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

NCT Number: NCT05205161

Date: 01 November 2021

Clinical Study Protocol	
Study Intervention	AZD0466
Study Code	D8242C00001
Version	2.0
Date	01 November 2021

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 Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Numbers:	**IND 142050** **EudraCT 2021-003410-39**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D8242C00001

Amendment Number: 1

Study Intervention: AZD0466

Study Phase: I/II

Short Title: A Phase I/II Study of AZD0466 as Monotherapy or in Combination with Anticancer Agents in Advanced Non-Hodgkin Lymphoma

Study Physician Name and Contact Information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	01 November 2021
Original Protocol	21 July 2021

Amendment 1, Dated 01 November 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was amended to include FDA recommendations. In addition to the updates based on FDA feedback the protocol was also amended to clarify inconsistencies throughout the protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.2 Schema	Figure 1 Overall Study Schema was updated to correct the number of patients in Cohort B2 R/R FL/MZL.	Clarification (typographical error correction).	Non-substantial
Section 4.5 Criteria for Stopping or Pausing the Study Recruitment	A new section 'Section 4.5 Criteria for Stopping or Pausing the Study Recruitment' was added to the protocol.	This section has been added to include a rule-based, study-wide stopping criteria, for guidance on when this study may stop or pause enrolment.	Substantial
Section 5.1 Inclusion Criteria	Inclusion criterion no 6 was updated to clarify at least one measurable FDG-PET avid lesion (except for MZL).	Updated for clarity since MZL patients have variable FDG-PET avidity, this criterion may not be applicable. Therefore, for MZL patients with FDG-PET non-avid lesion a CT scan is required.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 5.2 Exclusion Criteria	Exclusion criterion no 2 was added to the 'Core' exclusion criteria section (guidance for both Parts A and B), to exclude patients with risk of TLS according to Howard modification of Cairo-Bishop criteria and/or the presence of bulky disease.	Updated to clarify that this exclusion criterion is also applicable for Part B (not only Part A).	Substantial
	Exclusion criterion no 8, was updated to clarify that patients with known concurrent infection with CMV will be excluded.	Updated to exclude patients with known concurrent infection with CMV, since patients with controlled CMV infection may be at risk of subsequent uncontrolled infections and potential drug-drug interactions with antiviral treatments.	Non-substantial
	Exclusion criterion no 9 was updated to clarify that fully recovered patients (defined as no on-going COVID-19 symptoms, except loss of sense of smell/taste) who present persistence of positive PCR test with a negative antigen test and the presence of IgG antibodies, may be included in the study.	Updated for clarity to ensure that patients that are fully recovered from COVID-19 are not excluded from the study.	Non-substantial
	Exclusion criterion no 14, was updated to increase the period that patients must have stopped immunosuppression therapy from 4 weeks to 2 months.	Immunosuppressive therapy should be discontinued a minimum of 2 months prior to study intervention.	Substantial
Section 6.5.1 Permitted Concomitant Medications and Treatments	Table 5 Permitted Concomitant Medications and Treatments, was updated to clarify that prophylactic and therapeutic anti-microbials are allowed under supportive care, provided that they are not in the list of prohibited concomitant medications.	Updated to clarify that antimicrobial prophylaxis and therapy is permitted provided that they are not in the list of prohibited concomitant medications (Section 6.5.2).	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.6.6.1 Dose Modifications	The section was updated to clarify that dose frequency changes are not possible during ramp-up.	Updated to clarify that dose frequency changes can only occur at the target dose.	Non-substantial
	The section was updated to clarify permitted dose modifications (dose reduction and frequency change) and to clarify that a single event of CTCAE Grade 3 or 4 haemorrhage and any intracranial haemorrhage or haematoma, will result in discontinuation of study intervention.	To specify how many recurrences of a particular toxicity are permitted before the study intervention should be discontinued.	Substantial
	Table 6 Dose Frequency Changes was updated for clarity.	Clarification.	Non-substantial
Section 6.6.6.2 Dose Modifications Based on Haematologic Parameters	The section was updated to clarify the requirements for patients prior to each cycle.	Clarification.	Non-substantial
	Table 8 Recommended Dose Modifications for Haematologic Toxicities, was updated to specify the actions to be taken with regard to dose modification in the event of haematologic toxicities, and to include the number of recurrences of a particular toxicity that are permitted before the study intervention will be discontinued.	To specify how many recurrences of a particular toxicity are permitted before the study intervention should be discontinued. To specify to the investigator which action (eg, dose modification, study intervention discontinuation) should be taken in the event of a specific toxicity.	Substantial
Section 6.6.6.3 Dose Modifications Based on Non-haematologic Parameters	Table 9 Dose Modifications for Non-haematologic Toxicities, was updated to specify the actions to be taken with regards to dose modification in the event of non-haematologic toxicities, and to include the number of recurrences of a particular toxicity are permitted before the study intervention will be discontinued.	To specify how many recurrences of a particular toxicity are permitted before the study intervention should be discontinued. To specify to the investigator which action (eg, dose modification, study intervention discontinuation) should be taken in the event of a specific toxicity.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.6.6.4 Dose Modifications for Hepatotoxicity	Table 10 Dose Modification for Hepatotoxicity in Patients with Normal Baseline Liver Function, was updated to specify the actions to be taken with regards to dose modification in the event of hepatotoxicity in patients with normal baseline liver function, and to include the number of recurrences of a particular toxicity that are permitted before the study intervention will be discontinued.	To specify how many recurrences of a particular toxicity are permitted before the study intervention should be discontinued. To specify to the investigator which action (eg, dose modification, study intervention discontinuation) should be taken in the event of a specific toxicity.	Substantial
	Table 11 Dose Modification for Hepatotoxicity in Patients with Abnormal Baseline Liver Function, was added to specify the actions to be taken with regards to dose modification in the event of hepatotoxicity in patients with abnormal baseline liver function, and to include the number of recurrences of a particular toxicity that are permitted before the study intervention will be discontinued.	To specify how many recurrences of a particular toxicity are permitted before the study intervention should be discontinued. To specify to the investigator which action (eg, dose modification, study intervention discontinuation) should be taken in the event of a specific toxicity.	Substantial
Section 6.6.7 Resumption of Treatment	The section was updated to remove the specific treatment resumption criteria, instead referring to Section 6.6.6 and the corresponding tables.	The text is redundant since this is now described in Section 6.6.6.	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments	Table 12 Laboratory Safety Variables, was updated to remove footnote c.	Clarification (typographical error correction).	Non-substantial
Section 8.3.10 Reporting of Serious Adverse Events	This section was updated to remove 'the mandated' from the last paragraph.	Clarification (typographical error correction).	Non-substantial
Section 10.1.2 Schema	Figure 2 Module 1 Schema, was updated to correct the number of patients in Cohort B2 R/R FL/MZL.	Clarification (typographical error correction).	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 10.1.3 Schedule of Activities	Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1, was updated to include details on prophylaxis for Tumour Lysis Syndrome.	Clarification regarding the management of TLS prophylaxis.	Non-substantial
	Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1, was updated to include a footnote to clarify that MZL patients with FDG-PET non-avid lesion, only require a CT scan.	Updated for clarity since MZL has variable PET avidity, this criterion is not applicable.	Substantial
	Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1, was updated to include B-symptoms collection at Screening and every tumour assessment scan.	Clarification.	Non-substantial
	Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1, was updated to include a footnote to clarify that troponin T may be collected using a standard assay instead of troponin I, provided the results remain within normal range; However, if an abnormal troponin T value is recorded, collection of troponin I will be required thereafter.	Clarification.	Non-substantial
Section 10.1.3 Schedule of Activities	Table 14 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up, was updated to clarify that safety ECGs will be done on Day 1 of every even cycle from Cycle 4.	Clarification (typographical error correction).	Non-substantial
	Table 14 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up, was updated to include details on prophylaxis for Tumour Lysis Syndrome.	Clarification regarding the management of TLS prophylaxis.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Table 14 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up, was updated to include B-symptoms collection at Screening and every tumour assessment scan.	Clarification.	Non-substantial
	Table 14 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up, was updated to include a footnote to clarify that troponin T may be collected using a standard assay instead of troponin I, provided the results remain within normal range; However, if an abnormal troponin T value is recorded, collection of troponin I will be required thereafter.		
Section 10.5.1.2 Additional Inclusion Criteria for Cohort B2 (R/R FL or MZL)	Inclusion criterion no 1 was updated to clarify that patients must have a histologically confirmed diagnosis of FL Grade 1, 2, or 3a OR histologically confirmed MZL including splenic, nodal, and extranodal subtypes, as assessed by Investigator or local pathologist with documented active disease requiring systemic treatment.	For patients with indolent lymphomas, they must meet criteria requiring systemic treatment.	Substantial
Section 10.5.1.3 Additional Inclusion Criteria for Cohort B3 (R/R DLBCL)	Inclusion criterion no 1 was updated to clarify that patients must have histologically confirmed DLBCL (including transformed FL) OR FL Grade 3b.	Clarify that Cohort B3 (R/R DLBCL) will include patients with transformed FL.	Substantial
Section 10.5.2.1 Additional Exclusion Criteria for Part A	Section 10.5.2.1 Additional Exclusion Criteria for Part A was removed.	The section was removed since the addition of exclusion criterion no 2 in 'Section 5.2 Exclusion Criteria' made the text redundant.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 10.6.6.1 Starting Dose, Dose Escalation Scheme and Stopping Criteria	Table 15 Decision Rules Based on mTPI-2 for Dose Escalation, was updated to reduce the number of patients in the table at the current dose level from 12 to 9 since a maximum number of 9 patients will be dosed per cohort.	Clarification (only a maximum of 9 patients will be dosed).	Non-substantial
Section 10.6.6.2 Dose Expansion	Section was updated to clarify that AZD0466 will be administered based on a weekly dosing schedule for 2 years following an initial ramp up during week 1.	Clarification (typographical error correction).	Non-substantial
Section 10.6.6.3 Definition of DLT	The DLT haematologic toxicity CTCAE Grade 4 neutropenia lasting > 7 days was updated to remove 'despite growth factor support'.	Grade 4 neutropenia lasting > 7 days should be considered a DLT in the presence or absence of growth factor support.	Substantial
	The list of DLTs was updated to included 'Any CTCAE Grade 5 AEs'.	Any CTCAE Grade 5 AEs should be a DLT.	Substantial
Section 10.8.2.3 Electrocardiograms	The section was updated to remove arrhythmia assessment from electrocardiogram Holter monitoring.	Arrhythmia analysis is not required for PK purposes. Electrocardiograms for safety will be performed as indicated in Section 8.2.3.	Non-substantial
	Table 16 Part A and Part B Safety ECG and Holter ECG Extraction, was updated to indicate that at C1D8, triplicate ECGs (instead of single ECG) are required for safety purpose. The Holter monitor is being used for PK purpose.	Arrhythmia analysis is not required for PK purposes.	Non-substantial
Section 10.8.6.4 Whole Blood for Minimal/Measurable Residual Disease (Part A and Part B)	Table 19 Whole Blood for Minimal/Measurable Residual Disease (Part A and Part B), was updated to change the layout of the table to ensure consistency with the rest of the tables.	Consistency and clarity.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 10.8.6.5 Whole Blood for Circulating Free/Circulating Tumour DNA Analysis (Part A and Part B)	Table 20 Whole Blood for [redacted] (Part A and Part B), was updated to change the layout of the table to ensure consistency with the rest of the tables.	Consistency and clarity.	Non-substantial
Appendix F Management of Specific Adverse Events	Table F27 Risk Assessment for Tumour Lysis Syndrome, was updated for clarity.	Clarification.	Non-substantial
Appendix M Disease Prognostic Scores	Appendix M Disease Prognostic Scores was added to the protocol.	Clarity, provide reference for all investigators.	Non-substantial
Throughout Protocol	Minor typographical, and editorial changes were made throughout the clinical study protocol.	Clarity and consistency	Non-substantial

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1 PROTOCOL SUMMARY – CORE

1.1 Synopsis

Protocol 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

Short Title:

A Phase I/II Study of AZD0466 as Monotherapy or in Combination with Anticancer Agents in Advanced Non-Hodgkin Lymphoma

Rationale:

Non-Hodgkin lymphoma is a heterogeneous group of disorders involving malignant clonal proliferation of lymphoid cells in lymphoreticular sites. A subgroup of NHL is B-NHL, which includes indolent diseases such as FL and MZL that evolve slowly, with a median survival of 8 to 10 years. In contrast, more aggressive B-NHL diseases such as DLBCL and MCL, if left untreated, have a median survival of 6 months. Despite different available treatment options, a subset of patients who receive current therapies relapse.

Overexpression of pro-survival proteins, like Bcl-2 and Bcl-xL have been associated with tumour initiation, progression, and resistance to various current therapies. Bcl-2 was first identified as an oncogene in a FL cell line with a t(14;18) translocation followed by MCL, DLBCL, and MZL. Similarly, Bcl-xL overexpression was reported in FL, DLBCL, and MCL. Importantly, recent studies demonstrated Bcl-2 and/or Bcl-xL overexpression in primary samples of patients with DLBCL, FL, or MCL to correlate with poor prognosis.

This study will investigate the safety, tolerability, PK, and efficacy of AZD0466, a dual Bcl-2/Bcl-xL inhibitor, in patients with advanced B-NHL who have failed prior therapy(ies), are not eligible for curative treatment options, and for whom there is no standard therapy available.

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 patients 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 patients with R/R B-NHL	• ORR Endpoint based on revised response criteria for malignant lymphoma (Cheson et al 2014)
Secondary	
Part B	
• To assess the safety and tolerability of AZD0466 as monotherapy or in combination with anticancer agents in patients 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 patients 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)
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

AE = adverse event; B-NHL = B-cell non-Hodgkin lymphoma; CR = complete response; 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, see Section 3 of the CSP.

Overall Design:

The study consists of individual modules, each evaluating the safety and tolerability of AZD0466 as monotherapy or with a specific combination treatment. The initial components are the core protocol, which contains information applicable to all modules, and Module 1.

Module 1 will evaluate the safety, tolerability, PK, and preliminary efficacy of AZD0466 monotherapy and will include 2 parts. Part A consists of dose escalation and Part B of dose expansion cohorts. Part A will enrol patients with advanced B-NHL and once the RP2D has

been determined, Part B may open to further explore the preliminary anticancer efficacy of AZD0466 monotherapy in patients with selected lymphoid malignancies, including R/R MCL (Cohort B1), R/R FL or MZL (Cohort B2), and R/R DLBCL (Cohort B3).

An SRC (Appendix A 5) will review emerging data from evaluable patients in each cohort in Module 1 to monitor safety data on an ongoing basis.

This protocol has a modular design with the potential for future treatment arms to be added, as described in Section 4.1.4.

Disclosure Statement:

This is a non-randomised, open-label, dose escalation and expansion study.

Number of Patients:

In Module 1 Part A, a minimum of [redacted] patients will be enrolled in a dose cohort and evaluated through the DLT evaluation period of 28 days before a dose escalation/dose expansion/de-escalation decision can be made (unless unacceptable toxicity is encountered prior to enrolment of [redacted] patients). The maximum number of patients at any given dose cohort will be capped at [redacted] patients.

In Module 1 Part B, up to [redacted] patients will be enrolled ([redacted] patients for Cohort B1 and for Cohort B2, and [redacted] patients for Cohort B3).

Intervention Groups and Duration:

All patients will receive AZD0466. Treatment will continue for 2 years or until disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue study intervention, whichever occurs first. For patients who are responding and do not experience unacceptable toxicities, continuation of treatment may be considered by the Investigator and Sponsor.

Patients in Module 1 will receive AZD0466 monotherapy. Patients enrolled into subsequent modules incorporated via protocol amendment may receive AZD0466 in combination with other anticancer treatments.

Data Monitoring Committee:

This study will utilise an SRC, as described in Appendix A 5.

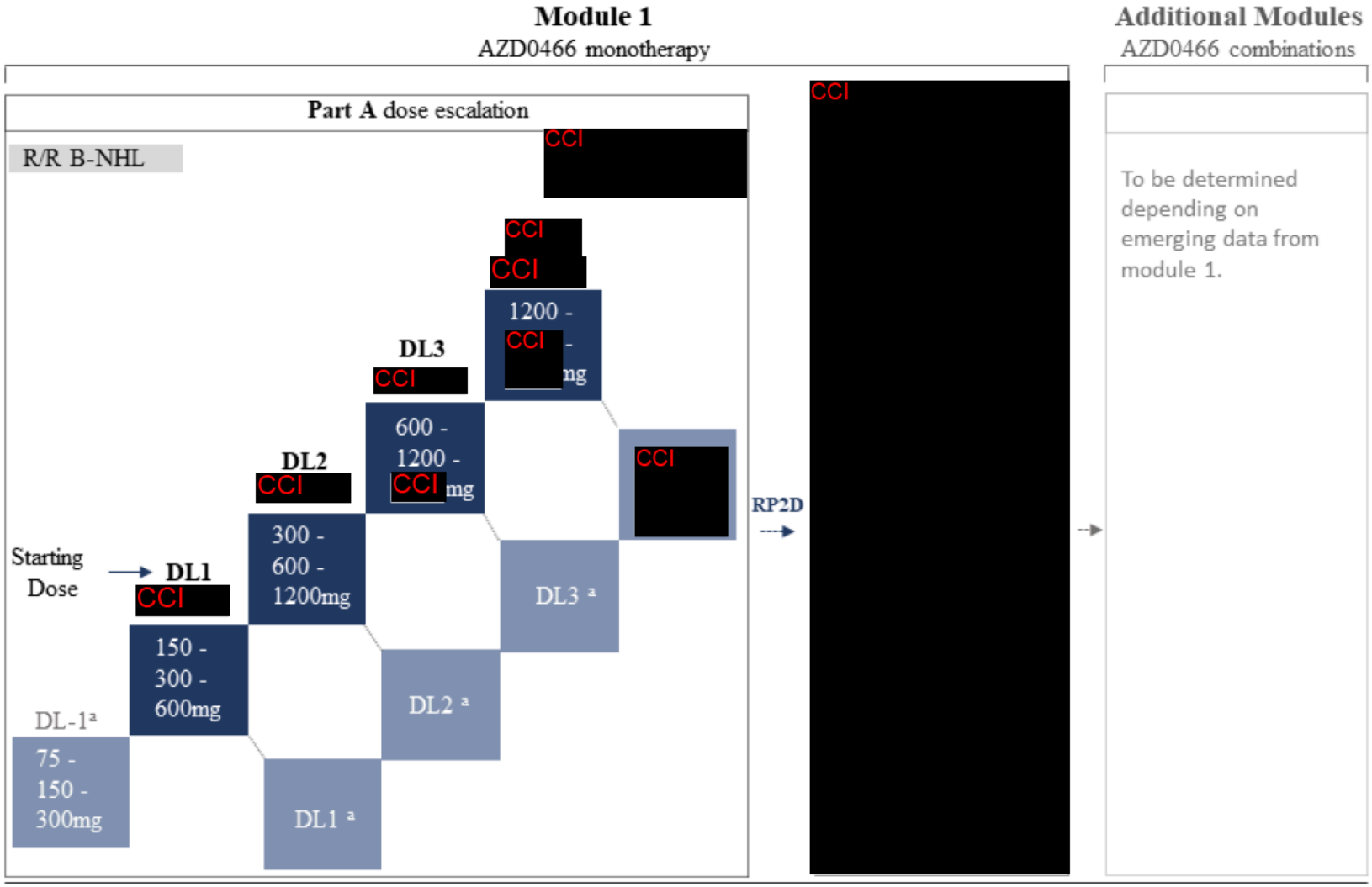
Statistical Methods:

Refer to the relevant individual modules for statistical considerations in this study.

1.2 Schema

The overall study schema is shown in Figure 1. Refer to the relevant individual modules for additional design information.

Figure 1 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.
B-NHL = B-cell non-Hodgkin lymphoma; 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.

1.3 Schedule of Activities

Refer to the individual SoAs for each study module within the respective protocol section (eg, Section 10.1.3 for Module 1).

2 INTRODUCTION – CORE

AZD0466 is a drug-dendrimer conjugate consisting of an active moiety AZD4320, covalently conjugated to a [redacted] dendrimer that gradually releases the active moiety by hydrolysis. AZD0466 is being developed for the treatment of B-NHL, including MCL, DLBCL, FL, and MZL.

2.1 Study Rationale

Non-Hodgkin lymphoma is a heterogeneous group of disorders involving malignant clonal proliferation of lymphoid cells in lymphoreticular sites. A subgroup of NHL is B-NHL, which includes indolent diseases such as FL and MZL that evolve slowly, with a median survival of 8 to 10 years. In contrast, more aggressive B-NHL diseases such as DLBCL and MCL, if left untreated, have a median survival of 6 months. Despite different available treatment options, a subset of patients who receive current therapies relapse.

Overexpression of pro-survival proteins, like Bcl-2 and Bcl-xL have been associated with tumour initiation, progression, and resistance to various current therapies (Czabotar et al 2014, Delbridge and Strasser 2015). Bcl-2 was first identified as an oncogene in a FL cell line with a t(14;18) translocation (Vaux et al 1988) followed by MCL (Rimokh et al 1993), DLBCL (Monni et al 1999), and MZL (Meda et al 2003). Similarly, Bcl-xL overexpression was reported in FL, DLBCL (Xerri et al 1996), and MCL (Rummel et al 2004). Importantly, recent studies demonstrated Bcl-2 and/or Bcl-xL overexpression in primary samples of patients with DLBCL (Tsuyama et al 2017), FL (Correia et al 2015), or MCL (Yi et al 2015) to correlate with poor prognosis.

This study will investigate the safety, tolerability, PK, and efficacy of AZD0466, a dual Bcl-2/Bcl-xL inhibitor, in patients with advanced B-NHL who have failed prior therapy(ies), are not eligible for curative treatment options, and for whom there is no standard therapy available.

2.2 Background

2.2.1 Disease Background

Globally, NHL is the most common haematologic malignancy, with more than 500 000 new cases diagnosed in 2018 (Bray et al 2018). Incidence rates of NHL tend to be higher in North America, Western Europe, Northern Europe, and Australia as compared with the rest of world. In the US, NHL is the seventh most common cancer, representing 4.3% of all new cancer cases (Siegel et al 2020). Between 1975 and 2011, the incidence of new cases of NHL in the US has nearly doubled from 11 to 20 cases per 100 000 people, but the proportion of deaths has slowly decreased (NCI 2017). In 2020, it is estimated that there will be nearly 80 000 new cases of NHL, with a median age at diagnosis of 67 years, and an estimated 20 000 deaths related to this disease in the US (Howlader 2020, Siegel et al 2020).

Non-Hodgkin lymphoma is a heterogeneous group of disorders involving malignant clonal proliferation of lymphoid cells in lymphoreticular sites, including the lymph nodes, bone marrow, spleen, liver, and gastrointestinal tract. The biologic heterogeneity of B-cell malignancies is reflected in the clinical course and outcome of individual diseases. Indolent diseases such as FL and MZL evolve slowly, with a median survival of 8 to 10 years. In contrast, more aggressive diseases such as DLBCL and MCL, if left untreated, have a median survival of 6 months.

Diffuse large B-cell lymphoma is the most common type of NHL, accounting for approximately 30% to 40% of all NHL diagnoses, followed by FL (20% to 25%), and MCL (6% to 10%) (Siegel et al 2020).

Although 60% of patients with DLBCL are cured with immunochemotherapy, the remaining patients develop recurrent or progressive disease and often succumb to the disease. Diffuse large B-cell lymphoma is a heterogeneous disease that is further classified into transcriptionally defined activated B-cell and germinal center B-cell subtypes. Recent genomic studies have uncovered a multitude of genetic abnormalities predictive of poor outcome in DLBCL, including MYC rearrangement, Bcl-2 and B-cell lymphoma overexpression, and *TP53* mutations. These alterations contribute to the initiation and maintenance of the tumour clone by disrupting critical biologic functions (Chapuy et al 2018).

Mantle cell lymphoma is generally an aggressive NHL with a poor prognosis, with a subset of patients presenting with more indolent disease. Nearly all patients relapse after first-line therapy and even though new advances such as novel targeted therapy and immunotherapy have changed the treatment landscape, relapsed or refractory MCL remains a disease of high unmet medical need (Lynch and Acharya 2021).

