A Modular Phase I/II, Open-Label, Multi-centre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of AZD0466 Monotherapy or in Combination in Patients with Advanced Haematological Malignancies

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Study dates:	First patient enrolled: 11 June 2021 Last patient last visit: 08 August 2023 The analyses presented in this report are based on a clinical data lock date of 20 December 2023 Date of early study termination: 28 July 2023 (Due to safety concerns and lack of efficacy for AZD0466)
Phase of development:	Clinical pharmacology (I)/Therapeutic exploratory (II)
International Co-ordinating Investigator:	*Nitin Jain, MD* *Anderson Cancer Centre, The University of Texas, 1515 Holcombe Blvd, Houston, Texas, USA*
Sponsor's Responsible Medical Officer:	PPD

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

Rationale for Authoring a Synoptic Clinical Study Report (CSR)

This was a modular, Phase I/II study of AZD0466 as monotherapy or in combination with other treatments in patients with advanced haematological malignancies.

Due to the determination of an important new safety issue of troponin elevations on 06 June 2023, AstraZeneca placed the NIMBLE study on voluntary hold on 16 June 2023, followed by a Food and Drug Administration-imposed partial clinical hold on 21 June 2023.

A thorough evaluation was performed of all patient data considering the cases of troponin elevation and myocardial oedema/myocarditis in this study. Based on this review, potential AZD0466-induced myocardial injury was classified as an important identified risk. In addition, the D8242C00001 study, evaluating the use of AZD0466 in patients with Non-Hodgkin Lymphoma (NHL) showed similar findings at dose levels consistent with observations from the NIMBLE study. Regarding efficacy, to date AZD0466 was not able to demonstrate meaningful clinical activity in either study. After careful evaluation of the risk-benefit ratio, AstraZeneca concluded to prematurely terminate both the NIMBLE and NHL studies as well as further development of AZD0466. Therefore, the data captured in this study is presented in a synoptic CSR format.

Study Centre(s)

Module 1 of this study was conducted at 14 sites in 6 countries (Australia, France, Germany, Italy, South Korea, and United States of America [USA]).

Module 2 of this study was conducted at 6 sites in 2 countries (Australia and USA).

Publications

The following publications were available at the time of writing this report:

- Arslan et al. Safety and Tolerability of AZD0466 as Monotherapy for Patients with Advanced Hematologic Malignancies. Results from a Phase I/II Trial. Blood. 2023;142(Suppl 1):5907.
- Marconi et al. P537: Safety and Tolerability of AZD0466 as Monotherapy for Patients with Advanced Hematological Malignancies – Preliminary Results From an Ongoing Phase I/II Trial. Hemasphere. 2023 Aug;7(Suppl 3):927-928.
- Arslan et al. Safety and Tolerability of AZD0466 as Monotherapy for Patients with Advance Hematological Malignancies. Preliminary Results from an Ongoing Phase I/II Trial. Blood. 2022;140(Suppl 1):9091-9093.
- Konopleva et al. NIMBLE: A Phase I/II Study of AZD0466 Monotherapy or in Combination in Patients with Advanced Hematological Malignancies. Blood. 2021;138(Suppl 1):2353.

Objectives and Criteria for Evaluation

Table 1 Objectives and Endpoints

Objectives	Endpoints/Variables
Objectives and Endpoints for Both Modules 1 and 2	
Primary	
• To assess the safety and tolerability of AZD0466 in patients with advanced haematological malignancies.	• Incidence of AEs and SAEs. • Changes from baseline in laboratory findings, physical examinations, performance status, electrocardiograms, and vital signs.
Secondary	
• To characterize the PK profile of AZD0466 following intravenous administration (via PK profiles of the active moiety AZD4320 in plasma).	• Plasma concentrations and derived PK parameters for total and released AZD4320.
Module 1 (Only) Objectives and Endpoints	
Primary	
• To assess the safety and tolerability of AZD0466 in patients with advanced haematological malignancies.	• DLT. • MTD. • RP2D and schedule.
Secondary	
Complete Response Rate (CR+CRi)	
• To estimate the preliminary antitumor activity of AZD0466 by assessment of complete response rate (CR+CRi) in patients with advanced haematological malignancies.	• Complete response rate (CR+CRi) was defined as the proportion of patients who have a CR or CRi, as determined by criteria described in Appendix J, Appendix K and Appendix O of the CSP). • The analysis planned to include all dosed patients as intended. • Data obtained from first dose up until progression, or the last evaluable assessment in the absence of progression, was to be included in the assessment of CR+CRi, regardless of whether the patient withdrew from study treatment. Patients who went off treatment without a response or progression, received a subsequent therapy, and then responded were not to be included as responders in this evaluation. • The measure of interest was the estimate of CR+CRi.

