A Phase 1, Open-Label, Multicentre, Non-Randomized Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of AZD4573, a Potent and Selective CDK9 Inhibitor, in Subjects with Relapsed or Refractory Haematological Malignancies

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Primary Objective:Assess the safety and explore the biologically effective dose (BED) and/or the maximum tolerated dose (MTD) and/or the recommended Phase II dose (RP2D) of AZD4573 in patients with relapsed or refractory haematological...

Ethical review	Approved WMO
Status	Completed
Health condition type	Lymphomas NEC
Study type	Interventional

Summary

ID

NL-OMON50684

Source
ToetsingOnline

Brief title
AZD4573

Condition

- Lymphomas NEC

Synonym
Relapsed or Refractory Haematological Malignancies - Some sort of blood cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Blood cancer, CDK 9 Inhibitor, FIH, Relapsed or Refractory Haematological Malignancies

Outcome measures

Primary outcome

Safety parameters:

Frequency, severity, and relationship to study drug of any treatment-emergent adverse events or abnormalities of laboratory tests; DLTs; vital signs; ECGs; serious adverse events (SAEs); and adverse events leading to discontinuation of study treatment.

Pharmacokinetic parameters:

The following PK sampling timepoints applies to those patients enrolled into Cohorts 2A/B and 3A/B: schedules can be found in protocol synopsis.

The timing of these samples may be adjusted, dependent upon ongoing PK analysis and interpretation. PK parameters to be estimated include maximum concentration (Cmax), area under the curve (AUC), half-life clearance and volume of distribution. Additional parameters may be calculated as appropriate.

Surplus plasma samples may be analysed for potential metabolites of AZD4573. The data from this sample analysis may be pooled and these data will be exploratory and the results of any analysis may not be available at the end of the study. The results of this analysis if undertaken may not be reported in the final clinical study report (CSR).

For Cohorts 1-3, ECGs will be collected for central analysis according to the schedule below:

• Screening (Single ECG only)

• Cycles A-D and Cycle 1, Day 1 (triplicate ECGs):

* Pre-dose (up to 2 hours prior to infusion) and 1, 2, 4, 7 (7 for Cohort 2 only), 8 (8 for Cohort 3 only), 10, and 24 hours (i.e., Day 2) after starting the infusion (triplicate ECG will only be taken at each dosing day during which a patient is receiving a dose to which the patient was not exposed to previously, otherwise single ECGs apply).

• Cycles 2-8: On Day 1 of each cycle, within 30 minutes after the end of infusion (Single ECG only)

• Safety-follow up visit (Single ECG only)

Pharmacodynamic and Biomarker Parameters:

Whole blood samples for immediate on-site peripheral blood mononuclear cell (PBMC) isolation will be collected from all patients at screening and Day 1 of each new dose (i.e., any dose which the patient had not been previously exposed to).

The timing of these samples may be adjusted dependent upon ongoing PK and pharmacodynamic analysis and interpretation.

For each new dose, samples will be collected at the following time points:

• Pre-dose (up to 2 hours prior to infusion), 2, 4, 7 (7 for Cohort 2 only), 8 (8 for Cohorts 3 to 5 only) and 24 hours after starting the infusion.

Additional Exploratory Biomarker Parameters:

Archival tumour tissue (blocks or slides) will be required, if available, from all enrolled patients. Additional bone marrow aspirate from samples taken at screening, and/or any time on study (i.e., disease assessment/confirmation of complete response), will be used for exploratory biomarker testing.

An optional bone marrow aspirate collection or tumour biopsy is requested at disease progression.

For all patients in Arm B (e.g., patients with AML, ALL, CLL, who are likely to have significant levels of tumour cells in their peripheral blood) an additional whole blood sample for exploratory biomarkers will be taken at:

• Screening

• Pre-dose for Cycle A (up to 2 hours prior to infusion)

• Cohort 3B only: Pre-dose on Cycle B, Day 1 and Cycle C, Day 1 (up to 2 hours prior to infusion)

• Cohort 3B only: Pre-dose, Cycle 1 Day 1 (up to 2 hours prior to infusion)

• Disease progression

These tissues (i.e., blood, archived tumour tissue, bone marrow aspirates and tumour biopsies) will be used to assess potential biomarkers of response and/or resistance (and if appropriate, pharmacodynamic responses) to AZD4573.

