Official Title: A Phase II/III, Randomised, Multicentre Study of MOR00208 with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL) Who Are Not Eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT) – [B-MIND]

NCT Number: NCT02763319

Document Date: MOR208C204 (B-MIND) CTP Amendment No. 8 10-Apr-2024

B-MIND

CLINICAL TRIAL PROTOCOL

A Phase II/III, Randomised, Multicentre Study of MOR00208 with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL) Who Are Not Eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT) – [B-MIND]

Brief Description of Study:	Open-label, randomised trial to evaluate the efficacy and safety of MOR00208 with bendamustine (BEN) versus rituximab (RTX) with BEN in adult patients with R-R DLBCL
Phase of Development:	Phase II/III
Sponsor:	Incyte Corporation
Sponsor's Address:	1801 Augustine Cut-Off Wilmington, DE 19803 USA
Study Protocol Number:	MOR208C204
IND No.:	114,856
EudraCT No.:	2014-004689-11
Date of Protocol:	10-Apr-2024 (Version 11.0)

INVESTIGATOR'S AGREEMENT

I have read the MOR208C204 Protocol Amendment 8 (dated 10-Apr-2024) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

PROTOCOL HISTORY

Version	Date
Amended Protocol CTP v11.0	10-Apr-2024
Amended Protocol CTP v10.0	02-Dec-2022
Amended Protocol CTP v9.0	22-Dec-2021
Amended Protocol CTP v8.0	14-Feb-2019
Amended Protocol CTP v7.0	23-Aug-2017
Amended Protocol CTP v6.0	21-Jul-2017
Amended Protocol CTP v5.0	05-Apr-2017
Amended Protocol CTP v4.0	21-Nov-2016
Amended Protocol CTP v3.0	04-Mar-2016
Amended Protocol CTP v2.0	18-Dec-2015
Original Protocol CTP v1.0	25-Nov-2015

Amended Protocol CTP v11.0 (10-Apr-2024)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to update the sponsorship from MorphoSys AG to Incyte Corporation.

1. **Title Page; Investigator's Agreement; Section 1, Protocol Synopsis; Section 5, Study Purpose/Rationale; Section 8.4, End of Study; Section 11.2, Adverse Event and Serious Adverse Event Recording and Reporting; Section 11.3, Pregnancies; Section 13, Statistical Methods and Planned Analyses; Section 14.4, Regulatory and Ethical Considerations, Including the Informed Consent Process; Section 14.5, Quality Control (Study Monitoring); Section 14.8, Publication Policy; Section 16.3, Appendix C: Overview of published data on NKCC as a prognostic factor in DLBCL and FL**

   Description of change: Updated the sponsorship from MorphoSys AG to Incyte Corporation.

   Rationale for change: Change in sponsorship.

2. **Incorporation of administrative changes.** Other administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

1 PROTOCOL SYNOPSIS

Title of Study	A Phase II/III, Randomised, Multicentre Study of MOR00208 with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL) Who Are Not Eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT) – [B-MIND]
Protocol Number	MOR208C204
IND Number	114,856
EudraCT Number	2014-004689-11
Sponsor	Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE USA 19803
Study Phase	Phase II/III
Background and Study Rationale	Despite advances in the first-line treatment of diffuse large B-cell lymphoma (DLBCL), 30–40% of patients either relapse or have refractory disease. Approximately 50% of patients with relapsed or refractory (R-R) DLBCL do not achieve a long-term remission with subsequent therapy as they either relapse after intensified chemotherapeutic treatment, including high-dose chemotherapy (HDC) and autologous stem-cell transplantation (ASCT), or are not eligible for an intensified treatment regimen. Patients with R-R DLBCL failing intensified second-line therapy, or those who are ineligible for such therapy, constitute an unmet medical need as the median overall survival (OS) for this population is less than one year with currently available therapies. MOR00208 is an Fc-enhanced, humanised, monoclonal antibody (mAb) with significantly enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP) and direct cytotoxic effects (apoptosis) compared with its non-enhanced parental antibody. Results of in vitro experiments suggest that MOR00208 leads to stronger ADCC-mediated target cell lysis in comparison to Rituximab (RTX) under conditions in which natural killer (NK) cells are limited. Based on the assumption that in patients with low baseline natural cell count (NKCC), NK cell numbers at the tumour site will not out-number the number of tumour cells, the in vitro data support the hypothesis that MOR00208 could have higher tumour killing capacity compared to rituximab in patients with a peripheral NK cell count of 100 or less NK cells/µL. MOR00208 has shown preliminary efficacy and acceptable toxicity in patients with R-R DLBCL, follicular lymphoma and other indolent non-Hodgkin lymphomas (NHLs). MOR00208 is expected to significantly increase the clinical efficacy of established chemotherapeutic regimens for R-R DLBCL such as bendamustine (BEN).

	MOR00208 or tafasitamab[1] (trade name Monjuvi) has been authorized for marketing in the US under the provision of accelerated approval on 31-Jul-2020 and under the trade name Minjuvi in Canada (19-Aug-2021), EU (26-Aug-2021) and UK (08-Oct-2021) as conditional approvals in 2021 in patients with R/R DLBCL. This is a randomised, open-label clinical trial to compare the safety and efficacy of MOR00208 with BEN versus rituximab (RTX) with BEN, an accepted standard of care for this patient population.
Study Objectives	**PRIMARY OBJECTIVE:** To determine the efficacy of a combination of MOR00208 with BEN versus a combination of RTX with BEN in terms of progression-free survival (PFS) in: • Adult patients with R-R DLBCL (overall population) • A subgroup of adult patients with R-R DLBCL with low baseline peripheral blood NK-cell count (NKCC-low), defined as 100 or less NK cells per µl blood at baseline. **SECONDARY OBJECTIVES:** 1. To determine and compare both study arms, MOR00208 with BEN versus RTX with BEN, for the overall population and NKCC-low subgroup in terms of: a) best objective response rate (ORR = complete response [CR] + partial response [PR]) based on the best response achieved at any time during the study b) duration of response (DoR) c) overall survival (OS) d) disease control rate (DCR = CR + PR + stable disease [SD]) e) time to progression (TTP) f) time to next treatment (TTNT) g) safety, based on the frequency, incidence and severity of adverse events (AEs) h) quality of life (QoL), using the EORTC QLQ-C30 and EQ-5D-5L questionnaires 2. To assess the potential immunogenicity of MOR00208 (anti-MOR00208 antibody formation) 3. To assess the pharmacokinetic (PK) profile of MOR00208. **EXPLORATORY OBJECTIVES:** [redacted]

[1] Tafasitamab is the recommended INN and USAN for MOR00208. Tafasitamab is also known under the names XmAb®5574, MOR208, MOR00208, Monjuvi and Minjuvi. MOR00208 was not replaced in this document as this is an ongoing trial.

Study Endpoints	**CO-PRIMARY ENDPOINTS:** 1. PFS in the overall study population (FAS) 2. PFS in the NKCC-low subgroup **SECONDARY ENDPOINTS:** 3. Best ORR, DoR, OS, DCR, TTP and TTNT 4. Frequency, incidence and severity of AEs 5. QoL 6. Anti-MOR00208 antibody formation 7. PK of MOR00208 8. [redacted] The secondary endpoints will be analysed in the overall population (FAS) and NKCC-low subgroup.
Design and Methodology/Patient Population	This is a randomised, two-arm, multicentre, open-label phase II/III efficacy and safety study of MOR00208 in combination with BEN versus RTX in combination with BEN given to adult patients who have relapsed after or are refractory to at least one but no more than three prior systemic therapies and have failed, or are not candidates for HDC and ASCT, and have thus exhausted their therapeutic options of demonstrated clinical benefit. At least one prior therapy line must have included a CD20-targeted therapy (e.g. RTX). Patients with R-R DLBCL who meet all the inclusion criteria and have none of the exclusion criteria will be enrolled and randomly assigned to one of two parallel treatment groups in a ratio of 1:1. Baseline NKCC will be determined by flow cytometry. Histological confirmation of DLBCL diagnosis (post-randomisation) will be performed by a central pathologist. The study will be performed according to a group-sequential, adaptive design with possible sample size adjustment after a planned interim analysis with 50 percent information rate. The trial will be conducted at approximately 180 sites worldwide. As the combination of MOR00208 and BEN will be systematically evaluated for the first time in a clinical trial, the trial includes an Initial Safety Evaluation (Phase II part of the trial) which will enable the Independent Data Monitoring Committee (IDMC) to conclude whether the combination treatments are safe. In the course of Initial Safety Evaluation, the first three patients in both investigational arms will be dosed sequentially with at least a 48 hours lag period between the enrolments of two consecutive patients as counted from Cycle 1 Day 4 (C1D4). After completion of the first treatment week (C1D8) by the third consecutive patient in each arm (approximately 6 patients in total) the safety data will be reviewed by the IDMC.

	Following a positive recommendation of the IDMC, seven additional patients in each arm may be dosed in parallel (approximately 14 patients in total). An additional IDMC review will take place after the last of 10 patients in each arm (approximately 20 patients in total) have completed C3D1 visit in their respective treatment allocation arm (complete Initial Safety Evaluation). The exact number of patients eligible for evaluation depends on the treatment allocation within the randomisation blocks. For a schematic presentation of study outline, see Figure 1 and Figure 2 in the protocol Should the IDMC maintain their initial recommendation that the combination treatments are safe, the trial may proceed further with recruitment (Phase III part of the trial). Subsequent IDMC meetings will be called for as outlined in the IDMC Charter throughout the entire trial. Each IDMC review will encompass the number, frequency, severity and type of AEs, as well as clinical laboratory biochemistry and haematology parameters and other relevant safety data. The IDMC will also advise the sponsor whether the trial design requires modifications or has met the pre-defined trial stopping criteria. Further details are provided in Sections 9.8 and 14.1 and the IDMC Charter. For the purpose of the primary efficacy endpoint analysis, the disease response assessments will be made centrally by an Independent Radiology/Clinical Review Committee (IRC; see Section 14.2).
Inclusion/Exclusion Criteria	**INCLUSION CRITERIA:** Eligible patients must meet the following criteria to be enrolled in the study: **Diagnosis/Trial Population** 1. Age ≥18 years • For Singapore only: age ≥21 years 2. Histologically confirmed diagnosis, according to the World Health Organization (WHO, 2008) classification, of: a) Diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) b) T cell/histiocyte rich large B-cell lymphoma (THRLBCL) c) Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL) d) Composite lymphoma with a DLBCL component with a DLBCL relapse subsequent to DLBCL treatment e) Disease transformed from an earlier diagnosis of low-grade lymphoma (i.e. an indolent pathology such as follicular lymphoma, marginal zone lymphoma) into DLBCL with a DLBCL relapse subsequent to DLBCL treatment.