Most indolent lymphomas are mature B-cell lymphomas, including the most common subtype FL, followed by MZL (approximately 12% of all NHLs) (Denlinger et al 2018). Despite the relatively slow-progressing nature of this disease and the recent treatment advances in this setting, most indolent NHLs remain incurable and are associated with a reduced life expectancy. A subset of patients suffers from early relapse or treatment refractory disease.

2.2.2 AZD0466

Apoptosis is a cellular process necessary in the development and maintenance of tissue homeostasis and dysregulation leads to a variety of pathologies, including cancer. The importance of apoptosis in regulating tumour growth was first identified in 1972 (Kerr et al 1972) and is considered one of the critical hallmarks of cancer (Hanahan and Weinberg 2000). Proteins of the Bcl-2 family regulate the intrinsic apoptosis pathway.

Under normal conditions, apoptosis is prevented by binding of pro-survival proteins (including Bcl-2 and Bcl-xL) to and inhibiting the pro-apoptotic proteins (Bak and Bax). However, under conditions of cell stress such as DNA damage, the apoptosis blockade is overridden. Pro-apoptotic proteins are upregulated, and bind and sequester pro-survival proteins. With removal of pro-survival proteins, the pro-apoptotic proteins are released to activate the apoptotic pathway (Czabotar et al 2014).

Overexpression of pro-survival proteins deregulates this intricate balance, blocking apoptosis even under conditions of cell stress. Thus, pro-survival Bcl-2 family proteins like Bcl-2 and Bcl-xL have been associated with tumour initiation, progression, and resistance to various current therapies (Czabotar et al 2014, Delbridge and Strasser 2015).

AZD0466 is a drug-dendrimer conjugate consisting of an active moiety AZD4320 (a dual Bcl-2/Bcl-xL inhibitor), covalently conjugated to a CCI dendrimer that gradually releases the active moiety by hydrolysis. CCI

CCI .

CCI

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD0466 is provided in the AZD0466 Investigator's Brochure.

2.3 Benefit/Risk Assessment

AZD0466 has been administered to 9 patients with advanced solid malignancies at doses declared tolerable (50, 100, and 200 mg) in the first-in-human study (D8240C00003). No DLTs have been recorded and enrolment has now closed (data on file, AstraZeneca).

More detailed information about the known and expected benefits and potential risks of AZD0466 can be found in the AZD0466 Investigator's Brochure.

2.3.1 Risk Assessment

Potential risks of AZD0466 may be anticipated due to its mechanism of action as a dual Bcl-2/Bcl-xL-specific inhibitor, published literature on clinical use of Bcl-2 and Bcl-2/Bcl-xL inhibitors, and observations from nonclinical studies of AZD0466 (drug-dendrimer conjugate) and AZD4320 (active moiety). No safety findings have emerged from the first-in-human AZD0466 study in solid tumours (D8240C00003) that would preclude investigation of AZD0466 in patients with advanced NHL.

The risks associated with AZD0466 and mitigation strategy are summarised in Table 1.

The dosing schedule for AZD0466 utilises an intra-patient dose ramp-up schedule to mitigate the risk of TLS (Roberts et al 2016). This CSP incorporates mandatory safety monitoring procedures (Section 8.2 and Section 8.3), dose modification guidelines (Section 6.6), and additional guidance for management of specific AEs (Appendix F).

Table 1 AZD0466 Risk Assessment

Potential risk of clinical significance	Summary of data/ rationale for risk	Mitigation strategy
Risks		
Important potential risks: • Thrombocytopenia • Hepatotoxicity • Cardiovascular toxicity (QRS changes/myocardial oedema) Potential risks: • Tumour lysis syndrome • Hypocellularity of bone marrow, lymphoid tissue (neutropenia, lymphopenia, anaemia) • Thymus and spleen effects • Pancreatic toxicity • Drug-drug interactions • Reproductive toxicity • Infusion related reaction	Risks identified based on nonclinical data available to date and evaluated by AstraZeneca.	These risks are monitored via routine pharmacovigilance and managed via routine risk minimisation activities and standard treatment practices. Further details of these risks can be found in the AZD0466 Investigator's Brochure. Risk minimisation activities are reflected in the CSP-specific inclusion and exclusion criteria (Section 5.1 and Section 5.2), alongside the safety monitoring strategy (Section 8.2 and Section 8.3), dose modification guidance (Section 6.6), toxicity management guidelines (Appendix F) and concomitant medication guidance (Section 6.5).
Study procedures		
Infusion site reactions	As with other drugs administered intravenously, local infusion site reactions (eg, infusion pain, infusion site reaction, skin, or vein irritation) may occur.	These reactions can be managed according to local institutional guidelines. Implantable port insertions (eg, Portacath) may be considered.

CSP = clinical study protocol.

2.3.2 Benefit Assessment

AZD0466 has dose-dependent in vivo antitumour activity as a single agent across a range of human tumour xenograft and patient-derived models, including haematological malignancies. Enhanced nonclinical activity has also been observed for AZD0466 in combination with many standard of care anticancer therapies. Refer to Section 4.1 and Appendix A of the AZD0466 Investigator's Brochure for further details.

2.3.3 Overall Benefit/Risk Conclusion

A high unmet medical need remains for additional treatment options for patients with advanced B-NHL. AZD0466 has the potential to provide meaningful clinical benefit. Considering the measures taken to minimise risk to patients participating in this study, the benefit-risk assessment supports the proposed study.

3 OBJECTIVES AND ENDPOINTS – CORE

The objectives and endpoints for the core protocol are provided in Table 2. Refer to the relevant individual module for additional objectives and endpoints.

Table 2 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 patients 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 patients with R/R B-NHL	• ORR Endpoint based on revised response criteria for malignant lymphoma (Cheson et al 2014)
Secondary	
Part B	
• To assess the safety and tolerability of AZD0466 as monotherapy or in combination with anticancer agents in patients 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 patients 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)
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
Exploratory	
Part B	
• CCI [redacted]	• CCI [redacted]

Table 2 Objectives and Endpoints

Objectives	Endpoints
CCI	
• CCI	• CCI
• CCI	• CCI
• CCI	• CCI • CCI

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

4 STUDY DESIGN – CORE

4.1 Overall Design

This is a modular Phase I/II, open-label, dose escalation and expansion, multicentre study that evaluates the safety, tolerability, PK, and preliminary efficacy of AZD0466 as monotherapy or in combination with other anticancer agents in patients with advanced NHL. The overall study design is shown in Figure 1.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The Investigator should confirm this with the designated Study Physician.
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix L.

4.1.2 Modular Protocol Structure

The structure of the protocol will follow a modular design. Information common to the overall study, including study objectives, rationale, core inclusion and exclusion criteria, safety assessments, and AE reporting can be found in this core protocol module (ie, Sections 1 to 9). Module-specific information including design and SoA can be found in subsequent sections.

4.1.3 Module Naming Conventions

Initially, the study will include one module (Module 1) to evaluate the safety, tolerability, PK, and preliminary efficacy of AZD0466 monotherapy. Module 1 will include 2 parts; Part A dose escalation and Part B dose expansion. Part A will enrol patients with R/R B-NHL and once the RP2D has been determined, Part B may open to patients with selected lymphoid malignancies, including R/R MCL (Cohort B1), R/R FL or MZL (Cohort B2), and R/R DLBCL (Cohort B3).

Module	Tumour type	Intervention	CSP section
Module 1	Advanced NHL • Part A dose escalation: R/R B-NHL • Part B dose expansion: R/R MCL, R/R FL and MZL, and R/R DLBCL	AZD0466 monotherapy	Section 10

4.1.4 Regulatory Amendment for Additional Modules

To support amendment of the CSP for additional modules, the Sponsor will provide a summary of all nonclinical and clinical data to support the proposed new combination and dosing schedule; this will include updating the following:

- Study objectives
- Background information providing rationale for the proposed patient population(s) and the proposed treatment plan(s)
- Study eligibility criteria
- A detailed description of the proposed study intervention plans
- A revised schedule of patient assessments
- A summary of safety data from the completed or ongoing cohort(s)/modules(s) and the proposed toxicity management plans for the proposed new combination
- A description of any dose modifications and the data (clinical safety information, clinical PK data, and nonclinical data) that support the safety of the proposed dose modifications for the regimen in question
- A clearly stated sample size and justification for the proposed sample size based on the objectives for that specific cohort/module

- A detailed description of the method and performance characteristics of any test that will be used to identify the patient population to be enrolled in the cohort/module, if the population will be selected based on a diagnostic assay

4.1.4.1 Europe and Rest of World

Prior to activating a new module, the Sponsor will provide a substantial amendment to the CSP for review and approval by regulatory authorities.

4.1.4.2 United States of America

The Sponsor will provide an amendment to the FDA 60 days in advance of planned enrolment into a new module for any combination involving a drug for which the RP2D has not been determined for the proposed dosage regimen to be employed, or at least 30 days in advance of a planned enrolment into a module for drugs where the RP2D has been determined for the proposed dosage regimen to be employed.

4.2 Scientific Rationale for Study Design

This study will investigate AZD0466 as monotherapy or in combination with other anticancer therapies in patients with R/R B-NHL who have failed prior therapy(ies), are not eligible for curative treatment options, and for whom there is no standard therapy available. The study is modular in design; the core protocol will contain study information applicable to all patients in this study. Initially, one module will open (Module 1) and will evaluate the safety, tolerability, PK, and preliminary efficacy of AZD0466 as monotherapy.

Module 1 will consist of Part A dose escalation and Part B dose expansion. Due to its mechanism of action, a potential risk of AZD0466 includes TLS (Davids et al 2017). Therefore, an intra-patient ramp-up will be incorporated in Part A dose escalation to mitigate against the risk of TLS in R/R B-NHL patients. During dose escalation, patients at high risk of TLS with high tumour burden and/or bulky disease (> 10 cm) will be excluded. Once a RP2D has been determined and with emerging patient data from Part A, Part B dose expansion may open to selected lymphoma patients. Part B will consist of 3 cohorts: Cohort B1 will enrol R/R MCL patients, Cohort B2 will enrol R/R FL and MZL patients, and Cohort B3 will enrol R/R DLBCL patients.

As the mechanism of action of AZD0466 and in vivo data suggest that combining AZD0466 with other anticancer treatments may result in enhanced activity, it is anticipated that the study may evolve to incorporate additional modules to allow further evaluation of AZD0466 in combination with anticancer agents.

Refer to the relevant individual modules for details.

4.3 Justification for Dose

Refer to the relevant individual modules for information on dose justification.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the SoA for the last patient in the study globally.

The end of module is defined as the last scheduled visit or contact of the last patient enrolled in the module.

Details of planned data analyses are provided in each of the study modules. The results from each module will be reported to regulatory authorities within 1 year of the end of each module.

A patient is considered to have completed the study if he/she has completed all phases of a study module including last visit or the last scheduled procedure shown in the SoA including follow-up for OS.

Patients who continue to demonstrate clinical benefit after a 2-year treatment period will be eligible to receive AZD0466 via a roll-over study requiring approval by the responsible health authority and ethics committee or through another mechanism at the discretion of the Sponsor.

Patients may be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings. The study may be terminated at individual centres if the study procedures are not being performed according to ICH GCP or if the recruitment rate does not allow for completion of the study in the planned timeframe.

4.5 Criteria for Stopping or Pausing the Study Recruitment

AstraZeneca reserves the right to pause recruitment, temporarily suspend or permanently terminate this study or components of the study at any time. AstraZeneca may at any point during the study, pause enrolment if at least one of the following occurs:

- Fatal event deemed related to study intervention by the Sponsor and in discussion with the SRC (probable or certain causality based on World Health Organization-The Uppsala Monitoring Centre [WHO-UMC] after full etiological work-up). This will also result in a comprehensive review of safety.
- Unexpected and life-threatening events deemed related to study intervention by the Sponsor and in discussion with the SRC. Note: As thrombocytopenia is an on-target effect it will be further addressed at the time of the SRC (Part A) or the safety interim analysis (Part B) and will not be considered as stopping criteria.

- Sponsor decision that study patients are placed at undue safety risk (also covered in Section 4.4)
- Sponsor decision to discontinue the development of the study intervention in the proposed indications.

During Part A of Module 1, AZD0466 monotherapy dose escalation, AstraZeneca pharmacovigilance process and the SRC will evaluate toxicities study-wide (including evaluation of previous doses). During Part B of Module 1, AZD0466 monotherapy dose expansion, a safety analysis will be performed at the time of the first interim analysis in each cohort (Cohort B1 at CCI patients, Cohort B2 at CCI patients and Cohort B3 at CCI patients), pooling safety data from all available patients. The study recruitment may be paused, pending investigation by the Sponsor and in discussion with SRC, if > CCI % of patients experience safety events that meet the DLT criteria, see Section 10.6.6.3 (including AEs of special interest [Section 8.3.6]), the SRC, will decide to stop the study, modify the study, or continue the study, based on the overall risk benefit of the agent. Throughout the expansions, the AZ safety team and the SRC, will regularly review cumulative safety data including, but not limited to, toxicities that meet the DLT criteria.

5 STUDY POPULATION – CORE

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the core criteria below and all criteria from the relevant individual modules apply. Where specific module criteria differ from core inclusion criteria, the most stringent criteria should be applied.

Informed Consent

1 Provision of signed and dated written informed consent, as described in Appendix A, prior to any study-specific procedures, sampling, and analyses. Informed consent includes compliance with the requirements and restrictions listed in the ICF and in this CSP.

Age

2 Patient must be aged ≥ 18 years at the time of signing the informed consent. In some countries, parental consent may be required in addition to an assent form for patients who are 18 years of age.

Type of Patient and Disease Characteristics

3 Patient must have histologically documented diagnosis of B-NHL as defined by a B-cell neoplasm in the World Health Organisation classification scheme except as noted in the exclusion criteria.

4 Patient has relapsed after or failed to respond to at least 2 but no more than 5 prior systemic treatment regimens (including investigational therapy) and for whom there is no available therapy expected to improve survival (eg, standard chemotherapy, autologous SCT, CAR-T cell therapy).

5 Documented active disease requiring treatment that is relapsed or refractory defined as:

- Recurrence/relapse of disease after response to prior line(s) of therapy.
- Progressive disease (refractory) on/after completion of the treatment regimen preceding entry into the study.

6 Must have at least one measurable FDG-PET avid lesion (except for MZL), based on bi-dimensional assessment on PET and CT/MRI scan. A measurable lesion is defined as:

- For nodal lesions: longest diameter > 1.5 cm
- For extranodal lesions: longest diameter > 1 cm

7 ECOG performance status score ≤ 2. Performance status must not have deteriorated by ≥ 2 levels within 2 weeks after providing informed consent.

8 Adequate haematologic, hepatic, and renal function as defined in Table 3.

Table 3 Criteria for Adequate Organ and Marrow Function

Parameter		Criteria
Haematologic	Haemoglobin	≥ 8.0 g/dL (5.59 mmol/L) with no whole blood transfusions within 14 days prior first dose of AZD0466
	Platelet count	≥ 75 × 10^9/L (≥ 100 × 10^9/L for Module 1 Part A) with no platelet transfusions within 7 days prior to first dose of AZD0466
	ANC	≥ 1.0 × 10^9/L. The use of growth factors is not permitted within 14 days prior to first dose of AZD0466 (long-acting pegylated growth factors are not permitted during study intervention).
Coagulation	INR	< 1.5 × ULN
Hepatic	Total bilirubin	≤ 1.5 × ULN (or ≤ 3.0 × ULN in presence of Gilbert's syndrome)
		≤ 3 × ULN if the patient has Gilbert's syndrome
	ALT and AST	≤ 2.5 × ULN
Pancreatic	Lipase and amylase	≤ 1.5 × ULN and absence of clinical pancreatitis
Renal	Serum creatinine OR Calculated creatinine clearance	≤ 1.5 × ULN ≥ 50 mL/min by the Cockcroft-Gault equation (Cockcroft and Gault 1976) or the estimated glomerular filtration rate ≥ 50 mL/min/1.73 m^2 using the MDRD formula

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; INR= international normalised ratio; MDRD = Modification of Diet in Renal Disease; ULN = upper limit of normal.

9 Adequate cardiac function as demonstrated by left ventricular ejection fraction > 50% on screening cardiac multigated acquisition, magnetic resonance imaging, or echocardiogram.

Reproduction

10 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Female patients:

- Female patients of childbearing potential must be willing to use 2 forms of highly reliable methods of contraception (Appendix I) from the time of screening until 6 months after the last dose of study intervention or patients must have evidence of an inability to bear children by fulfilling 1 of the following criteria at screening:
  - Postmenopausal, defined as aged > 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments.
  - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.

- Female patients must not be lactating, breastfeeding, and must have a negative pregnancy test (serum) prior to start of dosing.

(b) Male patients:

- Male patients must be willing to use barrier contraception (ie, condoms) and refrain from sperm donation from the time of screening until 6 months after the last dose of study intervention. If not done previously, storage of sperm before receiving AZD0466 will be advised to male patients with a desire to have children.

Other

11 Willing and able to participate in all required study evaluations and procedures including receiving IV administration of study intervention and admission to the hospital, when required, for administration of study intervention and/or monitoring.

12 All patients must be willing to undergo an incisional or excisional lymph node or tissue biopsy or to provide a lymph node or tissue biopsy from the most recent available archival tissue.

13 For inclusion in the optional genetic component of the study, patients must fulfil the following additional criteria:

– Provision of signed, written, and dated informed consent for genetic research. If a patient declines to participate in the genetic component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this protocol, as long as they consented to the main study.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the core criteria below and any criteria from the relevant individual modules apply.

Medical Conditions

1 Diagnosis of post-transplant lymphoproliferative disease, Richter's transformation, Burkitt's lymphoma, Burkitt-like lymphoma, lymphoblastic lymphoma/leukaemia, chronic lymphocytic leukaemia, small lymphocytic lymphoma.

2 High risk of TLS according to Howard modification of Cairo-Bishop criteria and/or the presence of bulky disease (defined as any lesion ≥ 10 cm on the screening CT scan).

3 Unresolved toxicity from prior anticancer therapy of CTCAE Grade ≥ 2. Patients with Grade 2 neuropathy or Grade 2 alopecia are eligible.

4 Active idiopathic thrombocytopenic purpura.

5 Active CNS involvement by lymphoma, leptomeningeal disease, or spinal cord compression. Patients with a prior history of CNS localisation of lymphoma who received treatment are eligible provided that there is no evidence of CNS involvement at study entry as documented by cerebrospinal fluid cytology and/or brain MRI.

6 Known history of infection with human immunodeficiency virus.

7 Known serologic status reflecting active hepatitis B or C infection.

- Patients who are anti-HBc antibody positive and who are surface antigen negative will need to have a negative PCR result before enrolment. Those who are hepatitis B surface antigen positive, or hepatitis B PCR positive will be excluded.
- Patients who are hepatitis C antibody positive will need to have a negative PCR result before enrolment. Those who are hepatitis C PCR positive will be excluded.

8 Known concurrent infection with CMV.

9 Patients must be tested for SARS-CoV-2 and those with active infection detected using either molecular or antigen tests in accordance with local testing guidelines will be excluded. Please note: Fully recovered patients (defined as no ongoing COVID-19 symptoms, except loss of sense of smell/taste) who present persistence of positive PCR test with a negative antigen test and the presence of IgG antibodies, may be included in the study.

10 As judged by the Investigator:

- Any evidence of severe or uncontrolled systemic diseases, (eg, severe hepatic impairment, interstitial lung disease [bilateral, diffuse, parenchymal lung disease]).
- Current unstable or uncompensated respiratory or cardiac conditions.
- Uncontrolled hypertension.
- History of, or active, bleeding diatheses (eg, haemophilia or von Willebrand disease).
- Uncontrolled active systemic fungal, bacterial, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

11 Any of the following cardiac criteria at screening:

- Patients with a history of myocarditis within one year of study entry, or heart failure New York Heart Association Functional Classification Class 3 or 4 (Appendix J).
- Mean resting corrected QT interval (QTcF) ≥ 470 msec obtained from 3 ECGs, in the absence of a cardiac pacemaker.
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age.
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (eg, complete left bundle branch block, third-degree heart block,

intermittent or persistent bundle branch block, atrioventricular block II to III, or clinically significant sinus pause).

12 History of another life-threatening malignancy ≤ 2 years prior to first dose of study intervention. **The following are permitted**:

- Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and considered to be at low risk of recurrence by the treating physician.
- Adequately treated lentigo malignant melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer.
- Adequately treated carcinoma in situ without current evidence of disease.

13 Any of the following procedures or any of the following conditions currently or in the 6 months prior to the first dose of study intervention:

- Coronary artery bypass graft
- Angioplasty
- Vascular stent
- Myocardial infarction
- Angina pectoris
- Haemorrhagic or thrombotic stroke, including transient ischaemic attacks or any other CNS bleeding

Prior/Concomitant Therapy

14 Treatment with any of the following:

- Radiotherapy less than 2 weeks prior to the first dose of study intervention. Radiation therapy for palliative care to focal sites is allowed.
- Any investigational agents or study drugs from a previous clinical study within ≤ 14 days or 5 half-lives (whichever is shorter) prior to the first dose of study intervention, with the exception of strong CYP3A inducers or inhibitors as outlined in Section 6.5.2. Treatment with high-dose steroids for primary malignancy control is permitted, but must be discontinued at least 2 days prior to the first dose of study intervention.
- Any other chemotherapy, immunotherapy, immunosuppressant medication (other than corticosteroids) or anticancer agents within 21 days of the first dose of study intervention. A longer washout may be required for drugs with a long half-life (eg, biologics) as agreed by the Sponsor.
- Prior allogenic HSCT within 6 months from the first dose of study intervention (patients > 6 months after allogenic HSCT are eligible in the absence of active graft-

versus host disease and concomitant immune-suppressive therapy). Eligible patients must have stopped immunosuppression at least 2 months prior to study entry.

- Prior cellular therapies such as CAR-T and/or autologous HSCT within 3 months prior to the first dose of study intervention.
- Major surgery (excluding placement of vascular access) ≤ 21 days, or minor surgical procedures ≤ 7 days, prior to the first dose of study intervention. No waiting is required following implantable port or catheter placement.
- Prescription or non-prescription drugs or other products known to be sensitive substrates of BCRP, OCT2, OAT3, OATP1B1, OATP1B3, CYP2B6, CYP2C8, CYP2C9 or CYP2D6, or reversible moderate or strong CYP3A inhibitors, which cannot be discontinued within 5 half-lives of the first dose of study intervention and withheld throughout the study until 14 days after the last dose of AZD0466 (Section 6.5.2).
- Moderate or strong mechanism-based inhibitors or inducers of CYP3A4 which cannot be discontinued within 5 half-lives plus 12 days of the drug prior to the first dose of study intervention and withheld until 14 days after the last dose of AZD0466.
- Concurrent anticoagulation therapy, including aspirin, which cannot be stopped.
- Medications with known risk of Torsades de Pointes (Appendix H) within 5 half-lives of the first dose of study intervention and continuing until 5 half-lives after the last dose of AZD0466. Some of the medications listed as a possible risk of Torsades de Pointes may be allowed at the Investigator's discretion after approval by the Study Physician when the patient has unmet medical need to continue receiving prohibited medication(s), no suitable alternative treatments are available, and the benefit-risk ratio is acceptable in the Investigator's opinion.

15 Administration of a live, attenuated vaccine within 4 weeks before first dose of study intervention.

16 Administration of inactivated vaccines or protein/RNA immunogen vaccines, including COVID-19 vaccines, within 7 days before first dose of study intervention.

Prior/Concurrent Clinical Study Experience

17 Patients with a known hypersensitivity to polyethylene glycol, pegylated products, or drugs with a similar chemical structure or class to AZD0466 or other BH3 mimetic.

Other Exclusions

18 Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

19 Judgement by the Investigator or Study Physician that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

20 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Patients should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids from 14 days before the first dose of study intervention until 14 days after the last dose of study intervention.

