Clinical Study Report Synopsis	
Drug Substance	AZD4573
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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

Study dates:
First patient enrolled: 24 October 2017
Last patient last visit: 30 September 2021
The analyses presented in this report were based on a clinical data lock date of 26 July 2022

Phase of development:
Clinical pharmacology (I)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted at 11 sites in the European Union (EU) overall: Germany (4 sites), The Netherlands (2 sites), and the United Kingdom (5 sites).

Publications

At the time of writing this report, the following publication has been published:

Rule S, Kater AP, Brümmendorf TH, Fegan C, Kaiser M, Radford JA, et al. A Phase 1, open-label, multicenter, 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 hematological malignancies. J Clin Oncol. 2018;36:15(suppl):TPS7588.

Objectives and criteria for evaluation

Table S1 Objectives and endpoints

Objectives	Endpoints
Primary	
• Assess the safety and explore the BED and/or MTD [a] of AZD4573 in patients with relapsed or refractory haematological malignancies	• BED [a]: dose that indicated clinical benefit, selected for future clinical studies • MTD [a]: highest dose at which < 33% of patients (Cohorts 1 and 2 [Arm A and Arm B]) or < 25% of patients (Cohort 3 [Arm A and Arm B]) experienced a DLT during the DLT observation period • Incidences of DLTs • AEs, abnormal laboratory test results, vital signs, creatinine clearance and ECG changes
Secondary	
• Assess the plasma PK of AZD4573	• AZD4573 concentrations and PK parameters in Cohorts 1 and 2 (Arm A and Arm B) only
• Assess preliminary tumour response/activity of AZD4573	• ORR, DoR, PFS, OS

[a] Based on the early safety profile, observation of DLTs, and PK data at doses ranging from [redacted] it was anticipated that the RP2D would be much lower than originally predicted [redacted] from the preclinical modelling data. Following a review of the available data by the SRC, it was determined that doses above [redacted] would not be explored. Based on the risk-benefit profile, additional cohorts for doses between [redacted] were not explored, and as a result, BED and MTD were not determined.

Exploratory endpoints were defined in the CSP (Appendix 16.1.1) but are not reported in this CSR.

AE = adverse event; BED = biologically effective dose; CSR = clinical study report; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); RP2D = recommended Phase 2 dose; SRC = safety review committee.

Study design

This Phase 1 study was a multicentre, open-label, first in human, non-randomised, dose-escalation study including an intra-patient ramp-up, designed to determine the biologically effective dose (BED) and/or maximum tolerated dose (MTD), safety, tolerability, pharmacokinetics (PK), and preliminary tumour response/activity of AZD4573, and to recommend dose(s) for evaluation in future clinical studies (recommended Phase 2 dose [RP2D]) in patients with relapsed or refractory haematological malignancies. Ultimately, only RP2D was determined; BED and MTD were not determined.

The study consisted of 2 parallel arms (Arm A and Arm B). Individual patients were enrolled and allocated to the most appropriate dosing cohort according to the patient's diagnosis at screening (Arm A or Arm B). The number of patients planned to be enrolled was based on the desire to obtain adequate tolerability, safety and PK data while exposing as few patients as possible to AZD4573 and related study procedures. As of the final clinical study protocol (CSP) (v7.0 [Amendment 6] [Appendix 16.1.1]), the anticipated sample size for the study was up to 48 patients.

Patients could include but were not limited to those with the following disease diagnoses:

- **Arm A:** All comers with relapsed or refractory haematological malignancies (excluding acute myeloid leukaemia [AML], acute lymphocytic leukaemia [ALL], high-risk myelodysplastic syndrome [MDS], chronic myelomonocytic leukaemia [CMML], chronic lymphocytic leukaemia [CLL] and Richter's syndrome) eg, non-Hodgkin lymphoma (NHL) (B-cell, T-cell), small lymphocytic lymphoma (SLL) and multiple myeloma (MM)
- **Arm B:** Relapsed or refractory AML/secondary AML, ALL, high-risk MDS (according to revised international prognostic scoring system), CMML, CLL, and Richter's syndrome.

Patients in Arm B were most likely to have significant levels of tumour cells in their peripheral blood and an increased risk of tumour lysis syndrome (TLS) due to disease burden.

The initial dosing period consisted of an intra-patient, dose-escalation ramp-up period. Given the potential for patients in Arm B to have an increased risk of TLS, Arm A was initiated first to assess safety and tolerability of AZD4573, prior to enrolling patients in Arm B at the same intra-patient ramp-up doses. The intra-patient ramp-up period was defined as Cycles A to D, in which each ramp-up dose was a new cycle. The target dose was defined as starting at Cycle 1 following the ramp-up period.