3. Fresh tumour tissue for central pathology review must be provided as an adjunct to participation in this study. Should it not be possible to obtain a fresh tumour tissue sample, archival paraffin embedded tumour tissue acquired ≤3 years prior to screening for this protocol must be available for this purpose.
4. Patients must have:
   a) R-R DLBCL (for definitions, see Section 8.1 of the protocol)
   b) at least one bidimensionally measurable disease site. The lesion must have a greatest transverse diameter of ≥1.5 cm and greatest perpendicular diameter of ≥1.0 cm at baseline. The lesion must be positive on PET scan (for definition, see Juweid et al. (2007)).
   c) received at least one, but no more than three previous systemic therapy lines for the treatment of DLBCL (for further details see Sections 8.6 and 9.5). At least one previous therapy line must have included a CD20-targeted therapy (e.g. RTX).
   d) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
5. Patients after failure of ASCT or patients considered in the opinion of the investigator currently not eligible for HDC with subsequent ASCT. Documentation of the reason for ineligibility for ASCT must be present in the patient's source data (for details, see Section 8.6).

Laboratory Values

6. Patients must meet the following laboratory criteria at Screening:
   a) absolute neutrophil count (ANC) ≥1.5 × 10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow aspiration and bone marrow biopsy required for Screening)
   b) platelet count ≥90 × 10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow aspiration and bone marrow biopsy required for Screening) and absence of active bleeding
   c) total serum bilirubin ≤2.5 × upper limit of normal (ULN) unless secondary to Gilbert's syndrome (or pattern consistent with Gilbert's) or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is ≤5 x ULN (see exclusion criterion 6e)
   d) alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase ≤3 × ULN or <5 × ULN in cases of documented liver involvement by lymphoma
   e) serum creatinine ≤2.0 x ULN **or** creatinine clearance must be ≥40 mL/min calculated using a standard Cockcroft-Gault formula (Cockroft & Gault, 1976; see Appendix A to the protocol)
7. For a female of childbearing potential (FCBP; for definition see Section 8.9), a negative pregnancy test must be confirmed before enrolment. An FCBP must commit to take highly effective contraceptive precautions (see Appendix B) without interruption during the study and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later. An FCBP

must refrain from breastfeeding and donating blood or oocytes during the course of the study and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later. Restrictions concerning blood donations apply as well to females who are not of childbearing potential. (**Applicable in Republic of Korea**: an FCBP must commit to take highly effective contraceptive precautions (see Appendix B) without interruption and refrain from breastfeeding and donating blood or oocytes during the course of the study and for 6 months after the last dose of MOR00208, 6 months after the last dose of BEN or 12 months after the last dose of RTX, whichever is later.).

8. Males must use an effective barrier method of contraception without interruption during the study and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later, if the patient is sexually active with an FCBP. Males must refrain from donating blood or sperm during study participation and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later. (**Applicable in Republic of Korea**: males must refrain from donating blood or sperm and, if the patient is sexually active with an FCBP, must use an effective barrier method of contraception without interruption during the study and for 6 months after the last dose of MOR00208, 6 months after the last dose of BEN or 12 months after the last dose of RTX, whichever is later).
9. In the opinion of the investigator, the patients must:
   a) be able to comply with all study-related procedures, medication use, and evaluations
   b) be able to understand and give informed consent
   c) not be considered to be potentially unreliable and/or not cooperative.

EXCLUSION CRITERIA:

Eligible patients must not have any of the following to be enrolled in the study:

Exclusionary Diagnosis Criteria

1. Patients who have:
   a) any other histological type of lymphoma including, e.g., primary mediastinal (thymic) large B-cell lymphoma (PMBL) or Burkitt's lymphoma
   b) primary refractory DLBCL (for definition, see Section 8.1)
   c) patients with known "double/triple hit" DLBCL genetics, characterised by simultaneous detection of *MYC* with *BCL2* and/or *BCL6* translocation, as defined by fluorescence *in situ* hybridisation (FISH). *MYC*, *BCL2*, *BCL6* testing prior to study enrolment is not required.
   d) central nervous system (CNS) lymphoma involvement in present or past medical history

	Exclusionary Previous and Current Treatment Criteria 2. Patients who had a major surgery (for definition, see Section 8.1) less than 30 days prior to Day 1 dosing 3. Patients who have, within 14 days prior to Day 1 dosing: a) not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma-specific therapy (for exceptions see Section 9.5.3) b) received live vaccines (for definition, see Section 8.6) c) required parenteral antimicrobial therapy for active, intercurrent systemic infections 4. Patients who: a) in the opinion of the investigator, have not recovered sufficiently from the adverse toxic effects of prior therapies, major surgeries (for definition, see Section 8.1) or significant traumatic injuries b) were previously treated with CD19-targeted therapy or BEN c) have a history of previous severe allergic reactions to compounds of similar biological or chemical composition to MOR00208, RTX, murine proteins or BEN, or the excipients contained in the study drug formulations d) have undergone ASCT within a period of ≤3 months prior to signing the informed consent form. Patients who have a more distant history of ASCT must exhibit full haematological recovery before enrolment into the study. e) have undergone previous allogeneic stem cell transplantation f) concurrently use other anticancer or experimental treatments (for exceptions see Section 9.5.3) **Exclusionary Medical History Criteria** 5. Prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥3 years prior to Screening. Exceptions to the ≥3-year time limit include history of the following: a) basal cell carcinoma of the skin b) squamous cell carcinoma of the skin c) carcinoma *in situ* of the cervix d) carcinoma *in situ* of the breast e) carcinoma *in situ* of the bladder f) incidental histological finding of prostate cancer (Tumour/Node/Metastasis [TNM] stage of T1a or T1b) 6. Patients with: a) positive hepatitis B and/or C serology (for definitions, see Section 8.6) b) known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV) c) evidence of active, severe uncontrolled systemic infections (e.g., tuberculosis, opportunistic infections) or sepsis d) a history or evidence of severely immunocompromised state e) a history or evidence of severe hepatic impairment (total serum bilirubin > 3 mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion 6c)

	f) a history or evidence of clinically significant cardiovascular, cerebrovascular, CNS and/or other disease that, in the investigator's opinion, would preclude participation in the study or compromise the patient's ability to give informed consent (for additional explanations, see Section 8.6).
Investigational Drug(s) (Name, Description)	MOR00208 (an Fc-enhanced, humanised, monoclonal antibody targeting the B-cell surface antigen CD19), Bendamustine (BEN: e.g. Levact®/ Treanda®) and Rituximab (RTX: e.g. MabThera®/Rituxan®).
Dose, Route of Administration, Treatment Regimen	Treatment with study drugs (MOR00208 with BEN or RTX with BEN) will be offered in 28-day cycles at specified time points at protocol-prescribed dose levels for a maximum of six cycles. Thereafter, patients with a response of at least PR at the end of Cycle 6, as per local disease response assessment, will continue antibody monotherapy treatment (MOR00208 or RTX) in accordance with their original treatment allocation until disease progression. Treatment may be stopped due to recurrence/disease progression, unacceptable toxicity, death or discontinuation for any other reason, whichever comes first. In the case of local confirmation of disease recurrence/progression, it is up to the investigator to decide according to the individual risk/benefit ratio if the patient should continue further antibody treatment (RTX or MOR00208) in accordance with the initial treatment allocation for up to 24 months in total (for details, see Section 9.1 of the protocol). **MOR00208 dose:** 12 mg/kg intravenously (IV) Cycle 1-3: MOR00208 will be administered on Day 1, Day 8, Day 15 and Day 22 of each cycle. Additionally, a loading dose will be administered on Day 4 of Cycle 1. Cycle 4-until disease progression: MOR00208 will be administered on Day 1 and Day 15 of each cycle. **RTX dose:** 375 mg/m^2 IV RTX will be administered on Day 1 of each cycle, with a pre-planned treatment interval of at least 28-days to the subsequent RTX administration. **BEN dose:** 90 mg/m^2 IV BEN will be administered on Days 2+3 of Cycle 1. BEN administration will be repeated on Days 1+2 or Days 2+3 of the subsequent cycles, with a pre-planned treatment interval of at least 28-days between the commencements of two succeeding cycles (for additional information see Section 9.1.3). BEN dose may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. In the case of early BEN discontinuation, the antibody treatment should continue unless contraindicated. Detailed guidance on how to manage haematological and/or other toxicities is provided in Section 9.4 of the protocol.