Additional plasma samples will be collected from all patients, to assess exploratory biomarkers at the timepoints below:

• Screening

• For each dose during ramp-up Cycles A-D:

* Pre-dose (within 2 hours before start of dosing)

* 4 hours after start of the infusion (± 30 minutes)

* 10 hours after start of the infusion (± 1 hour)

* 24 hours (i.e., Day 2) after start of infusion (± 1 hour)

• Samples also to be taken at 96 hours (2/+12 hours) post start of infusion and pre-dose the following infusion (within 4 hours) if patient has increases in LFTs/bilirubin (defined as any elevated transaminases of Grade 3 or above or fulfilling potential Hy*s Law criteria) and chemistry panel testing is being performed

For any elevated LFTs/bilirubin that is observed with subsequent dosing with AZD4573, liver safety biomarker sampling should be performed using the timepoints outlined above (exception of screening sample not required).

Efficacy parameters:

• Overall response rate (ORR)

• Duration of response (DOR)

• Progression-free survival PFS)

• Overall survival (OS)

• Minimal residual disease (MRD) for applicable histologies/disease indications

(e.g., CLL)

Secondary outcome

n.a.

Study description

Background summary

Cyclin-dependent kinases (CDKs) represent a family of closely related serine/threonine kinases that bind to their cognate regulatory subunits, known as cyclins, to form active heterodimeric complexes. Several CDK/cyclin complexes play crucial roles in regulating cell cycle progression (CDK1, 2, 4, 6), however more recently they have also been implicated in transcription and mRNA processing (Lim and Kaldis 2013).

Regulation of transcription is a complex process governed in part through activity of CDK9 (Bywater et al. 2013). Following successful transcription initiation, RNA polymerase II (RNAP2) pauses downstream of the transcription start site, which serves as a checkpoint and allows for the rapid, synchronous activation of genes and integration of multiple regulatory signals before proper elongation can proceed (Gilchrist et al. 2010, Adelman and Lis. 2012). To release RNAP2 from this pause and permit subsequent elongation, multiple CDK9-mediated phosphorylation events are required. First, phosphorylation of the elongation repressive complex DRB Sensitivity Inducing Factor-Negative Elongation Factor (DSIF-NELF) results in the dissociation of NELF from RNAP2 while converting DSIF to a positive elongation factor. CDK9 also phosphorylates the carboxyl-terminal domain (CTD) of RNAP2, which is comprised of 52 heptapeptide repeats (YSPTSPS), at the serine 2 (Ser2) position in the final step before elongation can proceed (Sanso and Fisher 2013).

As an integral node of the transcription regulatory network, CDK9 represents a potential target for cancer therapy. Short-term inhibition of CDK9 results in transient transcriptional repression and rapid downregulation of genes with short-lived mRNAs and labile proteins (Booher et al. 2014). This therefore

provides a therapeutic opportunity to treat tumours preferentially dependent on target key driver oncogenes which are rapidly turned over without having broad toxicity related to general transcriptional repression. Two such genes are Myeloid Cell Leukaemia 1 (MCL1) and MYC (Yang et al. 1996, Stewart et al. 2010, Hann and Eisenman 1984). Mcl-1 is an anti-apoptotic member of the B-cell Lymphoma-2 (Bcl-2) family, and its amplification and overexpression have been linked to increased survival of and chemotherapy resistance in various cancers. c-Myc is a proto-oncogenic transcription factor that coordinates diverse transcription programs and is overexpressed through amplification or genomic rearrangement in multiple indications. Given the pivotal role played by Mcl-1 and c Myc in tumour cell growth and survival and tumour maintenance, depletion of these oncoproteins in specific tumour contexts results in rapid cell death and tumour regressions. CDK9 therefore represents an intriguing target to indirectly and transiently reduce the level of these oncoproteins through transcription regulation to drive oncogene addicted tumour cells toward cell death, while sparing normal cells and tissues not dependent on these and other short half-life pro-tumour survival proteins.

Several multi-CDK inhibitors have been progressed in clinical trials, including Dinaciclib which is able to reduce levels of Mcl-1 in relapsed/refractory chronic lymphocytic leukaemia (rrCLL) patients and induce clinical responses attributed to CDK9 inhibition (Flynn et al. 2015). However, a more potent and selective CDK9 inhibitor which has appropriate pharmacokinetics for tuneable target engagement and an optimal dose/schedule, leading to improved efficacy as single agent or in combination and/or therapeutic index, is warranted.