The intention was 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 initial dosing schedule for AZD4573 was [redacted] days on/[redacted] days off. For all cohorts, the initial number of ramp-ups planned was 4 doses (3 ramp-up doses and 1 target dose) and the ramp-up process for all cohorts was the same (ie, each dose level was to be given on Days 1 and 2, followed by a 12-day drug free period before the next dose was given).

In Cohort 1, the initial starting dose was [redacted] for both Arms A and B, so patients received [redacted] on Days [redacted] followed by a [redacted]-day drug free period. The next dose administered was [redacted] given on Days [redacted] followed by a [redacted] day drug free period. The next dose was [redacted] given on Days 1 and 2, followed by a [redacted] day drug free period. At the end of the intra-patient ramp-up dosing, the patients reached the target dose level of [redacted], given on Days [redacted] followed by a [redacted]-day drug free period (ie, [redacted] days on, [redacted] days off). Once the target dose of [redacted] in Cohort 1 (or an alternative dose in Cohort 1 and other cohorts) was reached, the plan was for each subsequent cycle to be [redacted] days) in length. Patients would then remain at that target dose level for the remainder of the study or until documented evidence of disease progression or unacceptable toxicity.

After 5 patients were dosed in the study, it was clear that due to toxicity, delivering AZD4573 over [redacted] consecutive days would not be possible for all patients. The main toxicities that precluded consecutive dosing were intermittent, short-lasting diarrhoea (Grades 1 to 3, occurring approximately from 8 hours after dosing and leading to significant weight loss in some patients), transient neutropenia, and thrombocytopenia which were Grade 2 to 4 events and required interruptions to treatment after Day [redacted] These toxicities were expected on-target effects of AZD4573 based on preclinical data.

From the emerging and preliminary PK data from the first patients dosed with [redacted] AZD4573, it was observed that the half-life was significantly longer (4 to 7 hours) than that predicted by the preclinical modelling data (1.7 hours). In addition, it was noted that 2 patients were < [redacted] in weight, and it was not clear whether the severity of the toxicities observed were due to low weight patients having higher AZD4573 exposures in comparison with higher weight patients receiving the same dose. Therefore, a decision was made as an additional safety step to lower the starting dose to [redacted] only for those patients < [redacted] in weight. Two patients were dosed at a starting dose of [redacted] and none or very few toxicities (only Grade 1 events) were observed. Going forwards, [redacted] starting dose was no longer used for patients < [redacted] in weight (it was only used for the 2 patients described above).

As a result of the emerging safety/PK profile, and upon discussion and agreement with the Safety Review Committee (SRC) (02 March 2018), it was agreed that [redacted] days of consecutive dosing did not allow for sufficient time for patients to recover from drug-related toxicity. As such, a decision was made to adapt the dosing schedule for all new patients from [redacted] days on[redacted]

days off, to [redacted] dosing, but to still adhere to the [redacted] week dose-limiting toxicity (DLT) observation period.