Supply, Preparation and Administration	**MOR00208 DP** (drug product) is a lyophilisate supplied in single-use 20 mL glass vials. Each vial contains 200 mg of MOR00208 for reconstitution with 5 mL water for injection (WFI). Reconstitution yields 40 mg/mL MOR00208 in 25 mM sodium citrate, 200 mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 200 mg of MOR00208 in 5 mL of reconstituted solution. MOR00208 will be diluted into a 250 mL infusion bag containing 0.9% (w/v) sodium chloride for injection. **BEN** will be available from commercial drug supplies (e.g. Levact®/ Treanda®). **RTX** will be available from commercial drug supplies (e.g. MabThera®/ Rituxan®).
Efficacy Assessments	The primary efficacy endpoint, PFS, will be evaluated centrally by the Independent Radiology/Clinical Review Committee (IRC) that will apply the Cheson criteria (Cheson et al. 2007). The review process will be defined in the IRC Charter. The secondary efficacy endpoints will include best ORR, DoR, OS, DCR, TTP and TTNT. Results of local disease response assessments as per Cheson criteria will also be available.
Safety Assessments	The safety and tolerability of study drug treatments will be evaluated by means of AE reports (frequency, incidence and severity), performance status, physical examinations, 12-lead resting electrocardiograms (ECGs), and laboratory safety evaluations. Laboratory and AE toxicities will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (or higher).
Pharmacokinetics	The PK profile of MOR00208 will be investigated during the course of the study.
Biomarker Assessments	Blood and tumour specimens for the analysis of exploratory biomarkers will be collected throughout the study and will be characterised for markers which are important in the mechanism of action of, or could predict response to, the study drugs. [redacted] are planned to be investigated during the course of the study.
Sample Size Estimation and Simulations	The primary objective of the study is to detect a statistically significant difference in PFS for the experimental treatment arm relative to the comparator arm in the overall study population (FAS) and in the NKCC-low subgroup (i.e., the study has two co-primary endpoints). Based on previously published data (Ohmachi et al. 2013, Vacirca et al. 2014), it is anticipated that the median PFS in the MOR00208 with BEN group will equal 7.0 months versus 4.9 months in the comparator standard treatment

	RTX with BEN group (hazard ratio [HR] of 0.70) in the overall population. A two-stage, group-sequential, adaptive design with one interim analysis will be applied using the O'Brien-Fleming approach and the inverse normal method for preserving the overall type I error rate (Wassmer 2006). A total number of 256 PFS events are required based on a HR of 0.70 with 80% power at final analysis for the FAS, using a two-sided log-rank test at 4.8% alpha level and a 1:1 randomisation ratio between the two treatment groups. To generate the required number of events, 286 evaluable patients would need to be enrolled, with assumed accrual duration of 18 months and a Follow-Up of 12 months. Applying a 13% drop-out rate would result in a total number of enrolled patients of approximately 330. An interim analysis is planned after the observation of 50% of the required events, i.e., after 128 PFS events. The HRs will be calculated and three outcomes will be possible based on the interim result: The study may be stopped due to futility, the study may continue with the minimum planned number of 330 patients (to obtain 256 PFS events), or the sample size may be increased to 450 patients (to obtain 369 PFS events). Early stopping for efficacy is not allowed. The sample size was increased to 450 patients based on the IDMC recommendation. The study includes a co-primary endpoint (PFS in the NKCC-low subgroup), following the emergence of data showing the importance of NKCC as a prognostic factor, and potentially a predictive factor for antibody efficacy in DLBCL. For confirmatory hypothesis testing, the p-values of the statistical tests for the primary and key secondary endpoint will be combined from stage I (information up to Interim Analysis) and stage II (information between interim analysis and final analysis) of the study using the inverse normal method for the overall population (FAS) and the NKCC-low subgroup. The family-wise error rate will be maintained at 4.8% by splitting the alpha between FAS and NKCC-low subgroup adequately.

2 TABLE OF CONTENTS

2.1 Overall Table of Contents

2.2 List of Tables

(Excluding those in the appendix)

2.3 List of Figures

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABC	Activated B-cell
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cell-mediated phagocytosis
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukaemia
ALT	Alanine transaminase
ANC	Absolute neutrophil count
anti-HBc	Hepatitis B virus core antibody
anti-HCV	Hepatitis C virus antibody
ASCT	Autologous stem-cell transplantation
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (class)
BCL2/6	B-cell CLL/lymphoma 2/6
BCR	B-cell antigen receptor
BEN	Bendamustine
bpm	Beats per minute (heart rate)
BSA	Body surface area
BSC	Best supportive care
C1D4	Cycle 1 Day 4
CDC	Complement dependent cytotoxicity
CD16/19/20	Cluster of differentiation 16/19/20
CHOP	Cyclophosphamide, hydroxydaunorubicin (also referred to as doxorubicin or adriamycin), oncovin (vincristine) and prednisone or prednisolone
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPH	Cox proportional hazards
CR	Complete response/remission
CRO	Contract research organisation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DA-EPOCH-R	Dose-adjusted EPOCH-R (etoposide, prednisone, oncovin [vincristine], cyclophosphamide and hydroxydaunorubicin [doxorubicin] plus rituximab)

DCR	Disease control rate
DHAP	Cisplatin, cytarabine, dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusion capacity of the lung for carbon monoxide
DNA	Deoxyribonucleic acid
DoR	Duration of response
DP	Drug product
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOT	End of treatment
EQ-5D-5L	EuroQol five dimensions quality of life questionnaire, 5 levels
ESHAP	Etoposide, methylprednisone, cytarabine, cisplatin
EudraCT	European Union Drug Regulating Authorities Clinical Trials register
FAS	Full analysis set
FCBP	Female of childbearing potential
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FEV-1	Forced expiratory volume in 1 second
FISH	Fluorescence *in situ* hybridisation
FL	Follicular lymphoma
FNA	Fine needle aspirate
FU	Follow-up
FVC	Forced vital capacity
GCB	Germinal centre B-cell
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
HBsAb	Hepatitis B virus surface antibody
HBsAg	Hepatitis B virus surface antigen

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDC	High-dose chemotherapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
IAS	Immunogenicity analysis set
IB	Investigator's Brochure
ICE	Ifosfamide, carboplatin, etoposide
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	Investigational New Drug application
INN	International Non-proprietary Name
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Radiology/Clinical Review Committee
IRR	Infusion-related reaction
IRT	Interactive response technology
IV	Intravenous(ly)
L	Limited (physical examination)
LDH	Lactate dehydrogenase
LEN	Lenalidomide
mAb	Monoclonal antibody
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MYC	v-myc avian myelocytomatosis viral oncogene homolog
NAb	Neutralising antibody
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NKCC	Natural killer cell count
NKCC-high	High baseline natural killer cell count
NKCC-low	Low baseline natural killer cell count
NOS	Not otherwise specified

NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	Objective response rate (complete response + partial response)
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PKAS	PK analysis set
PLT	Platelet
PMBL	Primary mediastinal large B-cell lymphoma
p.o.	*per os*, by mouth
PPS	Per-protocol set
PR	Partial response/remission
PR (ECG)	PR interval
QoL	Quality of life
QRS	QRS interval
QT	QT interval
QTc	Corrected QT interval
QTcB	Bazett's QT interval correction
QTcF	Fridericia's QT interval correction
R	Randomization
RBC	Red blood cell
R-CHOP	Rituximab plus cyclophosphamide, hydroxydaunorubicin (also referred to as doxorubicin or adriamycin), oncovin (vincristine) and prednisone or prednisolone
RNA	Ribonucleic acid
rpm	Respirations per minute (respiration rate)
RR (ECG)	Relative rate
R-R CLL	Relapsed or refractory chronic lymphocytic leukaemia
R-R DLBCL	Relapsed or refractory diffuse large B-cell lymphoma
R-R NHL	Relapsed or refractory non-Hodgkin lymphoma
RTX	Rituximab
SAE	Serious adverse event
SAF	Safety analysis set

SAP	Statistical Analysis Plan
SCID	Severe combined immunodeficiency
SD	Stable disease
SLL	Small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard operating procedure
SPD	Sum of the product of the diameters
SPM	Second primary malignancy
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
THRLBCL	T cell/histiocyte rich large B-cell lymphoma
TLS	Tumour lysis syndrome
TNM	Tumour/Node/Metastasis
TTP	Time to progression
TTNT	Time to next treatment
ULN	Upper limit of normal
US	United States
USAN	United States Adopted Name
VAS	Visual analogue scale
VIM	Etoposide, ifosfamide, methotrexate or mitoxantrone
WBC	White blood cell
WFI	Water for injection
WHO	World Health Organization
β-HCG	Beta-human chorionic gonadotropin

4 BACKGROUND

4.1 Overview of Non-Hodgkin Lymphomas

Non-Hodgkin lymphomas (NHLs) account for approximately 5% of all new cancer cases and comprise a heterogeneous group of lymphoproliferative malignancies, which in 90% of cases are derived from B-cells.

Diffuse large B-cell lymphoma (DLBCL), the most common NHL, accounts for approximately 30% of NHLs (Armitage and Weisenburger 1998, Swerdlow et al. 2008) and comprises 60% of all new lymphomas in the elderly (Thieblemont and Coiffier 2007). There is a slight predominance of the male gender (55%) (Morton et al. 2006). DLBCL incidence increases with age, with a median age at diagnosis of 64 years (Shenoy et al. 2011).

At present, DLBCL not otherwise specified (NOS) can be further subdivided into at least two molecular groups by gene expression profiling: germinal centre B-cell (GCB) and activated B-cell (ABC) subtypes (Rosenwald et al. 2002, Lenz et al. 2008).

4.2 Treatment of DLBCL

First-line treatment ensuing immediately after diagnosis and staging of DLBCL and comprising rituximab (RTX) combined with CHOP chemotherapy (R-CHOP: RTX plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is currently the standard of care (Coiffier et al. 2002, Feugier et al. 2005, Habermann et al. 2006). The R-CHOP regimen is a "platform" combination therapy, which may be modified in order to increase its therapeutic efficacy, e.g. DA-EPOCH-R (dose-adjusted etoposide, prednisone, oncovin, cyclo-phosphamide and hydroxydaunorubicin plus rituximab; Wilson et al. (2012). Nevertheless, even with the availability of R-CHOP-like treatment regimens, approximately 40–50% of patients will ultimately succumb to the disease, with 30–40% of patients relapsing and 10% having a diagnosis of primary progressive disease or being non-responders (Pfreundschuh et al. 2008, Pfreundschuh et al. 2011).

