4.1 Inclusion criteria

For inclusion in the study, subjects must fulfil all of the following criteria:

1. Provision of signed and dated, written informed consent prior to any study-specific procedures, sampling and analyses.

If a subject declines to participate in any voluntary exploratory research and/or genetic component of the study, there will be no penalty or loss of benefit to the subject and he/she will not be excluded from other aspects of the study.

2. Men and women ≥18 years of age.

3. Subjects with histologically confirmed, relapsed or refractory haematological malignancies where in the opinion of the treating Investigator,a clinical trial is the best option for next treatment based on prior response and/or tolerability to standard of care. Subjects will include but are not limited to the following:

Arm A

- B-cell Non-Hodgkin lymphoma
- T-cell Non-Hodgkin lymphoma
- Small lymphocytic lymphoma (SLL)
- Multiple myeloma (MM)

Arm B

- CLL (chronic lymphocytic leukaemia)
- Richter's syndrome
- AML/secondary AML
- ALL

- High-risk myelodysplastic syndrome (MDS) (according to revised International prognostic scoring system IPSS-R).

- CMML (chronic myelomonocytic leukemia)

NOTE: AML/ALL subjects must have pathologically confirmed first or second relapsed or primary refractory AML using the World Health Organization (WHO) definition or ELN (European LeukaemiaNET) recommendations. A bone marrow blast count of >5% will be sufficient in the appropriate setting of a subject with a prior diagnosis of AML/ALL.

NOTE: AML subjects with acute promyelocytic leukemia (APL) (FAB subtype M3) will be excluded.

NOTE: Subjects >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 treating Investigator.

4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

5. Must have received at least 2 prior lines of therapy (with the exception of untreated AML, as outlined above) for the treatment of current disease 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) or European Society for Medical Oncology (ESMO) guidelines of each respective disease/indication for guidance.

NOTE: For some disease indications, for example Richter's syndrome, failure of first-line therapy (e.g., R-CHOP) would be sufficient to consider a subject for enrollment 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 subjects may be discussed between Sponsor and treating Investigator and considered on a case by case basis for enrollment into the study, and decisions to enroll such subjects will be documented in writing.

6. Documented active disease requiring treatment per respective NCCN/ESMO guideline that is relapsed or refractory defined as:

• Recurrence of disease after response to prior line(s) of therapy

• Or progressive disease after completion of the treatment regimen preceding entry into the study

7. Adequate hematologic function (Note: does not apply to acute leukaemias, CLL, Richter's syndrome or high-risk MDS), defined as:

• Absolute neutrophil count (ANC) ≥1000 cells/mm3 (1.0 x 109/L).

• Platelet count ≥75,000 cells/mm3 (75 x 109/L) or ≥35,000 cells/mm3 (35 x 109/L) with bone marrow involvement.

NOTE: For AML/ALL/MDS/CMMLCLL/Richter's syndrome, subjects with platelet counts < 10 x 109/L and/or neutropenia <0.1 x 109/L may be enrolled (adequate platelet support should be ensured as per Institutional guidelines).

NOTE: For AML and CMML subjects, WBC must be <10,000/ul, Treatment with hydroxyurea (HU) prior to study entry to achieve this level is permitted in AML subjects, as long as there is 8-24 hours between the start of study drug and use of HU.

8. Adequate hepatic and renal function at screening defined as:

• Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x upper limit of normal (ULN), except for those subjects with liver involvement/infiltration due to disease.

• Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin).

• Serum creatinine <2.0 mg/dL OR 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 <5mg/dL at the time of treatment initiation. NOTE: TLS prophylaxis/management (e.g., rasburicase, IV fluid), is permitted at any time during screening and treatment.

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:

• Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

• 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 (ie, 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 subjects 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 48 hours (24 hours per infusion – e.g., Day 1 and 2 dosing would require 48 hours admission) 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, subjects must fulfil the following additional criteria:

• Provision of signed, written, and dated informed consent for genetic research. If a subject declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the subject. The subject 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 / tumor biopsy at progression (optional):

For inclusion in the optional bone marrow aspirate / tumor biopsy component of the study, subjects must fulfil the following additional criteria:

• Provision of signed, written, and dated informed consent for a bone marrow aspirate or tumour biopsy at disease progression. If a subject 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 subject. The subject will not be excluded from other aspects of the study described in this protocol, so long as they consented to the main study.

• Presence of superficial lymphadenopathy for the lymph node biopsy (applies only to CLL and lymphoma).

4.2 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled

1. Treatment with any of the following:

− Any investigational agents from a previous clinical study within 4 half-lives of said prior investigational agent(s) with regard to the first dose of study treatment on this protocol.

− Any other chemotherapy, immunotherapy or anticancer agents within 2 weeks of the first dose of investigational product.

− Any hematopoietic growth factors (e.g., filgrastim; [G-CSF] or sargramostin [GM-CSF]) within 7 days of the first dose of investigational product or pegylated G-CSF (pegfilgrastim) or darbepoetin within 14 days of the first dose of investigational product.

− Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of investigational product.

2. Subjects with asecretory myeloma

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, CNS lymphoma, leptomeningeal disease or spinal cord compression.

5. History of prior nonhematologic malignancy except for the following:

(a) 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.

(b) Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled nonmelanomatous skin cancer.

(c) 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., haemophilia 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. Serologic status reflecting active hepatitis B or C infection.

(a) Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative PCR result before enrollment . Those who are hepatitis B surface antigen positive or hepatitis B PCR positive will be excluded.

(b) Subjects who are hepatitis C antibody positive will need to have a negative PCR result before enrollment . Those who are hepatitis C PCR positive will be excluded.

9. Active CMV infection (positive CMV IgM and/or positive PCR result).

10. Undergone any of the following procedures or experienced any of the following conditions currently or in the preceding 6 months:

(a) coronary artery bypass graft

(b) angioplasty

(c) vascular stent

(d) myocardial infarction

(e) angina pectoris

(f) congestive heart failure (New York Heart Association Class ≥2)

(g) ventricular arrhythmias requiring continuous therapy

(h) atrial fibrillation, which is uncontrolled

(i) haemorrhagic or thrombotic stroke, including transient ischemic attacks or any other central nervous system bleeding.

11. Hyperuricemia >10mg/dL.

<u>NOTE:</u> If hyperuricemia of any kind is present at screening, standard of care (SoC) therapy should be administered (including IV fluid, rasburicase +/- allopurinol).

12. Any of the following cardiac criteria:

− Mean resting corrected QT interval (QTcF) ≥470 msec obtained from 3 electrocardiograms (ECGs).

− Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle branch block, third degree heart block).

− 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 or during the scheduled ECG assessments.

13. History of severe allergic or anaphylactic reactions to BH3 mimetics or history of hypersensitivity to active or inactive excipients of AZD4573.

14. History of adrenal gland insufficiency or pancreatitis.

15. Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.

In addition, the following is considered a criterion for exclusion from the optional genetic research:

• Previous allogeneic bone marrow transplant