Title: A Modular Phase I/II, Open-label, Dose Escalation and Expansion, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of AZD0466 as Monotherapy or in Combination with Anticancer Agents in Patients with Advanced Non-Hodgkin Lymphoma

Sponsor Study Code: D8242C00001

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Synoptic Clinical Study Report Synopsis	
Drug Substance	AZD0466
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A Modular Phase I/II, Open-label, Dose Escalation and Expansion, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of AZD0466 as Monotherapy or in Combination with Anticancer Agents in Patients with Advanced Non-Hodgkin Lymphoma

Study dates:
First participant enrolled: 05 July 2022
Last participant last visit: 17 August 2023
Reason for early study termination: Due to unfavourable risk-benefit ratio
The analyses presented in this report are based on a clinical data lock date of 23 January 2024.

Phase of development:
Clinical pharmacology (I)
Therapeutic exploratory (II)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centre(s)

A total of 24 sites in 8 countries were activated in the study, and a total of 10 sites in 7 countries screened participants: 1 in Australia, 1 in France, 1 in Italy, 1 in Portugal, 2 in South Korea, 3 in Spain, and 1 in the United States (US).

Publications

The following publication for Module 1 was available at the time of writing this report:

- Chong et al. AZD0466 in Patients with Advanced Non-Hodgkin Lymphoma: Efficacy and Safety in an Open-label Phase 1 Trial. Cancer Res. 2024,84(7_Supplement):CT146.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A	
To assess the safety and tolerability and identify the MTD and/or RP2D of AZD0466 as monotherapy or in combination with anticancer agents in participants with R/R B-NHL	Incidence of AEs and DLTs Changes from baseline in laboratory parameters, electrocardiograms, and vital signs
Part B	
To assess the preliminary efficacy of AZD0466 as monotherapy or in combination with other anticancer agents in participants with R/R B-NHL	ORR Endpoint based on revised response criteria for malignant lymphoma (Cheson et al 2014) [a]
Secondary	
Part B	
To assess the safety and tolerability of AZD0466 as monotherapy or in combination with anticancer agents in participants with R/R B-NHL	Incidence of AEs and SAEs Changes from baseline in laboratory parameters, physical examinations, performance status, electrocardiograms, and vital signs
To assess the efficacy of AZD0466 as monotherapy or in combination with anticancer agents by evaluation of tumour response and OS in participants with R/R B-NHL	CR rate DoR TTR PFS OS Tumour response endpoints based on revised response criteria for malignant lymphoma (Cheson et al 2014) [a]
Part A and Part B	
To characterise the PK profile of study drug(s)	Plasma concentrations and derived PK parameters for study drug(s), to be specified for each module

[a] Cheson BD et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

AE = adverse event; B-NHL = B-cell non-Hodgkin lymphoma; CR = complete response; CSP = clinical study protocol; DLT = dose-limiting toxicity; DoR = duration of response; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RP2D = recommended Phase II dose; R/R = relapsed/refractory; SAE = serious adverse event; TTR = time to response.

For exploratory objectives and endpoints, refer to study protocol (version 2.0) in Appendix 16.1.1. None of the protocol-defined exploratory objectives are reported in this report. However, for Part A the best objective response rate was done as an exploratory analysis.

Study Design

The study was planned to consist of individual modules, each evaluating the safety and tolerability of AZD0466 as monotherapy or with a specific combination treatment. The initial components of the study protocol were the core protocol (which contained information applicable to all modules) and Module 1.

Module 1 was to evaluate the safety, tolerability, PK, and preliminary efficacy of AZD0466 monotherapy and included 2 parts:

- Part A: Phase I monotherapy dose escalation in participants with advanced B-cell non-Hodgkin lymphoma (B-NHL) to assess safety and tolerability and determine dose(s) and schedule(s) of AZD0466 treatment to be evaluated in Part B.
- Part B: Phase II cohort expansion(s) in selected participant disease groups to assess preliminary anti-tumour efficacy of AZD0466 treatment.