5.3.2 Caffeine, Alcohol, and Tobacco

Patients should refrain from consumption of red wine, which has components (such as, resveratrol) that have been reported to inhibit CYP3A4. There are no caffeine or tobacco restrictions.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only one time of rescreening is allowed in the study. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed. Unused samples will be destroyed.

6 STUDY INTERVENTION – CORE

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilised by a study patient according to the study protocol.

6.1 Study Intervention(s) Administered

All patients will receive treatment with the investigational product AZD0466 (Table 4). The AZD0466 drug product is provided with a custom solvent. The custom solvent is supplied to reconstitute AZD0466 drug product and subsequently dilute to lower concentrations, if needed, for clinical dosing.

Dosing details for AZD0466 administered as monotherapy or in combination with other anticancer agents are included in the relevant individual modules and associated handling instructions.

Table 4 Investigational Product: AZD0466

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(s)	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 level(s)	Refer to the relevant individual modules. The MTD and/or RP2D dose to be decided in Module 1 Part A.
Route of administration	Intravenous
Use	Experimental
IMP or NIMP	IMP
Sourcing	AstraZeneca R&D
Packaging and labelling	AZD0466 powder for concentrate for solution for infusion will be provided in CCI mg vials. Each vial will be labelled as per country requirement. Solvent for AZD0466 powder for concentrate for solution for infusion will be provided in CCI mL vials. Each vial will be labelled as per country requirement.

[a] AZD0466 powder for concentrate for solution for infusion CCI mg/vial is 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 may be further diluted with custom solvent to produce AZD0466 solution for infusion for clinical dosing. Multiple vials of drug product and custom solvent may 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.

6.2 Preparation/Handling/Storage/Accountability

Only patients enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

6.2.1 AZD0466 Preparation and Administration

'AZD0466 Powder for Concentrate for Solution for Infusion' and 'Solvent for AZD0466 Powder for Concentrate for Solution for Infusion' should be prepared and administered according to the handling instructions available at the study centres.

Preparation of the dosing solutions must occur under aseptic conditions. Preparation and dosing of AZD0466 should not occur at temperatures exceeding 25°C (refer to handling instructions for allowable excursions). Administration, including 1-hour (+10 minutes) infusion time, must be completed within 3 hours of initial reconstitution (ie, addition of custom solvent to the powder).

AZD0466 doses must be administered at least 72 hours apart.

The in-use stability period is limited due to the stability of the reconstituted material. Close dialogue between the pharmacy and research staff will be required to ensure that the material is administered as quickly as possible following reconstitution, and within the in-use period/conditions stipulated.

6.2.2 Storage

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

All study interventions should be kept in a secure place under appropriate storage conditions. Refer to the product label for specific storage conditions.

6.2.3 Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction of drugs to AstraZeneca. Unused drugs should be destroyed according to local guidelines, and the certificate of delivery destruction should be signed. Destruction

should not take place until approved by the responsible person at AstraZeneca. All study supplies and associated documentation will be regularly reviewed and verified by the site monitor before destruction.

Further guidance and information for the final disposition of unused study intervention is provided in the Pharmacy Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label, non-randomised study; no blinding is required. If an unscheduled assessment is performed and the patient has not progressed, provided the assessment was performed within the visit window, subsequent assessments should be performed at the scheduled visits. This schedule is to be followed to minimise any unintentional bias caused by some patients being assessed at a different frequency than others.

6.3.1 Methods for Assigning Treatment Groups

Refer to the relevant individual modules for details regarding treatment group assignment.

When the study intervention is provided centrally by AstraZeneca, the IRT will provide the kit identification number to be allocated to the patient at the treatment allocation visit and subsequent treatment visits.

6.4 Study Intervention Compliance

When patients are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Any changes from the dosing schedule, dose reductions and dose discontinuations should be recorded in the eCRF. The reason should also be documented.

Use of doses in excess of that specified in the protocol is considered to be an overdose. Overdose procedures to be followed in the event of overdose are described in Section 8.4.

6.4.1 Treatment Compliance for AZD0466

AZD0466 is administered by IV infusion and patients will receive AZD0466 directly from the Investigator or designee, under medical supervision. The date and time of dose administration will be recorded in the source documents and in the eCRF.

The Investigator or pharmacist must retain records of all study interventions administered at the site. The Study Physician will check these records to confirm compliance with the protocol administration schedule.

6.5 Concomitant Therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Concomitant Medications and Treatments

Permitted concomitant medications and treatments are listed in Table 5.

Table 5 Permitted Concomitant Medications and Treatments

Supportive medication/drug class	Usage
Antiemetics (see Appendix H)	• Permitted for the treatment of nausea and vomiting and may be administered prophylactically for recurrent events • Routine pre-medication with antiemetics for all patients is not advised
Intrathecal CNS prophylaxis	May be continued
Low-dose prednisone (≤ 10 mg) or equivalent dose of alternative	Permitted
Supportive care (including prophylactic and therapeutic anti-microbials provided they are not on the prohibited concomitant medication list [Section 6.5.2]), blood transfusions, and other medications necessary for the patient's wellbeing	May be given at the discretion of the Investigator
Erythropoietin	• Patients already receiving erythropoietin at the time of screening for the study may continue to receive it, provided they have been receiving it for > 1 month at the time study intervention is started • Prophylactic erythropoietin should not be started before Cycle 2

Table 5 Permitted Concomitant Medications and Treatments

Supportive medication/drug class	Usage
G-CSF or GM-CSF	Primary or secondary prophylactic use of G-CSFs may be used to treat emergent neutropenia as indicated by the current ASCO guideline and according to Investigator's clinical judgement. The use of long-acting pegylated G-CSF (eg, pegfilgrastim) is not permitted during study intervention.
RANKL inhibitors and/or bisphosphonates	Permitted for the treatment of osteopenia, as recommended according to practice guidelines
Allopurinol	Mandatory for TLS prophylaxis, with dosing and schedule as per institutional guidelines
Rasburicase	Should be considered based on Appendix F and institutional guidelines
Diuretics	• Use with care • Prophylactic use should be considered only if patients have signs of volume overload
Acetaminophen (paracetamol)	Restricted to 3 grams per day or the maximum dose approved locally (if < 3 g/day) during the study
Inactivated vaccines or protein/RNA immunogen vaccines	Permitted. Note: Use of live attenuated vaccines (eg, influenza vaccine delivered as nasal spray) is prohibited
Implanted pacemaker (at study entry)	Patient is eligible at Investigator's discretion

ASCO = American Society of Clinical Oncology; CNS = central nervous system; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; RANKL = receptor activator of nuclear factor kappa-B ligand; TLS = tumour lysis syndrome.

6.5.2 Prohibited Concomitant Medications and Treatments

AZD0466 is an investigational drug for which no data on in vivo interactions are currently available. In vitro data have shown that the principal CYP enzyme responsible for the Phase I metabolism of AZD0466 is CYP3A4. In addition, in vitro data suggest AZD0466 has the potential to cause drug interactions through inhibition of CYP2B6, CYP2C8, CYP2C9, CYP2D6, OATP1B1, OATP1B3, OAT3, OCT2, and BCRP.

- Besides those specified in individual modules, other anticancer agents, investigational agents, and radiotherapy should not be given while the patient is receiving study intervention. Radiation therapy for palliative care to focal sites is allowed.
- Due to potential drug-drug interactions, the following medications should not be administered while the patient is receiving AZD0466, and in the 14 days after the completion of study intervention. In addition, each type of the medications below should not be given within the specified time prior to starting AZD0466 treatment. For a

comprehensive list of clinical inhibitors, inducers, and substrates, refer to the FDA website (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers) or contact the AstraZeneca Study Team.

5 half-lives of each medication plus 12 days for the medications below:	
Strong inducers of CYP3A	Apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenytoin, rifabutin, rifampin, rifapentine, St. John's wort, and ivosidenib
Moderate inducers of CYP3A	Bosentan, dabrafenib, efavirenz, etravirine, genistein, lersivirine, lesinurad, lopinavir, modafinil, nafcillin, phenobarbital, primidone, ritonavir, semagacestat, talviraline, telotristat ethyl, thioridazine, tipranavir, enasidenib, and midostaurin
Mechanism-based strong inhibitors of CYP3A	Boceprevir, cobicistat, conivaptan, ritonavir, grapefruit juice, itraconazole, ketoconazole, lopinavir, saquinavir, telaprevir, troleandomycin, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir, montelukast, pioglitazone, rosiglitazone, phenytoin, mibefradil, ribociclib, telithromycin, and midostaurin
Mechanism-based moderate inhibitors of CYP3A	Amprenavir, conivaptan, crizotinib, cyclosporine, erythromycin, imatinib, letermovir, nilotinib, tofisopam, and verapamil

5 half-lives of each medication for the following medications:	
Reversible strong inhibitors of CYP3A	Danoprevir, elvitegravir, indinavir, paritaprevir (ombitasvir and/or dasabuvir), posaconazole, tipranavir, and voriconazole
Reversible moderate inhibitors of CYP3A	Aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, dronedarone, faldaprevir, fluconazole, fluvoxamine, isavuconazole, Magnolia vine (Schisandra sphenanthera), and netupitant
Substrates of CYP2B6	Bupropion.
Substrates of CYP2C8	Repaglinide
Substrates of CYP2C9	Celecoxib, glimepiride, tolbutamide, and warfarin
Substrates of CYP2D6	Atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine, amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, and trimipramine.
Substrates of OATP1B1 and OATP1B3	Asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel, fexofenadine, glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, and simvastatin acid.
Substrates of OAT3	Adefovir, cefaclor, ceftizoxime, famotidine, furosemide, ganciclovir, methotrexate, oseltamivir carboxylate, and penicillin G.
Substrates of OCT2	Dofetilide and metformin
Substrates of BCPR	Rosuvastatin and sulfasalazine

6.6 Dose Modification and Toxicity Management

6.6.1 Starting Dose, Dose Escalation Scheme and Stopping Criteria

Refer to the relevant individual modules.

6.6.2 Dose Expansion

Refer to the relevant individual modules.

6.6.3 Definition of DLT

Refer to the relevant individual modules.

6.6.4 Definition of Maximum Tolerated Dose

Refer to the relevant individual modules.

6.6.5 Definition of DLT Evaluable Patient

Refer to the relevant individual modules.

6.6.6 Dose Escalation Committee

This study will utilise an SRC, as described in Appendix A 5.

6.6.6.1 Dose Modifications

AZD0466 may be withheld and the dose reduced due to haematologic or non-haematologic toxicities. In general, no AZD0466 dose modification is required if a patient experiences a Grade 1 or Grade 2 AEs. However, AZD0466 treatment should be modified or discontinued when the AEs described in this section are observed.

AZD0466 dose modification is at the discretion of the Investigator. However, some considerations have been provided.

- For platelet and liver changes, consider Q2W (Table 6) and at second occurrence, consider triggering dose reductions (Table 7).
- For AEs other than platelet and liver-related toxicities, consider reducing the dose (Table 7).
- Dose modifications can be done in two ways, which include dose reduction and frequency change (from weekly to bi-weekly schedule). Frequency changes are not possible during ramp-up. A maximum of 3 dose modifications is acceptable, except for CTCAE Grade 3 or 4 haemorrhage and any intracranial haemorrhage or haematoma, of which only one event is allowed. See Table 8, Table 9, Table 10, and Table 11.

Table 6 Dose Frequency Changes

Table 7 Dose Reduction Modifications

6.6.6.2 Dose Modifications Based on Haematologic Parameters

If a patient experiences a clinically significant and/or **unacceptable haematologic toxicity** (including a DLT) considered by the Investigator to be related to study intervention and not attributable to the disease (or to disease-related processes) under investigation, dosing in subsequent cycles will be withheld and may subsequently be restarted at one lower dose (equivalent to one dose reduction) and supportive therapy (Appendix F) administered as

required. Recommended dose modifications for haematologic toxicities associated with AZD0466 observed in patients with haematologic malignancies are shown in Table 8.

Prior to the start of the next treatment cycle, patients must have a recovery of neutrophils > 1000/μL and platelets > 75 000/μL.

Table 8 Recommended Dose Modifications for Haematologic Toxicities

Toxicity grade	Occurrence	Action
Grade 3 or 4 neutropenia	Cycle 1	• Continue AZD0466 • Consider introducing growth factors (eg, G-CSF) after discussion with the Study Physician and continue to monitor ANC • If Grade 4 >7 days, discontinue AZD0466
	Cycle 2 and subsequent cycles	• Withhold AZD0466 until ANC resolution to $\geq 1.0 \times 10^9$/L • Consider introducing growth factors (eg, G-CSF) and continue to monitor ANC • If resolution occurs in ≤ 14 days, restart AZD0466 at **same dose level**, after discussion with Study Physician • If resolution occurs in > 14 days but ≤ 21 days, restart AZD0466 at **one lower dose** (Table 7). A maximum of 3 dose reductions is permitted • Discontinue AZD0466 if no resolution to ANC $\geq 1.0 \times 10^9$/L in < 21 days
Febrile neutropenia/neutropenic infection (any grade lasting > 2 days)	Cycle 1	• Consider introducing growth factors (eg, G-CSF), evaluate patient for infection, and begin antibiotic treatment per institutional guidelines • Withhold AZD0466 until infection is resolved, and antibiotics are no longer required (except prophylactic antibiotics), and ANC $\geq 1.0 \times 10^9$/L • Restart at **current dose** after discussion with Study Physician
	Cycle 2 and subsequent cycles	• Consider introducing growth factors (eg, G-CSF), evaluate patient for infection, and begin antibiotic treatment per institutional guidelines • Withhold AZD0466 up to 21 days until infection is resolved, and antibiotics are no longer required (except prophylactic antibiotics), and ANC $\geq 1.0 \times 10^9$/L ° On first occurrence, restart AZD0466 **at one lower dose** (Table 7), after discussion with Study Physician ° On second occurrence, consider restart AZD0466 at **one lower dose than the previous dose** (Table 7), after discussion with Study Physician ° On third occurrence, restart AZD0466 at **one lower dose than the previous dose** (Table 7), after discussion with Study Physician unless there is no clear evidence of clinical benefit, then consider discontinuing AZD0466

Table 8 Recommended Dose Modifications for Haematologic Toxicities

Toxicity grade	Occurrence	Action
CTCAE Grade ≥ 3 thrombocytopenia without the presence of significant bleeding	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤1 • Restart AZD0466 at **one lower dose** (Table 7) if values resolve to CTCAE Grade ≤ 1 within 14 days • Discontinue AZD0466 if the above criteria are not met
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤1 • Restart AZD0466 **following the Q2W schedule** (Table 6) if values resolve to CTCAE Grade ≤ 1 within 14 days • Discontinue AZD0466 if the above criteria are not met
	Third occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 • Restart AZD0466 **at one lower dose, maintaining the Q2W schedule** (Table 6 and Table 7) if values resolve to CTCAE Grade ≤ 1 within 14 days, there is clear evidence of clinical benefit and after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
	Fourth occurrence	• Discontinue AZD0466
Presence of significant bleeding events with or without thrombocytopenia, such as: • Grade 3 or 4 haemorrhage • Any intracranial haemorrhage or haematoma	Any	• Maintain platelets at ≥ 50 × 10^9/L until resolution of bleeding • Discontinue AZD0466

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor; Q2W = every 2 weeks.

6.6.6.3 Dose Modifications Based on Non-haematologic Parameters

Dose modifications for non-haematologic toxicities may occur at any time and the management are shown Table 9. Special considerations for TLS and specific AEs are included in Appendix F.

Dose modifications for changes in hepatic biochemistry are summarised in Section 6.6.6.4.

If a patient experiences a clinically significant and/or unacceptable non-haematologic toxicity (including a DLT), considered by the Investigator to be related to study intervention, and not attributable to the disease (or to disease-related processes) under investigation, dosing will be withheld or the dose reduced and supportive therapy administered as required.

Table 9 Dose Modifications for Non-haematologic Toxicities

Event	Occurrence	Action with AZD0466
Non-haematologic toxicities (except hepatic and cardiac changes, see Sections 6.6.6.4 and 6.6.6.5)		
CTCAE Grade 1 non-haematologic toxicities	Any	None
CTCAE Grade 2 non-haematologic toxicities	First occurrence	None
	Second occurrence	• Withhold AZD0466 until resolution to CTCAE Grade ≤ 1 or baseline. Maximum dose hold 21 days • Restart AZD0466 **at same dose level** • Discontinue AZD0466 if no resolution to CTCAE Grade ≤ 1 or baseline in ≤ 21 days
	On third and subsequent occurrences	• Withhold AZD0466 until resolution to CTCAE Grade ≤ 1 or baseline. Maximum dose hold 21 days • Restart AZD0466 **at one lower dose** (Table 7). A maximum of 3 dose reductions is permitted • Discontinue AZD0466 if no resolution to CTCAE Grade ≤ 1 or baseline in < 21 days
CTCAE Grade 3 non-haematologic toxicities	First occurrence	• Withhold AZD0466 until resolution to CTCAE Grade ≤ 1 or baseline • Supportive therapy should be given as per institutional guidelines • If resolution occurs in ≤ 7 days, restart AZD0466 at the **same dose** level, after discussion with Study Physician • If no resolution in ≤ 7 days, withhold AZD0466 for up to a total of 21 days • If resolution occurs in > 7 days but ≤ 21 days, restart AZD0466 at **one lower dose** (Table 7) • Discontinue AZD0466 if no resolution to CTCAE Grade ≤ 1 in < 21 days
	Second and subsequent occurrences	• Withhold AZD0466 and provide supportive therapy as per institutional guidelines • If resolution occurs in ≤ 7 days, restart AZD0466 at one lower dose (Table 7), after discussion with Study Physician • If no resolution in ≤ 7 days, withhold AZD0466 for up to a total of 21 days • If resolution to CTCAE Grade ≤ 1 in > 7 days but ≤ 21 days restart AZD0466 at **one lower dose than the previous dose** (Table 7) if there is clear evidence of clinical benefit and after discussion with Study Physician. A maximum of 3 dose reductions is permitted • Discontinue AZD0466 if no resolution to CTCAE Grade ≤ 1 in ≤ 21 days.
CTCAE Grade 4 non-haematologic toxicities	Any	• Discontinue AZD0466

CTCAE = Common Terminology Criteria for Adverse Events; Q2W = every 2 weeks.

6.6.6.4 Dose Modifications for Hepatotoxicity

AZD0466 dosing should be modified if a patient with normal or abnormal baseline liver function experiences a clinically significant and/or unacceptable change in hepatic biochemistry (including a DLT) described in Table 10 and Table 11 that is considered by the Investigator to be related to study intervention and not attributable to the disease (or to disease-related processes) under investigation.

Table 10 Dose Modification for Hepatotoxicity in Patients with Normal Baseline Liver Function

Event	Occurrence	Action with AZD0466
ALT and/or AST > 5 × ULN and ≤ 8 × ULN without concomitant elevation in bilirubin	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 at **same dose level** if all values resolve to baseline or Grade ≤ 1 within 14 days • Discontinue AZD0466 if the above criteria are not met
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 at **one lower dose** (Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days • Discontinue AZD0466 if the above criteria are not met
	Third occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 **following the Q2W schedule** (Table 6) if all values resolve to baseline or Grade ≤ 1 within 14 days and after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
	Fourth occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 at **one lower dose than the previous dose, maintaining the Q2W schedule** (Table 6 and Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days, there is clear evidence of clinical benefit and after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
ALT and/or AST > 8 × ULN and ≤ 20 × ULN without concomitant elevation in bilirubin	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤1 or baseline • Restart AZD0466 at **one lower dose** (Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days • Discontinue AZD0466 if the above criteria are not met
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤1 or baseline • Restart AZD0466 **following the Q2W schedule** (Table 6) if all values resolve to baseline or Grade ≤ 1 within 14 days and after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met

Table 10 Dose Modification for Hepatotoxicity in Patients with Normal Baseline Liver Function

Event	Occurrence	Action with AZD0466
	Third occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤1 or baseline • Restart AZD0466 at **one lower dose than the previous dose, maintaining the Q2W schedule** (Table 6 and Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days, there is clear evidence of clinical benefit and after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
ALT and/or AST ≥ 3 × ULN with concomitant elevation in bilirubin ≥ 2 × ULN	Any occurrence	• Discontinue AZD0466. Refer to Appendix E for process to follow in order to identify and appropriately report episodes of potential Hy's Law
ALT and/or AST > 20 × ULN	Any occurrence	• Discontinue AZD0466

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal; Q2W = every 2 weeks.

Table 11 Dose Modification for Hepatotoxicity in Patients with Abnormal Baseline Liver Function

Event	Occurrence	Action with AZD0466
ALT and/or AST > 3.5 × ULN and ≤ 5 × ULN, without concomitant elevation in bilirubin	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 at **same dose level** if all values resolve to baseline or CTCAE Grade ≤ 1 within 14 days • Discontinue AZD0466 if the above criteria are not met
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 at **one lower dose** (Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days • Discontinue AZD0466 if the above criteria are not met
	Third occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 **following the Q2W schedule** (Table 6) if all values resolve to baseline or Grade ≤ 1 within 14 days, after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met

Table 11 Dose Modification for Hepatotoxicity in Patients with Abnormal Baseline Liver Function

Event	Occurrence	Action with AZD0466
	Fourth occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 at **one lower dose than the previous dose, maintaining the Q2W schedule** (Table 6 and Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days, there is clear evidence of clinical benefit and, after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
ALT and/or AST > 5 × ULN and ≤ 8 × ULN, without concomitant elevation in bilirubin	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 at **one lower dose** (Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 restart **following the Q2W schedule** (Table 6) if all values resolve to baseline or Grade ≤ 1 within 14 days, after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
	Third occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤ 1 or baseline • Restart AZD0466 restart at **one lower dose than the previous dose, maintaining the Q2W schedule** (Table 6 and Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days and there is clear evidence of clinical benefit and after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
ALT and/or AST > 8 × and ≤ 20 × ULN, without concomitant elevation in bilirubin	First occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤1 or baseline • Restart AZD0466 at **one lower dose** (Table 7) **AND following the Q2W schedule** (Table 6) if all values resolve to baseline or Grade ≤ 1 within 14 days, after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
	Second occurrence	• Withhold AZD0466 until values return to CTCAE Grade ≤1 or baseline • Restart AZD0466 at **one lower dose than the previous dose, maintaining the Q2W schedule** (Table 6 and Table 7) if all values resolve to baseline or Grade ≤ 1 within 14 days and there is clear evidence of clinical benefit and after discussion with Study Physician • Discontinue AZD0466 if the above criteria are not met
	Third occurrence	• Discontinue AZD0466

Table 11 Dose Modification for Hepatotoxicity in Patients with Abnormal Baseline Liver Function

Event	Occurrence	Action with AZD0466
ALT and/or AST ≥ 3 × baseline with concomitant elevation in bilirubin ≥ 2 × baseline	Any occurrence	• Discontinue AZD0466, refer to Appendix E for process to follow in order to identify and appropriately report episodes of potential Hy's Law
ALT and/or AST > 20 × ULN	Any occurrence	• Discontinue AZD0466

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal; Q2W = every 2 weeks.

6.6.6.5 Cardiac Findings

AZD0466 should be withheld if any of the following occur at any time during study intervention:

- Symptomatic tachycardia
- Symptomatic hypotension
- QTcF shortening by 60 milliseconds compared to baseline, or interval value < 340 milliseconds, confirmed on at least 2 separate ECGs recorded 5 minutes apart
- QTcF prolongation of > 500 milliseconds or QTcF prolongation from baseline by 60 milliseconds, confirmed on at least 2 separate ECGs recorded 5 minutes apart
- Any other cardiac findings of CTCAE Grade ≥ 2 or considered by the Investigator to be clinically significant.
- AZD0466 should be permanently discontinued if a CTCAE Grade ≥ 3 cardiac AE of any duration occurs during study intervention, if considered by the Investigator to be related to study intervention.

Further investigation of the cardiac findings should be considered, including referral to a cardiac specialist. Patients should be monitored closely. AZD0466 may be restarted after resolution of cardiac findings to the patient's baseline at the discretion of the Investigator and after discussion with the Study Physician.