Patients progressing or relapsing after first-line treatment will be evaluated for their eligibility for intensified salvage treatment strategies which can lead to long-term remissions. Examples of such salvage chemotherapy include DHAP (cisplatin, cytarabine, dexamethasone), VIM (etoposide, ifosfamide, methotrexate or mitoxantrone), ICE (ifosfamide, carboplatin, etoposide) and ESHAP (etoposide, methylprednisone, cytarabine, cisplatin). For patients with chemotherapy-sensitive disease, autologous stem-cell transplantation (ASCT) as consolidation therapy significantly improves the outcome of second-line therapy. Approximately 10–50% of patients treated with an intensified regimen in second-line achieve a long-term remission and cure (Philip et al. 1995).

Unfortunately, only approximately 50% of patients with relapsed or refractory (R-R) DLBCL are eligible for an intensified treatment strategy, due mainly to cardiac comorbidities, decreased haematopoietic reserve, reduced hepatic function or advanced age, restricting the benefit of this aggressive approach to a relatively small subset of patients (Morrison et al. 2014). Similarly,

only younger and fit patients can be evaluated for allogeneic stem cell transplantation (Truelove et al. 2014).

Several treatment regimens have been described for patients that relapse after intensified second-line treatment or who are not eligible for an intensified second-line regimen. Despite recent advances, the treatment options for patients who have relapsed or progressed after second-line treatment of DLBCL, or who are not eligible for ASCT remain limited.

On 31 July 2020, the U.S. Food and Drug Administration (FDA) authorized tafasitamab-cxix (Monjuvi®) in combination with lenalidomide for marketing under the provision of accelerated approval for the treatment of adult patients with R/R DLBCL. Tafasitamab-cxix (Minjuvi®) has also been approved for marketing (conditional approval) in EU (26 August 2021), in UK (08 October 2021) and in Canada (19 August 2021) in combination with lenalidomide for the treatment of adult patients with R/R DLBCL.

Although RTX is widely used in the treatment of R-R DLBCL following RTX-based first-line therapy, clinical studies have demonstrated that patients who have received prior RTX are less likely to respond to RTX-containing salvage therapies (Martin et al. 2008, Gisselbrecht et al. 2010). Therefore, the development of more effective salvage therapy is essential to improve long-term outcomes.

Monoclonal antibody (mAb) therapy may have the potential to improve objective response rates (ORRs) and overall survival (OS) in this setting without increasing haematological toxicity. This possibility is supported by data from studies investigating CD19 mAbs, including MDX-1342, SAR3419 and MEDI-551 (Bargou et al. 2008, Viardot et al. 2011, Younes et al. 2012, Matlawska-Wasowska et al. 2013, Ribrag et al. 2014).

4.3 Bendamustine in DLBCL Treatment

Bendamustine (BEN) is a chemotherapeutic agent, synthesised as a hybrid of a purine analogue and an alkylator. It has been demonstrated *in vitro* that BEN is active in cell lines which are resistant to several other alkylating agents (Balfour and Goa 2001, Leoni et al. 2008). The mechanism of action of BEN is not fully elucidated but involves two separate metabolic pathways, one leading to deoxyribonucleic acid (DNA) damage, provoking apoptosis and another leading to the disruption of cell division. The latter mechanism is known as mitotic catastrophe. The dual effect may be attributable to the chemical structure of the BEN moiety, which comprises a 2-chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain (Leoni et al. 2008, Leoni 2011).

BEN is approved in several countries worldwide for the treatment of patients with relapsed refractory indolent lymphomas, chronic lymphocytic leukaemia (CLL) and in some countries, for multiple myeloma.

BEN was studied as monotherapy and in combination with other chemotherapeutic and/or biological agents (e.g. RTX) in R-R aggressive NHL, yielding ORRs from 32% to 62.7%, with median progression-free survival (PFS) times between 3.6 and 6.7 months. Similarly, the

combination of BEN and RTX used as first-line treatment in patients not eligible for intensive chemotherapy regimens achieved an ORR of 69%, including long-lasting complete remissions, and a median PFS of 7.7 months (Weidmann et al. 2002, Ogura et al. 2011, Horn et al. 2012, Rigacci et al. 2012, Walter et al. 2012, Ohmachi et al. 2013, Vacirca et al. 2014).
Therefore, it may be concluded that RTX with BEN compares favourably in terms of efficacy with other regimens for this difficult-to-treat patient population (Colosia et al. 2014). It is especially relevant given that the combination of RTX with BEN demonstrates a manageable toxicity profile and can therefore be used in elderly patients and/or patients with comorbidities. In the two largest and most recently published studies in R-R DLBCL, the combination of RTX with BEN evoked predominantly haematological toxicities including neutropenia, leukopenia, thrombocytopenia and anaemia. The myelosuppression was largely reversible. Common non-haematological adverse events (AEs) included gastrointestinal symptoms (e.g., diarrhoea, constipation, nausea), infections and fatigue (Ohmachi et al. 2013, Vacirca et al. 2014).

Due to its favourable efficacy and advantageous toxicity profile the combination of RTX with BEN became a standard of care for the treatment of patients with DLBCL over recent years.

4.4 Overview of natural killer (NK) cells in lymphoma, relevance to MOR00208

Several published studies have evaluated clinical outcomes in relation to high or low baseline NKCC in first-line patients, e.g., patients newly diagnosed with DLBCL (Kim et al. 2014, Klanova et al. 2017) or previously untreated patients with follicular lymphoma (FL) (He et al. 2016, Klanova et al. 2017).

In the MOR208C201 study a cut-off 100 NK cells/µL was prognostic for the treatment outcome of MOR00208 monotherapy in DLBCL and FL, while other blood cell populations such as lymphocytes and T cells showed no association with the treatment outcome. Even though a multivariate analysis was not conducted due to the small sample size, a stratified analysis did not reveal any obvious confounding of the NKCC subgroups with any other key baseline characteristics. Therefore, NKCC potentially is an independent factor for the treatment outcome of MOR00208.

Similar to the observation for MOR00208, the majority of the published studies for anti-CD20 antibodies also reported a NKCC cut-off of 100 cells/µL, which showed independent prognostic value. The cut-off was generally based on maximized differences in PFS and/or OS between patients with baseline NKCC-low and NKCC-high included in the respective studies (Kim et al. 2014, He et al. 2016, Klanova et al. 2017).

In two large phase III trials in patients with NHL – the GOYA trial (NCT01287741) in patients with newly diagnosed DLBCL and the GALLIUM trial (NCT01332968) in patients with previously untreated FL – the prognostic cut-off of 100 NK cells/µL was also useful to predict superiority of an Fc-enhanced anti-CD20 monoclonal antibody (obinutuzumab) versus a non-enhanced anti CD20 monoclonal antibody (RTX). This demonstrates that a NKCC cut-off

identified via the prognostic effect can be also useful to predict superiority of one monoclonal antibody over another.

The sponsor conducted pre-clinical experiments to investigate the in vitro ADCC activity of the Fc-enhanced CD19-specific antibody MOR00208 in comparison to the CD20-specific antibody rituximab for a range of effector to target (E:T) ratios of NK cells and B-cell tumour cell lines derived from DLBCL, mantle cell lymphoma (MCL) and chronic lymphocytic leukaemia (CLL).

The results of these in vitro experiments suggest that MOR00208 leads to stronger ADCC--mediated target cell lysis in comparison to RTX under conditions in which NK cells are limited. Based on the assumption that in patients with low baseline NKCC, NK cell numbers at the tumour site will not out-number the number of tumour cells, these data support the hypothesis that MOR00208 could have higher tumour killing capacity compared to rituximab in patients with a peripheral NK cell count of 100 or less NK cells/µL.

4.5 Overview of CD19 expression in DLBCL and treatment with MOR00208

4.5.1 The B-cell Differentiation Antigen CD19 in Lymphoma

The differentiation antigen CD19 is a 556-amino acid, type I transmembrane cell-surface protein with an important role in both normal and malignant B-cell physiology. CD19 belongs to the immunoglobulin (Ig) superfamily and is the dominant signal transducing member of the B-cell antigen receptor (BCR) co-receptor complex, which also includes complement receptor, CD21, the tetraspanin family protein, CD81, and the interferon-induced transmembrane protein, CD225 (Carter et al. 2002).

CD19 is expressed early in B-cell development at the late pro-B or early pre-B stage, just before the Ig heavy chain gene rearrangement, and is present throughout B-cell maturation until terminal differentiation into plasma cells (Anderson et al. 1984). As a low-affinity antigen receptor, CD19 functions to decrease the antigen concentration threshold necessary to trigger B-cell division and differentiation. Patients with a homozygous mutation in the CD19 gene (*CD19*) exhibit decreased B-cell activation in response to mitogen stimulation and are hypogammaglobulinaemic, with normal numbers of bone marrow and circulating B -lymphocytes (van Zelm et al. 2006). CD19 regulates B-cell proliferation and development through BCR-dependent and independent mechanisms (Leslie and Younes 2013). There are emerging data that suggest that CD19 plays a BCR-independent role in malignant B-cell proliferation by stabilising concentrations of the MYC oncoprotein (Poe et al. 2012). Importantly, CD19 expression is maintained in lymphomas which show a down-regulation of CD20 expression following anti-CD20 therapy (Chu et al. 2002).

4.5.2 MOR00208 Background and Preclinical Data

MOR00208 (synonyms: XmAb®5574, MOR208) is an Fc-enhanced mAb that binds to the human B-cell surface antigen CD19. MOR00208 possesses significantly increased tumour cytotoxicity when compared with the parental, non-enhanced, murine 4G7 CD19 antibody. The increased binding of MOR00208 to Fc gamma receptors (FcγR), due to the engineered

mutations, significantly enhances *in vitro* antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP), and direct cytotoxic effects (apoptosis) on the tumour cells compared with the non-enhanced parental murine antibody. MOR00208 has not been shown to mediate complement-dependent cytotoxicity (CDC).