The primary objective for Part A was to assess the safety and tolerability and identify the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of AZD0466 as monotherapy in participants with R/R B-NHL. The primary objective for Part B was to estimate objective response rate (ORR) by applying revised Lugano classification 2014 response criteria.

This protocol had a modular design with the potential for future treatment arms to be added. A Safety Review Committee reviewed emerging data from evaluable participants in each cohort of dose escalation in Module 1 to monitor safety data on an ongoing basis. At the time of study termination, the protocol only consisted of Module 1. Part B of Module 1 was not conducted.

Target Population and Sample Size

Module 1 Part A included male and female participants aged 18 or older with advanced B-NHL. Once the RP2D had been determined, Part B was to be opened to further explore the

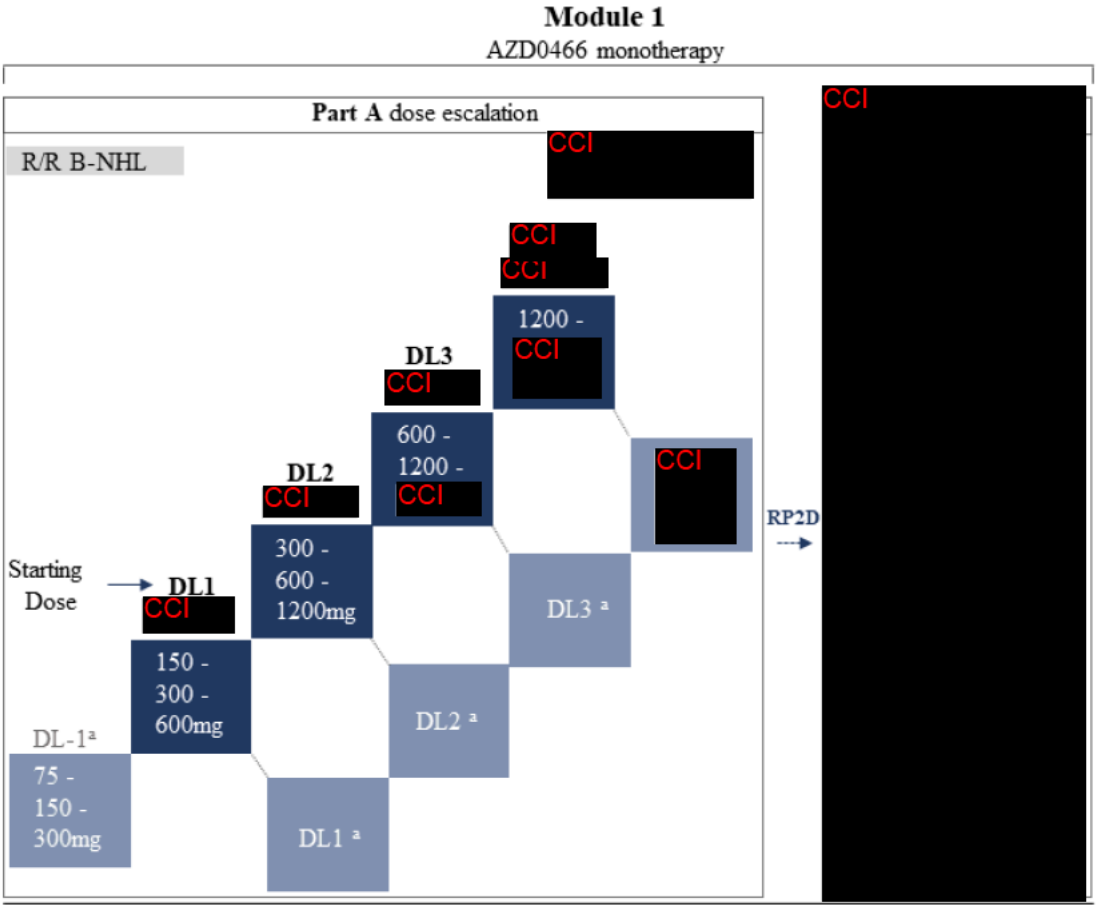
preliminary anticancer efficacy of AZD0466 monotherapy in participants with selected lymphoid malignancies, including R/R mantle cell lymphoma (MCL) (Cohort B1), R/R follicular lymphoma (FL) or marginal zone lymphoma (MZL) (Cohort B2), and R/R diffuse large B-cell lymphoma (DLBCL) (Cohort B3).