6.6.6.6 Infusion Site Reactions

As with other drugs administered intravenously, local infusion site reactions (eg infusion pain, infusion site reaction, skin irritation, or vein irritation) may occur. For CTCAE Grade ≥2 reactions, the infusion of AZD0466 should be stopped; if the patient recovers without issue, a full dose may be considered at the next scheduled infusion. For CTCAE Grade 1 or transient reactions with recovery within 15 minutes, AZD0466 infusion may be restarted if timings permit it to be completed within the 3-hour window of stability.

6.6.6.7 Progressive Disease

Permanently discontinue AZD0466 in the absence of clinical benefit after discussion with the Study Physician (Appendix J).

6.6.7 Resumption of Treatment

Refer to Section 6.6.6 (Table 8 to Table 11). Contact the Study Physician to discuss action with AZD0466 for any scenario not described.

6.7 Intervention After the End of the Study

No intervention is planned after the end of the study. However, provisions will be in place for patients still enrolled at the end of the trial to continue to receive study intervention if, in the opinion of the Investigator, they are continuing to receive benefit from treatment.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with study intervention may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits and assessments per its protocol. Any patient who would be proposed to move to such a study would be asked to sign a new ICF.

Subsequent anticancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent anticancer therapies should be recorded in the clinical database.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL – CORE

7.1 Discontinuation of Study Intervention

It may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, patients will continue to have follow-up assessments per the SoA.

Note that discontinuation from study intervention is NOT the same thing as withdrawal from the study.

Patients will be permanently discontinued from study intervention if the following criteria are met:

- Patient decision. The patient is at any time free to discontinue study intervention, without prejudice to further treatment. A patient who discontinues study intervention is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments.
- Investigator decision.
- Occurrence of any AE that, in the opinion of the Investigator or AstraZeneca contraindicates further dosing.
- Pregnancy or intent to become pregnant.
- Patients incorrectly initiated on study intervention. When the reason does not impact safety, consider the risk/benefit to the patient of stopping treatment.
- Noncompliance with the CSP that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from study intervention (eg, refusal to adhere to scheduled visits).
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Decision to modify the development plan of the drug.
- Initiation of alternative anticancer therapy including another investigational agent.
- Confirmed disease progression (Appendix J).
- Death.

All patients who are discontinued from study intervention should complete protocol-specified procedures for discontinuation of study intervention and follow-up procedures. Discontinued patients will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

The EoT visit should be performed as soon as the patient is permanently discontinued from study intervention. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Patients may withdraw from any aspects of the optional exploratory research at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Appendix C 2.

7.1.1 Procedures for Discontinuation of Study Intervention

Discontinuation of study intervention does not affect the patient's participation in the study. A patient who decides to discontinue the study intervention will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the CSP. If the patient does not agree to continue to attend study visits in person, where possible, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. The approach taken should be recorded in the medical records. A patient who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of study intervention, regardless of the reason, will be identified as having permanently discontinued treatment, followed by entry into follow-up. Patients who have permanently discontinued from further receipt of study intervention will need to be recorded in the IRT.

All patients will be followed for survival until the end of the study. Survival information may be obtained via telephone contact with the patient, patient's family, or by contact with the patient's current physician. Patients who decline to return to the site for evaluations should be contacted by telephone, following the timing and procedures indicated in the SoA, as an alternative.

7.2 Patient Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA. Refer to the SoA for data

to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

  - The patient will discontinue the study intervention and be withdrawn from the study at that time.

- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

Patients who are withdrawn from the study but are evaluable per the definition of DLT evaluable (Section 10.6.6.5) will not be replaced. Patients who do not experience a DLT (Section 10.6.6.3) can be replaced if the patient withdraws before the end of the DLT window. Any patient who is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable patients.

7.2.1 Procedures for Withdrawal from Study

Patients who withdraw from the study will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen by an Investigator and undergo the assessments and procedures scheduled for the post-study assessment. Adverse events should be followed.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients enrolled in the study, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES – CORE

The study assessments listed in this section apply to all modules. Safety assessments specific to each module will be listed in the respective sections. Study procedures and their timing are summarised in the SoA of each individual module. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

Adherence to the study requirements, including those specified in the SoA for each module, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Enrolment and Screening

At enrolment, each potential patient will provide informed consent prior to starting any study-specific procedures (see Appendix A 3). Screening will occur for up to 28 days from the date of enrolment. Every effort should be made to minimise the time between treatment assignment and dosing, preferably within 14 days. Patients who fail to meet the eligibility criteria will be recorded as a "screen failure". Each potential patient is assigned a unique patient number. If a patient withdraws from the study, the patient number cannot be reused.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all core and module-specific eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. The common screening forms will be considered as core protocol in the EDC system.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the appropriate time frame relative to the first dose of study intervention, as defined in the SoA.

Demographic data and other characteristics will be recorded and will include gender, race, and ethnicity according to local regulations. A standard medical history, medication history, and surgical history will be obtained during review of the selection criteria. This will include the date of initial diagnosis of the disease under study, disease assessment within 28 days prior to the first dose of AZD0466, prognostic indices/disease profiling (if available from local laboratory results) for each disease indication, and all prior anticancer treatments (including responses and duration of response) for the disease under study.

Disease assessments and other clinical data obtained as standard of care prior to consent may be used for the study, provided the assessments fall within the protocol-specified period prior to the first dose of study intervention.

Follow-up Period

The EoT assessment will be performed at the time study intervention is permanently discontinued. In addition, patients should be followed for 28 days after the last dose of study intervention for any new AEs, follow-up of existing AEs, and other study assessments. Patients should also be asked about concomitant medications at this follow-up. Patients will continue to be followed until disease progression or withdrawal of consent. All patients should be followed for survival every 3 months after the last clinic visit until withdrawal of consent or end of study for the purpose of assessing survival status (see Section 7.1). Patients who achieve CR should be followed for relapse of disease until death.

8.1 Efficacy Assessments

Efficacy assessments will be performed as indicated in the SoA in the relevant individual module until disease progression or relapse, start of a new anticancer therapy, death, lost to follow-up, or withdrawal of consent.

Disease status at baseline and during the study will be evaluated by using:

- Physical examination: attention to node-bearing areas, including Waldeyer's ring, and to the size of liver and spleen
- Total body CT scan, FDG-PET scan, MRI
- Brain imaging (MRI with contrast will be performed at screening only if there is a prior history of CNS involvement or if there are neurologic signs or symptoms present or as clinically indicated during the study)
- Bone marrow biopsy and/or aspirate (Section 8.1.1)
- Endoscopic and histopathologic assessments (eg, tumour biopsy, cytology), if applicable

8.1.1 Bone Marrow Assessments

For all patients, a baseline (before first dose of study intervention) bone marrow biopsy and/or aspirate is required at screening to assess bone marrow involvement by lymphoma. The baseline bone marrow aspirate/biopsy will be used to confirm disease status and profiling utilising technologies including, but not limited to, genomics, cytogenetics, transcriptomics, epigenomics, proteomics, and/or imaging. A portion of bone marrow sample may be used for assessing CCI .

Bone marrow biopsies/aspirates will be read at each site's local laboratory and will be performed as clinically indicated while on study (ie, to confirm CR [if bone marrow was involved by lymphoma at baseline, within 14 days after the respective radiological assessment] and/or per standard of care). If bone marrow involvement before the start of the study was unknown, a bone marrow evaluation must be conducted to confirm a CR.

Patients with a negative bone marrow aspirate/biopsy (ie, no lymphoma involvement) at screening, and patients with a PR, SD, or PD at any disease response assessment timepoint do not require a follow-up bone marrow aspirate/biopsy. Locally obtained results should be entered into the eCRF.

CCI

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

8.1.2 Imaging Assessments

During the screening period, an FDG-PET scan covering the whole body from base of skull to mid-thigh will be performed to assess the measurability of disease and will serve as baseline (Day -28 to Day -1). Information on extranodal involvement will also be recorded.

Any imaging assessments performed as part of standard of care within 5 weeks of the ICF signature, may be considered as baseline assessments for the study, provided that no anticancer treatment has been administered between the date of the assessment and the start of study intervention (with the only exception of low-dose steroids given for symptom control) and in the absence of significant clinical worsening of the patient based on the Investigator's opinion.

Subsequent radiological assessment, ie, CT scans with contrast (unless contraindicated) covering neck, chest, abdomen, and pelvis and any other disease sites will be performed every 8 weeks (± 7 days) until Week 24 (ie, Weeks 8, 16, and 24), every 12 weeks (± 7 days) until Week 48 (ie, Weeks 36 and 48), and thereafter every 16 weeks (± 7 days) for R/R DLBCL and R/R MCL, and every 24 weeks (± 7 days) for R/R FL and MZL.

Positron emission tomography scans covering whole body from base of skull to mid-thigh (or PET/CT scans) are mandatory on Week 8 (± 7 days), Week 24 (± 7 days), and Week 48 (± 7 days), and thereafter once a year to confirm CR or as clinically indicated. Newly documented CT-based CR should be confirmed by a negative PET scan within a window of 14 days; patients with confirmed CR can be subsequently followed up with CT with IV contrast only. More frequent PET-CT scans can be performed when clinically indicated at the Investigator's discretion.

Efficacy assessments will be performed until disease progression or relapse, start of a new anticancer therapy, death, lost to follow-up, or withdrawal of consent, following the schedule indicated in the SoA in the relevant individual modules. If clinically indicated, unscheduled imaging assessments can be performed at any timepoint during the study.

If a PET/CT is not available, an independent PET and a diagnostic-quality CT scan can be used. If PET and CT scans are done on the same day, the PET must be performed prior to the contrast-enhanced CT not to compromise the PET read-out. The CT portion of a PET/CT may be submitted in lieu of a dedicated CT; however, certain radiographic requirements are needed for acceptance, as described in the Site Radiology Manual, provided separately from this CSP.

Magnetic resonance imaging may be used for imaging assessments if a contrast CT scan is contraindicated or unobtainable (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations).

Brain MRI or brain CT with contrast (if possible) will be performed at screening only if there is a prior history of CNS involvement or if there are neurologic signs or symptoms present and/or as clinically indicated during the study.

No anticancer treatment other than study intervention can be implemented between the earliest date of baseline scans or bone marrow assessment and the start of study intervention. Patients should have radiographic tumour measurements done at the participating study centre or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given patient throughout the study.

Sites will be required to store electronic copies of all scans, and the Sponsor will arrange for centralised storage of all imaging data. All imaging assessments, including unscheduled visit scans, will be collected on an ongoing basis, and sent to the Sponsor or designee for storage.

The centralised storage of imaging data would be for possible independent centralised third-party blinded review of disease assessments. At the discretion of the Sponsor, an independent central review of all scans used in the assessment of tumours may be conducted.

Guidelines for imaging collection and storage will be provided in a separate document. The management of patients will be based solely upon the results of assessment conducted by the Investigator per protocol.

8.1.3 Disease Response Assessment

8.1.3.1 Revised Lugano 2014 Classification for Non-Hodgkin Lymphomas

Disease response assessment will be evaluated using the revised Lugano classification 2014 response criteria (Cheson et al 2014) as detailed in Appendix K. The overall disease response as determined by the Investigator will be used for primary and secondary endpoints.

8.1.4 Other Disease-specific Assessments

8.1.4.1 Endoscopy

Endoscopy with adequate tissue sampling for histopathologic analysis is mandatory to confirm CR for any patients with a documented history of gastrointestinal involvement. After CR is confirmed histologically, subsequent endoscopic assessments are not mandatory for disease evaluation, unless there is suspicion of a new or recurrent gastrointestinal involvement.

8.1.4.2 CCI

CCI

CCI

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8.1.4.3 B-symptoms

B-symptoms are constitutional symptoms defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months
- Fevers > 100.5°F or 38.0°C for ≥ 2 weeks without other evidence of infection
- Night sweats for > 1 month without evidence of infection
- B-symptoms should not be reported as AEs and will be collected at each disease response assessment during treatment and as clinically indicated

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

The physical examination includes, at a minimum, the general appearance of the patient, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat,

lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. The lymphatic system examination will include examination of palpable lymph nodes and spleen and liver below the costal margin on the respective side. Only physicians should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given patient.

Physical examination will be performed at timepoints specified in the SoA in the relevant individual module. Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs (see Section 8.3.4 for details).

8.2.2 Vital Signs

Vital signs (including blood pressure, pulse, pulse oxygen saturation, and body temperature) will be assessed at timelines as specified in the SoA in the relevant individual module. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones). Vital signs will be measured in a semi-supine position after 10 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

On PK sampling days, blood pressure readings to be taken at each PK sample timepoint. All blood pressure readings can be taken ±10 minutes from the designated PK sample collection.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.5.

8.2.3 Electrocardiograms

Digital 12-lead ECGs (triplicate ECGs, all 3 within a 5-minute time period) will be obtained after the patient has been resting in a supine position for at least 10 minutes. A single safety ECG will be collected if a Holter continuous ECG (for PK purpose) is being collected simultaneously. If a clinically significant abnormality is noted, triplicate safety ECGs are advised to be collected.

Safety ECGs will be performed at timepoints specified in the SoA of the relevant individual module. Safety ECGs will be measured before vital signs and prior to PK blood draws at matched PK sample timepoints. If an unscheduled ECG is done at any time, then an electrolyte panel (Section 8.2.4) must be collected to coincide with ECG testing.

A standardised ECG machine provided by the central ECG vendor should be used and the patient should be examined using the same machine throughout the study, where feasible. In case the centrally provided ECG machine is unavailable or technical issues occur that preclude

correct measurement, local ECGs (using the site owned device) may be performed instead. Standard ECG parameters to be determined will include HR/RR, PR, QRS, QT, and QTcF (QT interval corrected for HR using Fridericia's formula) intervals.

After the ECGs have been recorded, the Investigator or designated physician will review each of the ECGs at all timepoints for the presence of abnormalities (including rhythm, ECG intervals, or repolarisation abnormalities) and may refer to a local cardiologist if appropriate. A paper copy of the ECG should be filed in the patient's medical records. For all ECGs, an overall evaluation and interpretation should be recorded by the Investigator or designated physician. Any clinically significant abnormalities detected require a confirmatory ECG.

Refer to Section 6.6.6.5 for management of cardiac findings and cardiovascular parameters that require treatment to be withheld or increased monitoring.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, urinalysis, viral serology, pregnancy, and other laboratory tests will be taken at the visits indicated in the SoA of the relevant individual module. Collection times begin from the start of the infusion.

The date and time of each collection will be recorded in the appropriate eCRF. Following SRC review of emerging data, the timing of laboratory safety assessment samples may be adjusted for subsequent cohorts. Additional sampling times may be added or removed if indicated by the emerging data.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF. Laboratory values will be repeated, confirmed, and followed up as appropriate.

Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.5.

All laboratory safety analyses, including clinical chemistry, haematology, and urinalysis, will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The laboratory safety variables listed in Table 12 will be measured.

Table 12 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)		Clinical Chemistry (serum or plasma)	
Haemoglobin (Hb)		Creatinine	Chloride
Leukocyte count (WBC count)		Bilirubin, total	Cortisol [a]
Leukocyte differential count		Alkaline phosphatase	TSH [a]
Neutrophils		AST	Bicarbonate
Lymphocytes		ALT	BUN/urea nitrogen
Eosinophils		Amylase [b]	Lipase [b]
Platelet count		Albumin	LDH
Urinalysis		Potassium	Phosphate
Hb/erythrocytes/blood		Calcium, total	Uric acid
pH	Ketones	Sodium	Troponin I [a]
Protein/albumin	Bilirubin	BNP (or NTproBNP) [a]	
Glucose		Magnesium	Glucose
Microscopy (red and white blood cells, bacteria, casts, and crystals) only if urinalysis is abnormal		Total protein	ACTH [a]
Coagulation		Cholesterol	GGT
International normalised ratio (INR)		Triglycerides	Ferritin
Activated partial thromboplastin time (aPPT)		High-density lipoprotein (HDL)	Creatine kinase (CK)
Prothrombin time (PT)		Low-density lipoprotein (LDL)	
Fibrinogen		**Pregnancy test (females of childbearing potential only)**	
Viral Serology		Urine human chorionic gonadotropin (hCG)	Serum beta hCG
Hepatitis B and C	CMV	**Others**	
SARS-CoV-2		Serum immunoglobulins [a]	Beta-2 microglobulin [a]

[a] At screening, at target dose (predose timepoint) and then as clinically indicated and at end of treatment visit.
[b] Collected at screening, pre-infusion on each dosing day, and end of treatment visit.
Lipids: triglycerides, high density lipoprotein, low density lipoprotein, and cholesterol.
ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV = cytomegalovirus; GGT = gamma-glutamyltransferase; LDH = lactate dehydrogenase; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TSH = thyroid-stimulating hormone; WBC = white blood cell.

NB. In case a patient shows an AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN, refer to Appendix E for further instructions.

8.2.4.1 Troponin I and Brain Natriuretic Peptide

Blood samples for troponin I and BNP or NTproBNP measurements will be collected, as specified in the SoA within the relevant module and below:

- Screening
- Target dose pre-infusion (C1D8 – pre-infusion)
- As clinically indicated
- EoT visit

Troponin T may be collected using a standard assay instead of troponin I, provided the results remain within normal range. However, if an abnormal troponin T value is recorded, collection of troponin I will be required thereafter, as it is more cardiac-specific. Dosing with AZD0466 must not occur until results are obtained and are normal. If an unscheduled ECG is performed, an electrolyte panel (ie, calcium, magnesium, potassium, and troponin I) must be done to coincide with the ECG assessment, including referral to a cardiac specialist. Isolated troponin elevations are not sufficient to trigger dosing changes and should be evaluated in the context of other cardiac findings.

8.2.5 Other Safety Assessments

8.2.5.1 Cardiac MUGA/MRI/ECHO

A cardiac MUGA/MRI/ECHO to assess LVEF will be conducted. The modality of the cardiac function assessments must be consistent within a patient ie, if ECHO is used for the screening assessment then ECHO should also be conducted at subsequent assessments. A 28-day follow-up assessment will be required if an on treatment assessment was abnormal at the time of discontinuation of study intervention, to confirm reversibility of the abnormality. The patients should also be examined using the same machine and operator whenever possible.

Unscheduled assessments should be performed as clinically indicated, including after a clinically significant ECG finding (T wave inversion/flattening, significant QRS amplitude changes or symptomatic patient, etc). In case of any T wave abnormality, the ECHO, MRI, or MUGA should be repeated at the EoT visit to address the question of recovery during the off-treatment period.

Cardiac MUGA/MRI/ECHO should be performed as specified in the SoA.

8.2.5.2 ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the timepoints specified in the SoA of the relevant individual modules based on the following:

0	Fully active; able to carry out all usual activities without restrictions
1	Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)
2	Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; unable to carry out any self-care and totally confined to bed or chair
5	Dead

Any significant change from baseline or screening must be reported as an AE, as described in Section 8.3.5.

8.3 Adverse Events and Serious Adverse Events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported to the Investigator by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative). The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from the time of signature of the ICF throughout the treatment period and including the follow-up period (28 days after the last dose of the study intervention). If an event that starts after the defined safety follow-up period noted above is considered to be due to late-onset toxicity to study intervention, it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to AstraZeneca or its designee within 24 hours. The Investigator will submit any updated SAE data to AstraZeneca within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix B.

If the Investigator becomes aware of an SAE with a suspected causal relationship to study intervention that occurs after the end of the clinical study in a patient treated by him/her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and non-SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 28 days after the last dose of study intervention), but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade/changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the investigational product(s) (yes or no)
- Action taken with regard to investigational product
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of the SAE
- Probable cause of death

- Date of death
- Autopsy performed

The grading scales found in the revised NCI CTCAE v5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE v5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

8.3.3 Causality Collection

The Investigator should assess causal relationship between each study intervention (AZD0466 and combination treatment) and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests, vital signs, and ECGs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, DLT criteria, are the reason for discontinuation of study intervention, or are considered to be clinically relevant as judged by the Investigator (which may include but is not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or dose interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Adverse Events of Special Interest

An AESI is an AE, serious or non-serious, that is of scientific and medical interest specific to the understanding of the study intervention and may require closer monitoring, with collecting of additional information by the Investigator and reporting these to the Sponsor. The rapid reporting of AESIs by the Investigator allows ongoing surveillance of these events in order to further characterise and understand them in relation to the use of the study intervention. All AESIs should be recorded in the eCRF as soon as possible, preferably within 24 hours. All AESIs that are also serious (ie, are SAEs) should be reported to AstraZeneca Patient Safety within 24 hours, as per safety reporting requirements.

In this study, the following are considered to be AESIs:

- Tumour lysis syndrome (Appendix G)
- Hepatotoxicity, including potential Hy's Law, DILI, and bilirubin increase with transaminase (ALT or AST or both ALT and AST) increase
- QRS amplitude decrease

8.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.8 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing lesions to the primary disease under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.9 Disease Under Study

Symptoms of disease under study are those that might be expected to occur as a direct result of the advanced haematologic malignancy. Events that are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

8.3.10 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff on how to proceed.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such.

For further guidance on the definition of a SAE, refer to Appendix B of the CSP.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

Where hospitalisation for longer than 24 hours is required, it should be noted that if this is due to occurrence of an AE then the event must be reported as an SAE, per definition. However, if it is purely for the purposes of extended observation then this does not qualify as an SAE and does not need to be reported.

8.3.11 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy that is discovered before the study patient has received any study intervention.

8.3.11.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly/birth defect) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.10) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

When the eCRF module is used include the following: The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.11.2 Paternal Exposure

The outcome of any conception occurring from the date of the first dose until 6 months after the last dose of study intervention should be followed up and documented. Information on the pregnancy of a patient's partner must be obtained directly from the patient's partner. Therefore, prior to obtaining information on the pregnancy, the Investigator must obtain the consent of the patient's partner.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly), occurring from the date of the first dose until 6 months after the last dose of study intervention should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

If pregnancy occurs in a patient's partner within the timeframe specified above, Investigators or other site personnel will inform the appropriate Sponsor representative immediately, or no later than 24 hours of when he or she becomes aware of it.

The same timelines apply when outcome information is available. Detailed instructions on reporting pregnancies are provided in the Investigator manual separate from this CSP.

8.3.12 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study intervention and have been identified after the patient's inclusion in this study.

8.3.13 Deaths

All deaths that occur during the study or within the protocol-defined follow-up period after the administration of the last dose of study intervention should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the Study Physician at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the Study Physician as an SAE within 24 hours. It should also be documented in the eCRF module. The SAE report should contain a

comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF module. A postmortem may be helpful in the assessment of the cause of death, and if performed, a copy of the postmortem results (with translation of essential details into English) should be reported in an expedited fashion to the Sponsor representative within the usual timeframes.
- Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.3.14 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-threatening or follow-up Fatal/Life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.10) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of AZD0466 greater than the highest dose intended for the individual patient at that timepoint in the CSP will be considered an overdose. For example, during ramp-up, doses exceeding the specified dose at that timepoint will also be classified as an overdose, even if the dose administered is less than the target dose for that patient.

Investigators should be advised that any patient who receives a higher dose of AZD0466 than that intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly. There are no data available on overdose with AZD0466 and there is no known antidote.

Overdose should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.10) and **within 30 days** for all other overdoses.

Refer to the relevant individual modules for overdose information on module-specific study interventions.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, refer to Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

AZD0466 exposure is evaluated indirectly by AZD4320 concentration measurement. The term ‘total’ AZD4320 is defined as the sum of dendrimer-conjugated AZD4320 and released AZD4320. ‘Released’ AZD4320 in the plasma is the sum of protein bound and unbound AZD4320, which is not dendrimer-conjugated.

Samples for determination of AZD4320 concentrations in plasma (and/or urine) will be analysed by a suitable vendor on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analysed.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the clinical study report but separately in a Bioanalytical Report.

Refer to the relevant individual modules for details of collection schedule and procedures for PK sample collection.

8.5.2 Pharmacodynamics

Refer to the relevant individual modules for details of collection schedule and procedures for pharmacodynamic sample collection.

8.6 Human Biological Sample Biomarkers

8.6.1 CCI [redacted]

Refer to the relevant individual modules for details.

8.6.2 CCI [redacted]

CCI [redacted].

8.6.3 Other Study-related CCI [redacted]

Refer to the relevant individual modules for details.

8.7 CCI [redacted]

CCI [redacted] research is also part of this study as specified in the SoA of the relevant individual module and is subject to agreement in the ICF addendum.