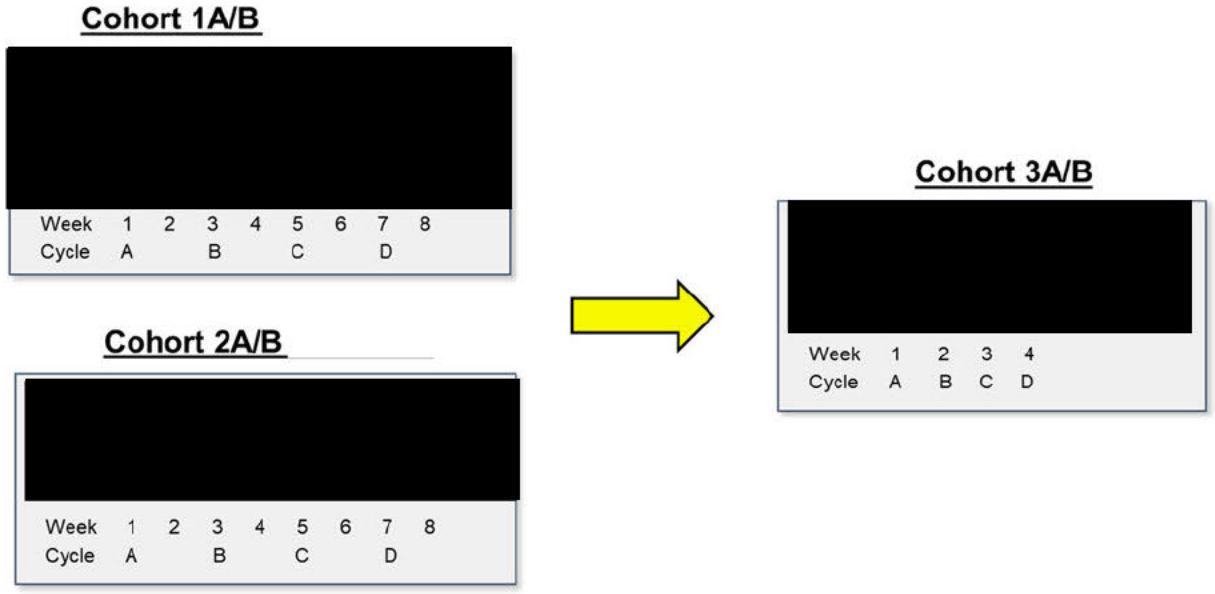
Given the patient population of multiply relapsed or refractory disease, it became clear based on emerging data from the first and second cohorts that not all patients would complete the [redacted]-week DLT observation period, due to progression of disease. Several patients needed to be replaced in Cohorts 1 and 2 (Arms A and B) due to disease progression. Upon discussion during safety calls with the investigators and during a SRC meeting (26 June 2018), it was agreed that the intra-patient ramp-up period and the 8-week DLT observation period was too long and did not appear to effectively mitigate for the risk of TLS. Under EU CSP version 5.0 (Amendment 4), the number of ramp-ups and effectively the DLT observation period was reduced for Cohort 3 patients (see Table S2).

Evaluation of the dosing and schedule used for cohorts in Arms A and B was driven by establishing acceptable safety and tolerability at the prior dose level and schedule per the SRC evaluation. In addition, available PK/pharmacodynamic data and preliminary evidence of efficacy could be considered in the decision to continue the most appropriate dosing and schedule.

A DLT-evaluable patient was a patient that received AZD4573 and either 1) received at least [redacted] doses of AZD4573 at the designated target dose level and completed appropriate safety evaluation requirements per the schedule of activities or 2) experienced a DLT. For reporting purposes, DLTs were as approved and documented by the SRC; DLTs were evaluated according to the criteria in the version of the CSP that the patient was enrolled under and re-evaluated at the end of the study according to criteria in CSP version 7.0.

A study schema is presented in Figure S1 and dosing schedules for all cohorts included in Arm A and Arm B are shown in Table S2.

Figure S1 Study schema



For Cohort 1A/B the dosing frequency was changed from [redacted] off study treatment in [redacted]

Table S2 Dosing schedules for Arm A and Arm B, Cohorts 1 to 3

Arm, Cohort	AZD4573 dosing schedule	DLT observation period [a]	Cycle length
Arm A, Cohort 1 + Arm B, Cohort 1	[redacted]	8 weeks	Ramp-up: 2 weeks After ramp-up: 3 weeks
Arm A, Cohort 2 + Arm B, Cohort 2	[redacted]	8 weeks	
Arm A, Cohort 3 + Arm B, Cohort 3	[redacted]	4 weeks	Ramp-up: 1 week After ramp-up: 3 weeks

[a] The DLT observation period could be extended to incorporate any dosing delay(s), as long as no dosing delay constituted a DLT (a delay due to drug-related toxicity for > 28 consecutive days for an 8-week DLT period, or > 21 consecutive days for a 4week DLT period). The DLT observation period was to end on the original planned day (8 weeks after first dose for Cohorts 1 and 2, or 4 weeks after first dose for Cohort 3) or 1 week after the last ramp-up dose, whichever was later.

[b] As a result of the emerging safety/PK profile, and upon discussion and agreement with the SRC, it was agreed that [redacted]

Patients eligible for treatment had the following disease diagnoses at screening:

Cohort 1: Arm A (DLBCL) and Arm B (AML/secondary AML, HCL)

Cohort 2: Arm A (DLBCL, MCL, MM) and Arm B (AML/secondary AML, CLL, CMML, ALL)

Cohort 3: Arm A (MM) and Arm B (AML/secondary AML, CLL, CMML)

ALL = acute lymphocytic leukaemia; AML = acute myeloid leukaemia; CLL = chronic lymphocytic leukaemia; CMML = chronic myelomonocytic leukaemia; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; HCL = hairy cell leukaemia; MCL = mantle cell leukaemia; MM = multiple myeloma; PK = pharmacokinetic(s); SRC = safety review committee.

