetic transaminase (AST), alanine aminotransferase or serum glutamic pyruvic transaminase (ALT) *2.5 x institutional ULN unless liver metastases are present in which case it must be *5x ULN
8. Eastern Cooperative Oncology Group (ECOG) performance status * 2.
9. Patients must have a life expectancy *12 weeks.
10. 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 the first treatment period in Part A. Postmenopausal is defined as:
* Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
* Luteinising hormone and follicle-stimulating hormone levels in the postmenopausal range for women under 50 years of age
* 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. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
12. Patients must be on a stable concomitant medication regimen (with the exception of electrolyte supplements), defined as no changes in medication or in dose within 2 weeks prior to start of olaparib dosing, except for bisphosphonates, denosumab and corticosteroids, which should be stable for at least 4 weeks prior to start of olaparib dosing.

Exclusion criteria

Patients must 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, its agents and/or staff at the study site).
2. Previous enrolment in the present study.
3. Participation in another clinical study with an investigational medicinal product (IP) during the last 14 days (or a longer period depending on the defined characteristics of the agent used).
4. Renal transplant and end stage renal disease (ESRD) patients.
5. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 2 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used). 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 4 weeks prior to treatment.
6. Patients who have received or are receiving inhibitors or inducers of CYP3A4 within the washout period.
7. For Part A only, drugs which affect creatinine clearance such as cephalosporin antibiotics, ascorbic acid, trimethoprim, cimetidine and quinine should not be used within the 7 days prior to dosing with olaparib.
8. Treatment in the previous 3 months with any drug known to have a well-defined potential for hepatotoxicity (eg, halothane).
9. Persistent toxicities (*CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia.
10. Patients with myelodysplatic syndrome/acute myeloid leukaemia.
11. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Patients with asymptomatic brain metastases or with symptomatic but stable brain metastases 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.

12. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of major surgery.
13. Patients considered a poor medical risk due to a serious uncontrolled medical disorder, non malignant systemic disease, uncontrolled seizures, or active uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive bilateral interstitial lung disease on high resolution computer tomography (HRCT) scan, or any psychiatric disorder that prohibits obtaining informed consent.
14. Patients with a history of heart failure or left ventricular dysfunction.
15. Patients who have gastric, gastro-oesophageal or oesophageal cancer.
16. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of olaparib.
17. Breastfeeding women.
18. Immunocompromised patients eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV).
19. Patients with known active hepatic disease (eg, hepatitis B or C).
20. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
21. Resting ECG at screening with measurable QTc >470 msec at 2 or more time points within a 24 hour period or family history of long QT syndrome.
22. Clinical judgment by the investigator that the patient should not participate in the study.

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):	21-01-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Olaparib
Generic name:	AZD2281

Ethics review

Approved WMO Date:	27-08-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-10-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-12-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-01-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	30-06-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2013-002225-30-NL
ClinicalTrials.gov	NCT01894256
CCMO	NL45346.068.13