In Module 1 Part A, approximately CCI participants were to be included, with a minimum of CCI participants per dose cohort. Participants were evaluated through the dose-limiting toxicity (DLT) evaluation period of 28 days before a dose escalation/dose expansion/de-escalation decision was made (unless unacceptable toxicity was encountered prior to enrolment of CCI participants). The maximum number of participants at any given dose cohort was capped at CCI participants.

In Module 1 Part B, up to CCI participants were to be included (CCI participants each for Cohort B1 and for Cohort B2, and CCI participants for Cohort B3). However, the study was terminated prior to the selection of the RP2D and did not initiate Module 1 Part B.

The overall study schema for Module 1, Part A (dose escalation) and Part B (dose expansion), as reproduced from the CSP, is presented in Figure S1.

Figure S1 Overall Study Schema



[a] Alternative dosing schedule; option of dose reduce and/or change in dosing schedule from weekly to every 2 weeks based on emerging safety data.

Note: AZD0466 doses shown in above figure are illustrative. Dose escalation was conducted so as to not be greater than a 2-fold increase of a dose declared tolerable by the SRC, or the maximum dose (CCI mg) as specified in Section 10.4.3 of the CSP (Appendix 16.1.1). One participant in DL3 received 2400 mg AZD0466 as the target dose as agreed upon by the SRC.

B-NHL = B-cell non-Hodgkin lymphoma; CSP = clinical study protocol; DL = dose level; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma; MTD = maximum tolerated dose; MZL = marginal zone lymphoma; RP2D = recommended Phase II dose; R/R = relapsed/refractory; SRC = Safety Review Committee.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Participants in Module 1 (Parts A and B) were to receive AZD0466 monotherapy.

Intervention Name	AZD0466
Dose Formulation	AZD0466 powder for concentrate for solution for infusion supplied with Solvent for AZD0466 powder for concentrate for solution for infusion
Unit Dose Strength	AZD0466 powder for concentrate for solution for infusion: CCI mg per vial [a] Solvent for AZD0466 powder for concentrate for solution for infusion: CCI mL per vial [a]
Dosage Levels	Participants of Module 1, Part A received AZD0466 target doses of 600, 1200, or 2400 mg once weekly on Cycle 1 Day 8 and thereafter in 28-day cycles following an intra-participant dose ramp-up on Day 1 and Day 4 in Cycle 1 (see CSP in Appendix 16.1.1).
Route of Administration	Intravenous
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided by AstraZeneca
Packaging and Labelling	AZD0466 powder for concentrate for solution for infusion was provided in CCI mg vials. Each vial was labelled as per country requirement. Solvent for AZD0466 powder for concentrate for solution for infusion was provided in CCI mL vials. Each vial was labelled as per country requirement.
Batch Numbers	AZD0466 powder: CCI (expiry CCI) and CCI (expiry CCI). Solvent for AZD0466 powder: CCI (expiry CCI) and CCI (expiry CCI)

[a] AZD0466 powder for concentrate for solution for infusion CCI mg/vial was intended to be reconstituted with CCI mL custom solvent to produce AZD0466 concentrate for solution for infusion, CCI 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.

IMP = investigational medicinal product; MTD = maximum tolerated dose; NIMP = non-investigational medicinal product; RP2D = recommended Phase II dose.

Duration of Treatment

For Module 1 Part A, cycle 1 consisted of a dose ramp-up on Day 1 and Day 4 to reach the target dose level on Day 8 and thereafter administered weekly at the target dose throughout the 28-day DLT period. Subsequent cycles were 28 days in duration, in which AZD0466 was administered once weekly. All participants were planned to be treated for 2 years until either disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reason(s) to discontinue study intervention, whichever occurred first. Module 1 Part B was not conducted.