Imaging was scheduled every 4 to 12 weeks (±7 days) depending on the disease indication. Response assessment per investigator was based upon the response assessment guidelines appropriate for each disease/indication eg, mantle cell lymphoma, NHL, CLL, SLL, T-cell lymphoma, and Richter syndrome (Cheson et al 2014), CLL (Hallek et al 2008), myeloma (Palumbo et al 2014), AML (Döhner et al 2010), and ALL (SWOG 2016).

Target population and sample size

The study included male and female patients aged ≥ 18 years with histologically confirmed, relapsed or refractory haematological malignancies, where in the opinion of the investigator, a clinical study was the best option for next treatment based on prior response and/or tolerability to standard of care.

The primary objective of this study was to investigate the safety and tolerability and thereby identify the MTD and/or BED of AZD4573 monotherapy and to recommend dose(s) for evaluation in future clinical studies. Hence the number of patients planned to be enrolled was based on the desire to obtain adequate tolerability, safety and PK data while exposing as few patients as possible to AZD4573 and related study procedures. The anticipated, planned sample size for the study at the time of final CSP (v7.0, Amendment 6) was up to 48 patients. Ultimately, only RP2D was determined; MTD and BED were not determined.

Investigational product: dosage, mode of administration and batch numbers

Table S3 Study treatment

Investigational product	Dosage form and strength	Manufacturer	Batch number (printed on label)	P LOT ID (Manufacturing lot number)
AZD4573	Sterile concentrate for solution for infusion. Each vial contains 1.5 mg/mL	AstraZeneca	L007176	007629 008416
			L008543	009868 011715
			L010029	012592

P = product; ID = identification.

Duration of treatment

AZD4573 was administered by intravenous infusion over [redacted] hours according to the dosing schedule for up to 8 cycles with or without treatment holidays (eg, 2 weeks on, 1 week off), provided AZD4573 was well tolerated and providing clinical benefit. Any patients who were deriving clinical benefit thereafter and wanted to continue AZD4573 beyond 8 cycles were assessed on a case-by-case basis as to whether or not continuing treatment was clinically justified.

During the intra-patient ramp-up period (Cycles A to D), cycle lengths were 2 weeks (14 days) for Cohorts 1 and 2 and 1 week (7 days) for Cohort 3. After the ramp-up period, cycle length was 3 weeks (21 days) for all cohorts.

Statistical methods

No formal statistical testing was performed. All data were summarised descriptively including tables, listings and graphs, as appropriate.

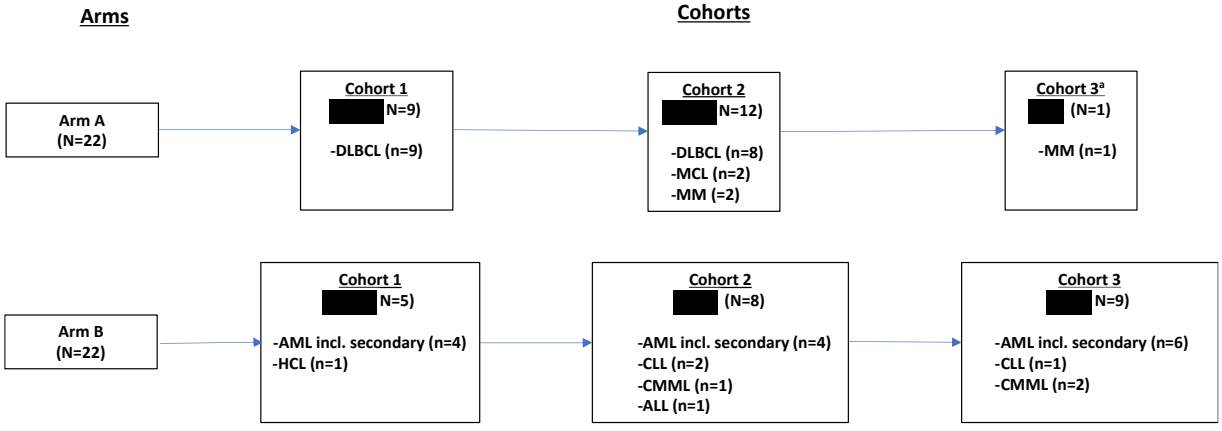
Study population

Sixty-six patients were enrolled (signed informed consent); of these 22 patients were screen failures and did not receive treatment. Forty-four patients were assigned to and received treatment (22 to Arm A and 22 to Arm B) at 11 study centres across 3 countries in the EU.