TTR	
• To estimate the preliminary antitumor activity of AZD0466 by assessment of time to complete response in patients advanced haematological malignancies.	• Time to response is defined as the time from date of first dose until the date of first documented CR or CRi. • The analysis included all dosed patients as intended, who have a complete remission. • Patients who went off study treatment without a clinical response and received a subsequent therapy and then responded were not to be included. • The measure of interest was median TTR.
DoR	
• To estimate the preliminary antitumor activity of AZD0466 by assessment of DoR in patients with advanced haematological malignancies.	• DoR was defined as the time from the date of first documented response (CR+CRi) until date of documented progression, relapse or failure per Appendix J and Appendix K of the CSP or death due to any cause. • The analysis was planned to include all dosed patients as intended who had a confirmed response (CR or CRi), regardless of whether the patient withdrew from study treatment or received another anti-cancer therapy. • The measure of interest was the percentiles of DoR.
OS	
• To estimate the preliminary antitumor activity of AZD0466 by assessment of OS in patients with advanced haematological malignancies.	• OS was defined as time from date of first dose until the date of death due to any cause. The comparison included all dosed patients as intended, regardless of whether the patient withdrew from therapy or received another anti-cancer therapy. • The measures of interest were the median OS and landmarks at 6 and 12 months of OS.
Module 2 (Only) Objectives and Endpoints	
Secondary	
• To assess the drug-drug interaction potential between AZD0466 and the azole antifungal voriconazole.	• AUC and Cmax of AZD4320 after administration of AZD0466 alone and in combination with voriconazole.

Abbreviations: AE, adverse events; AUC, area under the curve; Cmax, maximum concentration; CR, complete remission; CRi, incomplete haematological response; CSP, Clinical Study Protocol; DLT, dose-limiting toxicities; DoR, duration of response; MTD, maximum tolerated dose; OS, overall survival; PK, pharmacokinetics; RP2D, recommended Phase II dose; SAE, serious adverse event; TTR, time to response.

For the exploratory objectives and endpoints of Module 1 and 2, refer to the Clinical Study Protocol (CSP) in Appendix 16.1.1.

Study Design

The study consisted of individual modules, each evaluating the safety and tolerability of AZD0466 as monotherapy or with a specific combination treatment. The core CSP contained study information applicable to all patients in this study. Module 1 (AZD0466 monotherapy), and Module 2 (drug-drug interaction [DDI] study of AZD0466 with voriconazole) contained additional specific information applicable only to the individual modules.

Module 1 had 2 study parts: Part A consisted of dose-escalation cohorts and Part B was planned to consist of expansion cohorts. A Safety Review Committee (SRC) reviewed emerging data from evaluable patients in each cohort in Module 1 to monitor safety data on an ongoing basis. Module 1 Part B was not conducted.

Module 2 Cycle 1 had 3 periods which consisted of the DDI Part of the study and Cycle 2 and subsequent cycles consisted of AZD0466 monotherapy as the post-DDI Part. The SRC assessed the safety data from Module 2 that could have affected the conduct of Module 1. For more details, see Figure 4 in Section 12.1.5 of the CSP.

Target Population and Sample Size

This study aimed at including male and female patients aged 18 or older with a diagnosis of relapsed or refractory acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), or intermediate or higher risk myelodysplastic syndrome (myelodysplastic syndrome; Part A only) with active disease who had an Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤ 2, with a predicted life expectancy of ≥ 8 weeks.

Approximately 168 patients were planned to be assigned to study treatments across Modules 1 and 2. Patients per Module who were planned to receive treatment are described below:

- Module 1: AZD0466 monotherapy (n = 154 patients)
  - Part A dose-escalation cohorts:
    - Approximately 66 patients were planned to be included in Part A. Up to 48 patients were to be enrolled to yield approximately 36 dose-limiting toxicity (DLT)-evaluable patients.
  - Initiation of Part B depended on the evaluation of safety, tolerability, and pharmacokinetics (PK) in Part A. Part B dose expansion cohorts:
    - It was planned to enroll up to 88 patients.
- Module 2: AZD0466 and voriconazole DDI study
  - Approximately 10 (maximum 14) patients were planned to be assigned to study treatment in Module 2.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch numbers

Table 2 Study Treatment for Module 1

Study Treatment	AZD0466
Dosage Form	'AZD0466 powder for concentrate for solution for infusion' supplied with 'Solvent for AZD0466 powder for concentrate for solution for infusion'.
Unit Dose Strength(s)	• 'AZD0466 powder for concentrate for solution for infusion': 500 mg per vial. [0] • 'Solvent for AZD0466 powder for concentrate for solution for infusion': 20 mL per vial. [0]
Dose Levels	Single doses on various days: 300 mg, 600 mg, 1200 mg, 2400 mg, 3600 mg, and 5400 mg.
Route of Administration	Intravenous.
Provider	AstraZeneca R&D.
Batch Numbers	• USA: AZD0466 Drug Product: CCI ; Solvent: CCI . • Italy: AZD0466 Drug Product: CCI ; Solvent: CCI . • Australia: AZD0466 Drug Product: CCI ; Solvent: CCI . • France: ZD0466 Drug Product: CCI ; Solvent: CCI .