AZD4573 (formerly known as AZ13810325) is a potent inhibitor of CDK9 with nanomolar potency against the enzyme (IC50 <4 nM) and selectivity over other CDK family members (>5.8 fold). AZD4573 decreases pSer2RNAP2 levels linked to reduction of Mcl-1 and c-Myc and rapid and preferential induction of apoptosis in a broad range of human cancer cell lines derived from haematological malignancies. AZD4573 demonstrates significant antitumour activity in vivo associated with transient CDK9 inhibition across a range of tumour xenograft models as single agent when dosed intermittently and also demonstrated improved depth and duration of response when combined with a number of standard of care or other targeted agents in vivo.

The purpose of this study is to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PDx) and preliminary antitumour activity of AZD4573 in patients with relapsed or refractory haematological malignancies.

Study objective

Primary Objective:
Assess the safety and explore the biologically effective dose (BED) and/or the maximum tolerated dose (MTD) and/or the recommended Phase II dose (RP2D) of

AZD4573 in patients with relapsed or refractory haematological malignancies

Secondary Objective:
• Assess the plasma pharmacokinetics (PK) of AZD4573
• Assess preliminary tumour response/activity of AZD4573

Exploratory Objectives:
• Assess the pharmacodynamics (PDx) of AZD4573.
• Assess biomarkers that may correlate with AZD4573 mechanism of action, including response and/or resistance to AZD4573.

Exploratory analyses may be performed retrospectively after completion of the clinical trial itself. Where available prior to finalisation, results from exploratory analyses will be reported in the Clinical Study Report (CSR). Where testing is performed after the study has completed, these results may be added in a CSR addendum.

Study design

This study is a multicentre, open-label, first in human, non-randomised, phase 1, dose-escalation study including an intra-patient ramp-up.
The study consists of two, parallel dose escalation arms, namely:
• Patients with relapsed or refractory haematological malignancies (all comers excluding AML/ALL/high-risk MDS/CMML/CLL and Richter*s syndrome), herein referred to as Arm A.
• Patients with relapsed or refractory AML, ALL, high-risk MDS, CMML, CLL and Richter*s syndrome, herein referred to as Arm B.

Patients in Arm B are most likely to have significant levels of tumour cells in their peripheral blood and may have an increased risk of TLS due to disease burden.
The intention where feasible is for both Arm A and Arm B to follow the same ramp-up and dose escalation steps, unless otherwise indicated by the review of ongoing and emerging safety/efficacy data.
The ramp-up period is defined as Cycles A-D, in which each ramp-up dose is a new cycle. The target dose is defined as starting at Cycle 1 following the ramp-up period. See the dosing schedules table in protocol synopsis.

A Safety Review Committee (SRC) which includes the Principal Investigators, is in place and is tasked with the review of the available safety data (adverse events and available PK/PD data) prior to the SRC making decisions on opening next cohorts or changing the dose schedule. Refer to the current version of the SRC charter for specifics. All decisions are and will be documented in writing in the form of meeting minutes.
Given the potential for those subjects in Arm B to have an increased risk of TLS due to disease burden, Arm A Cohort 1 was started

At the time of protocol amendment 7.0, Cohorts 1A and 1B are completed. As of the IB data cut-off of 20 July 2019, no patients had yet been enrolled under the 4-week DLT period. If additional data are required on safety, tolerability or efficacy then cohort expansions at these doses/schedules may be opened or alternative doses/schedules explored, but the dose will be below 18 mg.
All available data from completed and ongoing cohorts will be used to explore safe and efficacious dose and schedules. Modelling may be used at the end of the study to support a Recommended Phase II Dose (RP2D).
The maximum tolerated dose (MTD) was originally defined as the highest dose level for which < 33% of the patients experience a DLT during the 8-week DLT review period; for cohorts with a 4-week DLT assessment period (Cohort 3) the definition is < 25% to reflect the shorter period of DLT evaluation. A biologically effective dose (BED) may be determined in addition to, or instead of, a MTD.
As per the latest IB data cut-off (20 July 2019), 30 patients have been dosed with AZD4573 as monotherapy (Cohort 1A [9], Cohort 1B [5], Cohort 2A [10], Cohort 2B [6]).