An overview of the dosing cohorts in both treatment arms is presented in Figure S2.

Based on the early safety profile, observation of DLTs, and PK data at doses ranging from [redacted] it was anticipated that the RP2D would be much lower than originally predicted [redacted] from the preclinical modelling data. Following a review of the available data by the SRC, it was determined that doses above [redacted] would not be explored. Based on the risk-benefit profile, additional cohorts for doses between [redacted] were not explored, and as a result, BED and MTD were not determined.

Figure S2 Overview of dosing cohorts



[a] Following enrolment and treatment of 1 patient, Arm A, Cohort 3 [redacted] was closed as it was concluded that [redacted] was a tolerated dose of AZD4573 monotherapy in Arm A patients.

The cohorts displayed above include patients assigned to and eligible for treatment.

ALL = acute lymphocytic leukaemia; AML = acute myeloid leukaemia; CLL = chronic lymphocytic leukaemia; CMML = chronic myelomonocytic leukaemia; DLBCL = diffuse large B-cell lymphoma; HCL = hairy cell leukaemia; MCL = mantle cell lymphoma; MM = multiple myeloma.

Overall

Forty-four patients received treatment during the study and all 44 patients (100%) discontinued study treatment. The most common reasons for discontinuation of study treatment were confirmed progressive disease (21 patients [47.7%]) and discontinuation due to an adverse event (10 patients [22.7%]). Twenty-five patients (56.8%) completed the safety follow-up visit.

Arm A

All 22 patients (100%) were treated: 9 patients in the [redacted] cohort (Cohort 1), 12 patients in the [redacted] cohort (Cohort 2) and 1 patient in [redacted] cohort (Cohort 3). All 22 patients (100%) discontinued study treatment with the most common reason for discontinuation being confirmed progressive disease (12 patients [54.5%]). One patient [redacted] cohort) discontinued study treatment due to a treatment-emergent adverse event (TEAE; the TEAE was assessed as causally related to AZD4573 by the investigator). Thirteen patients (59.1%) completed the safety follow-up visit.

Arm B

All 22 patients (100%) were treated: 5 patients in the [redacted] cohort (Cohort 1), 8 patients in the [redacted] cohort (Cohort 2) and 9 patients in the [redacted] cohort (Cohort 3). All 22 patients (100%) discontinued study treatment with the most common reason for discontinuation being confirmed progressive disease (9 patients [40.9%]). Nine patients (40.9%) discontinued study treatment due to a TEAE (in 4 patients the TEAE was assessed as causally related to AZD4573 by the investigator). Twelve patients (54.5%) completed the safety follow-up visit.

The demographic and baseline characteristics of the patients who received study treatment appropriately represented the intended population.

Overall

The median age was 69.0 years (range: 26.0 to 84.0 years) with 10 patients (22.7%) aged ≥ 75 years. Twenty-nine patients (65.9%) were male, and the majority were white (41 patients [93.2%]). The most common disease diagnoses were NHL: B-cell lymphoma (19 patients [43.2%] overall, all in Arm A) and de novo AML/secondary AML (14 patients [31.8%] overall, all in Arm B). Thirteen patients (29.5%) had an Eastern Cooperative Oncology Group

performance status (ECOG PS) of 0, 23 patients (52.3%) had an ECOG PS of 1, and 8 patients (18.2%) had an ECOG PS of 2.

Arm A

The median age was 63.5 years (range: 34.0 to 84.0 years) with 2 patients (9.1%) aged ≥ 75 years. Fifteen patients (68.2%) were male, and the majority were white (20 patients [90.9%]). The most common disease diagnosis was NHL: B-cell lymphoma (19 patients [86.4%]; of these 19 patients, 17 patients [77.3%] had diffuse large B-cell lymphoma [DLBCL]). Nine patients (40.9%) had an ECOG PS of 0, 8 patients (36.4%) had an ECOG PS of 1, and 5 patients (22.7%) had an ECOG PS of 2.

Arm B

The median age was 71.5 years (range: 26.0 to 82.0 years) with 8 patients (36.4%) aged ≥ 75 years. Fourteen patients (63.6%) were male, and the majority were white (21 patients [95.5%]). The most common disease diagnosis was de novo AML/secondary AML (14 patients [63.6%]). Four patients (18.2%) had an ECOG PS of 0, 15 patients (68.2%) had an ECOG PS of 1, and 3 patients (13.6%) had an ECOG PS of 2.