Abbreviation: R&D, Research & Development.

[a] AZD0466 powder for concentrate for solution for infusion 500 mg/vial was intended to be reconstituted with 20 mL custom solvent to produce AZD0466 concentrate for solution for infusion, 25 mg/mL. If required, AZD0466 concentrate for solution for infusion were permitted to be further diluted with custom solvent to produce AZD0466 solution for infusion for clinical dosing. Multiple vials of drug product and custom solvent were permitted to be used to achieve the required doses.

Table 3 Study Treatment for Module 2

Study Treatment	AZD0466	Voriconazole
Dosage Form	'AZD0466 powder for concentrate for solution for infusion' supplied with 'Solvent for AZD0466 powder for concentrate for solution for infusion'.	Film-coated tablet.
Unit Dose Strength(s)	'AZD0466 powder for concentrate for solution for infusion': 500 mg per vial [0] 'Solvent for AZD0466 powder for concentrate for solution for infusion': 20 mL per vial. [0]	50, 100, and 200 mg tablets.
Dose Levels	Dose levels of AZD0466 that were declared tolerable in Module 1 Part A: • 300 mg, 600 mg, 1200 mg, 2400 mg, and 3600 mg.	• Period 1: no voriconazole. • Period 2: voriconazole of 400 mg BID and 200 mg BID. • Period 3: voriconazole 200 mg BID.

Route of Administration	Intravenous.	Oral.
Provider	AstraZeneca R&D	Provided locally by the study site, subsidiary, or designee [b]
Batch Numbers:	• USA: AZD0466 Drug Product: CCI ; Solvent: CCI . • Australia: AZD0466 Drug Product: CCI ; Solvent: CCI .	Not applicable.

Abbreviations: BID, twice a day; R&D, Research & Development.

[a] AZD0466 powder for concentrate for solution for infusion 500 mg/vial was intended to be reconstituted with 20 mL custom solvent to produce AZD0466 concentrate for solution for infusion, 25 mg/mL. If required AZD0466 concentrate for solution for infusion were permitted to be further diluted with custom solvent to produce AZD0466 solution for infusion for clinical dosing. Multiple vials of drug product and custom solvent were permitted to be used to achieve the required doses.

[b] Under certain circumstances when local sourcing was not feasible treatment were permitted to be supplied centrally through AstraZeneca. In the event of central supply voriconazole was labeled as per country requirement for clinical trial use.

Duration of Treatment

For **Module 1, Part A** (Part B was not conducted), Cycle 1 comprised of 5 weeks (35 days) within an intra-patient ramp up period, followed by 28 days of observation during weekly administration at the target dose level (35-day DLT evaluation period). Subsequent cycles were to be 28 days in duration, in which AZD0466 was planned to be administered once weekly. All patients were planned to be treated until progressive disease, unacceptable toxicity, or withdrawal of consent.

For **Module 2**, Cycle 1 comprised of 3 weeks (21 days) with a period of intra-patient ramp up of AZD0466, a period of voriconazole administration only, and a period of concomitant AZD0466 and voriconazole; Cycle 2 and subsequent cycles were planned to be 28 days in duration with weekly AZD0466 administration, and a follow-up duration of 28 days. All patients were to be treated until progressive disease, unacceptable toxicity, or withdrawal of consent.

Statistical Methods

The Statistical Analysis Plan was finalized prior to database lock and includes a more technical and detailed description of the planned statistical analyses described below. Not all planned analyses were performed due to premature termination of the study.

In general, no formal hypothesis testing was planned. Descriptive statistics (including means, standard deviations, and medians for continuous variables, and proportions and confidence intervals for discrete variables) are used to summarize data by dose level, as appropriate. For

Module 1, data from Part A have been reported only, since Part B was not conducted due to premature termination of the study.

Safety and tolerability were primarily assessed in terms of adverse events (AEs), laboratory data, vital signs, and electrocardiogram (ECG) changes. The number of patients experiencing each AE is summarized by the Medical Dictionary for Regulatory Activities (MedDRA, version 26.1) system organ class, MedDRA preferred term (PT) and Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grade. The number and percentage of patients with treatment-emergent AEs in different categories (eg, causally related and CTCAE Grade ≥ 3) are summarized by dose level and events in each category are further summarized by MedDRA system organ class and PT, as appropriate.

Hematology, clinical chemistry, vital signs, ECG data, and left ventricular ejection fraction (LVEF) are summarized over time. For all laboratory variables which are included in the current version of CTCAE, the shift from baseline CTCAE Grade to the worst on-treatment CTCAE Grade is also summarized. For ECG, the shift for normal/abnormal classification from baseline to the last on-treatment assessment is summarized. ECOG PS scores were counted by their frequencies of changes from baseline to last on-treatment assessment.