Intervention

Intravenous injection of AZD4573 with monitoring afterwards, patients divided in different arms. Dose of IV injection modified in cohort-system as stated in the protocol.

Study burden and risks

This is the first time the study drug AZD4573 is used on humans. The study drug may cause side effects. Findings based on animal studies, which may potentially be observed in humans, and based on early findings in humans in this study are summarized below. Side effects can vary from mild to very serious and may vary from person to person. The patient may experience none, some, or all of those listed. It is also possible that unexpected side effects might occur.

• Tumour Lysis Syndrome (TLS)
This is a complication that can occur during the treatment of cancer, where large amounts of tumor cells are killed off (lysed) by the treatment. TLS can result in nausea and vomiting, but more seriously in, acute kidney failure, seizures, irregular heartbeat and death. The patient will be closely monitored for signs of TLS and given treatment to prevent serious complications, the patient may need to remain in the hospital for longer than specified above as per study doctor*s decision., so the doctor needs to follow the patient closely. If the patient experiences TLS after dosing, the patient may need to remain in hospital longer than 2 days as per study doctor decision.
• Diarrhoea
The patient may experience diarrhoea, at the time of, and in the hours

immediately after being given AZD4573. The study doctor will give the patient treatment to prevent this, as well as ensuring the patient stays well hydrated with intravenous fluids.
• Decrease in white blood cells
This means the patient has an increased risk for episodes of fever mostly caused by infections (bacterial, fungal, viral infections).
• Decreases in red blood cells and platelets
A decrease in platelets in the blood results in easy bruising, bleeding from the gums or blood in the stools. It can also lead to life- threatening bleeding anywhere in the body (which you will be monitored for). A decrease in red blood cells can result in dizziness and can make the patient feel tired.
• Effects on liver enzymes (an enzyme is a type of protein) and/or bilirubin (bilirubin is a yellow/orange substance in the blood made by normal breakdown of red blood cells)
Treatment with AZD4573 may cause an increase in blood levels of some liver enzymes and/or bilirubin. These increases usually are not associated with clinical symptoms and return to pre-treatment levels within 1 week, and most of the time within 3 days. It is not known whether these increases in liver enzymes and/or bilirubin can damage patients' liver in the long term. Liver enzymes and bilirubin levels will be monitored closely by the study doctor. If patients are affected by liver enzyme and/or bilirubin increases their doctor will discuss with them whether or not to continue with AZD4573 treatment based on their individual circumstances.
• Effects on pancreas enzyme levels
Transient changes in pancreas enzyme (enzymes are proteins that accelerate chemical reactions) tests results indicate abnormal pancreas function. This is usually without any symptoms. If you have any symptoms (e.g. pain) associated with pancreas enzyme elevations, you may need to undergo an ultrasound and/or a computer tomography (CT)-scan, because there may be an inflammation of your pancreas.
• Effects on adrenal gland function.
Initial changes to the adrenal gland function usually occur without any symptoms.The adrenal gland function will be tested regularly.
• Effects on the gastrointestinal system
Nausea and vomiting are common with AZD4573, your study doctor will give you treatment to help prevent and treat this. It is important that you remain well hydrated. You may experience bowel inflammation and possible weight loss.
• Possible effect on the heart
There has been a single case of possible mild heart attack in a patient taking AZD4573 that fully recovered. It is not known whether AZD4573 caused this. No other patients have experienced a heart attack whilst receiving AZD4573. Heart rate increase has also been noted in some patients; again, it is not known whether AZD4573 causes this. Your heart will be monitored closely during the course of the study by means of ECG and blood tests. Patients should inform their study doctor immediately if they experience any chest pain or palpitations.
• Concomitant mediation

AZD4573 can interact in the body with other concomitant drugs the patient might take, therefore these should be avoided (the study doctor will be able to provide further advice on this).

The physician will closely monitor the patients' health and if possible will treat the patient to minimize the symptoms. If needed the dose of AZD4573 will be changed. If needed the dose of the study drug will be changed.
There may be risks involved in taking this study drug AZD4573 that have not yet been discovered. There is always a risk involved in taking an investigational drug. If the patient suffers any side effects or injuries, or the condition gets worse, the patient needs to tell the study doctor immediately so he can receive appropriate care.