Summary of efficacy results

The overall response rate (ORR) in the response evaluable set (N=41) was 4.9% (80% confidence interval [CI]: 1.3%, 12.5%; 95% CI: 0.6%, 16.5%), with 2 patients, both in Arm A, and both in the DLBCL subset, having a response on study treatment (ORR Arm A: 10.0% [80% CI: 2.7%, 24.5%; 95% CI: 1.2%, 31.7%]; ORR in DLBCL subset: 13.3% [80% CI: 3.6%, 31.7%; 95% CI: 1.7%, 40.5%]). The 2 patients comprised 1 patient with DLBCL (unknown cell of origin) in the [redacted] with a complete response on Day 148 (approximately 21 weeks from first dose) that lasted 61 days, and 1 patient with DLBCL (germinal centre B-cell [GCB] cell of origin) in the [redacted] with a partial response on Day 136 (approximately 19 weeks from first dose) that lasted 72 days.

Fourteen deaths (31.8%; 7 deaths each in Arm A and Arm B) had occurred at the time of analysis. Median overall survival (OS) was 8.8 months overall (80% CI: 4.9, not reached; 95% CI: 3.8, not reached). In Arm A, median OS was not reached due to the short duration of follow-up; in Arm B, median OS was 8.8 months (80% CI: 2.2, not reached; 95% CI: 1.7, not reached).

Twenty-eight progression-free survival (PFS) events (63.6%; 16 in Arm A and 12 in Arm B) had occurred at the time of analysis. Median PFS was 2.1 months overall (80% CI: 1.7, 2.6; 95% CI: 1.2, 3.7); it was 2.4 months in Arm A (80% CI: 2.1, 3.8; 95% CI: 1.9, 4.5) and 1.1 months in Arm B (80% CI: 1.0, 1.7; 95% CI: 0.7, 2.6).

Summary of PK results

Following intravenous infusion of AZD4573, median t_{max} occurred between 1.00 and 3.07 hours across Day 1 of all cycles and cohorts generally coinciding with the end of infusion. Subsequently plasma concentrations declined in a generally biphasic manner with $t_{1/2}\lambda_z$ appearing to be independent of dose with geometric means of between 3.171 and 6.312 hours across all cohorts and visits. Between-subject-variability in exposure to AZD4573 was generally high (> 40%) based on geometric CV% for AUC_{inf}, AUC_{last}, and C_{max}.

Summary of safety results

Extent of exposure

Overall

The median duration of exposure to AZD4573 was 9.0 weeks (range: 1.0 to 130.1 weeks).

Arm A

The median duration of exposure to AZD4573 was 10.1 weeks (range: 1.0 to 130.1 weeks). In the [redacted] cohorts, 5 patients (55.6%%), 11 patients (91.7%) and 1 patient (100%) reached an actual maximum dose of [redacted] respectively.

Arm B

The median duration of exposure to AZD4573 was 5.2 weeks (range: 1.0 to 35.7 weeks). In the [redacted] cohorts, 3 patients (60.0%), 6 patients (75.0%), and 6 patients (66.7%) reached an actual maximum dose of [redacted] respectively.

Treatment-emergent adverse events and adverse events of special interest, DLTs, deaths, serious treatment-emergent adverse events and discontinuations of investigational product

Overall

Treatment-emergent adverse events (TEAEs) (any grade, regardless of causality) were reported in all 44 patients (100%); the most commonly reported TEAEs (≥ 40% of patients) by preferred term (PT) were diarrhoea (26 patients [59.1%]), pyrexia (23 patients [52.3%]), nausea (22 patients [50.0%]), and TLS (18 patients [40.9%]). Considering TLS events, laboratory TLS and clinical TLS events were reported in 17 patients (38.6%) and 3 patients (6.8%), respectively.

Grade 3 to 4 TEAEs were reported in 39 patients (88.6%); the most commonly reported (≥ 20% of patients) TEAEs with a maximum severity of Grade 3 to 4 by PT were TLS (18 patients [40.9%]), neutropenia (14 patients [31.8%]), and anaemia (10 patients [22.7%]).

Eighteen patients (40.9%) had adverse events of special interest (AESIs) of TLS, all of whom had Grade 3 to 4 events. Twenty-six patients (59.1%) had AESIs of neutropenia, 23 patients (52.3%) had AESIs of pyrexia, 17 patients (38.6%) had AESIs of hepatotoxicity, 11 patients

(25.0%) had AESIs of thrombocytopenia and 1 patient (2.3%) an AESI of myocardial ischaemia.