In Module 1, Part A, the safety assessments also included Cycle 1 DLTs for dose setting, and efficacy was planned to be assessed using the complete response rate, time to response (TTR), duration of response (DoR), and overall survival (OS).

The PK parameters and plasma concentrations were summarized for both modules (urine concentrations were planned to be summarized for Module 1 Part A) using the summary statistics: number of patients below lower limit of quantification (only for concentrations), geometric mean (gmean), geometric coefficient of variation %, arithmetic mean, arithmetic standard deviation, minimum, median, maximum, and number of observations.

In general, the Safety Set was used for the analysis of demographic data, baseline characteristics and all safety data. Additional summaries of demographics, baseline characteristics, and disease characteristics, are presented for the Evaluable for Response Set. The Evaluable for Response Set was to be used in the analysis of the complete response rate, TTR, and DoR. The Intention-to-Treat Set was also used in the analysis of complete response rate, and in the analysis of OS. The Dose-limiting Toxicity Evaluable Set was used for the assessment of DLTs. The Pharmacokinetic Set was used for the PK analyses. Listings of all data are presented for both modules. Figures describing summaries of safety and PK data are also presented, as appropriate.

Study Population

There was no data cut-off; the study database was closed on 20 December 2023.

Module 1 (Part A):

A total of 41 patients were screened, of which 32 patients were assigned and received study treatment in the Module 1 of the study. All 32 of the patients discontinued treatment. The most common reason for discontinuation was due to the condition under investigation worsened (56.3%), followed by Investigator decision (18.8%) and AEs (12.5%). There were 3 patients (9.4%) who had a possibly related AE leading to discontinuation which included by PT: myocarditis, troponin increased, troponin T increased. All 32 patients were withdrawn from the study, with the main reason being due to death (53.1%) and other (28.1%), followed by study terminated by AstraZeneca (12.5%).

Twenty-seven patients (84.4%) had a baseline disease type of AML/secondary AML: most of the patients (10 patients [31.3%]) had AML type at study entry listed as de novo AML, followed by 9 patients (28.1%) listed as secondary to chemotherapy, 6 patients (18.8%) as other, and 2 patients (6.3%) as prior history of myeloproliferative neoplasm.

Five patients (15.6%) had a baseline disease type of ALL: 4 were B-cell ALL and 1 was T-cell ALL.

The median age of the patients who received treatment was 67.5 years (range: 33 to 82 years); the majority were of White race (78.1%), male (53.1%), and most had their ethnicity described as not Hispanic or Latino (84.4%). At baseline, patients had an ECOG PS score of 0 (40.6%), 1 (46.9%), or 2 (9.4%).

A total of 24 patients (75.0%), who received treatment, had at least one important protocol deviation (PD) during the study. None of the identified important PDs were considered to have a major impact on the overall study results and conclusions, however, where deviations were considered to have a potential impact on individual PK parameter (if calculable) or concentration results, these were excluded from summary statistics and the reason provided in listings.

The medical and surgical history, and the prior anti-cancer and concomitant medications were as expected in the eligible study population. All of the patients (32) were on prior anti-cancer therapy:

- There were 11 patients (34.4%) who had prior allogeneic haematopoietic stem cell transplantation.
- There were 25 patients (78.1%) who received venetoclax in a prior line of therapy.
- Eight patients (25.0%) received 1 prior anti-cancer therapy line, 8 patients (25.0%) received 2 anti-cancer therapy lines, and 16 patients (50.0%) received > 2 prior anti-cancer therapy lines.

All prior cancer therapies were in line with the standard of care as per local practice or clinical trial for disease under study.

Module 2:

A total of 31 patients were screened, of which 16 patients were assigned and 14 patients received study treatment in the Module 2 of the study. All 14 of the patients discontinued treatment. The most common reason for discontinuation was due to the condition under investigation worsened (42.9%) and patient decision (28.6%), followed by AEs (14.3%) and Investigator decision (14.3%). There were 2 patients (14.3%) who had a possibly related AE leading to discontinuation, both for infusion related reaction. All 14 patients were withdrawn from the study, with the main reason being due to death (50.0%), and withdrawal by patient (28.6%), followed by lost to follow-up (7.1%), study terminated by AstraZeneca (7.1%), and other (7.1%).

Thirteen patients (92.9%) had a baseline disease type of AML/secondary AML: most of the patients (5 patients [35.7%]) had AML type at study entry listed as other, followed by 4 patients (28.6%) listed as de novo AML, 2 patients (14.3%) as prior history of myeloproliferative neoplasm, and 2 patients (6.3%) as secondary to chemotherapy.

One patient (7.1%) had a baseline disease type of ALL of B-cell lineage.