A CCI [redacted] will be collected from patients who have consented to participate in the CCI [redacted] component of the study. Participation is optional. Patients who do not wish to participate in the CCI [redacted] may still participate in the study. The mandatory saliva sample for CCI [redacted] is separate to this CCI [redacted] CCI [redacted].

Refer to Appendix D for information regarding the CCI [redacted]. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples, refer to Appendix D. See Appendix C for labelling, chain of custody, shipment, handling, and withdrawal of consent for donated biological samples.

8.8 Medical Resource Utilisation and Health Economics

Health economics/medical resource utilisation and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS – CORE

9.1 Statistical Hypotheses

No formal statistical hypothesis testing is planned.

9.2 Sample Size Determination

Refer to relevant individual modules for details of sample sizes.

9.3 Populations for Analyses

Refer to relevant individual modules for details of populations for analysis.

9.4 Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints that will be applicable across all modules.

9.4.1 General Considerations

Analyses will be performed by AstraZeneca or its representatives, including CROs. A comprehensive SAP will be developed and will describe the patient 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.

Unless stated otherwise, each module and cohort will be analysed separately.

Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total. All data collected will be listed.

Demographic and exposure data will be summarised on the safety population set. Safety data will be summarised on the safety population set. Pharmacokinetic data will be summarised based on the PK analysis set.

In general, the last observed measurement prior to first dose of study intervention will be considered the baseline measurement. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of first dose, when neither time nor a nominal pre-dose indicator are captured, will be considered prior to first dose if such procedures are required by the protocol to be conducted before the first dose.

Depending on the extent of any impact, summaries of data relating to patients diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study intervention, and other protocol deviations) may be generated. More detail will be provided in the SAP.

Demographic Data

Characteristics of the patients, including medical history and disease characteristics at baseline will be listed for each patient and summarised by dose group where appropriate. Reasons for discontinuation of study intervention will be listed including the study day of treatment discontinuation and will be summarised by dose group if appropriate.

Exposure

Exposure to study intervention, ie, total amount of study intervention received will be listed for all patients. Total exposure and total time on study (date of last dose minus date of first dose) will be summarised by the following: mean, standard deviation, minimum, maximum, median, and number of observations.

9.4.2 Efficacy Analyses

The efficacy endpoints for tumour response (ORR, DoR, and TTR) will be summarised on the evaluable for response population set. The efficacy endpoints for OS and PFS will be summarised on the Intent-to-treat Population Set.

Clinical responses will be listed and summarised by dose group and by appropriate response category. Clinical responses for ORR will be derived by applying revised Lugano classification 2014 response criteria (Cheson et al 2014).

Objective Response Rate

Objective response rate is defined as the proportion of patients achieving either CR or PR. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the patient withdraws from therapy. Patients who discontinue treatment without a response or progression, receive subsequent anti-lymphoma therapy and then respond will not be included as responders in the ORR.

The ORR will include data of all scans, regardless of whether it was scheduled or not.

ORR will be presented by the number and percentage of patients with a response (CR/PR) including 95% CIs based on exact binomial proportions.

Best objective response will also be summarised by n (%) for each category, with no formal statistical analysis presented.

Duration of Response

Duration of response will be defined as the time from the date of first documented response until the date of documented progression or death due to any cause in the absence of disease progression. The end of response should coincide with date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR.

The analysis will include all patients in the response-evaluable analysis set who had a response, regardless of whether the patient withdraws from therapy.

If a patient does not progress following a response, then their DoR will use the PFS censoring time.

Kaplan-Meier plots of DoR will be presented. Median DoR, including 95% CIs, will also be presented, calculated from the Kaplan-Meier curve. In addition, the number of patients still responding at 3, 6, and 12 months after initial response will also be presented. Swimmer plots that clearly show the profile of each patient who responds will also be produced.

Progression-free Survival

Progression-free survival is defined as the time from date of first dose to date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from treatment or receives another anti-lymphoma therapy prior to progression.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable assessment. The PFS time will always be derived based on scan/assessment dates and not on visit dates.

Kaplan-Meier plots of PFS will be presented. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (progression or death) will be provided along with the median PFS, its 95% CI, and the proportion of patients who were progression-free at 6, 12, and 18 months.

The treatment status at progression of patients at the time of analysis will be summarised. This will include the number and percentage of patients who were on treatment at the time of progression, the number and percentage of patients who discontinued study intervention prior to progression, the number and percentage of patients who have not progressed and were on treatment or discontinued treatment. This will also provide a distribution of number of days prior to progression for the patients who have discontinued treatment.

Overall Survival

Overall survival is defined as the time from date of first dose until death due to any case regardless of whether patient withdraws from treatment or receives another anti-lymphoma therapy. Any patient not known to have died at the time of analysis will be censored on the last recorded date on which the patient was known to be alive.

Note: Survival follow-up phone calls will be made in the week following the date of DCO for the analysis, if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO.

Overall survival data will be presented similarly to the presentation described for PFS.

Time to Objective Response

Time to objective response is defined as the time from date of first dose until the date of first documented objective response and will include all patients in the response-evaluable analysis set who had a response.

The TTR will be summarised (ie, number of patients [%] based upon the number of responders) by scheduled assessment timepoint that the response was first observed.

Additionally, descriptive summary statistics will also be presented. Associated Kaplan-Meier curves may also be presented.

9.4.3 Safety

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, and ECG changes. These will be collected for all patients. Safety will be presented using descriptive statistics unless otherwise stated.

All patients receiving a particular dose level within each part of the study will be grouped for summary and analysis and defined as a dose group.

9.4.3.1 Adverse Events

All patients who receive at least one dose of AZD0466 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities that will have been released for execution at AstraZeneca/designee.

Adverse events will be presented by system organ class and/or preferred term, covering number and percentage of patients reporting at least one event and number of events, where appropriate.

Only treatment-emergent AEs will be presented. Adverse events occurring prior to start of study intervention and post-treatment AEs will only be listed.

An overview of AEs will present the number and percentage of patients with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of treatment, AESIs, as well as AEs leading to withdrawal from study, as well as the number of individual occurrences in these categories.

Separate AE tables will be provided taking into consideration relationship as assessed by the Investigator, maximum CTCAE grading, seriousness, death and events leading to discontinuation of treatment as well as other action taken related to treatment, events of special interest, other significant AEs and timing of events.

An additional table will present number and percentage of patients with most common AEs. Most common (eg, frequency of > x%, ≥ x%) will be defined in the SAP.

Key patient information will be presented for patients with AEs with outcome of death, SAEs, AEs leading to discontinuation of treatment and AEs leading to treatment delay.

An AE listing for the safety analysis set will cover details for each individual AE.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to treatment discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematologic and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

Treatment-emergent Adverse Events

The following events are considered treatment-emergent:

- AEs with an onset date on or after the first dose of study intervention and within 30 days after last dose of study intervention or up to the day prior to start of subsequent therapy, whichever comes first.
- Worsening of pre-existing events on or after first dose of study intervention and within 30 days after last dose of study intervention or up to the day prior to start of subsequent therapy.

Full details of AE analyses will be provided in the SAP.

9.4.3.2 Other Safety Analyses

Detailed analyses will be provided in the SAP. Haematology, clinical chemistry, vital signs, ECG data (including QTc as calculated by Fridericia's formulae), and concomitant medications will be listed individually by patient and summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum, and number of observations will be used. Details of any deaths will be listed for all patients.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration, or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

9.4.4 Pharmacokinetic Analyses

Calculation or Derivation of Pharmacokinetic Variables

Pharmacokinetic analysis of the plasma concentration data for total and released AZD4320 and its metabolites (if available and appropriate), when applicable, will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara) performed by Covance on behalf of the Sponsor. The PK parameters are calculated/estimated according to AstraZeneca standards.

Pharmacokinetic analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded will be used in the database. If actual elapsed times are missing, nominal times may be used. Nominal sampling times may be used for any agreed interim PK parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where data allow, the following PK parameters for total and released AZD4320 will be derived from plasma and urine concentrations:

Plasma

C_{max}	Maximum observed plasma (peak) drug concentration
t_{max}	Time to reach peak or maximum observed concentration or response following drug administration
λz	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
$t_{1/2}\lambda z$	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve

C_{max}	Maximum observed plasma (peak) drug concentration
AUC_{0-24}	Partial area under the plasma concentration-time curve from time 0 to 24 hours after the start of infusion
AUC_{0-72}	Partial area under the plasma concentration-time curve from time 0 to 72 hours after the start of infusion
AUC_{last}	Area under the plasma concentration-curve from time 0 to the last quantifiable concentration
t_{last}	Time of last observed (quantifiable) concentration
C_{trough}	Concentration prior to dosing
Dose normalised AUC_{last}[a]	Area under the plasma concentration-time curve from time 0 to time of last quantifiable analyte concentration divided by the dose administered
Dose normalised AUC_{0-72}[a]	Area under the plasma concentration-time curve from time 0 to 72 hours after the start of infusion
Dose normalised C_{max}[a]	Maximum observed plasma (peak) drug concentration divided by the dose administered

[a] Calculated for total AZD4320 only.

The following diagnostic parameters for plasma PK analysis will be provided:

λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
Rsq	Statistical measure of fit for the regression used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)

Additional PK parameters may be calculated as appropriate.

Pharmacokinetic Summary Statistics

Plasma concentrations of AZD4320 will be summarised by nominal sample time. Plasma concentrations and derived PK parameters will be summarised by dose level and cohort. Plasma concentrations at each timepoint will be summarised according to dose and cohort by the following summary statistics:

- The geometric mean (g_{mean}, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- G_{mean} ± standard deviation (calculated as exp[μ±s])
- Arithmetic mean calculated using untransformed data

- Standard Deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for the estimated PK parameters, as appropriate:

- G_{mean}, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The PK data for AZD4320 will also be displayed graphically. Displays will include AZD4320 (total and released) plasma concentration patient profiles (on the linear and log scale) versus time and G_{mean} concentration (±standard deviation) versus time, stratified by dose.

Scatter plots of PK parameters versus dose, or log-dose, may also be considered to assess dose proportionality.

9.5 Interim Analyses

Refer to the relevant individual modules for details.

9.6 Data Monitoring Committee

This study will utilise an SRC, as described in Appendix A 5.

10 MODULE 1: AZD0466 MONOTHERAPY PART A (DOSE ESCALATION) AND PART B (DOSE EXPANSION)

10.1 Protocol Summary – Module 1

10.1.1 Synopsis

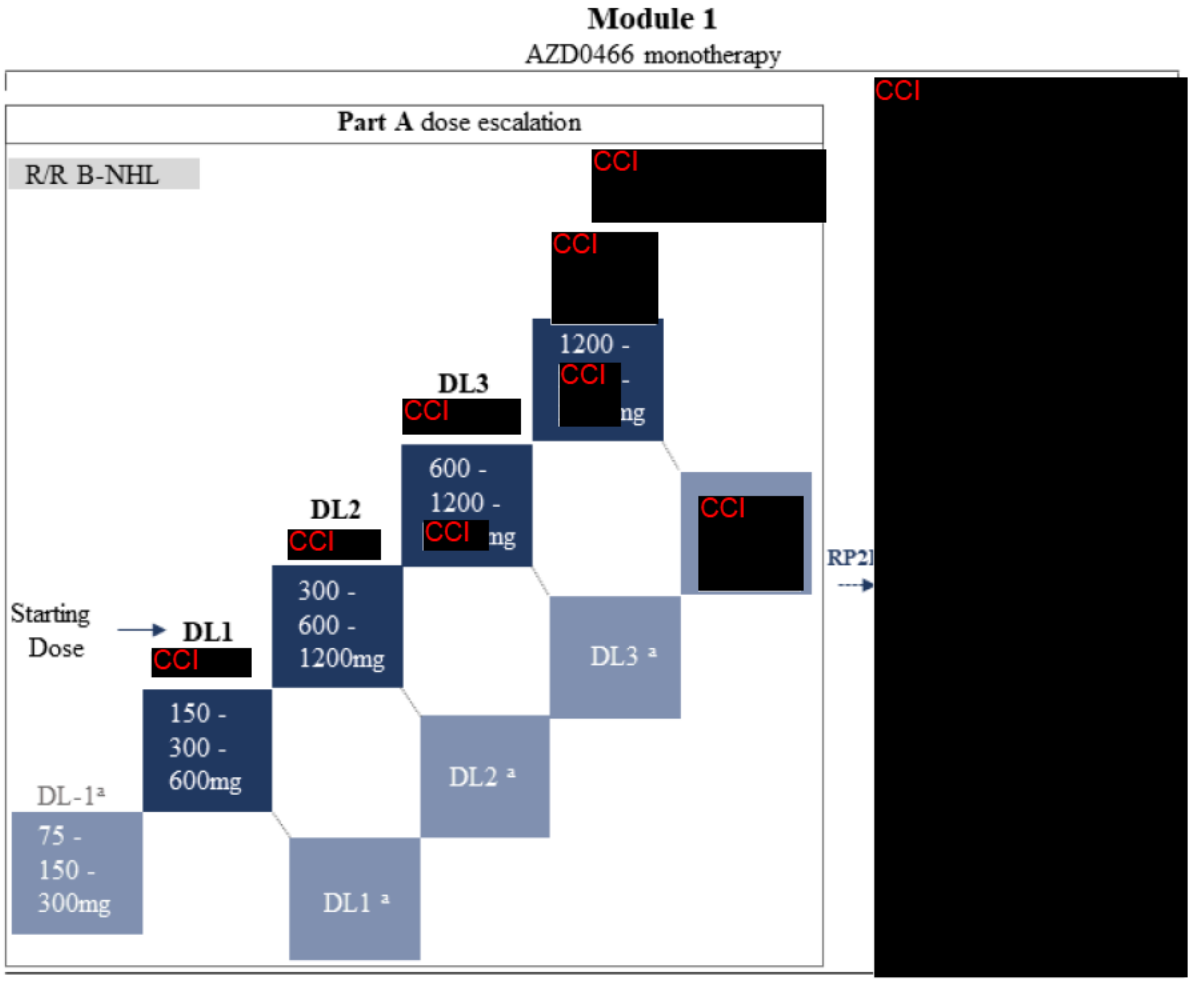
In addition to the core protocol (Sections 1 to 9), Module 1 contains the following information specific to AZD0466 monotherapy dose escalation and dose expansion:

- Schema (Section 10.1.2)
- SoAs (Section 10.1.3)
- Study design (Section 10.4)
- Inclusion and exclusion criteria (Section 10.5.1 and Section 10.5.2)
- Methods for assigning treatment groups (Section 10.6.3.1)
- Dose modification and toxicity management (Section 10.6.6)
- Assessment of ECGs (Section 10.8.2.3)
- Biological samples for PK and pharmacodynamic assessments (Section 10.8.5)
- Biological samples for biomarker assessments (Section 10.8.6)
- Statistical analyses (Section 10.9)

10.1.2 Schema

The schema for Module 1 Part A and Part B is illustrated in Figure 2.

Figure 2 Module 1 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.

B-NHL = B-cell non-Hodgkin lymphoma; 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.

10.1.3 Schedule of Activities

The SoA for Module 1 Part A and Part B is presented in Table 13 for screening and Cycle 1 and in Table 14 for Cycle 2 and beyond and follow-up.

Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1

Procedure	Screening	Cycle 1 (28 days)										Details in CSP section or appendix
		Ramp-up				Target dose						
Day	**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**9**	**10**	**11**	**15**	**22**	
Visit window		**± 2 days (unless indicated otherwise)**										
Informed consent	X											A 3
Inclusion and exclusion criteria	X											5.1, 5.2, 10.5.1, 10.5.2
Demography	X											8
Medical history	X											8
Disease characteristics	X											NA
Disease prognostic scores	X											Appendix M
Physical examination	X	X	X	X	X	X				X	X	8.2.1
Height	X											8.2.1
Weight	X	X				X					X	8.2.1
Vital signs	X	X	X	X	X	X	X			X	X	8.2.2
ECOG performance status	X	X										8.2.5.2
Concomitant medication	X	X	X	X	X	X				X	X	6.5
Adverse events	X	X	X	X	X	X	X			X	X	8.3
Safety ECGs (triplicate)	X	X	X	X	X	X	X			X	X	8.2.3, 10.8.2.3
24-hour continuous 12-lead ECG (Holter) recording for PK purpose						X [a]						8.2.3, 10.8.2.3
Cardiac MUGA/MRI/ECHO	X											8.2.5.1
Fresh or archival tumour sample	X	As clinically indicated										10.8.6.3

Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1

Procedure	Screening	Cycle 1 (28 days)										Details in CSP section or appendix
		Ramp-up				Target dose						
Day	**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**9**	**10**	**11**	**15**	**22**	
Visit window		**± 2 days (unless indicated otherwise)**										
Laboratory tests												
SARS-CoV-2 test	X											8.2.4
Pregnancy test (WOCBP)	X	X										8.2.4
Haematology	X	X		X		X				X	X	8.2.4
Clinical chemistry	X	X		X		X				X	X	8.2.4
Serum immunoglobulins	X					X						8.2.4
Beta-2 microglobulin	X					X						8.2.4
Amylase and lipase	X	X		X		X				X	X	8.2.4
Coagulation	X	X		X		X				X	X	8.2.4
Cortisol, ACTH, TSH	X					X						8.2.4
Troponin I [b]	X					X						8.2.4, 8.2.4.1
BNP (or NTproBNP)	X					X						8.2.4, 8.2.4.1
Hepatitis B and C	X	For patients with positive serology for HBV or HCV, HBV DNA or HCV RNA every 3 months										8.2.4
CMV	X											8.2.4
Urinalysis	X	X		X		X				X	X	8.2.4
Disease assessments												
CT scan	X											8.1.2
FDG-PET scan [c]	X											8.1.2
Bone marrow biopsy/aspirate	X											8.1.1
B-symptoms	X											8.2.4

Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1

Procedure	Screening	Cycle 1 (28 days)										Details in CSP section or appendix
		Ramp-up				Target dose						
Day	**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**9**	**10**	**11**	**15**	**22**	
Visit window		**± 2 days (unless indicated otherwise)**										
Endoscopy/histology	X (as clinically indicated)											8.1.4.1
Brain MRI/CT scan	X											8.1.2
Study intervention												
Administer AZD0466		X		X		X				X	X	6.1, 6.2.1
Prophylaxis for Tumour Lysis Syndrome												
Prophylaxis for TLS		X [d] (based on risk profile)		X [d] (based on risk profile)		X [d] (based on risk profile)				X [d] (based on risk profile)	X [d] (based on risk profile)	Appendix F
Pharmacokinetic assessments												
Blood samples for plasma PK		X [e]		X [e]		X [e]	X	X (Part A only)	X (Part A only)			10.8.5.1
Pharmacodynamic assessments												
Blood samples for locally collected PBMCs	X	X [e]	X (Part A only)			X [e]	X					10.8.5.2
Exploratory and biomarkers assessments												
CCI		X										10.8.6.1
Blood samples for CCI	X	X				X					X	8.1.4.2, 10.8.6.4
Blood samples for CCI	X	X				X					X	10.8.6.5
Blood samples for CCI	X	X				X	X					10.8.6.6

Table 13 Schedule of Activities for Module 1 Part A and Part B: Screening and Cycle 1

Procedure	Screening	Cycle 1 (28 days)										Details in CSP section or appendix
		Ramp-up				Target dose						
Day	**-28 to -1**	**1**	**2**	**4**	**5**	**8**	**9**	**10**	**11**	**15**	**22**	
Visit window		**± 2 days (unless indicated otherwise)**										
Blood samples for CCI	X	X				X	X					10.8.6.7
Blood samples for CCI	X	X										10.8.6.8, 10.8.6.9
Blood samples for CCI	X	X				X					X	10.8.6.10
Pharmacogenetic sampling (optional)												
CCI [f]		X										8.7

[a] Only applies to patients enrolled in cohorts for which the treatment dose has not been cleared by the Safety Review Committee in previous AZD0466 clinical studies. Sites will be notified which cohort(s) Holter monitoring will apply to.

[b] Troponin T may be collected using a standard assay instead of troponin I, provided the results remain within normal range; However, if an abnormal troponin T value is recorded, collection of troponin I will be required thereafter, as it is more cardiac-specific.

[c] Prophylaxis for TLS (hydration and anti-hyperuricaemic agents) is required for all patients receiving study intervention and should be implemented according to the TLS risk level. Prophylaxis is not provided by the study, is not given at the same frequency as the study intervention, and varies based on risk. See Appendix F, Appendix F 1.2 for details.

[d] More than one assessment to be performed at the visit.

[e] MZL patients with FDG-PET non-avid lesion, only require a CT scan.

[f] CCI .

ACTH = adrenocorticotropic hormone; BNP = brain natriuretic peptide; CCI ; CMV = cytomegalovirus; CR = complete response; CSP = clinical study protocol; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; HBV = hepatitis B virus; HCV = hepatitis C virus; MCL = mantle cell lymphoma; CCI MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; MZL = marginal zone lymphoma; NA = not applicable; NTproBNP = N-terminal pro brain natriuretic peptide; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PK = pharmacokinetics; R/R = relapsed/refractory; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLS = Tumour Lysis Syndrome; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

Table 14 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up

Procedures	Cycle 2 (28 days)		Cycle 3 and beyond (28 days)		EoT	Follow-up		Details in CSP section or appendix
Day	1	8/15/22	1	8/15/22		Post-treatment FU visit (28 days after last dose)	Q3M after post-treatment FU visit	
Visit window	± 2 days				± 7 days			
Physical examination	X	X	X	X	X			8.2.1
Weight	X	D15	X	D15	X			8.2.1
Vital signs	X	X	X	X	X			8.2.2
ECOG performance status	X		X		X			8.2.5.2
Concomitant medication	X	X	X	X	X	X		6.5
Adverse events	X	X	X	X	X	X		8.3
Safety ECGs (triplicate)	X	D8	Even cycles only beginning at C4		X			8.2.3, 10.8.2.3
Cardiac MUGA/MRI/ECHO		D8		D8, every 3 cycles from C5	X			8.2.5.1
Fresh tumour sample	As clinically indicated							10.8.6.3
Survival status						X	X	NA
Laboratory test								
SARS-CoV-2 test	X		X					8.2.4
Pregnancy test (WOCBP)	X		X		X			8.2.4
Haematology	X	X	X	X	X			8.2.4
Clinical chemistry	X	X	X	X	X			8.2.4
Serum immunoglobulins					X			8.2.4
Beta-2 microglobulin					X			8.2.4
Amylase and lipase	X	X	X	X	X			8.2.4
Coagulation	X	X	X	X	X			8.2.4
Cortisol, ACTH, TSH					X			8.2.4

Table 14 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up

Procedures	**Cycle 2 (28 days)**		**Cycle 3 and beyond (28 days)**		**EoT**	**Follow-up**		**Details in CSP section or appendix**
Day	**1**	**8/15/22**	**1**	**8/15/22**		**Post-treatment FU visit (28 days after last dose)**	**Q3M after post-treatment FU visit**	
Visit window	**± 2 days**				**± 7 days**			
Troponin I [a]					X			8.2.4
BNP (or NTproBNP)					X			8.2.4
Urinalysis	X	X	X	X	X			8.2.4
Disease assessments								
CT scan	Weeks 8, 16, 24, 36, 48 and thereafter every 24 weeks for R/R FL and MZL, and every 16 weeks for R/R MCL and R/R DLBCL, until disease progression							8.1.2
FDG-PET scan	Week 8, 24 and 48 and thereafter once a year. If confirmed CR, no further PET scans are required.							8.1.2
Bone marrow biopsy/aspirate	To confirm CR (if prior bone marrow involvement) or as clinically indicated							8.1.1
Endoscopy/histology	To confirm CR (if prior gastrointestinal involvement), or as clinically indicated							8.1.4.1
Brain MRI/CT scan	Only if clinically indicated							8.1.2
B-symptoms	To be collected at Screening, and every tumour assessment scan							8.1.4.3
Study intervention								
Administer AZD0466	X	X	X	X				6.1, 10.6.1
Prophylaxis for Tumour Lysis Syndrome								
Prophylaxis for TLS	X [b] (based on risk profile)	X [b] (based on risk profile)	X [b] (based on risk profile)	X [b] (based on risk profile)				Appendix F
Pharmacokinetic assessments								
Blood samples for plasma PK	X [c]		C3D1 [c], C5D1 [c]					10.8.5.1

Table 14 Schedule of Activities for Module 1 Part A and Part B: Cycle 2 and Beyond and Follow-up

Procedures	Cycle 2 (28 days)		Cycle 3 and beyond (28 days)		EoT	Follow-up		Details in CSP section or appendix
Day	1	8/15/22	1	8/15/22		Post-treatment FU visit (28 days after last dose)	Q3M after post-treatment FU visit	
Visit window	± 2 days				± 7 days			
Exploratory and biomarkers assessments								
Blood samples for CCI	X	D15 (Part B only)	C3D1, C5D1, C7D1, C9D1 (and at every tumour assessment scan)		X			8.1.4.2, 10.8.6.4
Blood samples for CCI	X	D15 (Part B only)	C3D1, C5D1, C7D1, C9D1 (and at every tumour assessment scan)		X			10.8.6.5
Blood samples for CCI	X		C3D1, C5D1 (and at every tumour assessment scan during Part B only)		X			10.8.6.6
Blood samples for CCI	X		C3D1, C5D1 (and at every tumour assessment scan during Part B only)		X			10.8.6.7
Blood samples for CCI	X		C3D1, C5D1 (and at every tumour assessment scan)		X			10.8.6.8, 10.8.6.9
Blood samples for CCI	X	D15	C3D1, C5D1, C7D1, C9D1 (and at every tumour assessment scan)		X			10.8.6.10

[a] Troponin T may be collected using a standard assay instead of troponin I, provided the results remain within normal range; However, if an abnormal troponin T value is recorded, collection of troponin I will be required thereafter, as it is more cardiac-specific.

