ISRCTN34386131 https://doi.org/10.1186/ISRCTN34386131

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 T-prolymphocytic leukaemia and mantle cell lymphoma

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

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-new-drug-olaparib-leukaemia-mantle-cell-lymphoma-that-has-stopped-responding-treatment-piclle

Contact information

Type(s)
Scientific

Contact name
Dr Guy Pratt

Contact details
School of Cancer Sciences
University of Birmingham
Birmingham
United Kingdom
B15 2TT

Additional identifiers

Protocol serial number
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

Primary study design
Interventional

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

Study type(s)
Treatment

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
Phase I/II

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

Primary outcome(s)
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.

Key secondary outcome(s)
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.

Completion date
01/03/2014

Eligibility

Key inclusion criteria
1. Relapsed or refractory chronic lymphocytic leukaemia (CLL), mantle cell lymphoma or T-prolymphocytic 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
2. 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)*
3. 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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

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
United Kingdom

England

Study participating centre
University of Birmingham
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University of Birmingham (UK)

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Leukaemia Research Fund (UK)

Results and Publications

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	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/08/2018		Yes	No
Plain English results			31/03/2022	No	Yes