The median age of the patients who received treatment was 69.5 years (range: 25 to 80 years); the majority were of White race (92.9%), and most had their ethnicity described as not Hispanic or Latino (85.7%). Gender was evenly split between male and females (50.0%). At baseline, patients had an ECOG PS score of 0 (14.3%), 1 (71.4%), or 2 (14.3%).

A total of 11 patients (78.6%) who received treatment had at least one important PD during the study. Important PDs impacted the overall study results and conclusions. Specifically, overdoses of AZD0466 on Cycle 1 Day 15 (C1D15) impacted interpretation of the role of voriconazole as a perpetrator of DDIs with AZD0466.

The medical and surgical history, and the prior anti-cancer and concomitant medications were as expected in the eligible study population. All of the patients (14) were on prior anti-cancer therapy:

- There were 3 patients (21.4%) who had prior allogeneic haematopoietic stem cell transplantation.
- There were 12 patients (85.7%) who received venetoclax in a prior line of therapy.
- Four patients (28.6%) received 1 prior anti-cancer therapy line, 1 patient (7.1%) received 2 prior anti-cancer therapy lines, and 9 patients (64.3%) received > 2 prior anti-cancer therapy lines.

All prior cancer therapies were in line with the standard of care as per local practice or clinical trial for disease under study.

Summary of Efficacy Results

Module 1 (Part A)

Preliminary antitumor activity of AZD0466 was assessed for patients in Module 1 (Part A) as a secondary objective. complete response rate was primarily assessed in the Evaluable Response Set, but also repeated in the Intention-to-Treat Set. Overall survival was assessed in the Intention-to-Treat Set.

- Twenty-three patients were evaluable for response. No patients with either AML or ALL had a complete response (CR + CRi), therefore TTR and DoR were not calculated.
- In total, of the 20 patients with AML, 5 patients (25.0%) had stable disease as best response, 6 patients (30.0%) had progressive disease, 5 patients (25.0%) had treatment failure due to resistant disease, 3 patients (15.0%) had no post-baseline assessment, and 1 patient (5.0%) had a haematological relapse. Similar results were seen in the Intention-to-Treat Set.
- In total, of the 3 patients with ALL, 2 patients (66.7%) had treatment failure due to resistant disease and 1 patient (33.3%) had no post-baseline assessment. Similar results were seen in the Intention-to-Treat Set.
- The median OS for the Intention-to-Treat Set was 3.2 months (95% confidence interval 2.1 months, 4.2 months).

Summary of Pharmacokinetic Results

Module 1 (Part A):

- Following weekly intravenous infusion of AZD0466 in Module 1 at target doses ranging from 300 to 5400 mg, all patients were systemically exposed to total and released AZD4320. PK was characterized (ie, PK parameters were calculated) for 31 patients; 3 of these were excluded from all PK summaries.
- Exposure to total AZD4320 generally increased with increasing dose. Overall, the increase in exposure represented a less than proportional increase in maximum concentration (Cmax) and a more than proportional increase in area under the curve (AUC). However, trends were inconsistent across dose groups, as dose-normalized exposure fluctuated, eg, Cmax was similar at 300 mg and 600 mg, but increased by 4-fold from 1200 mg to 2400 mg, and then decreased from 2400 mg to 3600 mg. Based on minimal data at 5400 mg, it appeared that Cmax and AUC increased in a slightly less than dose proportional manner from 3600 to 5400 mg.
- Total AZD4320 was characterized by a geometric mean t1/2 in the range of approximately 9 to 12 hours, consistent with no accumulation observed in total AZD4320 on C2D1 relative to C1D8.
- Released AZD4320 generally increased as dose increased, in terms of the partial area under the plasma concentration-time curve from time 0 to 72 hours after

- the start of infusion (AUC0-72) and Cmax. Overall, the data suggested a less than proportional increase in Cmax and a more than proportional increase in AUC. However, trends were inconsistent across dose groups; exposure decreased slightly from 3600 to 5400 mg for both AUC and Cmax, although geometric mean Cmax values were relatively similar at 300, 600, and 1200 mg.
- Released AZD4320 was measured at consistently lower levels compared to total (approximately ≤ 5%, as expected). Estimates of t½ were longer (approximately 20 hours) for released AZD4320, with no notable evidence of accumulation of released AZD4320 on C2D1 compared to C1D8.
- Renal excretion of unchanged AZD4320 is not a significant route of elimination. This is consistent with an estimated AZD4320 urinary excretion of 0.01% to 0.02% of the dose following administration of 2400 mg or 5400 mg AZD0466, with corresponding renal clearance values of 0.02 or 0.004 L/h (n = 3, where available data as deemed sufficient for estimation).