[b] Prophylaxis for TLS (hydration and anti-hyperuricaemic agents) is required for all patients receiving study intervention and should be implemented according to the TLS risk level. Prophylaxis is not provided by the study, is not given at the same frequency as the study intervention, and varies based on risk. See Appendix F, Appendix F 1.2 for details.

[c] More than one assessment to be performed at the visit.

ACTH = adrenocorticotropic hormone; C = Cycle; CCI; CSP = clinical study protocol; CR = complete response; CT = computed tomography; D = Day; DLBCL = diffuse large B-cell lymphoma; FDG = fluorodeoxyglucose; FL = follicular lymphoma; BNP = brain natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EoT = end of treatment; FU = follow-up; MCL = mantle cell lymphoma; CCI; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; MZL = marginal zone lymphoma; NA = not applicable; NTproBNP = N-terminal pro brain natriuretic peptide; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PK = pharmacokinetics; Q3M = every 3 months; R/R = relapsed/refractory; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLS = Tumour Lysis Syndrome; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

10.2 Introduction – Module 1

An overview of the disease under study, AZD0466, and benefit/risk assessment of AZD0466 is presented in Section 2 of the core protocol.

10.3 Objectives and Endpoints – Module 1

Refer to Section 3 of the core protocol.

10.4 Study Design – Module 1

10.4.1 Overall Design

Module 1 will evaluate the safety, tolerability, PK, and efficacy of AZD0466 as monotherapy. Module 1 comprises 2 parts: AZD0466 monotherapy dose escalation in patients with advanced B-NHL (Part A) followed by 3 independent dose expansion cohorts of patients with defined lymphoid malignancies (Part B). The Module 1 schema is illustrated in Figure 2.

- **Part A:** Phase 1 dose setting to assess the safety and tolerability and determine dose(s) and schedule(s) to be evaluated in Part B.
- **Part B:** Phase 1b/2a dose expansion to assess the efficacy of AZD0466 in 3 select patient populations: R/R MCL (Cohort B1), R/R FL or MZL (Cohort B2), and R/R DLBCL (Cohort B3).

An SRC will be responsible for making recommendations for dose escalation or dose de-escalation decisions after each dose level. The SRC will also assess all evaluable patients to establish the RP2D and determine if the study should progress to Part B. Refer to Appendix A 5 for details of the SRC.

Treatment will be administered in the outpatient setting with close monitoring. All patients will be treated until progressive disease or unacceptable toxicity or withdrawal of consent. All patients should be followed for survival every 3 months until death. Patients who discontinue treatment due to unacceptable AEs should be followed until resolution or stabilisation of the AE, then for response and survival. Patients who achieve a CR will be followed for relapse of disease until death.

10.4.2 Scientific Rationale for Study Design

Refer to Section 4.2 of the core protocol.

10.4.3 Justification for Dose

Validated PK models were used to predict human doses and exposures of AZD0466 expected to drive tumour regression. The predicted efficacious dose range of AZD0466 are expected to be CCI to CCI [redacted], or CCI to CCI [redacted] administered as a one-hour IV

infusion (based on a 60-kg patient). Further information on PK modelling of AZD0466 can be found in the Investigator's Brochure.

The first-in-human Study D8240C00003, now closed to enrolment, had demonstrated that weekly administration of AZD0466 200 mg IV is tolerated in patients with advanced solid malignancies (data on file, AstraZeneca). Subsequently, the 200 mg cohort in Study D8240C00003 was declared safe by the SRC.

The AZD0466 study, D8241C00001 for patients with advanced haematologic malignancies includes an intra-patient dose ramp-up, derived from the approach initially taken for venetoclax (a potent, selective inhibitor of Bcl-2) in patients with chronic lymphocytic leukaemia (Cheson et al 2017, Davids et al 2017) and AML (DiNardo et al 2018, DiNardo et al 2019). The AZD0466 schedule involves dose ramp-up in Cycle 1 from a starting dose on Day 1, with subsequent titration to the intermediate dose on Day 4, and to the target dose on Day 8, with weekly IV administration thereafter at the target dose.

At the time of writing, the AZD0466 Phase I/II D8241C00001 is actively enrolling patients with advanced leukaemias into the 300 mg cohort. The planned starting dose in this study will be adjusted based on emerging data from Study D8241C00001 and will not exceed the target dose of 600 mg (dose level 1). De-escalation to dose level -1 is included as part of the study design with a target dose level of 300 mg. Dose escalation will not be greater than a 2-fold increase of a dose declared tolerable by the SRC.

10.4.4 End of Study Definition

Refer to Section 4.4 of the core protocol.

10.5 Study Population – Module 1

10.5.1 Inclusion Criteria

Patients assigned to Module 1 must meet all of the criteria in the core protocol (Section 5.1) and all of the relevant criteria below.

10.5.1.1 Additional Inclusion Criteria for Cohort B1 (R/R MCL)

1 Histologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1, as assessed by Investigator or local pathologist.

2 Must have relapsed after or failed to respond to at least 2 prior lines of treatment, including one anti-CD20 mAb and a Bruton's tyrosine kinase inhibitor.

10.5.1.2 Additional Inclusion Criteria for Cohort B2 (R/R FL or MZL)

1 Histologically confirmed diagnosis of FL Grade 1, 2, or 3a OR histologically confirmed MZL including splenic, nodal, and extranodal subtypes, as assessed by Investigator or local pathologist with documented active disease requiring systemic treatment.

2 For FL patients: Previously received at least 2 prior systemic treatment regimens (including anti-CD20 mAb and an alkylating agent).

3 For MZL patients: Previously received at least 2 prior lines of systemic therapy including at least one anti-CD20 mAb-directed regimen either as monotherapy or as chemoimmunotherapy (*Helicobacter pylori* eradication and radiation therapy alone will not be considered a systemic treatment regimen).

10.5.1.3 Additional Inclusion Criteria for Cohort B3 (R/R DLBCL)

1 Histologically confirmed DLBCL (including transformed FL) OR FL Grade 3b.

2 Must have received 2 lines of systemic therapy including at least one anti-CD20 mAb-directed regimen and must have failed or are ineligible for stem cell transplantation (if indicated per local institutional guidelines).

10.5.2 Exclusion Criteria

Patients assigned to Module 1 must not meet any of the criteria in the core protocol (Section 5.2) and any of the criteria below.

10.5.2.1 Additional Exclusion Criteria for Cohort B1 (R/R MCL)

1 Patients with known blastoid or pleiomorphic variant at study entry/most recent relapse.

10.5.2.2 Additional Exclusion Criteria for Cohort B2 (R/R FL or MZL)

1 Histologically confirmed diagnosis of FL grade 3B.

2 Known transformation to aggressive lymphoma, eg, large cell lymphoma.

10.6 Study Intervention – Module 1

Information related to AZD0466 is provided in Section 6 of the core protocol. The following sections provide information specific to Module 1.

10.6.1 Study Intervention Administration

A description of AZD0466 is provided in Section 6.1 of the core protocol. Dose preparation is detailed in the Handling Instructions supplied to study centres.

10.6.2 Preparation/Handling/Storage/Accountability

Refer to the core protocol (Section 6.2) for a description of AZD0466.

10.6.3 Measures to Minimise Bias: Randomisation and Blinding

Refer to Section 6.3 of the core protocol and Module 1-specific information below.

10.6.3.1 Methods for Assigning Treatment Groups

In Module 1 Part A, the actual treatment given to patients will be determined by the sequentially opened cohorts. In Part B, as not all cohorts will be open at a given time, eligible patients can only be allocated to open cohorts. If only one cohort is open, treatment assignment can still occur.

10.6.4 Study Intervention Compliance

Refer to Section 6.4 of the core protocol.

10.6.5 Concomitant Therapy

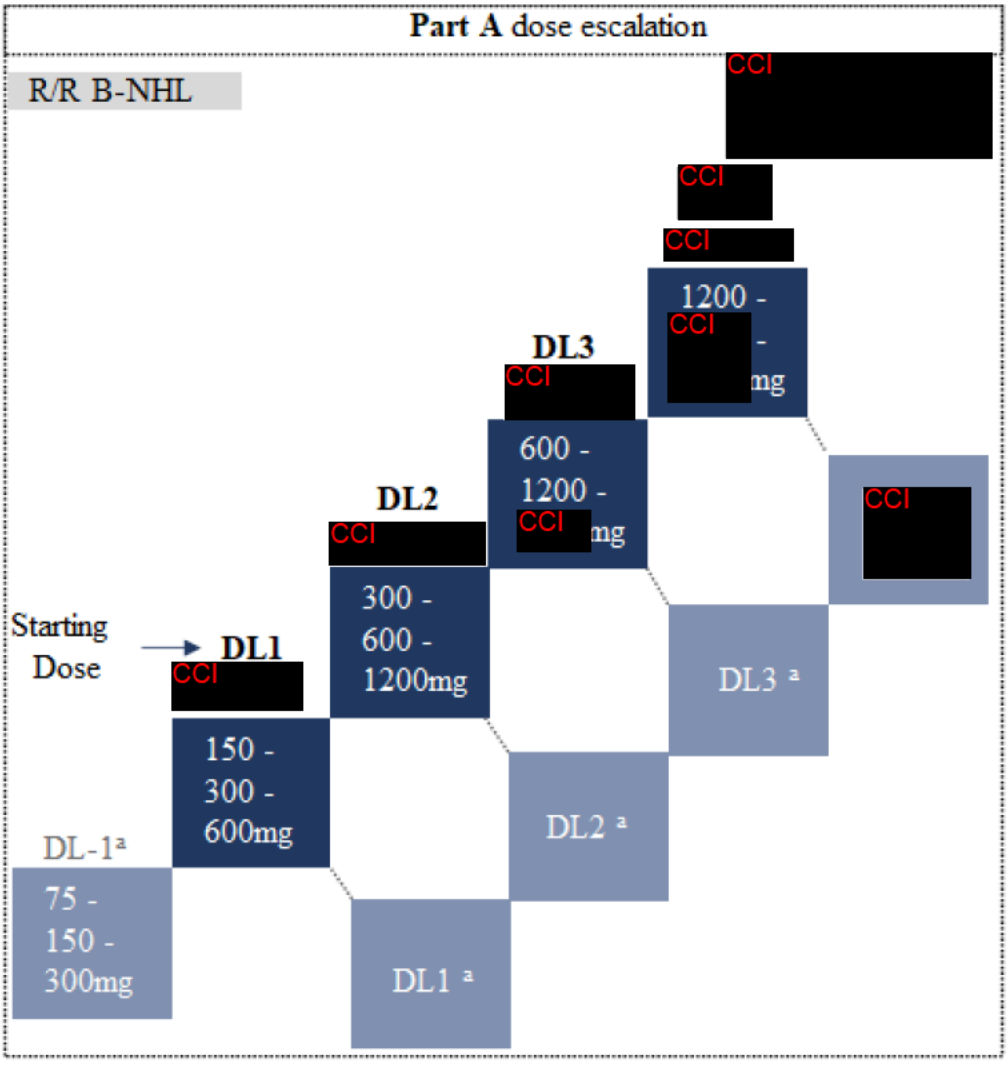
Refer to Section 6.5 of the core protocol.

10.6.6 Dose Modification and Toxicity Management

10.6.6.1 Starting Dose, Dose Escalation Scheme and Stopping Criteria

The dose escalation part of Module 1 (Part A) will enrol up to approximately [redacted] DLT evaluable patients with at least [redacted] DLT evaluable patients at each dose level. During Part A, up to [redacted] patients may be enrolled per dose level. The structure of the dose escalation part is shown in Figure 3.

Figure 3 Module 1 Part A Dose Escalation 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.

B-NHL = B-cell non-Hodgkin lymphoma; DL = dose level; MTD = maximum tolerated dose; R/R = relapsed/refractory.

Initial dose levels will be set according to nonclinical modelling and data from Studies D8240C00003 and D8241C00001 with an intra-patient dose ramp-up to mitigate the risk of TLS. The intra-patient ramp-ups will involve beginning at a specified lower dose and rapidly increase the dose to reach target value by Day 8. For example, in dose level 1, at Cycle 1 Day 1 AZD0466 will be administered at 150 mg followed by 300 mg at Cycle 1 Day 4 and reaching target dose of 600 mg at Cycle 1 Day 8. Thereafter, weekly dosing would continue at 600 mg. Each cycle is 28 days with Cycle 1 consisting of ramp-up to achieve the target dose level and then 3 doses at target level on Days 8, 15, and 22 with a 28-day DLT period (see Section 10.6.6.3).

The intra-patient dose escalation scheme and/or dose schedule for each cohort may be modified based on safety, PK, and pharmacodynamic findings of a previous dose level. If a dose level is declared not tolerated due to liver toxicity or cytopenias, the same dose level may be tested at a 2-weekly dosing schedule. Dose escalation from this point will be on a 2-weekly dosing schedule. Should the SRC determine this dose is not tolerated on a 2-weekly dosing schedule, the weekly dose level below will be considered the MTD.

The decisions on the adequacy of the dose escalation portion of the design were based on outcomes from an internal AstraZeneca simulation package which calculates estimates of the likelihood of selecting the true MTD under a range of different scenarios. Operating characteristics are presented in Table 15.

Table 15 Decision Rules Based on mTPI-2 for Dose Escalation

CCI

[redacted]

[a] Adapted from (Guo et al 2017) from E to S as a minimum of [redacted] evaluable patients are needed to make a dose escalation decision.

[b] Adapted from (Guo et al 2017) from D to S as a minimum of [redacted] evaluable patients are needed to make a dose de-escalation decision.

CCI [redacted]; DLT = dose-limiting toxicity; CCI [redacted]; CCI [redacted]; mTPI-2 = modified toxicity probability interval; CCI [redacted].

Source: Modified from (Guo et al 2017, Ji et al 2010).

A dose level will be considered as having unacceptable toxicity (with no additional patients to be enrolled at that dose level) if there is an estimated CCI [redacted] (P) of exceeding the target DLT rate of CCI [redacted] with at least [redacted] patients treated at that dose level.

If a 'stay' decision is made, additional patients may be enrolled (usually in cohorts of [redacted]) up to a maximum of [redacted] DLT evaluable patients for a given dose level and a maximum of CCI [redacted] DLT evaluable patients.

10.6.6.2 Dose Expansion

Cohorts may open either in parallel or sequentially at the Sponsor's discretion. The dose expansion part of the study (Part B) will enrol up to approximately [redacted] patients. After determining the RP2D in Module 1 Part A (dose escalation), the following separate cohorts may be opened at the RP2D in Module 1 Part B.

- **Cohort B1:** Approximately [redacted] response-evaluable patients with R/R MCL
- **Cohort B2:** Approximately [redacted] response-evaluable patients with R/R FL or MZL
- **Cohort B3:** Approximately [redacted] response-evaluable patients with R/R DLBCL

Following an initial ramp-up during Week 1, AZD0466 will be administered based on a weekly dosing schedule for 2 years or until disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue study intervention, whichever occurs first. In the event of liver or haematologic toxicities, a 2-weekly dosing schedule may be considered. In the absence of toxicities, a 2-weekly dosing schedule may also be considered after discussion with the Sponsor. For patients who are responding and do not experience unacceptable toxicities, continuation of treatment may be considered by the Investigator and Sponsor.

All patients should be followed for survival every 3 months until death. Patients who discontinue treatment due to unacceptable AEs should be followed until resolution or stabilisation of the AE, then for response and survival. Patients who achieve a CR will be followed for relapse of disease until death.

If the interim analysis of Part B meets the pre-set target value for monotherapy expansion in Cohorts B1 and B2, additional patients will be enrolled in these cohorts.

10.6.6.3 Definition of DLT

A DLT will be defined as the occurrence of any of the following during the 28-day DLT evaluation period in Cycle 1, unless unequivocally due to underlying malignancy or an extraneous cause:

- Haematologic toxicity:
  - CTCAE Grade 3 thrombocytopenia of any duration, associated with Grade ≥ 2 bleeding or requiring platelet transfusion
  - CTCAE Grade 4 thrombocytopenia lasting > 7 days
  - CTCAE Grade 4 anaemia
  - CTCAE Grade 4 neutropenia lasting > 7 days
  - CTCAE Grade ≥ 3 febrile neutropenia (ANC < 1.0×10^9/L, fever > 100.9°F [or > 38.3°C]) of any duration despite supportive care

- Non-haematologic toxicity:
  - Any CTCAE Grade 3 non-haematologic toxicity lasting > 7 days OR any CTCAE Grade 4 non-haematologic toxicity, with the exception of:
    - CTCAE Grade 4 nausea, vomiting, or diarrhoea lasting < 72 hours in the absence of maximum supportive therapy.
    - Elevation in serum amylase and/or lipase without clinical or radiographic evidence of pancreatitis.
    - CTCAE Grade 3 fatigue, asthenia, fever, anorexia, or constipation.
  - Any other cardiac findings of CTCAE Grade ≥ 2 if considered by the Investigator to be clinically significant. AZD0466 should be permanently discontinued if a CTCAE Grade ≥ 3 cardiac AE of any duration occurs at any time during study intervention, if considered by the Investigator to be related to study intervention.
  - Liver function test abnormalities meeting Hy's Law or potential Hy's Law criteria.
  - Cairo-Bishop Grade ≥ 3 clinical TLS (Appendix G) that occurs despite protocol-recommended management.
  - Cairo-Bishop Grade ≥ 3 laboratory TLS (Appendix G) with metabolic abnormalities that do not resolve within 5 days despite protocol-recommended management.
- Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care, results in a disruption of dosing schedule of more than 21 days or is judged to be a DLT by the SRC (toxicity that is clearly and directly related to the primary disease or to another aetiology is excluded from this definition).
- Any CTCAE Grade 5 AEs (please also see Section 4.5, study-wide stopping criteria)

Dose-limiting toxicities will not include the following:

- Transient isolated laboratory abnormalities which are not considered clinically significant and resolve to baseline within 72 hours without any intervention.
- Any documented infection, bleeding, or other direct complication of cytopenia due to active underlying disease.

Any event that meets the DLT criteria in the opinion of the Investigator should be reported to the Study Physician within 24 hours of knowledge of the event. Events will be assessed for DLT criteria according to the NCI CTCAE v5.0 except for TLS, which will be assessed for DLT criteria using the Howard et al 2011 modification of Cairo-Bishop 2004 criteria (Cairo and Bishop 2004, Howard et al 2011).

Any patient who is not evaluable for DLT assessment will be replaced, with the exception of a patient who experiences a DLT; these patients will not be replaced. Additional patients enrolled at a previously cleared dose level to provide supplemental safety, efficacy, PK, and pharmacodynamics data will not be replaced or evaluated for DLT in support of dose escalation decisions. However, these additional patients will be included in the determination of the MTD/RP2D upon completion of the dose escalation part.

10.6.6.4 Definition of Maximum Tolerated Dose

The MTD evaluation will be based on the DLT evaluable population. The MTD will be determined by isotonic regression analysis applied to DLT rates observed during the dose escalation phase. The estimated MTD will be selected as the dose with the smallest absolute value of difference between the estimated DLT rate and the target DLT rate of CCI% among all doses.

If 2 or more doses tie for the smallest difference, the following rules will be applied:

- If the estimated DLT rate is CCI% for all doses, then select the higher dose among the tied doses.
- In the case of dose levels with estimated toxicity of equal distance from the target toxicity of CCI% (tied dose levels), the following approach will be used (Ji et al 2010); among all tied dose levels the highest dose level with target toxicity CCI% will be selected, unless all tied dose levels have estimated toxicity CCI%, in which case the lowest dose level will be selected.
- If the estimated DLT rate for the tied doses are a combination of CCI% and CCI% then select the higher dose among the tied doses.
- If the estimated DLT rate is CCI% for all doses, then select the lower dose among the tied doses.

If the original dose schedule is rejected, the lower tested doses from the original schedule or doses from the revised schedule may be used.

10.6.6.5 Definition of DLT Evaluable Patient

A DLT evaluable patient is defined as a patient enrolled in Module 1 Part A (dose escalation), who has received at least 2 doses of AZD0466 at the target dose level (67% of Cycle 1 after ramp-up) and has completed safety follow-up through the DLT evaluation period, or has experienced a DLT.

10.6.6.6 Dose Escalation Committee

This study will utilise an SRC, as described in Appendix A 5.

10.6.6.7 Dose Modifications

Refer to Section 6.6.6.1 of the core protocol for AZD0466 dose modification and toxicity management guidelines.

10.6.6.8 Resumption of Treatment

Refer to Section 6.6.7 of the core protocol.

10.7 Discontinuation of Study Intervention and Patient Discontinuation/Withdrawal – Module 1

Refer to Section 7 of the core protocol.

10.8 Study Assessments and Procedures – Module 1

10.8.1 Efficacy Assessments

Refer to Section 8.1 of the core protocol.

10.8.2 Safety Assessments

10.8.2.1 Physical Examinations

Refer to Section 8.2.1 of the core protocol.

10.8.2.2 Vital Signs

Refer to Section 8.2.2 of the core protocol.

10.8.2.3 Electrocardiograms

Refer to Section 8.2.3 of the core protocol and to the Module 1-specific information below.

Twelve-lead centrally-read digital ECGs will be performed in triplicate, however, if safety ECGs are being collected at a matched timepoint as Holter ECGs (ECGs for PK purpose), single safety ECG is sufficient. If a single safety ECG is abnormal, triplicate safety ECGs are recommended.

Electrocardiograms will be performed at timepoints specified in the SoA and as indicated in Table 16 below.

