Table 5 Schedule of Assessments A – Cycles A-D and Cycles 1-6 (AZD4573 Monotherapy)

Assessment	Screen[a]	Intra-subject Dose Escalation/ramp-up (Cycles a-d – Cycle=14 days)[z]	Cycle 1-6 (28 Days)			Assess Disease Every 4 to 12 weeks from 1st Dose[aa]	30-Day SF[bb]	SOC LTF
		Days 1, 2, 15 & 16	Days					
		Visits	1&2	8	15&16			
		(±2 Days)	(±2 Days)			(±7 Days)	(+7 days)	
Informed consent[b]	X							
Inclusion/exclusion	X							
Medical history and demographics	X							
Physical examination[c]	X	X	X		X		X	
ECOG performance status	X	X	X				X	
Archived tumor block or slides (if available must submit)	Submit only once							
Vital signs[d] and weight	X	X	X		X		X	
B symptoms (for B-cell malignancies only)	X		X					
12-lead ECG[e]	X	Refer to footnote for schedule					X	
Cardiac troponin, cortisol, ACTH, TSH	X		X				X	

Assessment	Screen[a]	Intra-subject Dose Escalation/ramp-up (Cycles a-d – Cycle=14 days)[z]	Cycle 1-6 (28 Days)			Assess Disease Every 4 to 12 weeks from 1st Dose[aa]	30-Day SF[bb]	SOC LTF
		Days 1, 2, 15 & 16	Days					
		Visits	1&2	8	15&16			
		(±2 Days)	(±2 Days)			(±7 Days)	(+7 days)	
ECHO/MUGA[f]	X						X	
Hematology[g]	X	X	X	X	X		X	
Serum chemistry[h]	X	X	X	X	X		X	
TLS monitoring (admitted for at least 48 hours)[i]	X	X	(X)					
Urinalysis[j]	X	X	X	X	X		X	
Pregnancy testing (women of childbearing potential)	X	X	X				X	
Lipase/serum amylase	X	X	X	X	X		X	
Hepatitis serology[k]	X							
HBV PCR[l]	X	QM	QM				X	QM
HCV PCR[m]	X		Refer to footnote for schedule					
CMV testing[n]	X							
T/B/NK cell count	X		Day 1 of Cycles 1, 3, 6 and 8				X	
Serum immunoglobulins (IgA, IgM, IgG)	X		Day 1 of Cycles 1, 3, 6 and 8				X	

Assessment	**Screen[a]**	**Intra-subject Dose Escalation/ramp-up (Cycles a-d – Cycle=14 days)[z]**	**Cycle 1-6 (28 Days)**			**Assess Disease Every 4 to 12 weeks from 1st Dose[aa]**	**30-Day SF[bb]**	**SOC LTF**
		Days 1, 2, 15 & 16	**Days**					
		Visits	**1&2**	**8**	**15&16**			
		(±2 Days)	**(±2 Days)**			**(±7 Days)**	**(+7 days)**	
β_2-microglobulin (does not apply to MDS or AML/ALL).	X		Day 1 of Cycle 1, Cycle 3, Cycle 6, Cycle 8					
Concomitant medication	X	X	X	X	X		X	X[cc]
Adverse event evaluation[o]		X	X	X	X		X	X[cc]
AZD4573 plasma PK[p]		Refer to footnote for schedule						
24-hour urine collection (**Cohorts 3-5**) for PK			Day 1 of Cycle 1 target dose only (predose and 0-2, 2-6, 6-10 and 10-24 hours from start of infusion)					
Pharmacodynamic samples (blood)[q]	X	Refer to footnote for schedule						
Exploratory blood biomarker samples (blood; Arm B only)[r]	X	Before 1st dose				At disease progression	(X)	
Pharmacogenetics sample (**optional**)[s]		Before 1st dose						

Assessment	Screen[a]	Intra-subject Dose Escalation/ramp-up (Cycles a-d – Cycle=14 days)[z]	Cycle 1-6 (28 Days)			Assess Disease Every 4 to 12 weeks from 1st Dose[aa]	30-Day SF[bb]	SOC LTF
		Days 1, 2, 15 & 16	Days					
		Visits	1&2	8	15&16			
		(±2 Days)	(±2 Days)			(±7 Days)	(+7 days)	
Disease progression sample (**optional** bone marrow aspirate or tumor biopsy)[t]						At disease progression	(X)	
Skeletal survey (MM only)[u]	X	z				As clinically indicated and to confirm CR		
MM disease markers[v]	X					Q4W		
Bone marrow biopsy & aspirate[w]	X					As clinically indicated and to confirm CR		
Response assessments/radiologic scans[x]	X					Q12W		
AZD4573 intravenous[y]		X	X		X			
Disease progression follow-up								X[cc]