Module 2:

- Exposure to total and released AZD4320 was characterized in the presence and absence of voriconazole to assess the potential for a strong Cytochrome P450 3A4 (CYP3A4) inhibitor to alter AZD4320 disposition. Due to changes in target dose levels and PDs (overdose of AZD0466 on C1D15, missing dosing diaries for voriconazole, and missed PK samples), there were insufficient data to support statistical analysis; results were listed only.
- PK was characterized for 12 patients in Module 2 at target doses of 300 mg (1 patient, C1D1 only), 600 mg (3 patients), 1200 mg (4 patients), 2400 mg (3 patients), and 3600 mg (1 patient) AZD0466. Of these, 3 patients received the target dose on C1D15 rather than target dose/4 (2 patients at 600 mg, one patient at 1200 mg). Where PK results were available at the same dose level on C1D1 and C1D15, individual results were described here.
- At 150 mg (target dose of 600 mg), one patient was evaluable (ie, received the same AZD0466 dose with and without voriconazole). Exposure (AUC0-72) increased by 1.8-fold for total AZD4320 and by 1.5-fold for released AZD4320, for this patient, despite uncertainty in voriconazole administration (missing dose diary).
- At 300 mg (target dose of 1200 mg), 3 patients were evaluated at 300 mg on C1D15 (with voriconazole) and C1D1 (without voriconazole). For these patients, AZD4320 (total and released) was higher in the presence of voriconazole for 2 out of 3 patients; released AZD4320 increased by 30% for both patients, while total AZD4320 increased by 1.5- or 2-fold.
- At 600 mg (target dose of 2400 mg), 2 patients were evaluated at the target/4 dose level on C1D15 and C1D1. Changes in AZD4320 were < 2-fold for these patients. The largest change was a 35% increase in total AZD4320 AUC0-72 for one patient.
- Overall, while it was not possible to make statistical conclusions regarding the impact of voriconazole on AZD0466, available data support the approach. Administration of AZD0466 target dose/4 in the presence of voriconazole successfully maintained AZD4320 exposure at a level below the AUC0-72 associated with the corresponding

target dose, as determined during C1D8 of Module 1. Amongst available data, AZD4320 did not act as a sensitive CYP3A4 substrate; observed changes in exposure were no more than 2-fold.

- The statistical comparison comparing AZD0466 alone (Period 1) with AZD0466 + Voriconazole (Period 3) was not performed, as there was insufficient data available.

Summary of Safety Results

Module 1 (Part A):

- The median total treatment duration for AZD0466 was 4.10 weeks (range: 0.1 to 37.6 weeks). The median relative dose intensity of AZD0466 was 100% (range: 37.6 to 100.1%).
  - All of the patients had initiated at least 1 treatment cycle (100%), 12 patients (37.5%) initiated 2 treatment cycles, 3 patients (9.4%) each initiated treatment cycle 3 and 4, 2 patients (6.3%) each initiated treatment cycles 5 and 6, and 1 patient initiated treatment cycle 7 (3.1%).
- AEs were reported for 30 patients (93.8%).
  - The most frequently recorded AEs by PT were for hypokalaemia (12 patients [37.5%]), aspartate aminotransferase (AST) increased (11 patients [34.4%]), alanine aminotransferase (ALT) increased (10 patients [31.3%]), and nausea (10 patients [31.3%]).
- AEs considered to be possibly related by the Investigator were reported for 22 patients (68.8%).
  - The most frequently recorded possibly related AEs by PT were AST increased (9 patients [28.1%]), ALT increased (8 patients [25.0%]), gamma-glutamyltransferase increased (4 patients [12.5%]), and platelet count decreased (4 patients [12.5%]). Thrombocytopaenia was recorded in 2 patients (6.3%).
- Serious AEs (SAEs) were reported for 19 patients (59.4%).
  - No correlation was seen between dose and the frequency of SAEs: SAEs occurred in 100% of patients in the 300 mg group, 80.0% in the 3600 mg group, 60.0% in the 2400 mg group, 50% in the 5400 mg group, 42.9% in the 1200 mg group and 0.0% in the 600 mg group.
- SAEs considered to be possibly related by the Investigator were reported for 5 patients (15.6%).
  - Myocarditis (3600 mg and 5400 mg dose levels) and troponin increased (2400 mg and 5400 mg dose levels) were considered possibly related for 2 patients (6.3%), and ALT increased (2400 mg) and troponin T increased (3600 mg) were considered possibly related for 1 patient (3.1%) each.
- In Module 1, 25 patients (78.1%) experienced AEs of CTCAE Grade 3 or higher.