Statistical Methods

A comprehensive statistical analysis plan (SAP) was developed and described the participant populations to be included in the analyses, the analyses including any subgroup analyses or sensitivity analyses, and the procedures to account for missing, unused, and spurious data (see Appendix 16.1.9).

Due to early study termination, not all planned analyses were performed. Specifically for efficacy, as per the SAP, certain efficacy endpoints for Part B were considered for Part A as exploratory endpoints as data permitted. However, only the best objective response exploratory analysis was done for Part A due to early study termination.

In general, for Module 1, no formal hypothesis testing was planned. Descriptive statistics were used for all variables. Continuous variables were summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages were calculated out of the population total. Baseline was defined as the last non-missing value obtained prior to the first dose/administration of any study intervention. Figures describing summaries of safety and efficacy data are also presented for Module 1, as appropriate. Listings of data are also presented for Module 1.

The safety set, defined as all participants who received ≥ 1 dose of AZD0466, was used for all analyses of demographic data, baseline characteristics, and for all safety analyses. The Part A efficacy exploratory endpoint best objective response was analysed for the evaluable for response analysis set. The DLT evaluable set was used for the assessment of DLTs. The PK set was used for the PK analyses.

Analyses of all safety endpoints included treatment-emergent adverse events (TEAEs), laboratory data, vital signs, and electrocardiogram changes. In Module 1, Part A, the safety assessments also included DLTs that occurred during the 28-day DLT evaluable period.

TEAEs were defined as any AE with an onset date on or after the first dose date of AZD0466 or any ongoing AE that worsened in severity after the first dose date of AZD0466, and up to

30 days after the date of the last dose of AZD0466 or the first date starting subsequent therapy, whichever was earliest. Safety was presented using descriptive statistics unless otherwise stated. The safety analysis was done both by dose level and for the total population. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 system organ class, preferred term and Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) grade, and were described using the MedDRA preferred term unless otherwise stated.

Laboratory data (including clinical chemistry, haematology, coagulation and urinalysis), vital signs, and electrocardiogram data were summarised over time. For all laboratory variables which were included in the current version of CTCAE, the shift from baseline CTCAE grade to the worst on-treatment CTCAE grade was also summarised. The CTCAE grade for the clinical chemistry CTCAE grade change from baseline tables was based on the laboratory ranges associated with the CTCAE grade and not based on associated symptoms or treatment indication.

PK parameters and plasma concentrations were summarised for Module 1 Part A using the summary statistics: number of participants below lower limit of quantification (only for concentrations), geometric mean (gmean), geometric coefficient of variation (CV)%, arithmetic mean, arithmetic standard deviation (SD), minimum, median, maximum, and number of observations.

A modification from the SAP definition of total treatment duration was made: total duration of exposure is defined by last date of actual dosing (ie, a dose > 0 mg/L is given) in the last cycle plus 6 days (by default, the number of days in a cycle or until the next scheduled dose minus 1 day; there were 2 days between C1D1 and C1D4, 3 days between C1D4 and C1D8, and 6 days thereafter) minus the date of first treatment with AZD0466 plus 1 day (see Section 5.6.1.1 of the SAP, Appendix 16.1.9).

Study Population

Note: no participants were enrolled/screened in Module 1 Part B of this study, thus only results from Module 1 Part A will be presented in the rest of this report.

Of the 13 participants screened in the study, 6 participants were considered screen failures, and 7 participants were assigned to study treatment. Of the 7 participants assigned to treatment, all initiated treatment (3 participants at target dose of 600 mg AZD0466, 3 participants at target dose of 1200 mg AZD0466, and 1 participant at target dose of 2400 mg AZD0466 as approved by the SRC to escalate up to 2-fold prior dose level) and were included in the safety, PK, intention-to-treat, and DLT-evaluable sets; the evaluable for response set included 6 participants. The participant who was excluded from the evaluable for response set did not receive at least 2 doses of AZD0466 at the target dose level. At the time of planned

last participant last visit date (17 August 2023), all 7 participants had discontinued treatment, including 3/7 (42.9%) participants due to objective disease progression; 2/7 (28.6%) participants due to adverse events, and 1/7 (14.3%) participant each due to participant decision and study terminated by the Sponsor.

