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Efficacy and safety of olaparib in relapsed and refractory chronic lymphocytic leukaemia patients with an 11q deletion or ATM mutation and relapsed/refractory patients with Tprolymphocytic leukaemia and mantle cell lymphoma

Submission date 05/01/2010 Registration date 09/02/2010	Recruitment status No longer recruiting Overall study status Completed	[X] Prospectively registered	
		Protocol	
		[X] Results	
Last Edited 31/03/2022	Condition category Cancer	[_] Individual participant data	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-new-drugolaparib-leukaemia-mantle-cell-lymphoma-that-has-stopped-responding-treatment-piclle

Contact information

Type(s) Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers RG_08_160

Study information

Scientific Title

Phase I/II clinical trial to assess the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase (PARP) -inhibitor, in relapsed and refractory chronic lymphocytic leukaemia patients with an 11q deletion or ATM mutation and relapsed/refractory patients with T-prolymphocytic leukaemia and mantle cell lymphoma

Acronym

PICCLe

Study objectives

Poly (ADP-ribose) polymerase (PARP-1) is a principal component of the cellular response to deoxyribonucleic acid (DNA) single strand breaks (SSBs). Recent studies have shown that PARP inhibition is cytotoxic to cells with mutations in BRCA1 and BRCA2 genes that are defective in homologous recombination (HR) DNA repair. The rationale of these studies was that the generation of specific DNA lesions by PARP-1 inhibition requires a functional HR repair pathway for resolution. In the absence of functional components of HR machinery, such as BRCA1 or BRCA2, the use of the PARP1 inhibitor leads to the accumulation of unrepaired DNA lesions ultimately resulting in cell death, thus providing a mechanism for specific killing of BRCA1 /BRCA2 negative cells. These studies inferred that tumours with deficiencies in other components of HR repair, potentially, could be treated in a similar manner, using PARP inhibitors.

Ataxia telangiectasia mutated (ATM) also takes part in double strand break (DSB) repair by HR and ATM mutant cells are defective in HR repair. Consistent with this, it has subsequently been shown that PARP inhibition has a cytotoxic effect on cells in which levels of other components of HR DNA DSB repair have been reduced by siRNA - ATM, Rad51, Rad54, ATR, RPA1, DSS1, CHK1,2 and FANC genes.

There are a number of observations supporting the interaction of ATM and PARP-1 in response to DNA DSBs thus providing the rational for a chronic lymphocytic leukaemia (CLL) trial with the PARP inhibitor olaparib.

Ethics approval required

Old ethics approval format

Ethics approval(s) Oxford Research Ethics Committee, pending as of 05/01/2010

Study design Single-arm multicentre rolling phase I/II study

Primary study design Interventional

Secondary study design

Non randomised study

Study setting(s) Hospital

Study type(s) Treatment

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied

Chronic lymphocytic leukaemia

Interventions

Phase I:

Dose escalation study (cumulative 3 + 3 design) of the PARP inhibitor, olaparib (previously known as AZD2281 and KU-0059436). Two cohorts: 200 mg twice daily (bd) and 400 mg bd for a minimum of 8 weeks. Patients may continue to receive olaparib at the allocated dose for as long as there appears to be clinical benefit (at the discretion of the Investigator). The maximum tolerated dose (MTD) identified in phase I will be used as the dose of olaparib in phase II. All patients will be followed-up for a minimum of 5 years.

Phase II:

All patients will receive olaparib (at the dose defined in Phase I) continuously until disease progression or unacceptable toxicity is observed. Response will be assessed at week 16. All patients achieving stable disease, partial remission or complete remission will be offered further treatment with olaparib after 16 weeks.

Intervention Type

Drug

Phase I/II Phase I/II

Drug/device/biological/vaccine name(s) Olaparib

Primary outcome measure

Demonstration of sufficient efficacy in patients with ATM deficient, relapsed and refractory CLL to warrant further investigation in a phase III trial. Sufficient efficacy is defined as at least 20% of patients showing a clinical response (defined as either a complete remission or partial remission) after 16 weeks of therapy with olaparib.

For CLL patients, clinical response will be defined according to guidelines from the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL). Response for mantle cell lymphoma patients is classified according to the definitions recommended by the International Workshop to Standardise Response Criteria for non-Hodgkin's lymphomas. There are no published response criteria for T-PLL and response is defined as for CLL.