More specifically, in preclinical studies, MOR00208 has been shown to significantly enhance *in vitro* ADCC, ADCP, and direct cytotoxic effects (apoptosis) on CD19+ tumour cell lines spanning a broad range of human lymphomas and leukaemias (Burkitt's lymphoma, CLL, hairy cell leukaemia, CD19+ chronic myeloid leukaemia, DLBCL, and acute lymphoblastic leukaemia [ALL]) expressing levels of CD19 antigen ranging from 15,000 to 105,000 molecules/cell. Similar effects were also noted in relation to freshly isolated patient CLL or ALL cells and are also expected to translate to primary NHL cells, since the expression range reported for ALL and CLL B-cells covers the range observed for NHL B-cells (Ginaldi et al. 1998, Olejniczak et al. 2006). MOR00208 has also shown superior efficacy to its non-enhanced parental antibody in relation to its ability to induce a marked reduction in tumour growth, inhibit tumour growth rate and increase survival *in vivo* in xenograft models of human lymphoma in severe combined immunodeficiency (SCID) mice. (See relevant sections of Investigator's Brochure [IB].)

The pharmacodynamic (PD) interactions of MOR00208 in combination with fludarabine, BEN, and lenalidomide (LEN) used in the treatment of patients with CLL and NHL, were investigated in a human intravenous (IV) lymphoma model in SCID mice (see relevant sections of IB). In this orthotopic model for disseminated B-cell malignancies, the median survival was superior for all of the groups receiving MOR00208 combination therapy (with fludarabine, BEN or LEN) when compared with the groups receiving MOR00208 monotherapy. More specifically, MOR00208 (3.0 mg/kg) in combination with BEN (13.0, 16.0 mg/kg) was superior to either therapy alone in terms of increased median lifespan (26% versus 57%). The effect was classified as potentiation of the efficacy of MOR00208, as MOR00208 was the only drug amongst the combination partners tested that demonstrated a significant effect on survival as a single agent.

Tissue cross-reactivity studies have shown that the pattern and distribution of MOR00208 binding to cynomolgus monkey tissues closely parallels those of human tissues. Flow cytometry experiments show MOR00208 binding to human and cynomolgus monkey B-cells, but not to the B-cells of other common laboratory species (such as rat, mouse, rabbit and dog). Therefore, pharmacology studies were restricted to human and cynomolgus monkey cell-based *in vitro* systems, CD19+ human B-cell tumour xenograft models in SCID mice, and cynomolgus monkeys *in vivo*. In *in vivo* studies in cynomolgus monkeys, MOR00208 was shown to induce B-lymphocyte depletion in peripheral blood, bone marrow, spleen and inguinal lymph nodes. Cynomolgus monkeys were also judged to be the only relevant common laboratory species for toxicity studies.

The results of studies evaluating the pharmacokinetics (PK), PD and toxicity of MOR00208 in cynomolgus monkeys, are provided in the relevant sections of the IB. The findings in five preclinical studies were limited to the expected pharmacological effects of MOR00208, with no reports of unanticipated toxicity. The five studies, all conducted in cynomolgus monkeys included: a 26-week single 10.0 mg/kg dose, PK, PD and toxicity study; a 28-day single IV dose, dose-ranging (0.3, 1.0 and 3.0 mg/kg) PK/PD study; a 29-day, single-dose (3.0 mg/kg) study

comparing MOR00208 with two other CD19 antibodies with different Fc regions; an 8-week toxicity study in which MOR00208 was administered IV every 2 weeks at a dose of 2, 10 or 50 mg/kg for 8 consecutive weeks with a 90-day recovery period; and a 13-week toxicity study in which MOR00208 was administered IV weekly to sexually mature cynomolgus monkeys at doses of 10, 30 or 100 mg/kg for 13 consecutive weeks with a 132-day recovery period. The aim of the latter Good Laboratory Practice (GLP)-compliant, multiple-dose toxicology studies was to support the use of MOR00208 in human clinical studies. As an expected pharmacological effect, a reversible lack of germinal centres in lymphoid organs and markedly reduced peripheral CD20+ B cell counts were observed, which were consistent with lowered IgG levels in serum as well as a reversible reduction in the T-cell dependent antibody response. There were no MOR00208-related effects on body weight, clinical signs, food consumption, blood pressure, electrocardiography, respiratory rate, ophthalmology, neurobehavioural observations, haematology, coagulation, urine or cytokine analysis. MOR00208 had no effects on menstrual cycle length in females and no histopathology/microscopic changes to male and female reproductive organs. Overall, MOR00208 administration to the cynomolgus monkey was very well tolerated at doses up to 100 mg/kg. In addition, GLP-compliant tissue cross-reactivity studies were performed on normal tissue panels from human and cynomolgus monkey donors. No specific staining to structures other than the expected mononuclear leukocytes, lymphocytes and haematopoietic precursor cells was observed.

4.5.3 Clinical Experience with MOR00208

4.5.3.1 Protocol XmAb5574-01

A Phase 1 Study of XmAb®5574 to Evaluate the Safety, Tolerability, and Pharmacokinetics in Patients with Relapsed or Refractory Chronic Lymphocytic Leukaemia

The first study in humans was a phase I trial exploring the use of MOR00208 (also known as XmAb®5574 or MOR00208) in adult patients diagnosed according to International Workshop on CLL guidelines (Hallek et al. 2008) with active, treatment-requiring R-R CLL/small lymphocytic lymphoma (SLL). Results of the study were reported by (Woyach et al. 2014).

Twenty-seven patients were enrolled to 6 escalating dose levels, with expansion at the highest dose level of 12 mg/kg. Nine doses of MOR00208 were infused over 8 weeks. No maximal tolerated dose was reached, and the drug was generally well tolerated, with infusion-related reactions (IRRs) of grade 1 or 2 being the most common toxicities. Treatment-related grade 3 or 4 AEs occurred in five patients and included neutropenia, thrombocytopenia, increased aspartate aminotransferase (AST), febrile neutropenia, and tumour lysis syndrome (TLS). MOR00208 showed preliminary efficacy, with 18 patients (66.7%) responding by physical examination criteria and laboratory studies, and 8 patients (29.6%) responding by computed tomography (CT) criteria. MOR00208 showed a terminal elimination half-life of approximately 14 days. A dose of 12 mg/kg was recommended for use in subsequent studies.

4.5.3.2 Ongoing Studies

The following other studies are ongoing. Details of safety and efficacy data are reported in the IB:

Protocol MOR208C201
A Phase IIa, Open-Label, Multicenter Study of Single-Agent MOR00208, an Fc-Optimised Anti-CD19 Antibody, in Patients with Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma

Protocol MOR208C203 (L-MIND)
A Phase II, Single-Arm, Open-Label, Multicentre Study to Evaluate Safety and Efficacy of Lenalidomide Combined with MOR00208 in Patients with Relapsed or Refractory (R-R) Diffuse Large B-Cell Lymphoma

Protocol MOR208C205 (COSMOS)
A Phase II, Two-Cohort, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of MOR00208 Combined with Idelalisib or Venetoclax in Patients with Relapsed or Refractory CLL/SLL Previously Treated with Bruton's Tyrosine Kinase Inhibitor

Protocol MOR208C107 (First-MIND)
A Phase Ib, open-label, randomized study to assess safety and preliminary efficacy of Tafasitamab in addition to R-CHOP or Tafasitamab plus Lenalidomide in addition to R-CHOP in patients with newly diagnosed Diffuse Large B-Cell Lymphoma (DLBCL)

Protocol MOR208C310 (FrontMIND)
A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of tafasitamab plus lenalidomide in addition to R-CHOP versus R-CHOP in previously untreated, high-intermediate and high-risk patients with newly diagnosed diffuse large B-cell lymphoma

Protocol MOR208C414 (REALMIND)
A Phase IV, multicenter, observational study that will collect data on treatments and outcomes for patients in the US with relapsed or refractory diffuse large B-cell lymphoma who are starting second- or third-line therapy and are not receiving autologous stem cell transplant.

Protocol MOR208C115 (MINDway)
A Phase 1b/2, Open-Label, Multicenter Study to Evaluate the Safety and Pharmacokinetics of a Modified Tafasitamab IV Dosing Regimen Combined with Lenalidomide (LEN) in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Protocol INCMOR0208-101 (topMIND)
A Phase 1b/2a basket study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of combination therapy with the anti-CD19 monoclonal antibody tafasitamab and the PI3Kd

inhibitor parsaclisib in adult participants with relapsed/refractory (R/R) non-Hodgkin lymphoma or chronic lymphocytic leukemia

Protocol INCMOR0208-102 (J-MIND)
A Phase 1b Study of tafasitamab, tafasitamab plus lenalidomide, tafasitamab plus parsaclisib, and tafasitamab plus lenalidomide in combination with R-CHOP in Japanese participants with non-Hodgkin lymphoma.

Protocol INCMOR0208-301 (inMIND)
A Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of tafasitamab plus lenalidomide in addition to rituximab versus lenalidomide in addition to rituximab in patients with relapsed/refractory (R/R) follicular lymphoma grade 1 to 3a or R/R marginal zone lymphoma

Protocol MOR00208 IIT OSU-13031
Phase II Study of Tafasitamab in Combination with Lenalidomide for Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)/Prolymphocytic Leukemia (PLL), Including those who have Relapsed on Ibrutinib, or Patients with Untreated CLL/SLL/PLL

Protocol IIR_INT_DE_Hess_GOALII
A prospective, multicenter randomized phase II trial investigating Gemcitabine/Oxaliplatin/Rituximab with or without Tafasitamab (MOR208) for patients with relapsed/refractory Aggressive Lymphoma (GOAL II)

4.5.4 Safety of MOR00208

MOR00208 offers a novel mechanism of action that may add to the care of patients with NHL. Based on the available data from the completed clinical studies of MOR00208 (Protocol XmAb®5574-01 and MOR208C202), preliminary data from the ongoing clinical studies MOR208C201 (Jurczak et al. 2018), MOR208C203, MOR208C204 and MOR208C205, nonclinical studies and experiments, and literature data on CD19, the sponsor is of the opinion that the potential benefit of MOR00208 outweighs the potential risks. It is expected that the potential risks will be adequately controlled by the design of this trial (e.g. by the inclusion and exclusion criteria) and by frequent monitoring of potential adverse drug reactions throughout the entire study.