A total of 2/7 (28.6%) participants who received treatment had at least one important protocol deviation (PD) during the study, both due to the use of disallowed concomitant medications. None of the identified important PDs were considered to have a major impact on participant safety and the overall study results and conclusions.

The age of the participants who received treatment ranged from 26 to 79 years; the majority were of White (4/7 [57.1%] participants) race, were male (6/7 [85.7%] participants), and had an Eastern Cooperative Oncology Group performance status score of 0 (4/7 [57.1%] participants) or 1 (3/7 [42.9%] participants) at baseline. The majority of participants who received treatment had NHL classified as DLBCL (5/7 [71.4%] participants) and most had Stage II or IV disease according to the Lugano classification (3/7 [42.9%] participants each). The majority of participants (5/7 [71.4%] participants) had 3 prior lines of anti-cancer therapy.

The medical and surgical history were as expected in the current participant population and the prior cancer therapies were in line with the standard of care as per local practice.

Summary of Efficacy Results

- In total, 6 participants were evaluable for response.
  - One (16.7%) participant achieved a best objective response of partial response at the 1200 mg target dose level. The best objective responses for the remaining 5 (83.3%) participants included 3 (50.0%) participants with stable disease and 2 (33.3%) participants with progressive disease.
- At the time of study termination, limited evidence of anti-tumour activity was observed based on a small number of participants.

Summary of Pharmacokinetic Results

- No participant was excluded from the non-compartmental analysis.
- Limited data were available for 2400 mg, and therefore was not included in the PK observations context below.
- Following weekly intravenous infusion of AZD0466 in Module 1 at target doses ranging from 600 to 1200 mg, all participants were systemically exposed to total and released AZD4320 (active moiety of the AZD0466 dendrimer).
- Exposure to total AZD4320 increased with increasing dose; a dose increase by 2-fold from 600 to 1200 mg was associated with approximately 1.6-fold increase in total AZD4320 Cmax and AUC. There was no accumulation observed for total AZD4320 following multiple dosing (C2D1 compared to C1D8).

- Total AZD4320 was characterized by an arithmetic mean t½ in the range of approximately 11 to 12 hours.
- Released AZD4320 was measured at consistently lower levels compared to total (approximately < 5% of total, as expected). There was a slight trend toward a later tmax for released AZD4320, compared to total, most notably at higher dose levels, where tmax was 6 to 9 hours post dose for some participants.
- Exposure to released AZD4320 generally increased as dose increased; a dose increase by 2-fold from 600 to 1200 mg was associated with approximately 2-fold increase in Cmax and AUC. There was no consistent evidence of accumulation of released AZD4320 following multiple dosing (C2D1 compared to C1D8).
- Estimates of t½ were longer (around 15 hours) for released AZD4320 compared to total AZD4320 on C1D8.

