- Cohort 2: 9 mg → 12 mg → 18 mg → **30 mg**
- Cohort 3: 12 mg → 18 mg → 30 mg → **48 mg**
- Cohort 4: 18 mg → 36 mg→ 54 mg →**72 mg**
- Cohort 5: 18 mg → 36 mg → 72 mg → **102 mg**
- Cohort 6: TBC

The intrasubject dose escalation scheme and/or dose schedule for each cohort may be modified based on the safety and PK findings of a previous dose level.

### 5.1.2 Definition of dose-limiting toxicity

A cycle is defined as the period in which the subject is treated with AZD4573 on two consecutive days plus the respective recovery period. The recovery period will be a total of 12 days (for each 2-day consecutive dosing period) but may change, if emerging data indicates a change is warranted.

For the ramp-up period, a cycle is defined as 2 weeks (14 days) for each ramp-up and target dose. Thereafter, all treatment cycles will follow a 4-week (28 day) time-course. Regardless of cycle definition, subjects will be treated with AZD4573 on a 2 days on, 12 days off dosing schedule.

Although the plan is for subjects to receive AZD4573 on two consecutive days, every 2 weeks, it is possible that due to AEs or other reasons, that a subject does not receive treatment over 2 consecutive days, therefore, it may be that a subject receives AZD4573 on 2 days, every 2 weeks, this is permissible and the dosing days are recorded accordingly in the CRF.

Therefore, the DLT evaluation period during this study, will be 8 weeks. Any subject not completing the 8 week DLT period will be replaced.

A decision to stop recruitment will be agreed to by the SRC after review of the data from each cohort (see Section 5.1.5).

A DLT will be defined as the occurrence of any of the following, unless unequivocally due to underlying malignancy or an extraneous cause (applies to both dose escalation arms):

**Dose Escalation Arm A**

**DLT Criteria for all comers relapsed or refractory haematological malignancy subjects (excluding AML, high risk MDS, CMML, ALL, CLL and Richter's syndrome):**

- Any Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 non-hematologic toxicity except CTCAE Grade 3 nausea, vomiting, or diarrhoea that respond to medical management (e.g., by 1 or more severity grade within 72 hours) and Grade 3 elevations in serum lipase and amylase that returns to meet initial eligibility criteria within 72 hours.

- Any of the following haematological toxicities:
- - CTCAE Grade 4 thrombocytopenia lasting >3 days or Grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion.
- - CTCAE Grade 4 neutropenia with associated fever >38.3 C lasting > 7 days.
- Clinical, symptomatic TLS that occurs despite protocol-specified and/or local Institutional management will be considered a DLT.
- Grade ≥3 laboratory TLS will be considered a DLT if the metabolic abnormalities do not resolve to baseline within 72 hours despite protocol- required and/or local Institutional management.
- Dosing delay due to drug-related toxicity for >28 consecutive days.

**Dose Escalation Arm B**

**DLT Criteria for relapsed or refractory AML, high-risk MDS, CMML, ALL, CLL and Richter's syndrome subjects:**

- Any haematological toxicity in the absence of disease in the bone marrow, requiring treatment interruption for > 28 days.
- Any Grade ≥3 non-haematological toxicity with the exception of the following:
  - Grade 3 nausea, vomiting, or diarrhoea that is controlled within 72 hours.
  - Grade 3 elevations in ALT/AST that returns to meet initial eligibility criteria within 7 days.
  - Grade 3 elevations in serum lipase and amylase that returns to meet initial eligibility criteria within 72 hours.
  - Grade 3 infection which reaches recovery with appropriate treatment within 7 days.
- Clinical, symptomatic TLS that occurs despite protocol-specified and/or local Institutional management will be considered a DLT.
- Grade ≥3 laboratory TLS will be considered a DLT if the metabolic abnormalities do not resolve to baseline within 72 hours despite protocol- required and/or local Institutional management.

For both arms, a DLT excludes:

1. Alopecia of any grade.

2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

### 5.1.2 Definition of maximum tolerated dose (MTD)

A dose will be considered nontolerated and dose escalation will cease if 2 or more of up to 6 evaluable subjects experience a DLT at a given dose level. Once the nontolerated dose is defined the MTD will be confirmed at the previous dose level below the nontolerated dose or a dose between the nontolerated dose and the last tolerated dose may be investigated. Six evaluable subjects are required to determine the MTD.

### 5.1.3 Definition of Biologically Effective Dose (BED)

A biologically effective dose is defined as a dose selected based on the review of combined clinical datasets (e.g., reduction of leukaemic cells in peripheral blood); safety, efficacy, pharmacokinetic and pharmacodynamic data and any other supportive biomarker data that would indicate that a certain dose level tested indicated clinical benefit and would be a dose selected for future clinical studies.

### 5.1.4 Definition of evaluable subject

For decisions on dose escalation, an evaluable subject is defined as a subject that has received AZD4573 and either:

- has completed minimum safety evaluation requirements and has received at least 14 days of AZD4573 at the designated target dose level

or

- has experienced a DLT

### 5.1.5 Safety Review Committee (SRC)

After each dose level during the dose escalation phase of the study, a safety review committee (SRC) will evaluate the safety/tolerability and PK of AZD4573 to decide the next dose.

The SRC will consist of:

- Medical Monitor, who will chair the committee, or delegate
- Principal Investigator, or delegate, from each investigational site

In addition, one other physician from the following may be invited:

- Global Safety Physician or delegate
- Clinical Science representative or delegate