Secondary outcome measures

1. To investigate whether there is evidence of efficacy within relapsed/refractory CLL, mantle cell lymphoma and T-PLL patients dependent on the ATM status of the remaining ATM allele 2. To measure the progression free survival and overall survival of patients treated with olaparib 3. In all patients with CLL, MCL and T-PLL a secondary outcome will be to determine the safety, tolerability and toxicity of this treatment (graded according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v4.0)

All measured after the last patient has received at least 16 weeks of treatment.

Overall study start date 01/03/2010

Completion date

. 01/03/2014

Eligibility

Key inclusion criteria

1. Relapsed or refractory chronic lymphocytic leukaemia (CLL), mantle cell lymphoma or Tprolymphocytic leukaemia (T-PLL) patients (World Health Organization [WHO] Classification of Haematopoietic and Lymphoid Tissues, Fourth Edition) who are not considered to be appropriate for further conventional treatment

 CLL patients only: confirmation of chromosome 11q deletion by fluorescent in situ hybridisation (FISH) or an ATM mutation (ATM mutation requires the presence of both a predicted ATM mutation and demonstration of reduced ATM dependent phosphorylation)*
Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2

4. Aged 18 years or older, either sex

5. Written informed consent

6. Not known to be positive for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen and hepatitis C antibody

7. Estimated life expectancy of greater than 16 weeks

*Please note that confirmation of 11q deletion or an ATM mutation prior to registration is not required for CLL patients taking part in phase 1 (dose escalation phase). All other eligibility criteria apply to both phase 1 and phase 2.

Participant type(s)

Patient

Age group Adult

Lower age limit 18 Years

Sex Both

Target number of participants

Total final enrolment

15

Key exclusion criteria

1. Receiving treatment for CLL, mantle cell lymphoma or T-PLL including corticosteroids (greater than 10 mg prednisone/day or equivalent) or have received treatment for CLL, mantle cell lymphoma or T-PLL for the 4 weeks prior to study entry

2. Receiving corticosteroids (at a dose greater than 10 mg prednisone/day or equivalent) for other medical conditions

3. Previous treatment with a PARP-inhibitor, including olaparib

4. A known hypersensitivity to olaparib or any excipient of the product

5. Treatment with any investigational product within 28 days of registration

6. Receiving or have received the following inhibitors of CYP34A:

6.1. Azole antifungals

6.2. Macrolide antibiotics

6.3. Protease inhibitors

7. Impaired hepatic or renal function as defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2.5 x upper limit of normal (ULN), bilirubin greater than 2 x ULN, serum creatinine greater than 2 x ULN

8. Persisting (greater than 8 weeks) severe pancytopenia due to previous therapy rather than disease (neutrophils less than 0.5 x 10^9/L or platelets less than 50 x 10^9/L)

9. Central nervous system (CNS) involvement with CLL

10. Cardiac dysfunction as defined as: myocardial infarction within 6 months of study entry, New York Heart Association (NYHA) class III/IV heart failure, unstable angina, unstable cardiac arrhythmias

11. Any other malignancy which has been active or treated within the past 3 years, with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and non-melanoma skin lesions or endometrial carcinoma stage 1A grade 1

12. Unable to swallow orally administered medications

13. Patients with uncontrolled seizures

14. Active infection requiring systemic antibiotics, antifungal or antiviral drugs

15. Concurrent severe and/or uncontrolled medical condition (e.g. severe chronic obstructive pulmonary disease [COPD], severe Parkinsons's disease) or psychiatric condition

16. Women of child-bearing potential and men who have partners of child-bearing potential who are not willing to practise effective contraception for the duration of the study and for three months after the last study drug administration

17. Pregnancy or lactating women. Pre-menopausal women of child bearing potential must have a negative urine or serum pregnancy test within 7 days prior to registration.

Date of first enrolment

01/03/2010

Date of final enrolment 01/03/2014

Locations

Countries of recruitment England **Study participating centre University of Birmingham** Birmingham United Kingdom B15 2TT

Sponsor information

Organisation University of Birmingham (UK)

Sponsor details Research and Commercial Services Birmingham England United Kingdom B15 2TT

Sponsor type University/education

Website http://www.bham.ac.uk/

ROR https://ror.org/03angcq70

Funder(s)

Funder type Charity

Funder Name Leukaemia Research Fund (UK)

Results and Publications

Publication and dissemination plan

To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

Not provided at time of registration

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details results	Date created	Date added	Peer reviewed?	Patient-facing?
<u>Results article</u>		01/08/2018		Yes	No
<u>Plain English results</u>			31/03/2022	No	Yes