Abbreviated Clinical Study Report Synopsis	
Drug Substance	AZD0466
Study Code	D8240C00003
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NCT Number	NCT02740985

A Phase I, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Ascending Doses of AZD0466 in Patients with Advanced Hematologic or Solid Tumors

Study dates: First subject enrolled: 16 December 2019
Last subject last visit: 18 June 2021
The analyses presented in this report are based on a clinical data lock date of 20 December 2021

Phase of development: Clinical pharmacology (I)

International Co-ordinating Investigator: PPD
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Sponsor's Responsible Medical Officer: PPD
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This study was performed in compliance with International Council for Harmonisation Good Clinical Practice, including the archiving of essential documents.

Study Centers

The study was conducted at 2 sites in the USA.

Publications

None at the time of writing this report.

Objectives and Endpoints

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of AZD0466 participants with advanced hematologic and solid tumor malignancies.	Incidence of AEs, SAEs and DLTs Changes from baseline in laboratory data, vital signs, and ECG results
To determine the MTD/RP2D when given to patients with advanced hematologic and solid tumor malignancies.	The RP2D will be determined in discussion among the SRC. Observations related to PK, PD and AZD0466 toxicities may be included in the rationale supporting the RP2D
Secondary	
To characterize the PK profile of AZD0466 following IV administration (via PK profiles of the total/released active moiety AZD4320).	Indirect evaluation via individual subject concentration measurements of the Total/Released active moiety of AZD0466 (AZD4320) Estimated PK parameters of AZD4320 including C_{max} and AUC
To assess the preliminary tumor response of AZD0466 in patients with advanced hematologic and solid tumor malignancies.	RECIST 1.1 criteria for solid tumors Lugano (Cheson et al 2014) classification for lymphoma iwCLL guidelines for CLL (Hallek et al 2018) International Working Group Criteria (Palumbo et al 2014) for multiple myeloma Criteria adapted from Savona et al 2015 for MDS and MPN Criteria adapted from Döhner et al 2010 for CLL SWOG 2016 for acute lymphoblastic leukemia

AE, adverse event; AUC, area under the concentration-time curve; C_{max}, maximum observed concentration; DLT, dose-limiting toxicity; ECG, electrocardiogram; IV, intravenous(ly); MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; MTD, maximum tolerated dose; PD, pharmacodynamic(s); PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase II dose; SAE, serious adverse event; SWOG, Southwest Oncology Group.

Study Design

This was a first-time-in-human (FTIH), Phase 1, open-label, multicenter study to determine the safety, tolerability, maximum tolerated dose (MTD), recommended Phase II dose (RP2D),

and pharmacokinetics (PK) of AZD0466 in patients with advanced solid tumors, lymphoma and multiple myeloma at low risk (LR) of developing tumor lysis syndrome (TLS) as well as in participants at intermediate risk (IR) or high risk (HR) of TLS with hematologic malignancies for whom no standard therapy exists. AZD0466 is a drug-dendrimer conjugate that consists of an active moiety (AZD4320, a dual B-cell lymphoma-2/B-cell lymphoma extra-long (BCL-2/BCL-xL)-specific molecule) covalently conjugated to a pegylated poly-L-lysine type dendrimer, which gradually releases the small molecule by hydrolysis.

Arm A was to include participants at LR of TLS with advanced solid tumors, lymphoma or multiple myeloma.

Arm B was to include participants at IR to HR of TLS with hematological malignancies. Arm B was planned to open after completion of the 400 mg cohort in Arm A. However, following agreement with the Safety Review Committee (SRC) to commence enrollment and dosing of the Arm A 200 mg cohort, Arm A was closed prior to dose escalation to 400 mg AZD0466, and Arm B enrollment was not started.

Once an MTD/RP2D had been determined in the dose escalation portions of Arms A and B respectively, further disease-specific expansions (in solid and hematological malignancies) enrolling additional participants of histologically limited subtypes and at RP2D doses defined by protocol amendment were planned to be undertaken. However, as the study closed prior to determining the MTD/RP2D, disease-specific expansion cohorts were not opened.

Target Population and Sample Size

Arm A of this study was to include adults (aged ≥ 18 years) with histologically or cytologically confirmed advanced solid tumors, lymphoma, and multiple myeloma at LR of developing TLS. Participants must have had documented active disease requiring treatment that is relapsed or refractory as determined by Response Evaluation Criteria in Solid Tumours (RECIST)- or clinically-defined disease progression or recurrence.