Table 16 Module 1 Part A and Part B Safety ECG and Holter ECG Extraction

Study period	Day	Timepoint	Holter ECG extraction (for PK) [a]	Triplicate ECG (for safety)
Screening	-28 to -1	Baseline	--	X
Cycle 1	Day 1	Pre-infusion	--	X [b]
		End of the infusion (+ 10 min)	--	X [b]

Table 16 Module 1 Part A and Part B Safety ECG and Holter ECG Extraction

Study period	Day	Timepoint	Holter ECG extraction (for PK) [a]	Triplicate ECG (for safety)
	Day 2	24 hours after the start of the Day 1 infusion (± 2 hours)	--	X
	Day 4	Pre-infusion	--	X [b]
		End of the infusion (+ 10 min)	--	X [b]
	Day 5	24 hours after the start of the Day 4 infusion (± 2 hours)	--	X
	Day 8	Pre-infusion	X	X [b]
		30 min after start of infusion (± 5 min)	X	-
		End of the infusion (+ 10 min)	X	X [b]
		2 hours from start of Day 8 infusion (± 15 min)	X	-
		6 hours from start of Day 8 infusion (± 30 min)	X	-
		9 hours from start of Day 8 infusion (± 1 hour)	X	-
	Day 9	24 hours after the start of the Day 8 infusion (± 2 hours)	X	X [b]
	Day 15	Pre-infusion	--	X
		End of the infusion (+ 10 min)	--	X
	Day 22	Pre-infusion	--	X
		End of the infusion (+ 10 min)	--	X
Cycle 2	Day 1	Pre-infusion	--	X
		End of the infusion (+ 10 min)	--	X
	Day 8	Pre-infusion	--	X
		End of the infusion (+ 10 min)	--	X
Cycle 4 and beyond	Day 1	Pre-infusion	--	See footnote [c]
		End of the infusion (+ 10 min)	--	See footnote [c]
EoT		--	--	X

[a] Patients enrolled in cohorts for which the treatment dose has not been cleared by the SRC in previous AZD0466 clinical studies will require continuous recordings of 12-lead ECGs (Holter device) for PK modelling (see Section 10.8.5.1 for PK assessment timepoints)

[b] Triplicate ECGs will be collected before the PK sample is taken (see Section 10.8.5.1 for PK assessment timepoints).

[c] Beyond Cycle 4 ECGs will be collected on even Cycles only ie, Cycle 4, 6, 8 etc; Day 1: pre-infusion and at the end of the infusion (+10 minutes).

ECG = electrocardiogram; PK = pharmacokinetics; SRC = Safety Review Committee.

Continuous 12-lead ECG Recordings (Holter)

Patients enrolled in cohorts for which the treatment dose has not been cleared by the SRC in previous AZD0466 clinical studies will require continuous recordings of 12-lead ECGs (12-lead Holter devices) for the purpose of PK modelling. When electrocardiogram Holter monitoring is performed, extractions will capture PR, QRS, QT, QTcF, and RR intervals. Recording should be performed as specified in Table 13 of the SoA and Table 16 above, with recording commencing on C1D8 pre-infusion to cover the 24-hour timepoint (prior to PK sampling). The timing of ECGs may be altered depending on the emerging PK profile. The standardised 12-lead Holter device will be provided by the central ECG vendor who will provide the central ECG reads.

The 12-lead Holter devices will always be fitted and safely removed by the Investigator or a trained designee.

The schedule of continuous ECG recordings may be increased, reduced, or stopped at any time during the study, if supported by emerging data and with the agreement of the SRC.

10.8.2.4 Clinical Safety Laboratory Assessments

Refer to Section 8.2.4 of the core protocol.

10.8.2.5 Other Safety Assessments

Refer to Section 8.2 of the core protocol.

10.8.3 Adverse Events and Serious Adverse Events

Refer to Section 8.3 of the core protocol.

10.8.4 Overdose

Refer to Section 8.4 of the core protocol.

10.8.5 Human Biological Samples

10.8.5.1 Pharmacokinetics

Pharmacokinetic samples may be subjected to further analyses in order to further investigate the presence and/or identity of drug metabolites. These samples will be separate from the primary PK samples sent to the bioanalytical laboratory for analysis. Any results from such analyses will be reported separately from the CSR.

Blood Samples for Plasma Pharmacokinetics

Blood samples should be taken from a different part of body than where study intervention is being infused to prevent erroneous drug concentration readings. For example, if AZD0466 is

being infused into the patient's right arm, then the blood sample should be collected from the left arm.

Blood samples for plasma PK will be collected as outlined in Table 17 (collection time begins from start of infusion). The date and time of collection of each sample as well as sample processing time will be recorded. Details will be provided in Laboratory Manual.

Table 17 Pharmacokinetic Timepoints

Blood sample for plasma PK				
Cycle	**Day**	**Timepoint**	**Part A**	**Part B**
1	1	Pre-infusion	X	X
		End of the infusion (+ 10 min)	X	X
	4	Pre-infusion	X	X
		End of the infusion (+ 10 min)	X	X
	8	Pre-infusion	X	X
		30 min after start of infusion (± 5 min)	X	X
		End of the infusion (+ 10 min)	X	X
		2 hours from start of Day 8 infusion (± 15 min)	X	X
		6 hours from start of Day 8 infusion (± 30 min)	X	X
		9 hours from start of Day 8 infusion (± 1 hour)	X	X
	9	24 hours after the start of the Day 8 infusion (± 2 hours)	X	X
	10	48 hours after the start of the Day 8 infusion (± 3 hours)	X	
	11	72 hours after the start of the Day 8 infusion (± 7 hours)	X	
2	1	Pre-infusion	X	X
		End of the infusion (+ 10 min)	X	X
		2 hours from start of infusion (± 15 min)	X	X
		6 hours from start of infusion (± 30 min)	X	X
		9 hours from start of infusion (± 1 hour)	X	X
	2	24 hours after the start of the Day 1 infusion (± 2 hours)	X	X
3 & 5	1	Pre-infusion	X	X
		End of the infusion (+ 10 min)	X	X

PK = pharmacokinetics.

10.8.5.2 Pharmacodynamics

Whole Blood Samples for Locally Collected PBMCs (Part A and Part B)

Mandatory whole blood samples will be collected from all patients at the timepoints indicated in the SoA (Table 13 and Table 14) and as shown in Table 18 below. Assays will include, but are not limited to, pro-apoptotic:anti-apoptotic proteins complex disruption and caspase 3

cleavage assays. Peripheral blood mononuclear cell isolation should occur within 30 minutes of whole blood sample collection. Note: Collection time begins with the start of infusion.

Table 18 CCI

CCI

10.8.6 Human Biological Sample Biomarkers

10.8.6.1 CCI

Per local regulations, a CCI . It is important to assess whether CCI in the patient are CCI . The sample should be collected from patients before receiving study intervention. Details on sample processing, handling, and shipment are provided in the Laboratory Manual.

10.8.6.2 Bone Marrow (Part A and Part B)

Refer to Section 8.1.1 of the core protocol.

10.8.6.3 Tumour Tissue Samples (Part A and Part B)

The provision of an archival tumour biopsy sample FFPE tumour block is mandated, with sufficient material to produce approximately 20 slides. The sample age should be less than 3 months before the first dose of study intervention. If archival tumour biopsy FFPE blocks are not available, archival tumour biopsy FFPE unstained slides (20 unstained slides preferable, minimum 15 slides acceptable) must be provided that were obtained from the FFPE block generated that should not be older than 3 months prior to the first dose of study intervention. Archival tissues must have been obtained as a core biopsy and meet the specified criteria detailed in the Laboratory Manual. Associated pathology report(s) for archival tissue samples must be obtained at screening for all patients enrolled into the study.

If archival tumour FFPE blocks and/or FFPE unstained slides are not available, then a **fresh** biopsy is required at screening if medically accessible. Where clinically feasible, patients may also consent [redacted] Informed consent must be obtained from any patient who agrees to provide [redacted]

The tumour biopsy procedure will be performed by core needle, under radiological guidance, or surgically if the site of disease is superficial and palpable or visible. Tumour biopsies should be preferentially obtained from tumour tissues that are safely accessible, as determined by the Investigator, and are not obtained from sites that require significant risk procedures. Patients will undergo 6 core image-guided needle biopsies at each tumour sample timepoint. It is mandated that the core biopsy be removed directly from the tumour in situ and not cored from a surgically removed tumour. This is to ensure the best possible quality of the biopsy, as the blood/nutrient supply to the tumour is not disrupted prior to biopsy collection. **Fine-needle aspirate specimens are not acceptable**. Excisional biopsies can be accepted. Failure to obtain sufficient tumour sample after making best efforts to biopsy the tumour will not be considered a protocol deviation.

Sites should confirm adequacy of tumour biopsy material at the time of the procedure. The exact time that the biopsy was taken should be clearly noted in the associated documentation. For mandatory and [redacted] patients, the associated pathology report(s) for fresh tumour samples will be required at screening and requested on treatment for all patients enrolled into the study.

[redacted]

[redacted]

10.8.6.4 [redacted] will be collected as indicated in the SoA (Table 13 and Table 14) and as indicated in Table 19 below. Note: Collection time begins with the start of infusion.

Table 19 CCI

CCI

10.8.6.5 CCI

CCI will be collected to CCI with CCI or CCI or CCI to the CCI and to monitor CCI as indicated in the SoA (Table 13 and Table 14) and as indicated in Table 20 below. Note: Collection time begins with the start of infusion.

Table 20 CCI

CCI

10.8.6.6 CCI [redacted] CCI [redacted] at the timepoints indicated in the SoA (Table 13 and Table 14) and as shown in Table 21 below. Assays will include, but are not limited to, CCI [redacted], and CCI [redacted]. Note: Collection time begins with the start of infusion.

Table 21 CCI [redacted]

CCI [redacted]

10.8.6.7 CCI [redacted] CCI [redacted] at the timepoints indicated in the SoA (Table 13 and Table 14) and as shown in Table 22 below. Assays will include, but are not limited to, CCI [redacted] and CCI [redacted] CCI [redacted] Note: Collection time begins prior to the start of infusion.

Table 22 CCI [redacted]

CCI [redacted]

10.8.6.8 CCI [redacted] CCI [redacted] in the SoA (Table 13 and Table 14) and as indicated in Table 23 below. Analysis will include assessment of the CCI [redacted], CCI [redacted] and CCI [redacted]. Note: Collection time begins with the start of infusion.

Table 23 CCI [redacted] CCI [redacted]

10.8.6.9 CCI [redacted] CCI [redacted] at the timepoints indicated in the SoA (Table 13 and Table 14) and as indicated in Table 24 below to analyse CCI [redacted] such as CCI [redacted] and to perform CCI [redacted]. Note: Collection time begins with the start of infusion.

Table 24 CCI [redacted] CCI [redacted]

10.8.6.10 CCI [redacted] CCI [redacted], but not limited to, CCI [redacted] and for CCI [redacted] at the timepoints indicated in the SoA (Table 13 and Table 14) and as indicated in Table 25 below. Note: Collection time begins with the start of infusion.

Table 25 CCI [redacted]

CCI [redacted]

10.8.7 CCI [redacted]

Refer to Section 8.7 of the core protocol.

10.8.8 Medical Resource Utilisation and Health Economics

Refer to Section 8.8 of the core protocol.

10.9 Statistical Considerations – Module 1

10.9.1 Statistical Hypotheses

As stated in Section 9.1 of the core protocol, no formal statistical hypothesis testing is planned.

10.9.2 Sample Size Determination

Module 1 Part A (Dose Escalation)

The primary objective of Part A is to identify the MTD of AZD0466 monotherapy. In Module 1 Part A, a minimum of CCI patients will be enrolled in a dose cohort and evaluated through the DLT evaluation period of 28 days before a dose escalation/expansion/ de-escalation decision can be made (unless unacceptable toxicity is encountered prior to enrolment of CCI patients), while the maximum number of patients to be enrolled in any given dose cohort will be capped at CCI patients.

Dose escalation (or de-escalation) will be determined by an m-TPI2 with a target DLT rate of CCI % and an equivalence interval of (CCI %, CCI %). A dose level will be considered non-tolerated with no additional patients enrolled at that dose level, if it has an estimated CCI % or more probability (P) of exceeding the target DLT rate of CCI [redacted] %) with

at least [redacted] patients treated at that dose level. Five doses (DL-1, DL1 to DL4, start at DL1), [redacted] total patients, with a maximum of [redacted] being DLT evaluable at each dose level.

Module 1 Part B (Dose Expansion)

In Module 1 Part B, up to [redacted] patients will be enrolled ([redacted] patients in Cohorts B1 and B2, and [redacted] patients in Cohort B3).

Separate expansion cohorts will enrol 3 distinct populations of patients with lymphoma: R/R MCL (Cohort B1), R/R FL or MZL (Cohort B2), and R/R DLBCL (Cohort B3). Two of these expansion cohorts (B1 and B2) will recruit up to [redacted] patients, and the other (Cohort B3) will recruit approximately [redacted] patients. These sample sizes have been determined to ensure confidence intervals constructed around the complete ORR, as calculated after all patients have had the opportunity to complete 2 treatment cycles, will provide sufficient information to enable decisions to be made around the likely success of future studies in these patient populations, using methodology described in Frewer et al 2016 (Frewer et al 2016).

[redacted]

Two expansion cohorts in Part B (Cohorts B1 and B2) will have an internal interim analysis for futility, with the potential to stop or trigger a combination expansion, followed by a Sponsor decision towards further development if the cohort proceeds to full recruitment. During the interim analysis, enrolment may be paused in order to fully evaluate the results. Response-evaluable patients will include those that had at least 2 doses of AZD0466 at the target dose level. Contingent on the outcome of the interim analysis, recruitment will then continue to full recruitment. The number of patients to be assessed in each cohort in Part B is based on the operating characteristics of the cohort-specific decisions using the approach as described in Frewer et al 2016 (Frewer et al 2016).

For Cohorts B1 and B2, [redacted] Descriptive statements for these expansion cohorts are given below, with values for the final (and interim) analyses presented using brackets for the interim analysis:

For Cohort B1, [redacted]

CCI [redacted].

For Cohort B2, CCI [redacted]

10.9.3 Populations for Analyses

The analysis populations for Module 1 Part A and Part B are summarised in Table 26.

Table 26 Module 1 Part A and Part B Analysis Populations

Analysis population	Description
Safety	All patients who received at least 1 dose of AZD0466
Intent-to-treat	All patients who received at least 1 dose of AZD0466
Evaluable for Response	All patients who have received at least 2 doses of AZD0466 at the target dose level in Cycle 1
DLT Evaluable	Patients enrolled in dose escalation who have received at least 2 doses of AZD0466 at the target dose level (67% of target doses from Day 8 to Day 22 in Cycle 1) and have completed the safety follow-up through the DLT evaluation period or have experienced a DLT
Pharmacokinetics	Dosed patients with reportable plasma concentrations and no important AEs or protocol deviations that may impact PK

AE = adverse event; DLT = dose-limiting toxicity; PK = pharmacokinetics.

10.9.4 Statistical Analyses

10.9.4.1 General Considerations

For Module 1 Part A (dose escalation), a final analysis will be performed when the MTD has been determined and the last patient to be recruited has had the opportunity to complete 2 cycles of treatment or has discontinued or withdrawn from treatment. Response and survival data will continue to be collected for ongoing patients until this milestone is reached for the final patient.

For Module 1 Part B (dose expansion), an interim analysis will be performed, as described in Section 10.9.5. The final analysis of the expansion cohorts will be undertaken when either the last patient from all expansion cohorts has had the opportunity to complete 6 months of treatment, or all patients have withdrawn from the study or died. Thereafter, patients who remain on study intervention may remain on study intervention and individual patients will continue to be assessed for safety as specified in the CSP.

10.9.4.2 Efficacy Analyses

Refer to Section 9.4.2 of the core protocol.

10.9.4.3 Safety Analyses

Refer to Section 9.4.3 of the core protocol.

10.9.4.4 Pharmacokinetic Analyses

Refer to Section 9.4.4 of the core protocol.

10.9.5 Interim Analyses

An interim analysis will be performed for Module 1 Part B when the last patient per criteria above has had the opportunity to complete 2 cycles of treatment and is response-evaluable as per population definition. This analysis will include evaluation of clinical response and AEs leading to discontinuation.

10.9.6 Data Monitoring Committee

Refer to Section 9.6 of the core protocol.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

- For all studies except those utilising medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative "an individual, juridical, or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial", per ICH GCP E6(R2) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Patients must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

Patients who are rescreened are required to sign a new ICF.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorised designee will explain to each patient the objectives of the analysis to be done on the samples and any potential future use. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data Protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients, their family members, their general physician, any insurance company, any employer, or any other third party, unless required to do so by law; however, AstraZeneca may share data and biosamples with research partners.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A study-specific SRC will review the emerging data from the study and will monitor safety data on an ongoing basis.

The SRC will consist of:

- Study Chair, who will chair the committee, or delegate
- Principal Investigator or delegate from the investigational sites that have enrolled patients
- Study Physician for the study or delegate
- Medical Science Director or delegate

In addition, one other physician from the following may be invited:

- Global Safety Physician or delegate
- Senior Physician from another project.

The Study Pharmacokineticist, Study Statistician, Patient Safety Scientist, Clinical Project Manager, and other experts may also be invited as appropriate. The SRC Charter document for this study will define the exact membership, and who should be present for decisions to be made, how reviews will be performed and how the discussions will be documented.

Further internal or external experts may be consulted by the SRC, as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com, https://www.clinicaltrialsregister.eu and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All patient data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the construction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).
- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site activated and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

Patients from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definitions of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above

Adverse events for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the Investigational Product under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

The grading scales found in the revised National Cancer Institute CTCAE version 5 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet

- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IRT errors)
- Wrong drug administered to patient (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of, destroyed, or repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures patient’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for CCI to explore how CCI variations may affect CCI, and the CCI . This CCI may lead to better understanding of CCI, better CCI or CCI, and to the discovery of new CCI, or CCI. Therefore, where local regulations and IRB/IEC allow, a CCI will be collected for DNA analysis from consenting patients.
- This CCI may consist of the analysis of the structure of the patient´s DNA, ie, the entire genome.
- The results of CCI may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the CSP and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

Withdrawal of Consent for Genetic Research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for [redacted]

A [redacted] for this [redacted] will be obtained from the patients at enrolment. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE. If for any reason the sample is not drawn at Cycle 1 Day 1 pre-infusion, it may be taken at any visit outside of Cycle 1 until the last study visit. Only one sample should be collected per patient for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for [redacted] are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this [redacted] component, are outlined in Appendix A.

Informed Consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient Data Protection

- AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this [redacted] with other researchers, such as hospitals, academic organisations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review adverse event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study intervention.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local Laboratories Being Used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (see Section E 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

- Within one day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For patients that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the patient's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for patient follow-up (including any further laboratory testing), and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician
  - Complete the 3 Liver eCRF Modules as information becomes available

#A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to patients with liver involvement who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on study intervention occurrence of PHL criteria being met the Investigator will determine if there has been a **significant change** in the patients' condition# compared with the last visit where PHL criteria were met:

- If there is no significant change no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study intervention and at their first on study intervention visit as described in Section E 6 of this Appendix?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the patient's condition# compared with when PHL criteria were previously met#

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section E 4.2 for reporting PHL as an SAE

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 8 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory. The list may be modified based on clinical judgement. Any test results need to be recorded.

Hy's Law Lab Kit for Laboratories	
Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV
	HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
[c] CD-transferrin and transferrin are not available in China. Study teams should amend this list accordingly.

Appendix F Management of Specific Adverse Events

F 1 Guidance for Management of Tumour Lysis Syndrome

Tumour lysis syndrome is a known pharmacodynamic effect of antitumour therapy in haematologic malignancies including NHL. The inherent risk of TLS is dependent on the malignancy being treated and individual patient characteristics (Coiffier et al 2008).

The risk of TLS with AZD0466 in NHL patients is predicted to be highest for those with bulky disease (defined in the context of TLS as any lesion ≥ 10 cm on the screening CT scan) and elevated pretreatment lactate dehydrogenase levels, particularly in the presence of dehydration or compromised renal function.

While DLBCL, transformed lymphomas, and MCLs may be at higher risk of TLS as compared with follicular, marginal, and small cell lymphomas (Cairo et al 2010), any risk stratification based on tumour type must be considered along with the effectiveness of therapy (Howard et al 2011).

Recommendations for prophylaxis, management, dose modification, and adverse event reporting pertaining to TLS are summarised below.

F 1.1 Prophylaxis for Tumour Lysis Syndrome

Assessment of TLS risk is based on disease type, as summarised in Table F27.

Table F27 Risk Assessment for Tumour Lysis Syndrome

Risk of tumour lysis syndrome		
Low Risk Disease	**Intermediate Risk Disease (IRD)**	**High Risk Disease**
• DLBCL with LDH within normal limits (WNL) • Mantle cell lymphoma with LDH WNL • Transformed lymphoma with LDH WNL • Follicular lymphoma • Hodgkin lymphoma • Marginal zone B-cell lymphoma	• DLBCL with LDH greater than upper limit of normal (ULN) non-bulky • Mantle cell lymphoma with LDH greater than ULN non-bulky • Transformed lymphoma with LDH greater than ULN non-bulky	• DLBCL with LDH > 2 ULN greater than ULN or bulky disease • Mantle cell lymphoma with LDH > 2 ULN greater than ULN or bulky disease • Transformed lymphoma with LDH greater than ULN and bulky disease • IRD with uric acid, potassium, and/or phosphate > ULN

Renal dysfunction elevates the patient to the next risk level
DLBCL = diffuse large B-cell lymphoma; LDH: lactate dehydrogenase; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; TLS = tumour lysis syndrome; ULN = upper limit of normal.
Source: Risk classification adapted from MD Anderson Cancer Center guidance.

Prophylaxis for TLS (hydration and anti-hyperuricaemic agents) is required for all patients receiving study intervention and should be implemented according to the TLS risk level assessed for each patient (Table F27). Specific recommendations are outlined in this section, but details of management may vary per institutional practice. Patients with creatinine clearance < 80 mL/min, and patients with renal involvement from underlying disease and/or urinary outflow obstruction, may be at higher risk of TLS and complications of TLS, and should be managed accordingly. Hospitalisation may be considered for hydration management requirements at the Investigator's discretion.

Prophylaxis is summarised by TLS risk score in Table F28, according to the following principles:

- **Adequate oral fluid intake** (Table F28) is required for all patients receiving study intervention, in particular around the times of AZD0466 dosing, and patients should be encouraged to drink sufficient fluid (total of 1.5 to 2 L/day) before and after each infusion of AZD0466.
- **IV hydration** is required for patients with high risk of TLS and at Investigator's criteria. Additional IV hydration may be administered as clinically indicated in patients with diarrhoea and/or nausea and vomiting. Diuretics should be used with care and prophylactic use of diuretics should be used only if patients have signs of volume overload.
- Allopurinol (or other xanthine oxidase inhibitor) should be administered to all patients receiving study intervention and initiated at least one calendar day before the first dose of AZD0466. Allopurinol 100 to 300 mg every 8 hours is suggested, but allopurinol dose may require adjustment as described in the allopurinol prescribing information or institutional guidelines.
- **Rasburicase** should be considered as an alternative to allopurinol for patients with elevated uric acid at baseline, or high tumour burden. Rasburicase should be administered 4 hours prior to AZD0466 infusion, and as described in the rasburicase prescribing information.

Table F28 Recommended Prophylaxis for Tumour Lysis Syndrome

	Risk of tumour lysis syndrome		
	High	**Intermediate**	**Low**
Recommended prophylaxis			
Hydration	Increased hydration: oral 1.5 to 2 L/day and IV 150 to 200 mL/h Maintain urine output	From Cycle 1 Day 15: oral hydration 1.5 to 2 L/day; consider IV hydration based on risk of TLS	

Table F28 Recommended Prophylaxis for Tumour Lysis Syndrome

	Risk of tumour lysis syndrome		
	High	**Intermediate**	**Low**
Anti-hyperuricemics	Allopurinol 100 to 300 mg every 8 hours Early consideration of rasburicase [a] as an alternative, based on baseline uric acid and tumour burden		Allopurinol 100 to 300 mg every 8 hours
Criteria for use of rasburicase			
Serum uric acid at baseline	> 475.8 µmol/L [b] + 1 risk factor ≤ 475.8 µmol/L [b] + 2 risk factors	> 475.8 µmol/L [b] + 2 risk factors ≤ 475.8 µmol/L [b] + 3 risk factors	NA
Risk factors	Serum creatinine > 1.3 mg/dL (> 88.4 µmol/L) WBC > 50 $\times 10^9$/L LDH > 2× ULN		NA

[a] Rasburicase is contraindicated in patients with glucose-6 phosphate dehydrogenase deficiency, known hypersensitivity to rasburicase, haemolytic anaemia or methemoglobinemia
[b] Uric acid cutoff may be adjusted according to local guidance.
Recommended prophylaxis adapted from MD Anderson Cancer Center guidance (Coiffier et al 2008) and Cairo and Bishop (Cairo and Bishop 2004).
IV = intravenous; LDH = lactate dehydrogenase; TLS = tumour lysis syndrome; WBC = whited blood cell.