Abbreviations: ALL = acute lymphocytic leukaemia; AML = acute myeloid leukaemia; CLL = chronic lymphocytic leukaemia; CMV = cytomegalovirus; CR = complete remission; CT = computed tomography; ECG = electrocardiogram, ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; LTF = long-term follow-up; MM = multiple myeloma; MRI = magnetic resonance imaging; MUGA =

multigated acquisition; NK = natural killer; PCR = polymerase chain reaction; PET = positron-emission tomography; PK = pharmacokinetics; Q4W = every 4 weeks; Q12W = every 12 weeks; QM = every month; SFU = safety follow-up; SOC = standard of care.

a. Screening tests should be performed within 30 days before the first administration of study drug, unless otherwise indicated.
b. Informed consent must be obtained ≤30 days before first dose of study drug and must be obtained before any protocol-defined screening tests are done.
c. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter.
d. Vital signs (blood pressure and pulse rate) will be assessed after the subject has rested in the sitting position for at least 5 minutes. During the intrasubject ramp-up period and including the first administration of the first target dose (Cycles a-d), blood pressure and pulse rate will be measured at 1 hour from the start of the infusion and within 30 minutes, 4 hours and 6 hours of post-infusion. Thereafter, blood pressure and pulse rate will be measured within 30 minutes of ending the infusion. Temperature should be taken before administration of study drug.
e. Subjects should be in supine position and resting for ≥10 minutes before the ECGs. An ECG is required at screening and at each timepoint during the intrasubject ramp-up period including the first target dose (Cycles a-d) . During the intrasubject ramp-up and the first target dose, triplicate ECGs will be taken predose and 1, 2, 4, 7, 10 and 24 hours after the end of infusion. Beginning with Cycle 1, a single ECG will be taken within 30 minutes of ending the infusion on Day 1 of every subsequent cycle. Note: The timing and number of ECGs may be altered depending on the emerging PK and safety profile. A single ECG will be taken at the safety-follow up visit.
f. In addition to screening, an ECHO should be done within 14 days after an abnormal ECG finding (T wave inversion/flattening) or as soon as possible when clinically indicated. If an ECHO cannot be taken, a multigated acquisition (MUGA) scan to assess left ventricular ejection fraction (LVEF) will be done. In case of any T-wave abnormality, the ECHO (or MUGA) should be repeated at the 30-day follow up visit to address the question of recovery, during the off-treatment period.
g. Haematology includes complete blood count (CBC) with automated and/or manual differential including, but not limited to white blood cell count, haemoglobin, haematocrit, platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) or blast cells. Coagulation testing (aPTT/PT, fibrinogen. Haematology should be measured before dosing while subjects are receiving treatment. Haematology and coagulation testing to be performed on Days 1, 2, 5, 8, 12, 15, 16, 19, 22 and 26 (Note: haematology testing on Days 5, 12, 19, 22 and 26 will be during the ramp-up/DLT evaluation period only. Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted).
h. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, cholesterol, creatinine, C-reactive protein (CRP), glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, triglycerides, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Serum chemistry should be measured before dosing while subjects are receiving treatment. Clinical chemistry testing to be performed on Days 1, 2, 5, 8, 12, 15, 16, 19, 22 and 26 (Note: clinical chemistry testing on Days 5, 12, 19, 22 and 26 will be during the ramp-up/DLT evaluation period only. Investigator may take additional, unscheduled samples throughout the study if deemed clinically warranted).
i. Subjects considered at risk for TLS will be required to be admitted for 48 hours for each dose administration starting with the first ramp-up dose through to the first target dose level (inclusive) for every cohort. This will allow for collection of PKPD timepoints over 48 hours and also for monitoring of TLS. Monitoring for TLS includes, but not limited to checking BUN, creatinine, phosphate/phosphorus, uric acid, calcium, potassium and LDH levels at least every 6 hours from starting the infusion. Fluid balance must be monitored according to local institutional standards. Once a subject considered at risk for TLS reaches the target dose level, then admitting the subject for subsequent dose administration will be done at investigator discretion. Those subjects not considered to be at risk for TLS (based on treating Investigator's clinical judgement), will be required to be admitted to hospital for at least

48 hours for each dose administration up to the third ramp-up dose and thereafter be treated in the hospital in an out-patient setting at Investigator's discretion. These subjects may remain in hospital longer if deemed clinically necessary by the treating Investigator.

j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. On dosing days, urinalysis should be done pre and post-infusion.

k. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. In addition, any subjects testing positive for any hepatitis serology, must have polymerase chain reaction (PCR) testing for verification purposes.