Other risks and discomforts:
Blood draws
There is a small risk of side effects from drawing blood for the tests that the patient will have throughout the study. Drawing blood from a vein may cause local pain, bruising, fainting, and very rarely, infection at the site of the blood draw.

Injection site reaction
There is a small risk of side effects from receiving study drug directly into the vein by infusion, which may cause local pain, bruising, blood clot or infection at the site of injection.

Electrocardiogram (ECG)
After an ECG test, the 12 self-adhesive electrodes are removed from the skin. The patient may have mild irritation, slight redness, and itching at the places on the skin where the recording patches are placed. The patient may also have to have his chest shaved for this procedure.

Bone marrow biopsy and aspiration
The bone marrow biopsy and aspiration will be done at the hospital by a trained doctor. It may be done under local anaesthesia because bone marrow aspiration can cause brief but sharp pain. The patient will be fully awake during the procedure, but the aspiration and biopsy site will be numbed to reduce pain. If the patient feels anxious about pain, he may be given an IV medication so that the patient is either completely or partially sedated (asleep) during the bone marrow exam.

If this is the case, plan to have someone drive the patient home. Contact the doctor if the patient has:
• Bleeding that soaks through the bandage and does not stop with direct pressure
• A persistent fever
• Worsening pain or discomfort
• Swelling at the procedure site
• Increasing redness or drainage at the procedure site

Tumour Biopsy
A tumour biopsy in blood cancer can either be a bone marrow biopsy or a needle biopsy of lymph nodes. The lymph node biopsy will be done at the hospital by a trained doctor. The biopsy takes about 10 to 15 minutes.

There are risks involved with any type of surgical procedure. Notable risks from a lymph node biopsy include:
• tenderness around the biopsy site
• infection
• bleeding
• numbness caused by incidental nerve damage. Any numbness normally disappears within a couple of weeks.

Pain and tenderness can last for a few days after a biopsy. Contact the doctor if patients show signs of an infection or complications, including:
• fever
• chills
• swelling
• intense pain
• bleeding or discharge from the biopsy site

Echocardiogram (ECHO)
An ECHO, or ultrasound of the heart, is a non-invasive procedure that takes about 30 minutes and provides an image of the structures of the heart. During the ECHO, electrodes will be placed onto the chest. Then a transducer (a device that looks like a computer mouse) will be applied. You may feel slight pressure on the chest from

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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 signed and dated, written informed consent prior to any study-specific procedures, sampling and analyses.
2. Men and women >=18 years of age
3. Patients with histologically confirmed, relapsed or refractory haematological malignancies, with at least one measurable lesion >= 1.5 cm and where in the opinion of the Investigator, a clinical trial is the best option for next treatment based on prior response and/or tolerability to standard of care, e.g., but not limited to:
Arm A:
o B-cell Non-Hodgkin lymphoma
o T-cell Non-Hodgkin lymphoma
o Small lymphocytic lymphoma (SLL)
o Multiple myeloma (MM) , Arm B:
o CLL (chronic lymphocytic leukaemia)
o Richter*s syndrome
o AML/secondary AML
o ALL
o High-risk myelodysplastic syndrome (MDS) (according to revised International prognostic scoring system IPSS- R)
o CMML (chronic myelomonocytic leukaemia),
NOTE: AML/ALL patients must have pathologically confirmed first or second relapsed or primary refractory AML using the World Health Organization (WHO) definition or European LeukemiaNet (ELN) recommendations. A bone marrow blast count of >5% will be sufficient in the appropriate setting of a patient with a prior diagnosis of AML/ALL.
NOTE: AML patients with APL (acute promyelocytic leukaemia FAB subtype M3) will be excluded
NOTE: Patients >70 years of age with untreated AML who are considered unfit for