Nine patients (30.0%) had DLTs according to the CSP version the patients were enrolled under and 7 (23.3%) had DLTs according to CSP version 7.0. The RP2D dose was determined to be [redacted] for Arm A patients and [redacted] for Arm B patients.

Fourteen patients died: 7 due to disease progression, 4 due to TEAEs (none were assessed as causally related to AZD4573 by the investigator), 2 due to other reasons and 1 for whom the reason was unknown (further details provided below under Arm A and Arm B subheadings).

Serious TEAEs were reported in 39 patients (88.6%); the most commonly reported (≥ 3 patients) serious TEAEs by PT were pyrexia (13 patients [29.5%]), TLS (10 patients [22.7%]), febrile neutropenia (8 patients [18.2%]), dyspnoea (5 patients [11.4%]), drug-induced liver injury (4 patients [9.1%]), and blood bilirubin increased, diarrhoea, pneumonia, and sepsis (each in 3 patients [6.8%]).

Ten patients (22.7%) had a TEAE that led to discontinuation of AZD4573; in 5 patients the TEAEs were assessed as causally related to AZD4573 by the investigator.

No unexpected trends were observed in laboratory values (with the exception of the biochemical PHL patterns), vital signs and electrocardiograms on treatment and changes were as expected in these patient populations. There were no confirmed Hy's Law cases reported.

Arm A

Treatment-emergent adverse events (any grade, regardless of causality) were reported in all 22 patients (100%); the most commonly reported TEAEs (≥ 40% of patients) by PT were diarrhoea (15 patients [68.2%]), nausea (13 patients [59.1%]), pyrexia (12 patients [54.5%]), vomiting (11 patients [50.0%]), and anaemia and neutropenia (each in 10 patients [45.5%]).

Grade 3 to 4 TEAEs were reported in 21 patients (95.5%); the most commonly reported (≥ 20% of patients) TEAEs with a maximum severity of Grade 3 to 4 by PT were neutropenia (9 patients [40.9%]), TLS (8 patients [36.4%]), anaemia (5 patients [22.7%]), and neutrophil count decreased (5 patients [22.7%]).

Eight patients (36.4%) had AESIs of TLS, all of whom had Grade 3 to 4 events. Fifteen patients (68.2%) had AESIs of neutropenia, 12 patients (54.5%) had AESIs of pyrexia, 7 patients (31.8%) had AESIs of hepatotoxicity, and 7 patients (31.8%) had AESIs of thrombocytopenia.

DLTs were reported for 2 of 5 evaluable patients in the [redacted] (per the CSP version they were enrolled under and per CSP version 7.0): 1 patient had a DLT of Grade 3 TLS and

1 patient had a DLT of Grade 3 acute kidney injury. DLTs were reported for 2 of 8 evaluable patients in the [redacted] (per the CSP version they were enrolled under): 1 patient had a DLT of Grade 3 hepatic enzyme increased and 1 patient had DLTs of Grade 3 alanine aminotransferase increased and Grade 4 aspartate aminotransferase increased. No patients had a DLT per CSP version 7.0 criteria. DLTs were not reported in the 1 evaluable patient in the 9 mg cohort (per the CSP version they were enrolled under or per CSP version 7.0).

Seven patients died: 6 due to disease progression and 1 for whom the primary cause of death was recorded as 'patient refused further cancer therapy'(17 days from last dose). No patient in Arm A had a TEAE leading to death.

Serious TEAEs were reported in 18 patients (81.8%); the most commonly reported (≥ 3 patients) serious TEAEs by PT were pyrexia (7 patients [31.8%]), TLS (5 patients [22.7%]), dyspnoea (4 patients [18.2%]), and blood bilirubin increased (3 patients [13.6%]).

One patient had a TEAE (PT: tumour lysis syndrome) that led to discontinuation of AZD4573 and was assessed as causally related to AZD4573 by the investigator.

Arm B

Treatment-emergent adverse events (any grade, regardless of causality) were reported in all 22 patients (100%); the most commonly reported TEAEs (≥ 40% of patients) by PT were diarrhoea and pyrexia (each in 11 patients [50.0%]), TLS (10 patients [45.5%]), and nausea, blood bilirubin increased, and hypokalaemia (each in 9 patients [40.9%]).

Grade 3 to 4 TEAEs were reported in 18 patients (81.8%); the most commonly reported (≥ 20% of patients) TEAEs with a maximum severity of Grade 3 to 4 by PT were TLS (10 patients [45.5%]), febrile neutropenia (6 patients [27.3%]), anaemia (5 patients [22.7%]), and neutropenia (5 patients [22.7%]).