F 1.2 AZD0466 Dose Modifications for Tumour Lysis Syndrome

AZD0466 dose modifications for TLS are summarised in Table F29.

Table F29 AZD0466 Dose Modifications for Tumour Lysis Syndrome

Abnormality	**Action with AZD0466**
Laboratory findings (serum)	
Uric acid ≥ 475.8 µmol/L	• Initiate supportive therapy as per standard clinical practice, additional guidance provided in Table F30. • Delay AZD0466 for up to 7 days (if finding present before administration of AZD0466) • If resolution to within specified threshold in ≤ 7 days, restart at the same dose level • If resolution after 7 days restart AZD0466 at one lower dose
Potassium ≥ 6.0 mmol/L	
Phosphate ≥ 1.6 mmol/L (5.0 mg/dL) with ≥ 0.16 mmol/L (0.5 mg/dL) increase [a]	
Corrected calcium < 1.75 mmol/L	
Creatinine increase by > 26.5 µmol/L from baseline (creatinine > 1.5 × ULN if no baseline)	
All laboratory abnormalities must resolve to within specified threshold before AZD0466 is restarted	
Clinical findings	
Signs suggestive of clinical TLS (eg, acute kidney injury, cardiac arrhythmia/dysrhythmia [b], hypotension [c], heart failure [c])	• Initiate supportive therapy as per standard clinical practice • Delay AZD0466 for up to 14 days • AZD0466 at one lower dose following resolution

Table F29 AZD0466 Dose Modifications for Tumour Lysis Syndrome

Abnormality	Action with AZD0466
Symptoms suggestive of clinical TLS [b] (eg, oliguria [d], seizure, nausea, vomiting, muscle cramps [c], neuromuscular instability [c])	• For clinical TLS, initiate supportive therapy and withhold AZD0466 until resolution of symptoms • AZD0466 can be withheld up to 14 days • Restart AZD0466 at one lower dose • Patients should be encouraged to maintain oral hydration

[a] Recommended prophylaxis adapted from MD Anderson Cancer Center guidance and Cairo and Bishop 2004.
[b] Probably or definitely caused by hyperkalaemia or hypocalcaemia.
[c] Probably or definitely caused by hypocalcaemia.
[d] Average urine output of < 0.5 mL/kg/h, lasting for > 6 hours.
TLS = tumour lysis syndrome; ULN = upper limit of normal.

F 1.3 Treatment of Tumour Lysis Syndrome

Signs and symptoms of clinical TLS (including but not limited to acute kidney injury, oliguria, nausea, vomiting, seizure, muscle cramps, neuromuscular irritability, cardiac arrhythmia/dysrhythmia, hypotension, or heart failure) should be managed according to standard clinical practice. Additional IV hydration may be administered as clinically indicated in patients with diarrhoea and/or nausea and vomiting.

Recommendations for management of specific laboratory abnormalities is summarised in Table F30.

Table F30 Recommended Management of Electrolyte Abnormalities in Tumour Lysis Syndrome

Abnormality	Management recommendations
Hyperphosphataemia	
Moderate (≥ 2.1 mmol/L)	• Avoid IV and oral phosphate and limit dietary sources • Administer phosphate binder
Severe	Dialysis or haemofiltration may be required
Hypocalcaemia (≤ 1.75 mmol/L)	
Asymptomatic	• No therapy • Patients with acute hypocalcaemia and hyperphosphatemia should not receive calcium repletion until phosphate level has normalised
Symptomatic	• Calcium gluconate [a] 50 to 100 mg/kg by slow IV infusion with ECG monitoring
Calcium-phosphate product	
≥ 50 mg^2/dL^2	• Ensure hydration is maintained and alkalinisation is discontinued

Table F30 Recommended Management of Electrolyte Abnormalities in Tumour Lysis Syndrome

Abnormality	Management recommendations
Hyperkalaemia	
Moderate (≥ 6.0 to < 7.0 mmol/L) and asymptomatic	• Avoid IV and oral potassium • ECG monitoring • Administer sodium polystyrene sulfonate
Severe (≥ 7.0 mmol/L) or symptomatic	• As above, plus • Calcium gluconate[a] 100 to 200 mg/kg by slow IV infusion if concurrent ECG changes (including life-threatening arrhythmias) • Regular IV insulin and dextrose, monitor blood glucose closely • Consider sodium bicarbonate [a] if patient is acidaemic • Consider albuterol (to be avoided in patients with acute coronary disease) • Dialysis may be required
Renal dysfunction (uraemia)	• Fluid and electrolyte management • Uric acid and phosphate management • Adjust doses of renally excreted medication • Dialysis or haemofiltration may be required

[a] Sodium bicarbonate and calcium gluconate should not be administered through the same line.
Recommended management adapted from MD Anderson Cancer Center guidance and Coiffier et al 2008.
ECG, electrocardiogram; IV, intravenous.

Laboratory parameters indicating TLS (including blood urea nitrogen, creatinine, phosphate/phosphorus, uric acid, calcium, potassium, and LDH) will be evaluated. Fluid balance must be monitored per institutional standards. If more aggressive hydration management is indicated, patient hospitalisation will be considered at Investigator discretion. Allopurinol prophylaxis should be considered based on institutional guidelines.

F 1.4 Reporting Adverse Events of TLS

The Investigator will report TLS as an adverse event or serious adverse event of "laboratory TLS" or "clinical TLS" according to the classification of TLS in Appendix G 1. For the purposes of adverse event reporting, a CTCAE grade for TLS should also be recorded, as follows:

- CTCAE Grade 3: TLS present
- CTCAE Grade 4: TLS with life-threatening consequences; urgent intervention indicated
- CTCAE Grade 5: Death

Tumour lysis syndrome will also be graded according to Cairo-Bishop criteria for the purposes of dose-limiting toxicity assessment and summary of adverse events of special interest (Appendix G 2; Cairo and Bishop 2004).

F 2 Guidance for Management of Haematologic Changes

F 2.1 Thrombocytopenia and Haemorrhage

Platelet transfusions are permitted as per institutional standards. However, due to the mechanism of action of AZD0466, platelet transfusion may have limited efficacy within 24 to 48 hours after AZD0466 infusion.

AZD0466 should be withheld in presence of significant bleeding events with or without thrombocytopenia, such as:

- Grade 3 or 4 haemorrhage
- Any grade serious haemorrhage event
- Any grade intracranial haemorrhage or haematoma

However, if there is evidence that the patient is experiencing clinical benefit with AZD0466, restarting at a reduced dose may be considered following discussion with the Study Physician. AZD0466 should be discontinued if significant bleeding reoccurs.

Anticoagulants and aspirin are not allowed during the study; other anti-aggregants may be used with caution.

F 2.2 Neutropenia and Febrile Neutropenia

The use of G-CSF (eg, filgrastim) or GM-CSF (eg, sargramostim) may be used for management of severe neutropenia or febrile neutropenia, as indicated by the current American Society of Clinical Oncology guideline and according to Investigator's clinical judgement. The use of long-acting pegylated G-CSF (eg, pegfilgrastim) is not permitted during study intervention.

F 2.3 Anaemia

Patients already receiving erythropoietin at screening may continue to receive it during study intervention, provided they have been receiving erythropoietin for > 1 month at the time study intervention is started.

Prophylaxis in Cycle 1: Prophylactic erythropoietin should not be started during Cycle 1.

Prophylaxis in Cycle 2 and beyond: Prophylactic erythropoietin may be started during Cycle 2 or in subsequent cycles.

Use of the long-acting erythropoiesis-stimulating agent, darbepoetin, is not permitted during study intervention.

Blood transfusions may be administered at the discretion of the Investigator.

F 3 References

Cairo and Bishop 2004
Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

Coiffier et al 2008
Coiffier et al 2008. University of Texas MD Anderson Cancer Center 2018 Tumor lysis syndrome (TLS) in adult patients. 2018. Copyright University of Texas MD Anderson Cancer Center 2018.

Howard et al 2011
Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

Appendix G Classification of Tumour Lysis Syndrome

G 1 Classification

The criteria for classification of laboratory and clinical TLS in adults are described below. These criteria are based on the Howard et al 2011 (Howard et al 2011) modification of Cairo and Bishop 2004 (Cairo and Bishop 2004), and have been adapted from Cheson et al 2017 (Cheson et al 2017).

Clinical TLS assumes the laboratory evidence of metabolic changes and an adverse event that requires clinical intervention. Clinical TLS is defined as the presence of laboratory TLS and any one or more of the clinical criteria, as specified in Table G31 below.

Table G31 Criteria for Laboratory and Clinical Tumour Lysis Syndrome

Abnormality	Criteria
Laboratory TLS	
Two or more of the following metabolic abnormalities occurring during the same 24-hour period, and within 3 days before until 7 days after infusion of study intervention:	
Hyperuricaemia	Uric acid ≥ 475.8 µmol/L (≥ 8.0 mg/dL)
Hyperkalaemia	Potassium ≥ 6.0 mmol/L
Hyperphosphataemia	Phosphate ≥ 1.5 mmol/L (≥ 1.5 mg/dL)
Hypocalcaemia	Corrected calcium < 1.75 mmol/L (< 7.0 mg/dL), or Ionised calcium < 0.3 mmol/L
Clinical TLS	
Laboratory TLS plus one or more of the following:	
Acute kidney injury	Serum creatinine increase by > 26.5 µmol/L (or a single value > 1.5 × ULN if no baseline measurement), or oliguria (average urine output of < 0.5 mL/kg/h) lasting for > 6 hours
Cardiac arrhythmia/dysrhythmia or sudden death	Probably or definitely caused by hyperkalaemia or hypocalcaemia
Seizure	Probably or definitely caused by hypocalcaemia
Neuromuscular irritability, hypotension, or heart failure	Probably or definitely caused by hypocalcaemia

TLS = tumour lysis syndrome; ULN = upper limit of normal.

G 2 Grading

Tumour lysis syndrome should be graded according to the Cairo-Bishop criteria for the purposes of dose-limiting toxicity assessment (Cairo and Bishop 2004). The grade of the maximal clinical manifestation defines the overall grade of TLS, as summarised below in Table G32.

Table G32 Grading of Tumour Lysis Syndrome

Cairo-Bishop Grading for TLS						
Abnormality	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laboratory TLS	Absent	Present	Present	Present	Present	Present
Serum creatinine [a]	≤ 1.5 x ULN	1.5 x ULN	1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN	Death [b]
Cardiac arrhythmia [a]	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death [b]
Seizure [a]	None	--	One brief generalised seizure; seizures well controlled by anticonvulsants; infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalised seizures despite medical intervention	Seizure of any kind and prolonged, repetitive, or difficult to control (eg, status epilepticus, intractable epilepsy)	Death [b]

[a] Not directly or probably attributable to therapeutic agent.
[b] Probably or definitely attributable to clinical TLS.
Modified from Cairo and Bishop 2004.
ADL = activities of daily living; CHF = congestive heart failure; TLS = tumour lysis syndrome; ULN = upper limit of normal.

G 3 References

Cairo and Bishop 2004
Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

Cheson et al 2017
Cheson BD, Enschede SH, Cerri E, Desai M, Potluri J, Lamanna N et al. Tumor lysis syndrome in chronic lymphocytic leukemia with novel targeted agents. Oncologist. 2017;22(11):1283-91.

Howard et al 2011
Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

Appendix H Drugs That Prolong QT Interval and/or Induce Torsades De Pointes

Drugs with known or possible risk of Torsades de Pointes (cardiac arrhythmia due to drug-induced QTc prolongation) are withheld for 5 half-lives prior to the first dose of study intervention and will continue to be withheld during the study, and for 14 days after the last dose of AZD0466.

Table H33 Drugs with a Known Risk of Torsades de Pointes

Contraindicated drug	Withdrawal period prior to the start of study intervention
Aclarubicin, anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin.	2 days
Cilostazol, cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, sotalol, roxithromycin, sevoflurane, sparfloxacin, thioridazine	7 days
Azithromycin, bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine, citalopram, dronedarone, escitalopram, fluconazole, levomepromazine, levosulpiride	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	3 weeks [b]
Arsenic trioxide [a], ibogaine	3 weeks [b]
Pentamidine	3 weeks [b]
Astemizole, probucol, vandetanib	3 weeks [b]
Amiodarone, chloroquine	1 year

[a] Estimated value, as pharmacokinetics of arsenic trioxide have not been studied.
[b] The withdrawal period for these drugs will be 3 weeks prior to the start of study treatment, after discussion with the Study Physician regarding the risk/benefit ratio.

CredibleMeds® (www.crediblemeds.org) is the standard reference for drugs with known or possible risk of Torsades de Pointes. Since CredibleMeds® constantly assesses new drug information and updates its lists, sites should go directly to the crediblemeds.org website in real-time for reference. Patients receiving drugs listed in the “known” or “possible” categories at the time of eligibility assessment are prohibited from 14 days before the start of treatment until permanent discontinuation of treatment.

Some of the medications listed as a possible risk of Torsades de Pointes may be allowed at the Investigator’s discretion after approval by the Study Physician when the patient has unmet medical need to continue receiving prohibited medication(s), no suitable alternative treatments are available, and the benefit-risk ratio is acceptable in the Investigator’s opinion.

Appendix I Contraception Guidance

I 1 Definitions

- A female of childbearing potential is defined as a female who is not permanently surgically sterilised or postmenopausal.
- Surgical sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion (the term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).
- Postmenopausal is defined as amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
  - Women under 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments AND with luteinising hormone and follicle-stimulating hormone levels in the postmenopausal range
  - Women over 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments
- A highly effective method of contraception is defined as a method that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly.

I 2 Contraception Methods

Highly effective methods of contraception are described in Table I34.

Table I34 Highly Effective Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods

• Intrauterine device
• Intrauterine hormone-releasing system (UIS) [a]
• Bilateral tubal occlusion
• Vasectomized partner [b]
• Sexual abstinence [c]
	• Combined (oestrogen and progestogen containing hormonal contraception)
	  ° Oral (combined pill)
	  ° Injectable
	  ° Transdermal (patch)
	• Progestogen-only hormonal contraception associated with inhibition of ovulation [d]
	  ° Injectable
	  ° Implantable

[a] This is also considered a hormonal method.
[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the patient. However, periodic, or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method.

Appendix J New York Heart Association Functional Classification

Class	Patient Symptoms	Class	Objective Assessment
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).	A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).	B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.	C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.	D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Source: https://www heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

Appendix K Response Evaluation Criteria for Non-Hodgkin Lymphoma

Disease response assessment will be evaluated using the revised Lugano 2014 Classification for NHL (Cheson et al 2014).

Response assessments will be done by the Investigators following the revised Lugano 2014 Classification response criteria (Cheson et al 2014).

Tumour assessment will be made for target lesions (ie, measurable disease), non-target lesions (ie, non-measurable disease), organ enlargement (eg, spleen, liver), and new lesions on CT and combined with visual assessment of PET-CT for response assessment (Cheson et al 2014; Table K35).

K 1 Visual Interpretation of PET-CT Scans

Variation in FDG uptake in a nodal or extranodal sites indicative for lymphoma will be visually assessed using the Deauville 5-point scale.

Target Lesions

Up to a maximum of 6 dominant, measurable lymph nodal or extranodal lesions should be assessed as target lesions and documented at baseline and throughout the study.

A lesion will be considered measurable if:

- For nodal lesions: LDi > 1.5 cm
- For extranodal lesion: LDi > 1 cm

Lesions visible on PET but not on CT/MRI to be assigned as non-target lesions.

Target nodal or extranodal lesions nodes should be selected according to all of the following:

- They should be clearly measurable in at least 2 perpendicular dimensions
- If possible, they should be from disparate regions of the body
- They should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

The perpendicular long and short axis diameters will be measured and recorded in the transverse plane at baseline and follow-up.

For the selected target lymph nodal lesions, the sum of the product of the perpendicular diameters will be calculated with the percentage change from baseline for assessment of response and nadir for assessment of progression.

Non-target Lesions

All other lesions (including nodal, extranodal, and assessable disease) not selected as target lesions, as well as truly non-measurable sites of disease should be followed as non-measurable disease (eg, cutaneous, gastrointestinal, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites) and should be factored into the overall response assessment. Non-target lesions will be documented at baseline and throughout the study. Measurement of these lesions is not required to be documented on the eCRFs.

Spleen Involvement

Spleen will be considered to be normal if size of its vertical length (cranial-caudal measurement) is ≤ 13 cm. For patients with splenomegaly at baseline, spleen vertical length will be assessed at screening and all subsequent response evaluations.

Liver Involvement

Intrahepatic lesions should be considered as target, non-target, or new lesion as applicable. The presence of a diffuse or focal uptake with or without focal or disseminated nodules support liver involvement. Given variability in body habitus and the impact of numerous medical conditions, liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by lymphoma. For these reasons, liver size will not be collected in eCRFs.

Bone Marrow Involvement

Bone marrow involvement by lymphoma documented by aspirate and/or biopsy will be reported on the eCRF as present or absent.

Table K35 Response Assessment Criteria for Non-Hodgkin Lymphoma

Response and site	PET-CT-based response	CT-based response
Complete response:	**Complete metabolic response:**	**Complete radiologic response – all of the following:**
Lymph nodes and extralymphatic sites (target lesions)	Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No extralymphatic sites of disease (0 × 0 cm)
Non-measured lesion (non-target)	Not applicable	Absent/normal
Organ enlargement	Not applicable	Regress to normal; spleen vertical length is ≤ 13 cm
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Table K35 Response Assessment Criteria for Non-Hodgkin Lymphoma

Response and site	PET-CT-based response	CT-based response
Partial response:	**Partial metabolic response:**	**Partial remission – all of the following:**
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with or without a residual mass on 5PS	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease:	**No metabolic response:**	**Stable disease:**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Table K35 Response Assessment Criteria for Non-Hodgkin Lymphoma

Response and site	PET-CT-based response	CT-based response
Progressive disease:	**Progressive metabolic disease:**	**Progressive disease requiring at least 1 of the following:**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from visually determined nadir and/or	PPD progression: An individual node/lesion must be abnormal with: • LDi > 1.5 cm AND • Increase by ≥ 50% from PPD nadir AND • An increase in LDi or SDi from nadir ° 0.5 cm for lesions ≤ 2 cm ° 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (eg, infection, inflammation). If uncertain regarding aetiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone

Table K35 Response Assessment Criteria for Non-Hodgkin Lymphoma

Response and site	PET-CT-based response	CT-based response

marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy of myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Adapted from Table 3: Cheson et al 2014

5PS = Deauville 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

K 2 Assessment of New Lesions

Appearance of any new lesions > 1.5 cm in any axis during or at the end of therapy, even if all other lesions are decreasing should be considered progression. Increased FDG uptake in a previously unaffected site should only be considered progression after confirmation with other modalities (eg, CT, MRI, biopsy).

In patients with no history of pulmonary lymphoma, new nodules identified by CT are benign and should be considered negative for lymphoma. These lesions typically represent infectious or inflammatory lesions; therefore, if FDG positive, should not be considered positive for lymphoma in the absence of confirmatory tests, (eg, histology).

The presence or absence of new lesions will be recorded in the eCRF.

K 3 Overall Response Assessment

The efficacy endpoints are based on the overall response assessment, which is combining the radiological response from PET/CT scans, the bone marrow findings (if applicable) and any additional clinical finding, including cytologic or histopathologic findings for each disease response assessment during the study. The possible outcomes for ORR as CR, PR, SD, PD, Unknown. The Investigator-assessed ORR and respective date will be captured on the eCRF.

K 4 References

Cheson et al 2014
Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E 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.

Appendix L Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the patient's safety. If in doubt, please contact the Study Physician.

L 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on-site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections L 2 to L 5. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patients' next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

L 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The Investigator should confirm this with the designated Study Physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in the SoA of the respective modules, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a patient in addition to that detailed in Section 5.4.

L 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the patient's home/or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

L 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow AEs, concomitant medication, and ECOG performance status to be reported and documented.

L 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the patient themselves.

Appendix M Disease Prognostic Scores

M 1 Follicular Lymphoma Prognostic Scores

Table M36 FLIPI-1 Criteria

Category	Risk Factor
Age	≥ 60 years
Ann Arbor Stage	III-IV
Haemoglobin level	< 12 g/dL
Serum LDH level	> ULN
Number of nodal sites	≥ 5
Risk Group According to FLIPI Chart	**Number of Factors**
Low	0-1
Intermediate	2
High	≥ 3

FLIPI: follicular lymphoma international prognostic index; LDH: lactate dehydrogenase; ULN: upper limit of normal.
Source: (Solal-Céligny et al 2004)

Table M37 FLIPI-2 Criteria

Risk Factors	
Age	
Raised beta-2-microglobulin	
Haemoglobin < 12 mg/dL	
Longest diameter of largest involved node ≥ 6 cm	
Bone marrow involvement	
Risk Category and Prognosis	
FLIPI-2 Score	**FLIPI-2 Risk Category**
0	Low
1-2	Intermediate
3-5	High

FLIPI: follicular lymphoma international prognostic index.
Source: (Solal-Céligny et al 2004, Federico et al 2009)

M 2 Mantle Cell Lymphoma Prognostic Score

Table M38 Simplified MIPI

Point	Age	ECOG	LDH ULN	WBC (109/L)
0	<50	0-1	< 0.67	< 6.700
1	50-59	-	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000-1.49	1.000-14.999
3	≥70	-	≥ 1.5000	≥ 15000

ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; MIPI: Mantle cell lymphoma. International Prognostic Index; ULN: upper limit of normal; WBC: white blood cell.
Source: (Hoster et al 2008)

Table M39 Risk Category According to the MIPI

MIPI Score	Risk
0-3	Low
4-5	Intermediate
6-11	High

MIPI: Simplified Mantle cell lymphoma International Prognostic Index.
Source: (Hoster et al 2008)

M 3 Diffuse Large B-cell Lymphoma Prognostic Score

Table M40 International Prognostic Index

Category	Risk Factor
Age	> 60 years
Ann Arbor Stage	III-IV
Performance status	2-4
Serum LDH level	> ULN
Extranodal sites	> 1
Risk Group According to IPI Chart	**Number of Factors**
Low	0-1
Low-intermediate	2
High intermediate	3
High	4-5

LDH, lactate dehydrogenase
Source: International Non-Hodgkin's Lymphoma Prognostic Factors Project, NCCN Guidelines)

M 4 References

Federico et al 2009
Federico M, Bellei M, Marcheselli L, Luminari S, Lopez-Guillermo A, Vitolo U, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009;27(27):4555-62.

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International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993 Sep 30;329(14):987-94. doi: 10.1056/NEJM199309303291402. PMID: 8141877.2008;111(2):558-65.

NCCN Guidelines
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) B-Cell Lymphomas. Version 1.2021. Available from https://www.nccn.org/professionals/physician_gls/pdf/bcell.pdf (accessed 11 February 2021).

Solal-Céligny et al 2004
Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. Blood 2004;104(5):1258–65.

Appendix N Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
BCRP	breast cancer resistance protein
B-NHL	B-cell non-Hodgkin lymphoma
CAR-T	chimeric antigen receptor T cell
cfDNA	circulating free deoxyribonucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organisation
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumour deoxyribonucleic acid
CTEP	Cancer Therapy Evaluation Program
CYP	cytochrome P450
DCO	data cutoff
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
eCRF	electronic case report form
EDC	electronic data capture
EoT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FL	follicular lymphoma
GCP	Good Clinical Practice
HCP	healthcare provider
HL	Hy's Law
HSCT	haematopoietic stem cell transplantation
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous(ly)
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCL	mantle cell lymphoma
CCI	CCI
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease

Abbreviation or special term	Explanation
PET	positron emission tomography
PFS	progression-free survival
PHL	Potential Hy's Law
PK	pharmacokinetic(s)
PR	partial response
RP2D	recommended Phase II dose
R/R	relapsed/refractory
QTcF	QTc corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCT	stem cell transplantation
SD	stable disease
SoA	Schedule of Activities
SRC	Safety Review Committee
TBL	total bilirubin
TLS	tumour lysis syndrome
TPV	third-party vendor
TTR	time to response
ULN	upper limit of normal
US	United States

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