intensive treatment or who refuse intensive treatment, may be considered eligible for the study, upon consultation and agreement between the Sponsor and the Investigator.
NOTE: Patients with DLBCL subtypes such as Richter's syndrome, Transformed Follicular Lymphoma, Primary Mediastinal Lymphoma and High-grade lymphomas [e.g. double-hit]) are also eligible to be included in the Cohort 2A DLBCL expansion.
4. Eastern Cooperative Oncology Group (ECOG) performance status of <=2.
5. Must have received at least 2 prior lines of therapy for the treatment of current histology and a clinical trial is best option for next treatment based on prior response and/or tolerability to standard of care. Refer to National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines of each respective histology for guidance. NOTE: For some disease indications, for example Richter*s syndrome, failure of one therapy (e.g., R-CHOP) would be sufficient to consider a patient for enrolment in a study with an Investigational agent. Disease indications, where there may be no standard of care or standard of care options have been exhausted after failure of first line therapy, these patients may be discussed and considered by Sponsor and Investigator on a case by case basis for enrolment into the study and decisions to enrol such patients documented in writing.
6. Documented active disease requiring treatment per respective NCCN/ESMO guideline that is relapsed or refractory defined as:
o Recurrence of disease after response to prior line(s) of therapy
o or progressive disease after completion of the treatment regimen preceding entry into the study
7. Adequate haematologic function (Note: does not apply to acute leukaemias, CLL, Richter*s syndrome or high-risk MDS), defined as:
o Absolute neutrophil count (ANC) >=1000 cells/mm3 (1.0 x 109/L)
o Platelet count >=50,000 cells/mm3 (50 x 109/L) or >=35,000 cells/mm3 (35 x 109/L) with bone marrow involvement., NOTE: For AML/ALL/MDS/CMML/CLL/Richter*s syndrome, patients with platelet counts < 10 x 10^9/L and/or neutropenia <0.1 x 10^9/L may be enrolled. , NOTE: For AML/CMML patients, WBC must be <25,000/µl. Treatment with hydroxyurea (HU) prior to study entry and during ramp-up to achieve this level is permitted in AML patients, as long as there is 8-24 hours between the start of AZD4573 and use of HU.
8. Adequate hepatic and renal function at screening defined as:
o Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <=2.5 x upper limit of normal (ULN) except for those patients with liver involvement/infiltration due to disease
Note: If LFTs are elevated for any patient at study entry, investigator sites are to document, if known, the reason for LFT elevation (i.e., confirmed disease infiltration of the liver, or to document if unknown cause for elevation).
Patients with elevated LFTs at study entry must be discussed with the Sponsor prior to any decision on dosing with AZD4573.
o Bilirubin <=1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)

o Serum creatinine <=2.0 mg/dL OR <=1.5 x ULN (local reference), INR <1.5OR creatinine clearance >=50 mL/min as measured or calculated by Cockcroft and Gault equation [(140-Age) • Mass (kg)/(72 • creatinine mg/dL) • multiply by 0.85 if female])
9. Uric acid level < 5 mg/dl at the time of treatment initiation. (applies to all AZD4573 infusions) NOTE: TLS prophylaxis/management with rasburicase or allopurinol, and IV fluid is permitted at any time during screening and treatment. Rasburicase and allopurinol must not be co administered.
10. Lipase <=1.5 x ULN and serum amylase <=1.5 x ULN and no history of pancreatitis.
11. Heart function: EF>40% by echocardiogram or multi-gated acquisition scan (MUGA) at baseline (left ventricular ejection fraction [LVEF] >40%). Appropriate correction to be used, if a MUGA is performed.
12. Women should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test before start of dosing if of child-bearing potential or must have evidence of nonchildbearing potential by fulfilling one of the following criteria at screening:
o Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
o Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
13. Men should be willing to use barrier contraception (i.e., condoms) and refrain from sperm donation during and after the conduct of the trial. If not done previously, storage of sperm before receiving AZD4573 will be advised to male patients with a desire to have children.
14. Willing and able to participate in all required evaluations and procedures in this study protocol including receiving intravenous administration of study drug and being admitted, when required, for at least 24 hours during study drug administration, and willing and able to provide mandatory baseline bone marrow biopsy/aspirate.
Host genetics research study (optional):
For inclusion in the optional genetic component of the study, patients must fulfil the following additional criteria:
• Provision of signed, written, and dated informed consent for genetic research. If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the patientt. The patient will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study.
• Whole blood transfusion given within 120 days of genetic sample collection should be leukocyte depleted. Bone marrow aspirate/tumour biopsy on study (optional):
For inclusion in the optional bone marrow aspirate / tumour biopsy component of the study, patients must fulfil the following additional criteria:
1. Provision of signed, written, and dated informed consent for a bone marrow aspirate or tumour biopsy on study. If a patient declines to participate in the bone marrow aspirate/tumour biopsy component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded

from other aspects of the study described in this protocol, so long as they consented to the main study. Any additional bone marrow aspirate (i.e. from second draw) will be collected and sent to sponsor for exploratory biomarker testing
2. P