l. Subjects who are anti-HBc positive (or have a known history of HBV infection) should have a quantitative PCR test for HBV DNA performed during screening and monthly thereafter. Monthly monitoring should continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrolment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (eg, in the setting of rising transaminase levels).

m. Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should have quantitative PCR testing for HCV RNA performed during screening and Cycle 6. No further testing beyond Cycle 6 is necessary if PCR results are negative.

n. CMV testing at screening must include serology testing for CMV immunoglobulin G (IgG), CMV IgM, and CMV PCR testing.

o. A formal assessment of adverse events will occur at the visits marked in this table, but adverse events reported at any time during the study must also be recorded in the case report form (CRF).

p. Plasma samples for PK analysis will be taken at the following time points: Day 1: pre-dose (within 2 hours of start of infusion) and 0.5, 1, 2, 3, 4, 5, 7 and 10 hours after the start of the infusion; Day 2: Pre-dose (within 2 hours of start of infusion) and 1,2,4, 7, 10 and 24 hours after the start of the infusion, beginning with the first dose and at every dose ramp up including the first target dose level for each cohort (Cycles a-d). In addition, PK samples will be taken for all doses in each cohort for the duration of the study (Cycles 1-6, but no PK samples will be taken beyond cycle 6). Samples will be taken pre-dose (within 2 hours of the start of the infusion), immediately after the end of the infusion and 4 hours post infusion. The timing of these samples may be adjusted dependent upon ongoing PK analysis and interpretation.

q. Whole blood samples will be collected for immediate on-site peripheral blood mononuclear cells (PBMC) isolation. Samples will be collected at screening and on Day 1 at predose (within 2 hours of start of infusion) and 2, 4 and 7 hours post-dose and on Day 2; pre-dose (within 2 hours of start of infusion), 2 and 7 hours post-dose, after the start of the infusion beginning with the first dose and at every dose ramp up including the final dose level for each cohort. The timing and frequency of these samples may be adjusted dependent upon ongoing PK and pharmacodynamic analysis and interpretation.

r. For all subjects in Arm B (e.g., AML/ALL or CLL/Richter's syndrome) an additional whole blood sample will be taken at screening, predose (within 2 hours of start of infusion) and at disease progression. Note: the disease progression sample may be taken at the safety follow-up visit if not collected previously.

s. Pharmacogenetics sample: an optional blood sample for pharmacogenetics research will be taken from consenting subjects during screening.

t. An optional bone marrow aspirate collection or tumour biopsy is requested at disease progression from consenting subjects. Note: the disease progression sample may be taken at the safety follow-up visit if not collected previously.

u. Skeletal survey is required at baseline only for subjects with multiple myeloma. Whole body imaging (CT-PET) or whole body MRI as per local Institutional guidelines may be used as an alternative to a skeletal survey.

v. Refer to Section 6.9.4 of the protocol for a list of disease markers per disease indication

w. A baseline (before first dose of study drug) bone marrow biopsy and aspirate is required for all subjects. The baseline bone marrow aspirate/biopsy will be used for standard disease profiling (e.g. immunohistochemistry, flow cytometry, cytogenetics, fluorescence in situ hybridization (FISH), etc.). On

treatment bone marrow biopsies/aspirates at 8 weeks may be done for disease assessments on subjects in Arm B, in multiple myeloma subjects and in subjects with lymphoma who have documented evidence of bone marrow infiltration at screening. Additional biopsies may be done as clinically indicated and to confirm CR. Additional bone marrow aspirate (i.e., from a second draw) will be collected from all bone marrow collections, i.e. baselines, 8-wk disease assessment, and confirmation of response by the sponsor for exploratory biomarker testing.

x. Please refer to Section 6.9 for more detailed information regarding requirements for disease/indication specific response assessment measurements. Radiologic scans (i.e., contrast CT) will be repeated every 2-3 cycles (approximately every 8-12 weeks ±7 days depending on the disease indication). For subjects with lymphoma or CLL/Richter's syndrome/ALL, baseline tumour assessments will be performed using radiologic imaging by CT with contrast and PET-CT covering neck, chest, abdomen, and pelvis during the screening period. PET-CT (does not apply to CLL/Richter's syndrome/ALL) also will be repeated on the same schedule, when required, per Section 6.9 of the protocol. For subjects with baseline hepatosplenomegaly, the cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

y. Refer to the pharmacy manual for instructions on administration of AZD4573.

z. Refer to the protocol for the intrasubject dose escalation scheme for each cohort.

aa. Disease assessments will be done by the investigator using conventional response criteria as defined in the protocol for each respective disease/indication.

bb. The SFU visit will be performed 30 days (+7 days) after the last dose of all study drug. Tumour assessments will be repeated at this visit, if they have not been performed within the past 12 weeks.

cc. Subjects who discontinue study drug before documented disease progression will be followed according to standard of care until documented disease progression is captured in the Web Based Data Capture (WBDC) system. During this period, information will also be collected in the WBDC system on concomitant medications and procedures, including any new anticancer agents, and on any serious adverse events (SAEs) considered related to study drug or study procedures. The long-term follow up will not apply to subjects who withdraw consent or are lost to follow-up.