Arm A of this study was to enroll approximately 54 participants. In the absence of dose-limiting toxicities (DLTs), 8 cohorts of up to 6 evaluable participants (n = 48) were to be treated. However, whilst cohort size is usually capped at 6 evaluable participants, statistical simulations suggest an additional 6 participants (n = 54 final) may have been required to yield the desired degree of certainty to identify the actual MTD (undertaken at the discretion of the SRC).

The target population and sample size for Arm B has not been included in the Clinical Study Report (CSR) as enrollment was not started for this arm. See Section 7.2 from the CSP v4.0 for the Arm B target population and sample size.

Investigational Product: Dosage and Mode of Administration

AstraZeneca provided the Investigators with AZD0466 using designated distribution centers.

In Arm A, AZD0466 was to be initially administered intravenously (IV) over 1 hour, once weekly. For this arm, a cycle of study treatment was defined as 28 days and each cohort tested single dose levels with no intraparticipant dose ramp-up. The initial dose of AZD0466 was 50 mg, which was escalated to 100 mg, followed by 200 mg, before enrollment was closed. Doses could have been increased to a maximum of 3200 mg.

The dosage and mode of administration for Arm B has not been included in the CSR as enrollment was not started for this arm.

Duration of Treatment

Participants were to continue to receive AZD0466 as long as they were continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

Statistical Methods

Arm A was to include participants at low risk of TLS, enrolling participants with advanced solid tumors, lymphoma, and multiple myeloma to be treated under a Bayesian-informed dose escalation scheme.

The statistical methods for Arm B have not been included in the CSR as enrollment was not started for this arm. See Section 7 of the CSP v4.0 for Arm B statistical methods.

All participants who received a particular dose level were grouped together for summary and analysis and defined as a dose group. At a participant level, the baseline had been defined as the last non-missing value obtained prior to the first dose/administration of AZD0466.

All participants who received at least 1 dose of AZD0466 were to be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data were produced.

Plasma concentrations of AZD4320 were to be summarized by nominal sample time. Plasma concentrations and derived PK parameters were to be summarized by dose level.

Tumor response data were to be summarized for dosed patients with measurable disease at baseline and separately for dosed patients who only had nonmeasurable disease at baseline using the standard response criteria (RECIST 1.1 for advanced solid tumors). Tumor response data were to be listed and summarized by dose group.

Study Population

A total of 13 participants signed informed consent; of which, 4 were screen failures and 9 were assigned to treatment. All 9 participants received AZD0466; of which, 7 completed the study and 2 terminated the study (1 due to death [from disease progression], and 1 due to other [starting a new treatment]).

Summary of Efficacy Results

The best overall response in the 50 mg and 200 mg AZD0466 groups was disease progression, and all participants in the 100 mg AZD0466 group experienced a best overall response of stable disease. The best percentage change

from baseline in target lesion size in the 50 mg, 100 mg, and 200 mg AZD0466 groups were 2.8%, -10.5% (mean: -1.8%; median: -5.8%), and 5.7%, respectively (the means and medians were not calculable for the 50 mg and 200 mg AZD0466 groups).

Summary of Pharmacokinetic Results

- Total AZD4320 reached median t_{max} at the end of infusion and was eliminated in a biphasic manner with a $t_{1/2}$ λz of approximately 11 hours.
- Released AZD4320 appeared rapidly in plasma and the concentration–time profile generally followed that of the total AZD4320.
- Preliminary estimates of t½λz for released AZD4320 suggest a slower elimination than for total AZD4320 with t½λz estimates all longer than 20 hours.
- Released AZD4320 accounted for approximately 2% to 3% of the total AZD4320 exposure.
- Interparticipant variability in exposure for both analytes was generally moderate (25% to 40%) to high (> 40%) based upon geometric CV.
- The increase in C_{max}, AUC_{last}, and AUC_{inf} for both analytes appeared
- to be greater than proportional to dose.

Summary of Safety Results

- All participants experienced an adverse event (AE), and 8 participants experienced an AE possibly related to AZD0466.
- Due to the small sample size in this study, any AE that was experienced is considered very common (frequency ≥ 10%).
- No participants experienced a DLT.
- No patients experienced AEs of TLS.
- One death on study occurred and was related to disease under investigation only.
- There were no safety concerns due to clinical chemistry, hematology, vital signs, or electrocardiogram data.

Conclusions

- There were no safety or tolerability concerns following AZD0466 administration at 50, 100, or 200 mg IV once weekly.
- The RP2D was not determined as the study was halted prior to completing dose escalation due to a strategic decision to focus the AZD0466 program solely on hematological malignancies.
- The sample size in this study was too small to draw any efficacy conclusions.