Exclusion criteria

1. Treatment with any of the following:
o Any other chemotherapy, immunotherapy or anticancer agents, including investigational agents, within 2 weeks of the first dose of study treatment
o Any haematopoietic growth factors (e.g., filgrastim [granulocyte colony-stimulating factor; G-CSF], sargramostin [granulocyte-macrophage colony-stimulating factor; GM-CSF]) within 7 days of the first dose of study drug or pegylated G-CSF (pegfilgrastim) or darbepoetin within 14 days of the first dose of study drug
o Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment
Any full-dose level anti-coagulation treatment sufficiently prior to treatment that INR is <1.5 (DVT/PE prophylaxis dose is allowed)
o
2. Patients with asecetory mylema
3. With the exception of alopecia, any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment.
4. Presence of, or history of, central nervous system (CNS) lymphoma, leptomeningeal disease or spinal cord compression.
5. History of prior nonhaematologic malignancy except for the following:
o Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and felt to be at low risk for recurrence by treating physician.
o Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.
o Adequately treated carcinoma in situ without current evidence of disease.
6. As judged by the Investigator, any evidence of severe or uncontrolled systemic disease (e.g., severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease]), or current unstable or uncompensated respiratory or cardiac conditions, or uncontrolled hypertension, history of, or active, bleeding diatheses (e.g., hemophilia or von Willebrand disease) or uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment), or intravenous anti-infective treatment within 2 weeks before first dose of study drug.
7. Known history of infection with human immunodeficiency virus (HIV).
8. Serological evidence of active Hepatitis B infection

9. Undergone any of the following procedures or experienced any of the following conditions currently or in the preceding 6 months:
o coronary artery bypass graft
o angioplasty
o vascular stent - for the purposes of clarification, a patient who has had a cardiac stent or arterial stent currently or in the preceding 6 months will not be eligible for the study. However, a patient who has had a venous stent to prevent life-threatening conditions, currently or in the preceding 6 months, will be eligible for the study.
o myocardial infarction
o angina pectoris
o congestive heart failure (New York Heart Association Class >=2)
o ventricular arrhythmias requiring continuous therapy
o atrial fibrillation, which is uncontrolled
o haemorrhagic or thrombotic stroke, including transient ischemic attacks or any other central nervous system bleeding
10. Hyperuricaemia >10 mg/dL.
NOTE: If hyperuricaemia of any kind is present at screening, standard of care (SoC) therapy should be administered (including IV fluid and rasburicase or allopurinol). Rasburicase and allopurinol must not be co administered.
11. Any of the following cardiac criteria:
o Resting corrected QT interval (QTcF) >= 470 msec obtained from a single electrocardiogram (ECG).
o Any clinically important abnormalities in rhythm (except for patients with a pace maker in place), conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block).
o Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age. Concomitant medications known to prolong QTc should be used with caution and cannot be used starting with the first dose of study drug and through the DLT review period.
12. History of severe allergic or anaphylactic reactions to BH3 mimetics or history of hypersensitivity to active or inactive excipients of AZD4573.
13. Documented confirmation and treatment of adrenal gland insufficiency or pancreatitis.
14. Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.
15. Chronic use of systemic corticosteroids (prednisone or equivalent) >20mg/day whilst on study. Systemic corticosteroids at any dose, may be used during the screening period for symptom control, but must be tapered down, if necessary, to 20 mg/day prior to dosing with AZD4573. Doses of systemic corticosteroid > 20 mg/day may be used during the study if clinically indicated (e.g., for treatment of an AE/SAE), but again, the dose must be tapered back down to no greater than 20 mg/day upon resolution of the event, to avoid chronic use.
In addition, the following is considered a criterion for exclusion from the

optional genetic research:
• Previous allogeneic bone marrow transplant

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• Previous allogeneic bone marrow transplant

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	30-10-2017
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AZD4573
Generic name:	n.a.

Ethics review

Approved WMO

Date:	12-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	22-09-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2020
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	EUCTR2017-000817-22-NL
CCMO	NL62394.018.17

Study results

Date completed: 30-09-2021

Results posted: 23-02-2023

First publication
23-11-2022