Ten patients (45.5%) had AESIs of TLS, all of whom had Grade 3 to 4 events. Eleven patients (50.0%) had AESIs of neutropenia, 11 patients (50.0%) had AESIs of pyrexia 10 patients (45.5%) had AESIs of hepatotoxicity, 4 patients (18.2%) had AESIs of thrombocytopenia, and 1 patient (2.3%) had an AESI of myocardial ischaemia.

DLTs were reported for 2 of 4 evaluable patients in the [redacted] (per the CSP version they were enrolled under and per CSP version 7.0): 1 patient had a DLT of Grade 4 hypotension and 1 patient had a DLT of Grade 4 liver injury. DLTs were reported for 2 of 6 evaluable patients in the [redacted] (per the CSP version they were enrolled under and per CSP version 7.0): 1 patient had a DLT of Grade 4 TLS per the CSP version they were enrolled under and a DLT of Grade 4 hypotension per CSP version 7.0 criteria. The other patient had a DLT of Grade 4 TLS per the CSP version they were enrolled under and per CSP version 7.0 criteria. A DLT was reported in 1 of 6 evaluable patients in the [redacted] (per

the CSP version they were enrolled under and per CSP version 7.0): a DLT of Grade 4 hepatic enzyme increased.

Seven patients died, of which 4 patients died due to a TEAE (2 due to sepsis, 1 due to pneumonia and 1 due to pyrexia); none of these TEAEs were assessed as causally related to AZD4573 by the investigator. For the remaining 3 patients, 1 died due to disease progression, 1 due to a pulmonary infection (after the 30-day safety follow-up period), and for 1 patient the cause of death was 'unknown (patient was found dead in bed by a nurse)' (24 days from last dose).

Serious TEAEs were reported in 21 patients (95.5%); the most commonly reported ($\geq$ 3 patients) serious TEAEs by PT were febrile neutropenia (7 patients [31.8%]), pyrexia (6 patients [27.3%]), and TLS (5 patients [22.7%]).

Nine patients had TEAEs that led to discontinuation of AZD4573 comprising 2 events of pneumonia and 1 event each of febrile neutropenia, hepatic enzyme increased, hypotension, liver injury, myocardial infarction, pyrexia, and sepsis. Events in 4 patients (events of hypotension, hepatic enzyme increased, liver injury, and myocardial infarction) were assessed as causally related to AZD4573 by the investigator.

Conclusion(s)

- The study was designed to assess the safety and explore the BED and/or MTD of AZD4573 in patients with relapsed or refractory haematological malignancies.
- The demographic and baseline characteristics of the patients who received study treatment appropriately represented the intended population.
- A response on treatment was observed in 2 patients overall, both with DLBCL in Arm A (response evaluable analysis set ORR of 4.9% [80% CI: 1.3%, 12.5%]; ORR in Arm A of 10.0% [80% CI: 2.7%, 24.5%]; ORR in DLBCL subset of 13.3% [80% CI: 3.6%, 31.7%]). Median OS was 8.8 months overall (80% CI: 4.9, not reached) and was not reached in Arm A due to the short duration of follow-up. Median PFS was 2.1 months overall (80% CI: 1.7, 2.6).
- There are limitations regarding assessment of efficacy in this patient population since disease assessments were not consistently performed across patients using a pre-planned schedule.
- Following intravenous infusion of AZD4573, concentration reached C_{max} generally at the end of infusion, followed by a biphasic decline with mean $t_{1/2}$ λ_z between 3.171 and 6.312 hours.
- In Arm A, DLTs (per CSP version 7.0) were reported for 2 patients in the [redacted] cohort. In Arm B, DLTs were reported for 2 patients in the [redacted] cohort, 2 patients in [redacted] cohort, and 1 patient in the [redacted] cohort.
- Based on the risk-benefit profile, additional cohorts for doses between [redacted] were not explored, and as a result, BED and MTD were not determined. The RP2D dose was

determined to be [redacted] for Arm A patients and [redacted] for Arm B patients.

- AZD4573 had a manageable safety profile. The most common TEAEs across the study arms and cohorts were diarrhoea, pyrexia, and nausea. In those patients who experienced serious TEAEs, the most common events were pyrexia, TLS, and febrile neutropenia. The majority of TEAEs were considered to be manageable through supportive care and/or dose modification at the RP2D dose levels.

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