Summary of safety results

- Overall, the median duration of AZD0466 treatment was 7.29 weeks (range: 2.0 to 33.0 weeks). In the 600 mg AZD0466 cohort the median duration was 27.14 weeks (range: 7.3 to 33.0 weeks) and in the 1200 mg AZD0466 cohort it was 7.14 weeks (range: 7.0 to 9.0 weeks). The overall duration of AZD0466 treatment for the sole participant in the 2400 mg AZD0466 cohort was 2.0 weeks.
  - All participants had initiated at least 1 treatment cycle (100%): 6/7 (85.7%) participants initiated 2 treatment cycles, 2/7 (28.6%) participants initiated treatment cycles 3 through 6, and 1/7 (14.3%) participant initiated treatment cycles 7 through 9.
- The median relative dose intensity of AZD0466 treatment was 100% (range: 73.8% to 100%) in the 600 mg AZD0466 cohort and 88.57% (range: 70.4% to 100%) in the 1200 mg AZD0466 cohort. The overall relative dose intensity of AZD0466 treatment for the sole participant in the 2400 mg AZD0466 cohort was 100%.
- Overall, AEs were reported for all 7/7 (100%) participants and 6/7 (85.7%) participants experienced at least one AE that was assessed by the investigator as possibly related to AZD0466 treatment.
  - The most frequently reported TEAEs (experienced by 2 or more participants) that were assessed as possibly related to AZD0466 were platelet count decreased (total 4/7 participants), neutropenia or neutrophil count decreased (total 3/7 participants), and hypophosphatemia (2/7 participants) in both the 600 mg and 1200 mg AZD0466 cohorts.
- Overall, 4/7 (57.1%) participants experienced AEs of CTCAE Grade 3 or higher: 1/3 (33.3%) participants in the 600 mg AZD0466 cohort, 2/3 (66.7%) participants in the 1200 mg cohort, and 1/1 (100%) participant in the 2400 mg AZD0466 cohort.
  - CTCAE ≥ Grade 3 AEs included neutropenia, neutrophil count decreased, platelet count decreased, and troponin increased, all of which were assessed by the investigator as possibly related to AZD0466.

- A serious adverse event (SAE) of Grade 3 troponin increased was reported for the 1 participant in the 2400 mg AZD0466 cohort, assessed by the investigator as possibly related to AZD0466. This SAE led to treatment discontinuation. No SAEs were reported for the 600 and 1200 mg AZD0466 cohorts.
- Overall, 2/7 (28.6%) participants experienced AEs leading to discontinuation of AZD0466; 1/3 (33.3%) participants in the 1200 mg AZD0466 cohort experienced an AE of Grade 3 platelet count decrease, and 1/1 (100%) participant in the 2400 mg AZD0466 cohort experienced a SAE of Grade 3 troponin increased. Both participants recovered following discontinuation of AZD0466.
- Dose delays of AZD0466 due to AEs were reported for 1/3 (33.3%) participants in the 600 mg AZD0466 cohort and for 2/3 (66.7%) participants in the 1200 mg AZD0466 cohort. No AEs leading to dose reduction or infusion interruption of AZD0466 were reported.
- Overall, 1/7 (14.3%) participants in the DLT-evaluable set experienced a DLT: SAE of Grade 3 troponin increased in the 2400 mg AZD0466 cohort, which led to AZD0466 discontinuation.
- No Hy's law cases were reported. Overall, 1/7 (14.3%) participants in the 1200 mg AZD0466 cohort had laboratory abnormalities that met laboratory criteria for potential Hy's Law based on both bilirubin increase with transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) increased:
  - The participant had AST and ALT ≥ 3 × upper limit of normal (ULN) together with bilirubin ≥ 2 × ULN at the end of treatment visit and programmatically met potential Hy's Law criteria. These elevated enzymes were assessed by the investigator as due to progression of disease to the liver and was therefore not entered as a Hy's law case and the AE was removed in accordance with CRF completion guideline (no disease-related lab abnormalities or symptoms are to be reported as AEs).
- No deaths were reported for this study.
- Overall, AZD0466 at doses ≤ 1200 mg was clinically well tolerated, but a DLT of asymptomatic troponin elevation was observed at 2400 mg.
- No conclusions could be drawn for clinically relevant trends for laboratory results and vital signs given the small number of participants and limited data available. There were no concerns with the safety and tolerability of AZD0466 based on changes observed from baseline for laboratory parameters, physical examinations, performance status, electrocardiograms and vital signs, in the safety set participants.

Conclusion(s)

Seven patients with advanced B-NHL received one or more doses of AZD0466 in this Phase I study. Following reports of troponin elevation and myocardial oedema/myocarditis in the D8241C00001 study (NIMBLE), a thorough evaluation of all participant data was performed. Based on this review, potential AZD0466-induced myocardial injury was classified as an important identified risk. This study showed similar findings of troponin elevation at dose levels consistent with observations from the NIMBLE study and halted participant recruitment

for this study on 10 July 2023. 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.