Based on the safety data from the clinical studies listed above the anticipated possible risks associated with MOR00208 monotherapy include the following AEs with a suspected relationship to MOR00208 treatment (incidence ≥ 3 %):

- IRRs (mostly Grade 1/2)
- Febrile neutropenia
- Neutropenia
- Thrombocytopenia
- Tumour lysis syndrome

- Upper respiratory tract infections
- Lower respiratory tract infection (including pneumonia and bronchitis)
- Fatigue
- Chills
- Pyrexia
- Nausea
- Diarrhoea
- Headache
- Rash
- AST and ALT increases.

Since a major pharmacological effect of MOR00208 is B-cell depletion, the risks associated with the use of approved B-cell depleting therapeutics based on the labelling of other agents with similar effects should be considered. These may include: B-cell depletion, lymphopenia, neutropenia, hepatitis B reactivation, progressive multifocal leukoencephalopathy, mucocutaneous reactions and infections.

The anticipated risks associated with the administration of MOR00208 are described in detail in the MOR00208 IB.

5 STUDY PURPOSE/RATIONALE

Despite recent improvements in the management of DLBCL, approximately 30–40% of patients with DLBCL treated with R-CHOP relapse following initial immunochemotherapy (Coiffier et al. 2002, Feugier et al. 2005, Sehn et al. 2005, Habermann et al. 2006, Pfreundschuh et al. 2006, Pfreundschuh et al. 2011). Although a significant number of patients can be salvaged with high-dose chemotherapy (HDC) and subsequent ASCT, the majority will succumb to the disease. In particular, elderly and/or frail patients and those with multiple comorbidities are in need of novel therapeutic approaches as the intensified treatment regimens cannot be used in this population. Improving the therapeutic options for this group of patients is an important unmet medical need.

As RTX-based regimens have become standard first-line treatment in DLBCL, the efficacy of RTX combined with chemotherapy in the second-line setting has decreased and there is a need for new therapies in patients progressing or relapsing after first- or second-line RTX-based treatment. The CD19 antigen is an attractive target in DLBCL as CD19 is typically expressed in DLBCL cells, has a signalling function that contributes to the malignant phenotype and is not down-regulated in patients pre-treated with CD20-targeted agents. Thus, it might be possible to overcome the absolute or relative RTX resistance in R-R NHL by using MOR00208 instead of RTX and thereby to improve clinical outcome in the R-R NHL patient population.

The effects of MOR00208 appear to involve ADCC, ADCP, and direct cytotoxic activity (apoptosis). MOR00208 and BEN are active as single agents and in combination show synergistic antileukaemic and antilymphoma activity *in vivo* and *in vitro*.

MOR00208 demonstrated single-agent activity in R-R CLL/SLL, DLBCL, follicular lymphoma and other indolent NHLs (Woyach et al. 2014, Jurczak et al. 2015, Jurczak et al. 2016). MOR00208 elicits only mild haematological AEs and has a manageable toxicity profile. The predominant AEs are IRRs, a class effect of many therapeutic antibodies, which typically occur during the first to third application. Overall, MOR00208 is therefore considered to be a good candidate for combination with established treatments, such as BEN, in DLBCL.

BEN has one of the highest anti-lymphoma activities of single agents used to treat R-R DLBCL and is well tolerated in patients with DLBCL with a manageable, mainly haematological toxicity profile (Ohmachi et al. 2013, Colosia et al. 2014, Vacirca et al. 2014). As a result, the current open-label, randomised study was developed to evaluate the efficacy and safety of MOR00208 with BEN versus RTX with BEN in adult patients with R-R DLBCL. The main goal of this study is to offer such patients a novel treatment option taking into consideration that many patients are frail, of advanced age and/or have multiple comorbidities.

An International Consensus Panel has recommended that BEN should be administered at a dose of 90 mg/m^2, when combined with RTX in the treatment of aggressive NHL (Cheson et al. 2010, Cheson et al. 2016). The published studies indicated a consistent, manageable and comparable (between studies) toxicity profile for patients with DLBCL. Walter et al. (2012) have investigated BEN dose ranges from 60 through 120 mg/m^2 and came to the conclusion that 90 mg/m^2 is the maximum dose that can be achieved in the majority of patients. Several studies have confirmed that RTX with BEN 90 mg/m^2 is a highly active combination therapy and an AE profile comparison between the 120 mg/m^2 and 90 mg/m^2 dose levels clearly favoured the 90 mg/m^2 dose. Therefore, the combinations of RTX or MOR00208 with BEN (at 90 mg/m^2) were selected as the most appropriate comparator and experimental regimens for this study.

Since MOR00208 has not been previously studied in combination with BEN systematically in a clinical trial, an Initial Safety Evaluation will precede the main recruitment in this clinical trial. Accumulating data (as described in Section 4.4) after the study was initiated indicate that NKCC is an important prognostic factor in DLBCL and may also affect the anti-tumour activity of monoclonal antibodies directed at CD20 and/or CD19 differentially. Accordingly, the protocol was amended to enable the efficacy of MOR00208 plus BEN to be compared with the efficacy of RTX plus BEN in the NKCC-low subgroup of patients (defined at baseline), as well as in the overall population.

6 OBJECTIVES

6.1 Primary Objectives

To determine the efficacy of a combination of MOR00208 with BEN versus a combination of RTX with BEN in terms of PFS in:

- Adult patients with R-R DLBCL (overall population)
- A subgroup of adult patients with R-R DLBCL with low baseline peripheral blood NK -cell count (NKCC-low), defined as 100 or less NK cells per µl blood at baseline.

6.2 Secondary Objectives

Secondary objectives will be assessed for the overall population, and NKCC-low subgroup, as appropriate.

1. To determine and compare both study arms, MOR00208 with BEN versus RTX with BEN, in terms of:
   a) best objective response rate (ORR = complete response [CR] + partial response [PR]) based on the best response achieved at any time during the study
   b) duration of response (DoR)
   c) overall survival (OS)
   d) disease control rate (DCR = CR + PR + stable disease [SD])
   e) time to progression (TTP)
   f) time to next treatment (TTNT)
   g) safety, based on the frequency, incidence and severity of AEs
   h) quality of life (QoL), using the EORTC QLQ-C30 and EQ-5D-5L questionnaires
2. To assess the potential immunogenicity of MOR00208 (anti-MOR00208 antibody formation)
3. To assess the PK profile of MOR00208.

6.3 Exploratory Objectives

[redacted]

7 STUDY ENDPOINTS

7.1 Co-Primary Endpoints

1. PFS in the overall study population (FAS)
2. PFS in the NKCC-low subgroup

7.2 Secondary Endpoints

3. Best ORR, DoR, OS, DCR, TTP and TTNT
4. Frequency, incidence and severity of AEs
5. QoL
6. Anti-MOR00208 antibody formation
7. PK of MOR00208
8. [redacted]

The secondary endpoints will be analysed in the overall population (FAS) and NKCC-low subgroup.

8 INVESTIGATIONAL PLAN

8.1 Protocol-Specific Definitions

Relapsed/progressive/recurrent disease reflects the appearance of any new lesions or increase by ≥50% of previously involved sites from nadir according to the International Working Group response criteria (Cheson et al. 2007) after achieving at least a partial response to the most recent systemic therapy.

Disease refractory to last treatment is defined as having had less than a partial response to the most recently administered systemic therapy

Primary refractory disease is a disease

1) progressing in the course of the first line treatment as per International Working Group response criteria (Cheson et al. 2007)
2) showing a response of less than PR to first line treatment; or disease progression-within ≤ 6 months from the completion of first line therapy

For the purpose of the protocol-specific definition of **"primary refractory disease", "first line treatment"** is defined as an anti-CD-20 agent containing, standard anthracycline- or anthracenedione-based chemotherapy regimen. First line treatment refers specifically to DLBCL treatment.

Primary refractory DLBCL patients with radiologically confirmed responses to the second or, third line(s) of systemic therapy may be considered for study participation.

For the purpose of the protocol, **major surgery** is defined as any surgical procedure that involves in its course general anaesthesia or respiratory assistance. Intravascular access procedures e.g. central line placement or subcutaneous port placement, are not considered major surgery.

8.2 Study Design

This is a randomised, two-arm, multicentre, open-label, phase II/III efficacy and safety study of MOR00208 in combination with BEN versus RTX in combination with BEN. The study will enrol adult patients with DLBCL who have relapsed after, or are refractory to, at least one but no more than three prior systemic therapy lines (for further details see Section 8.6 and 9.5) and have failed or are not candidates for HDC and ASCT, and have thus exhausted their therapeutic options of demonstrated clinical benefit. At least one prior therapy line must have included a CD20-targeted therapy (e.g. RTX).

Patients with primary refractory DLBCL (for definition, see Section 8.1), patients with known "double/triple hit" DLBCL genetics or who have undergone previous allogeneic stem cell transplantation are not eligible for study participation. Additionally, patients with a history of ASCT within a period ≤3 months prior to signing the informed consent form (ICF) cannot be included in the study.

The combination of MOR00208 and BEN will be systematically evaluated for the first time in a clinical trial. Therefore, the trial includes an Initial Safety Evaluation, which will enable the Independent Data Monitoring Committee (IDMC) to conclude whether the combination treatment(s) are safe (see Figure 1). Further details are provided in Section 14.1 and the IDMC Charter.

