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

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

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

Summary

ID

NL-OMON45128

Source
ToetsingOnline

Brief title
Phase 1-Olaparib/Hepatic

Condition

- Other condition
- Hepatic and hepatobiliary disorders

Synonym
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: Hepatic function, Olaparib, Oncology, pharmacokinetics

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 measureable time point (AUC 0-t), area under the plasma

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

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

of distribution (Vz/F) and terminal rate constant (*z).

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 (PK) of olaparib after a single oral dose of 300 mg to patients with advanced solid tumours and mild or moderate hepatic impairment compared to those with normal hepatic function.
-The secondary objective is to investigate the safety and tolerability of single and multiple oral doses of olaparib in advanced solid tumour patients with mild or moderate hepatic impairment and in those with normal hepatic function.
-The exploratory objective of this study is to explore changes in protein binding of olaparib and the subsequent effects on its PK in patients with varying degrees of hepatic function.

Study design

This is a 2-part study in patients with advanced solid tumours. Part A will investigate the PK of olaparib in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function; Part B will allow patients with mild or moderate hepatic impairment or normal hepatic function continued access to olaparib after the PK phase and will provide additional safety data. Patients with normal hepatic function and mild hepatic impairment will be recruited before those with moderate hepatic impairment. Pharmacokinetic data and at least 3 months of safety data from at least 3 patients with mild hepatic impairment will be reviewed before recruiting patients with moderate hepatic 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 hepatic impairment dosed continuously with olaparib for 3 months raises safety concerns for the continuous dosing of patients with moderate hepatic impairment, then patients with moderate hepatic impairment will not enter the study.
Approximately 30 patients are planned to be enrolled with at least 24 evaluable patients required to complete Part A (8 patients with normal hepatic function, 8 with mild hepatic impairment [Child-Pugh A] and 8 with moderate hepatic impairment [Child-Pugh B]). An evaluable patient is defined as a patient having full PK sampling to 96 hours post-dose of olaparib. Groups will be recruited so that, if possible, at least 3 patients of each sex are in each group.
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 samples for the determination of olaparib will be collected during Part A.
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 their last dose in the last treatment period in Part A or 30 days (±7 days) after discontinuation of olaparib in Part B. If a patient discontinues investigational product (IP) 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) bd 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 hepatic impairment:
1. Patients must have stable mild hepatic impairment (as defined by Child-Pugh classification), for at least 1 month prior to the start of the study or stable moderate hepatic impairment (as defined by Child-Pugh classification), for at least 2 weeks prior to the start of the study, see Section 6.2.1.1. Patients with hepatic metastases and/or HCC are eligible for the study, providing the hepatic metastases or HCC are not the sole reason for any changes in liver function satisfying the criteria for mild or moderate hepatic impairment as defined by the Child Pugh criteria.
Patients must have globally impaired hepatic function to participate in the study.
For inclusion in the study as a patient with normal hepatic function, the following criteria must be met:
2. Negative result for serum hepatitis B surface antigen and hepatitis C antibody
3. Total bilirubin *1.5 x institutional upper limit of normal (ULN), albumin and prothrombin time within normal limits and must not have ascites (unless related to disease under study) or encephalopathy
4. 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 *5 x ULN
All patients must fulfill the following criteria:
5. Provision of written informed consent prior to any study specific procedures.
6. Patients must be *18 years of age.
7. Histologically or, where appropriate, cytologically confirmed malignant solid tumour

refractory or resistant to standard therapy or for which no suitable effective standard therapy exists. In case of HCC, histological or cytological confirmation is not required in the following situations, as per international guidelines of the scientific societies European Society for Medical Oncology (ESMO) and American Association for the Study of Liver Diseases (AASLD):
* Nodules >2 cm with a typical feature of HCC on a dynamic imaging technique, or any nodule associated with *-fetoprotein (AFP) concentration >400 ng/ml or rising AFP on sequential determinations, do not require biopsy but should be considered as proven HCC (Jelic et al
2010).
* Nodules >1 cm found on ultrasound screening of a cirrhotic liver should be investigated further with either 4-phase multi-detector CT scan or dynamic contrast enhanced MRI. If the appearances are typical of HCC (ie, hyper-vascular in the arterial phase with washout in the portal venous or delayed phase), the lesion should be treated as HCC. If the findings are not characteristic or the vascular profile is not typical, a second contrastenhanced study with the other imaging modality should be performed, or the lesion should be biopsied (level II) (Bruix et al 2011).
8. Normal organ and bone marrow function measured within 28 days prior to administration of IP as defined below:
* Haemoglobin *9.0 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 *75 x 109/L
* Serum creatinine *1.5 x institutional ULN
9. Calculated serum creatinine clearance >50 mL/min (using Cockcroft-Gault formula or by 24-hour urine collection)
10. Eastern Cooperative Oncology Group (ECOG) performance status * 2.
11. Patients must have a life expectancy *8 weeks.
12. 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).
13. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
14. 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 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, its agents and/or staff at the study site).
2. Previous enrolment in the present study.
3. Treatment with any investigational product (IP) during the last 14 days (or a longer period depending on the defined characteristics of the agent used).
4. Treatment in the previous 3 months before dosing in this study with any drug known to have a well defined potential for hepatoxicity (eg, halothane).
5. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 2 weeks prior to study treatment. 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 (see Section 5.6 for guidelines and washout periods).
7. Toxicities (*CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia.
8. 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.
9. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of major surgery.
10. 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.
11. Patients with a history of heart failure or left ventricular dysfunction.
12. Patients who have gastric, gastro-oesophageal or oesophageal cancer.
13. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders or significant gastrointestinal resection likely to interfere with the absorption of olaprib.
14. Breastfeeding women.
15. Immunocompromised patients eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV).
16. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
17. Resting ECG with measurable QTc >470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.
18. Clinical judgment by the investigator that the patient should not participate in the study.
In addition to exclusion criteria 1 to 18, patients with normal hepatic function should not enter the study if the following exclusion criterion is fulfilled:
19. History or presence of hepatic disease known to interfere with the absorption, distribution, metabolism or excretion of olaparib.

In addition to exclusion criteria 1 to 18, patients with mild or moderate hepatic impairment should not enter the study if the following exclusion criteria are fulfilled:
20. Patients with liver metastases or hepatic encephalopathy (as described in the Child Pugh Classification system, see Section 6.2.1.1).
21. Fluctuating or rapidly deteriorating hepatic function as indicated by widely varying or worsening of clinical and/or laboratory signs of hepatic impairment within the screening period (eg, advanced ascites, fever, active gastrointestinal bleeding).
22. Change in dose regimen of medically required medication within the last 2 weeks before screening and/or the use of disallowed co-medication in the 3 weeks prior to admission to the clinic.
23. Presence of a hepatocellular carcinoma or an acute liver disease caused by drug toxicity or by an infection.
24. Severe portal hypertension or surgical porto-systemic shunts.
25. Biliary obstruction or other causes of hepatic impairment not related to parenchymal disorder and/or disease of the liver.
26. Oesophageal variceal bleeding within the past 2 months.
27. Anticoagulant therapy with warfarin or related coumarins.

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):	13-03-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	14-08-2013
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:	05-12-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-12-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-10-2015
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)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-06-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-06-2017
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	EUCTR2013-002246-37-NL

Register	ID
ClinicalTrials.gov	NCT01894243
CCMO	NL45320.068.13