  - The most frequently reported AEs of CTCAE Grade 3 or higher (≥ 10% of patients) were febrile neutropaenia (18.8%), pneumonia (18.8%), platelet count decreased (15.6%), thrombocytopaenia (12.5%), and hypokalaemia (12.5%).
  - Overall, the maximum CTCAE Grade were recorded for AEs per patient for 14 patients (43.8%) at Grade 3, for 10 patients (31.3%) at Grade 4 and 1 patient (3.1%) at Grade 5 (fatal AE; however, this AE of cerebral haemorrhage was not considered to be possibly related to AZD0466).
  - Overall, the maximum CTCAE Grade were recorded for possibly related AEs per patient for 8 patients (25.0%) at Grade 3 and for 7 patients (21.9%) at Grade 4.
    - The reported possibly related AEs of Grade 3 intensity by PT were for febrile neutropaenia in 3 patients (9.4%), followed by hypokalaemia and ALT increased in 2 patients (6.3%) each, and hypomagnesaemia, diarrhoea, blood creatinine phosphokinase increase, gamma-glutamyltransferase increase, lipase increase, troponin T increase, and troponin increase in 1 patient (3.1%) each.
    - The reported possibly related AEs of Grade 4 intensity by PT were for platelet count decreased in 4 patients (12.5%), thrombocytopaenia in 2 patients (6.3%), and neutrophil count decreased in 1 patient (3.1%).

- Eighteen patients (56.3%) were hospitalized due to AEs. The most frequent AEs leading to hospitalizations were for pneumonia (5 patients [15.6%]), febrile neutropaenia (3 patients [9.4%]), and abdominal pain (2 patients [6.3%]).
- There were 4 patients (12.5%) who had AEs that led to discontinuation of AZD0466, 1 patient (3.4%) who had an AE leading to dose reduction of AZD0466, and 12 patients (37.5%) who had AEs leading to dose interruptions of AZD0466.
  - Three patients (9.4%) had possibly related AEs leading to discontinuation of AZD0466. These AEs were recorded by PT for myocarditis, troponin T increased, and troponin increased (1 patient [3.1%] each). All of these were recorded as SAEs.
- In total, 17 deaths (53.1%) were reported, with 16 deaths related to “the disease under investigation” and 1 death relating to “the disease under investigation and an AE with the outcome of death” (the AE of cerebral haemorrhage was not considered to be possibly related to AZD0466).
  - One participant (PPD) had CTCAE Grade 5 cerebral haemorrhage. The cerebral haemorrhage was attributed by the Investigator to AML and to thrombocytopaenia refractory to platelet transfusion (detection of anti-human leukocyte antigen antibodies before C1D1). The primary cause of death was reported as disease progression.
- Three patients (12.5%) in the DLT-evaluable Set had DLTs (2 patients in the 3600 mg and 1 patient in the 5400 mg dose levels). There were 2 AEs (8.3%) of myocarditis (both Grade 2) and 1 AE (4.2%) each for troponin T increased and troponin increased (both Grade 3).
- There were shifts from baseline values in CTCAE Grades for ALT and AST laboratory results. In Module 1, 12 patients (37.5%) had AEs of special interest (AESIs) that were

classified as “hepatotoxicity” (including by the PTs potential Hy’s Law, drug-induced liver injury, and bilirubin increase with transaminase [ALT or AST or both ALT and AST] increase):

  - Ten patients (31.3%) had ALT increased and 11 patients (34.4%) had AST increased.
  - No ALT/AST increase with concurrent bilirubin increased ie, no results met Hy’s Law criteria (Hy’s Law criteria, ie, ALT or AST values ≥ 3 × upper limit of normal [ULN] together with total bilirubin values ≥ 2 × ULN).

- There were 5 patients (15.6%) with QT corrected for heart rate by Fridericia's cube root formula (QTcF) > 470 ms, 3 patients (9.4%) > 480 ms, and 2 patients (6.3%) > 500 ms at any timepoint while on-treatment as compared with the change from baseline. There were 11 patients (34.4%) who had an increase in QTcF > 30 ms and 4 patients (12.5%) > 60 ms at any time while on-treatment as compared with the change from baseline. QTcF prolongations were asymptomatic.
- No patients had Grade 1 or higher decreases in LVEF.
- There were no clinically relevant trends observed for any other laboratory results, ECG variables, or vital signs.
- The maximum tolerated dose and the recommended Phase II dose and schedule were not determined as the study was terminated, including further development of AZD0466.

Module 2:

- The median total treatment duration for AZD0466 in Module 2 was 4.05 weeks (range: 0.6 to 8.3 weeks), while the median total treatment duration for voriconazole was 8.0 days (range: 1 to 9 days). The median relative dose intensity of AZD0466 was 100% (range: 1.3 to 137.5%). Two patients who received doses higher than the CSP intended dose on C1D15 during the DDI Part of the study; however, no related AEs were reported around the time of the higher dose administration.
  - All of the patients had initiated at least 1 treatment cycle (100%), 9 patients (64.3%) initiated 2 treatment cycles, and 2 patients (14.3%) initiated treatment cycle 3.
- AEs were reported for 13 patients (92.9%).
  - The most frequently recorded AEs by PT were for 6 patients (42.9%) each for anaemia, hematuria, and nausea.
- AEs considered to be possibly related by the Investigator were reported for 9 patients (64.3%).
  - The most frequently recorded possibly related AEs by PT were nausea (3 patients [21.4%]), AST increased (3 patients [21.4%]), ALT increased (2 patients [14.3%]), and infusion related reaction (2 patients [14.3%]).
- SAEs were reported for 9 patients (64.3%).
  - No correlation was seen between dose and the frequency of SAEs: SAEs occurred in 100% of patients in the 2400 mg dose group, 100% in the 300 mg group, 100% in the 3600 mg group, 66.7% in the 600 mg group, and 0.0% in the 1200 mg group.