The MOR208C204 trial will employ a parallel-group design, whereby patients will be randomly assigned to the two parallel treatment groups in a ratio of 1:1 (see Figure 2). The study will be performed according to a group-sequential, adaptive design with possible sample size adjustment after one planned interim analysis. The interim analysis will be carried out when 128 PFS events (50% of the planned 256 events) have been observed. If the study is continued until completion and no adaptation is made at interim analysis, the sample size will be approximately 330 patients.

In November 2019, the IDMC recommended to increase the sample size to 450 patients.

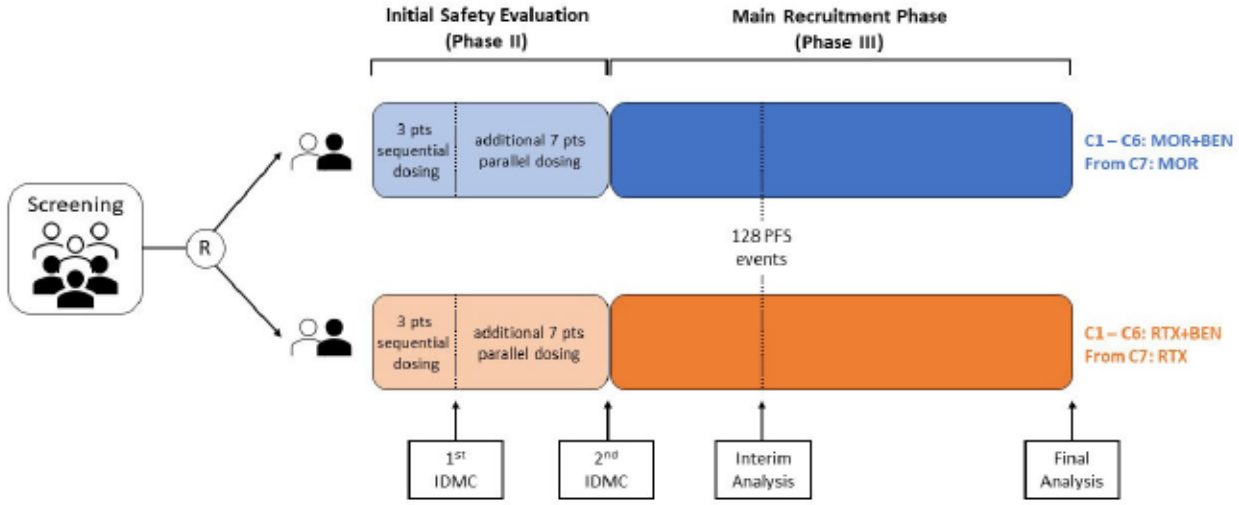


Figure 1: Recruitment and Study Flow

After screening, eligible patients will be randomized into one of two study arms. Patients will either receive MOR00208 + Bendamustine or Rituximab + Bendamustine from cycle 1 to cycle 6. From cycle 7 onwards, they may receive MOR00208 or Rituximab only.
During the initial safety evaluation phase of the trial the first 3 patients in both arms will be dosed sequentially with a 48-hour lag period between the enrolments of 2 consecutive patients (counted from C1D4). Following a positive recommendation of the IDMC, seven additional patients in each arm may be dosed in parallel. An additional IDMC review will take place after the last of 10 patients in each arm have completed C3D1 visit in their respective treatment allocation arm. Should the IDMC maintain their initial recommendation that the combination treatments are safe, the trial may proceed further with recruitment (Phase III part of the trial).
An interim analysis will be performed after 128 PFS events have been observed. The final sample size was adjusted after the interim analysis to N=450. The final analysis including but not limited to primary and secondary end point analyses will be conducted at the end of the trial.
Abbreviations: BEN = bendamustine; C = Cycle ; IDMC = Independent Data Monitoring Committee; MOR = MOR00208; R = randomisation (1:1); RTX = rituximab.

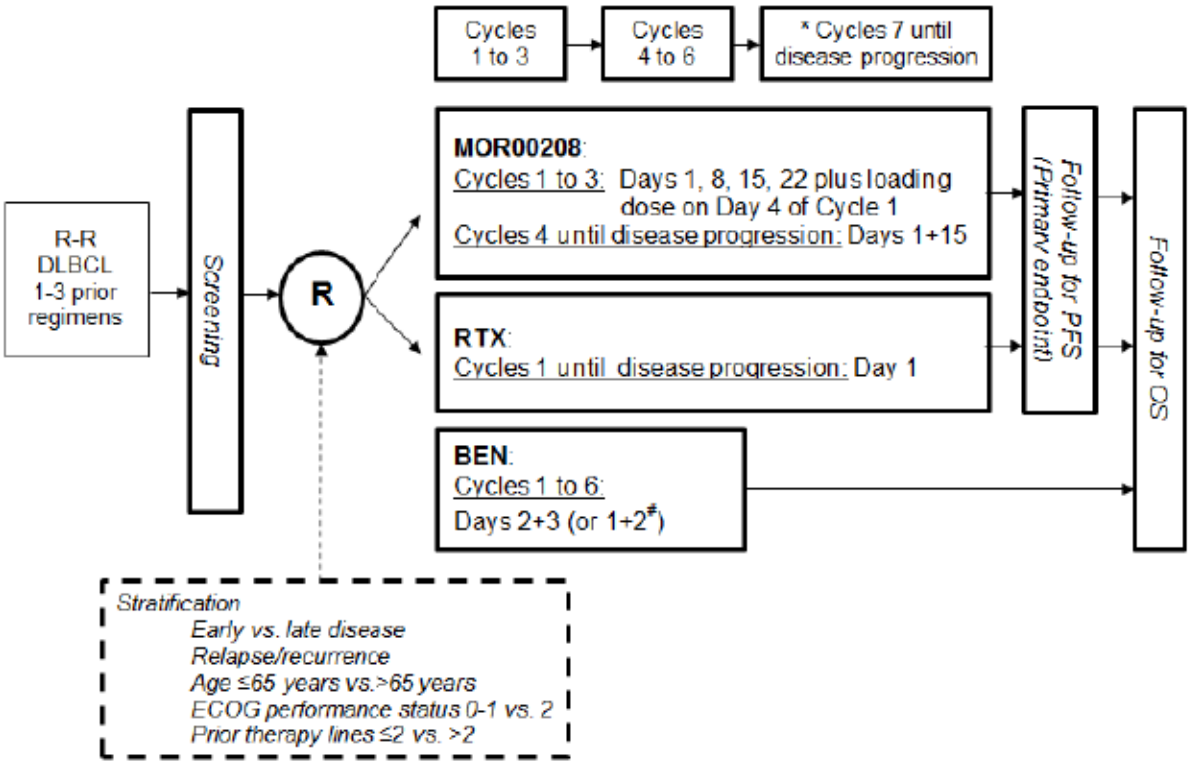


Figure 2: Study Design

*Subsequent to the completion of Combination Treatment, patients with an ongoing response of at least PR at the end of Cycle 6, as assessed locally, will continue antibody monotherapy treatment until disease progression in accordance with the initial treatment allocation (RTX or MOR00208).
#BEN is to be administered on Days 2+3 of Cycle 1. Subsequently, BEN can be administered on Days 1+2 or Days 2+3 according to institutional/patient/physician choice.
Note: Stratification will not be applied to patients randomised during Initial Safety Evaluation (see Figure 1).
Abbreviations: BEN = bendamustine; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PFS = progression-free survival; R-R DLBCL = relapsed or refractory diffuse large B-cell lymphoma; R = randomisation (1:1); RTX = rituximab.

8.3 Study Conduct

The trial will be conducted at approximately 180 sites worldwide.

The total study duration is expected to be approximately 4 years plus Follow-Up (assuming no sample size adjustment by the IDMC). The study duration for an individual patient includes Screening (up to 28 days from the signing of the ICF), Combination Treatment (maximum 6 months) followed by Antibody Monotherapy Treatment (until disease progression). After study treatment ends, each patient enters Follow-Up of an individually varying duration.

Follow-Up begins with the End of Treatment (EOT) visit. Patients will also have an on-site 30-day post-treatment safety evaluation visit (30-Day Safety Follow-Up visit). Follow-Up for the primary study endpoint, i.e. PFS, should be performed every 3 months until disease progression, withdrawal of consent or death, whichever comes first. After confirmed progression, patients should be followed up for OS.

Follow-Up for OS will be performed every 3 months from the date of EOT or the last Follow-Up Visit for the primary study endpoint (i.e. PFS), as applicable. The first Follow-Up for OS will be a clinic visit. Subsequent Follow-Up for OS visits may be phone contacts. For Follow-up of a patient who becomes eligible for "Further or Continued Antibody Treatment," please refer to Section 10.5.

8.4 End of Study

The end of the study is defined as 3 years after the last patient was randomized or after approximately 75% of patients have died, whichever occurs first. Upon study closure, the sponsor will notify the applicable regulatory agencies in accordance with local requirements.

8.5 Patient Selection Criteria

8.5.1 Inclusion Criteria

Eligible patients must meet the following criteria to be enrolled in the study:

Diagnosis/Trial Population

1. Age ≥18 years
    - For Singapore only: age ≥21 years
2. Histologically confirmed diagnosis, according to the World Health Organization (WHO, 2008) classification, of:
    a) Diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS)
    b) T cell/histiocyte rich large B-cell lymphoma (THRLBCL)
    c) Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL)
    d) Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse
    e) Disease transformed from an earlier diagnosis of low-grade lymphoma (i.e. an indolent pathology such as follicular lymphoma, marginal zone lymphoma) into DLBCL with a DLBCL relapse subsequent to DLBCL treatment.