Table 6 Schedule of Assessments B – AZD4573 Monotherapy (Cycle 7 onwards)

Assessments	Treatment Phase[l]
	Cycles 9, 12, 15, 18 and every 6 months thereafter (±7 days) Cycle=28 days
PE[a]/Vital signs[b]/Weight	X
ECOG status	X
Haematology[c]	X
Serum chemistry[d]	X
T/B/NK cell count	Every 6 months
Serum immunoglobulins (IgA, IgM, IgG)	Every 6 months
Disease progression sample (optional bone marrow aspirate and/or tumour biopsy)[e]	At disease progression
Bone marrow (biopsy/aspirate)[f]	to confirm CR or progression and at Investigator discretion
Exploratory blood biomarker sample (Arm B subjects only) [g]	At disease progression
AZD4573 Monotherapy[h]	X
Tumour assessment/ Radiologic assessment [i]	X

Assessments	**Treatment Phase[l]**
	Cycles 9, 12, 15, 18 and every 6 months thereafter (±7 days) Cycle=28 days
Concomitant medications	X
Adverse events [j]	X
Disease progression/new anticancer therapy follow-up[k]	Refer to footnote l

Abbreviations: CR = complete remission; CT = computed tomography; DFU = discontinuation follow-up; ECOG = Eastern Cooperative Oncology Group; Ig = immunoglobulin; LTF = long-term follow-up; PE = physical exam; NK = natural killer; QM = SOC = standard of care

a. Symptom-directed physical exams will be performed.
b. Vital signs - blood pressure and pulse will be assessed after the subject has rested in the sitting position, within 30 minutes of ending the infusion. Temperature should be taken before administration of study drug.
c. Haematology includes complete blood count (CBC), with automated and/or manual differential including, but not limited to, white blood cell count, haemoglobin, haematocrit, platelet count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC) or blast cells, coagulation testing (aPTT/PT, fibrinogen. Haematology should be measured pre-dose on each dosing day whilst subjects are receiving treatment with AZD4573.
d. Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, cholesterol, creatinine, C-reactive protein (CRP), glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, triglycerides, total bilirubin, total protein, and uric acid. If an unscheduled electrocardiogram (ECG) is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Serum chemistry to be measured pre-dose on each dosing day, whilst subjects are receiving treatment with AZD4573.
e. An optional bone marrow aspirate collection and/or tumour biopsy is requested at disease progression from consenting subjects. Note – the disease progression sample may be taken at the safety follow-up visit (refer to footnote k) if not collected previously at the time of progression.
f. Additional bone marrow biopsy/aspirate to be done at investigator discretion (i.e., to confirm CR and/or per standard of care). In these instances, additional bone marrow (i.e., from a second draw) will be collected from all bone marrow collections for exploratory biomarker testing by the Sponsor.
g. For all subjects in Arm B, an additional whole blood sample will be taken at disease progression. Note, the disease progression sample may be taken at the safety follow-up visit (refer to footnote k).
h. AZD4573 is to be administered as an absolute (flat) dose, 2-hour intravenous infusion over two days every 2 weeks. Please refer to the pharmacy manual for more detailed information on the drug produce and the administration guidelines. AZD4573 may be administered in an out-patient setting. Subjects who in the treating Investigator's opinion are considered to be at risk for TLS, may be hospitalized at Investigator discretion based on clinical experience with preceding cycles of treatment and local Institutional practice guidelines. Monitoring for TLS includes, but not limited to checking BUN, creatinine, phosphate/phosphorus, uric acid, calcium, potassium and LDH levels at least every 6 hours from starting the infusion. Fluid balance must be monitored according to local institutional standards.
i. Please refer to Section 6.9 for more detailed information regarding requirements for disease/indication specific response assessment measurements. Radiologic scans will be performed at Cycles 9, 12, 15 and 18 (±28 days depending on the disease indication) and then every 6 months thereafter (±7 days). Unscheduled radiologic scans may be performed at Investigator discretion if deemed clinically relevant.
j. A formal assessment of adverse events will occur at Cycles 9, 12, 15 and 18 and then every 6 months thereafter, but adverse events reported at any time during the study must also be recorded in the case report form (CRF).
k Refer to footnote l.
l. Please refer to schedule of assessments A for the assessments/procedures to be undertaken for the 30 day safety follow-up visit and SOC/LTF visit (including new anti-cancer therapy follow-up).