- SAEs considered to be possibly related by the Investigator were reported for 3 patients (21.4%).
  - All possibly related SAEs were reported for 1 patient each and included (by PT) pneumonia (2400 mg), thrombocytopaenia (2400 mg), and infusion related reaction (3600 mg).
- In Module 2, 13 patients (92.9%) experienced AEs of CTCAE Grade 3 or higher.
  - The most frequently reported AEs of CTCAE Grade 3 or higher (≥ 10% of patients) were anaemia (35.7%), febrile neutropaenia (28.6%), lymphocyte count decreased (28.6%), neutrophil count decreased (28.6%), platelet count decreased (21.4%), sepsis (21.4 %), pneumonia (21.4%), and muscular weakness (14.3%).
  - Overall, the maximum CTCAE Grade were recorded for AEs per patient for 4 patients (28.6%) at Grade 3, for 8 patients (57.1%) at Grade 4, and 1 patient (7.1%) at Grade 5 (Fatal AE; however, this AE of sepsis was not considered to be possibly related to AZD0466).
  - Overall, the maximum CTCAE Grade were recorded for possibly related AEs per patient for 1 patient (7.1%) at Grade 3 and 4 patients (28.6%) at Grade 4.
    - Grade 3 possibly related AEs were recorded by PT for 1 patient (25.0%) each for pneumonia and anaemia.
    - The possibly related AEs of Grade 4 intensity by PT were for thrombocytopaenia, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, white blood cell count increased, and infusion related reactions in 1 patient (7.1%) each.
- Eight patients (57.1%) were hospitalized due to AEs. The most frequent AEs leading to hospitalizations for 3 patients (21.4%) each were for pneumonia, sepsis, and febrile neutropaenia.
- There were 2 patients (14.3%) who had AEs that led to discontinuation of AZD0466 (none of these were recorded as SAEs), 2 patients (14.3%) who had an AEs leading to dose reduction of AZD0466, and 6 patients (42.9%) who had AEs leading to dose interruptions of AZD0466.
  - Both AEs leading to discontinuation of AZD0466 were considered to be possibly related to AZD0466 and both were recorded by PT as an infusion related reaction.
- In total, 7 deaths (50.0%) were reported, with 6 deaths related to “the disease under investigation” and 1 death relating to “the disease under investigation and an AE with the outcome of death” (the AE of sepsis was not considered to be possibly related to AZD0466).
  - One participant (PPD) had CTCAE Grade 5 sepsis which was not considered to be possibly related to AZD0466 by the Investigator and AstraZeneca. The primary cause of death was reported as disease progression secondary to an unrelated AE.

- In Module 2, 6 patients (42.9%) had AESIs that were classified as "hepatotoxicity including potential Hy's Law, drug-induced liver injury, and bilirubin increase with transaminase (ALT or AST or both ALT and AST) increase":
  - Five patients (35.7%) had AST increased, 4 patients (28.6%) had blood bilirubin increased, and 3 patients (21.4%) had ALT increased. While there were shifts from baseline in CTCAE Grades for various laboratory results, there were no other clinically relevant trends observed.
  - No ALT/AST increase occurred concurrent with bilirubin increased and no occurrences fulfilled the criteria for Hy's Law or potential Hy's Law (potential Hy's Law criteria, ie, ALT or AST values ≥ 3 × ULN together with total bilirubin values ≥ 2 × ULN).
- There was 1 patient (7.1%) with QTcF value > 470 ms and 5 patients (35.7%) with an increase in QTcF by > 30 ms at any time while on-treatment as compared with the change from baseline. QTcF prolongations were asymptomatic.
- No patients had Grade 1 or higher decreases in LVEF.
- There were no clinically relevant trends observed for changes in laboratory values, ECG variables, and vital signs.

Conclusion(s)

Forty-six patients with relapsed/refractory AML or ALL received one or more doses of AZD0466 in this Phase I study. Following reports of troponin elevation and myocardial oedema/myocarditis a thorough evaluation of all patient data was performed. Based on this review, potential AZD0466-induced myocardial injury was classified as an important identified risk. In addition, the D8242C00001 study, evaluating the use of AZD0466 in NHL showed similar findings at dose levels consistent with observations from the NIMBLE study. Regarding efficacy, to date AZD0466 was not able to demonstrate meaningful clinical activity in either study. After careful evaluation of the risk-benefit ratio, AstraZeneca concluded to prematurely terminate both the NIMBLE and NHL studies as well as further development of AZD0466. Therefore, the data captured in this study is presented in a synoptic CSR format.