3. Fresh tumour tissue for central pathology review must be provided as an adjunct to participation in this study. Should it not be possible to obtain a fresh tumour tissue sample, archival paraffin embedded tumour tissue acquired ≤3 years prior to screening for this protocol must be available for this purpose.
4. Patients must have:
   a) R-R DLBCL (for definitions, see Section 8.1 of the protocol)
   b) at least one bidimensionally measurable disease site. The lesion must have a greatest transverse diameter of ≥1.5 cm and greatest perpendicular diameter of ≥1.0 cm at baseline. The lesion must be positive on PET scan (for definition, see Juweid et al. (2007)).
   c) received at least one, but no more than three previous systemic therapy lines for the treatment of DLBCL (for further details see Sections 8.6 and 9.5). At least one previous therapy line must have included a CD20-targeted therapy (e.g. RTX).
   d) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
5. Patients after failure of ASCT or patients considered in the opinion of the investigator currently not eligible for HDC with subsequent ASCT. Documentation of the reason for ineligibility for ASCT must be present in the patient's source data (for details, see Section 8.6).

Laboratory Values

6. Patients must meet the following laboratory criteria at Screening:
   a) absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow aspiration and bone marrow biopsy required for Screening)
   b) platelet count $\geq 90 \times 10^9$/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by bone marrow aspiration and bone marrow biopsy required for Screening) and absence of active bleeding
   c) total serum bilirubin ≤2.5 × upper limit of normal (ULN) unless secondary to Gilbert's syndrome (or pattern consistent with Gilbert's) or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or documented liver involvement by lymphoma may be included if their total bilirubin is ≤5 x ULN (see exclusion criterion 6e)
   d) ALT, AST and alkaline phosphatase ≤3 × ULN or <5 × ULN in cases of documented liver involvement by lymphoma
   e) serum creatinine ≤ 2.0 ULN or creatinine clearance must be ≥40 mL/min, calculated using a standard Cockcroft-Gault formula (Cockroft & Gault, 1976; see Appendix A)
7. For a female of childbearing potential (FCBP; for definition see Section 8.9), a negative pregnancy test must be confirmed before enrolment. An FCBP must commit to take highly effective contraceptive precautions (see Appendix B) without interruption during the study and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later. An FCBP must refrain from breastfeeding and donating blood or oocytes during the course of the study and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later. (**Applicable in Republic of Korea**: an FCBP must commit to take highly effective contraceptive precautions (see Appendix B) without interruption and refrain from breastfeeding and donating blood or oocytes during the course

of the study and for 6 months after the last dose of MOR00208, 6 months after the last dose of BEN or 12 months after the last dose of RTX, whichever is later.).

8. Male patients must use an effective barrier method of contraception without interruption during the study and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later, if the patient is sexually active with an FCBP. Males must refrain from donating blood or sperm during the study participation and for 3, 6 or 12 months after the last dose of MOR00208, BEN or RTX respectively, whichever is later. (**Applicable in Republic of Korea**: males must refrain from donating blood or sperm, and if the patient is sexually active with a FCBP, must use an effective barrier method of contraception without interruption during the study and for 6 months after the last dose of MOR00208, 6 months after the last dose of BEN or 12 months after the last dose of RTX, whichever is later).
9. In the opinion of the investigator, the patients must:
   a) be able to comply with all study-related procedures, medication use, and evaluations
   b) be able to understand and give informed consent
   c) not be considered to be potentially unreliable and/or not cooperative.

8.5.2 Exclusion Criteria

Eligible patients must not have any of the following to be enrolled in the study:

Exclusionary Diagnosis Criteria

1. Patients who have:
   a) any other histological type of lymphoma including, e.g., primary mediastinal (thymic) large B-cell (PMBL) or Burkitt's lymphoma
   b) primary refractory DLBCL (for definition, see Section 8.1)
   c) patients with known "double/triple hit" DLBCL genetics characterised by simultaneous detection of *MYC* with *BCL2* and/or *BCL6* translocation, as defined by fluorescence *in situ* hybridisation (FISH). *MYC*, *BCL2*, *BCL6* testing prior to study enrolment is not required.
   d) central nervous system (CNS) lymphoma involvement in present or past medical history

Exclusionary Previous and Current Treatment Criteria

2. Patients who had a major surgery (for definition, see Section 8.1) less than 30 days prior to Day 1 dosing
3. Patients who have, within 14 days prior to Day 1 dosing:
   a) not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphoma-specific therapy (for exceptions see Section 9.5.3)
   b) received live vaccines (for definition, see Section 8.6)
   c) required parenteral antimicrobial therapy for active, intercurrent systemic infections
4. Patients who:
   a) in the opinion of the investigator, have not recovered sufficiently from the adverse toxic effects of prior therapies, major surgeries (for definition, see Section 8.1) or significant traumatic injuries
   b) were previously treated with CD19-targeted therapy or BEN

c) have a history of previous severe allergic reactions to compounds of similar biological or chemical composition to MOR00208, RTX, murine proteins or BEN, or the excipients contained in the study drug formulations
d) have undergone ASCT within a period of ≤3 months prior to signing the ICF. Patients who have a more distant history of ASCT must exhibit full haematological recovery before enrolment into the study.
e) have undergone previous allogeneic stem cell transplantation
f) concurrently use other anticancer or experimental treatments (for exceptions see Section 9.5.3)

Exclusionary Medical History Criteria

5. Prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥3 years prior to Screening. Exceptions to the ≥3-year time limit include history of the following:
   a) basal cell carcinoma of the skin
   b) squamous cell carcinoma of the skin
   c) carcinoma *in situ* of the cervix
   d) carcinoma *in situ* of the breast
   e) carcinoma *in situ* of the bladder
   f) incidental histological finding of prostate cancer (Tumour/Node/Metastasis [TNM] stage of T1a or T1b)
6. Patients with:
   a) positive hepatitis B and/or C serology (for definitions, see Section 8.6)
   b) known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)
   c) evidence of active, severe uncontrolled systemic infections (e.g., tuberculosis [TB], opportunistic infections) or sepsis
   d) a history or evidence of severely immunocompromised state
   e) a history or evidence of severe hepatic impairment (total serum bilirubin >3 mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion 6c)
   f) a history or evidence of clinically significant cardiovascular, cerebrovascular, CNS and/or other disease that, in the investigator's opinion, would preclude participation in the study or compromise the patient's ability to give informed consent (for additional explanations, see Section 8.6).

8.6 Additional Explanatory Information on Inclusion and Exclusion Criteria

Inclusion Criteria: Diagnosis/Trial Population

Inclusion *"2. Histologically confirmed diagnosis, according to the World Health Organization (WHO, 2008) classification, of:*

e) Disease transformed from an earlier diagnosis of low-grade lymphoma (i.e. an indolent pathology such as follicular lymphoma, marginal zone lymphoma) into DLBCL with a DLBCL relapse subsequent to DLBCL treatment"

Patients with Richter's transformation or Richter's syndrome are not eligible for study participation.

Inclusion *"5. Patients after failure of ASCT or patients considered in the opinion of the investigator currently not eligible for HDC with subsequent ASCT. Documentation of the reason for ineligibility for ASCT must be present in the patient's source data."*

As for the ASCT, the induction, consolidation, stem cell collection, preparative regimen including transplantation, and maintenance will be considered a single line of therapy.

For the purpose of this protocol, patients who are not candidates for HDC with ASCT are defined by meeting any of the following criteria as evidenced in the patient's source data:

1) Inadequate performance status (Karnofsky Performance Status ≤ 80%; see Appendix D)
2) Disease not responsive to salvage chemotherapy. Responsiveness is defined as a tumour demonstrating either CR or PR to salvage chemotherapy.
3) Inadequate major organ function:
   a) Symptomatic congestive heart failure
   b) Lung function-forced vital capacity (FVC), forced expiratory volume in 1 second (FEV-1), and corrected diffusion capacity of the lung for carbon monoxide (DLCO) ≤ 60%
   c) Renal function-creatinine clearance < 60 mL/min
   d) Liver function-total serum bilirubin and transaminases > 2 x ULN
   e) Serious active or uncontrolled microbial infections (e.g. TB)
4) History or evidence of significant co-morbid medical or psychiatric illness which would significantly compromise the patient's clinical care and chances of survival
5) Inability to collect adequate stem cell graft (e.g. < 1-2 x 10^6 $CD34^+$ cells free of tumour contamination/kg recipient body weight)

Inclusion Criteria: Laboratory values

Inclusion *"6. Patients must meet the following laboratory criteria at Screening:*
e) serum creatinine ≤2.0 x ULN or creatinine clearance must be ≥40 mL/min calculated using a standard Cockcroft-Gault formula (Cockcroft and Gault (1976); see Appendix A to the protocol)

Glomerular filtration rate can also be used in place of creatinine or creatinine clearance (CrCl).

Exclusion criteria: Exclusionary Diagnosis Criteria

Exclusion "*1. Patients who have:*
b) primary refractory DLBCL

Protocol MOR208C204 excludes primary refractory patients defined as patients who progress in the course of first line treatment or within 6 months of completion of first line treatment.

The protocol allows the inclusion of:

1) DLBCL patients with a history of primary refractory disease who were responsive to a later treatment line,

2) Patients with relapsed DLBCL and remission lasting more than 6 months of prior RTX-containing therapy

3) DLBCL patients who are not responding or progress early when treated in 2nd and 3rd line including RTX-containing regimens.

Exclusion criteria: Exclusionary Previous and Current Treatment
Exclusion "*3. Patients who have, within 14 days prior to Day 1 dosing:*
b) Received live vaccines"

Additional information: live vaccines (e.g. yellow fever vaccination) must not be administered to patients in this study. Vaccinations against influenza with inactivated virus or vaccination for pneumococcal diseases are allowed.

Exclusion criteria: Exclusionary Medical History
Exclusion "*6. Patients with:*
a) positive hepatitis B and/or C serology"

In the context of the exclusion criteria, seropositive for or active viral infection with HBV means:

1) Hepatitis B virus surface antigen (HBsAg) positive
2) HBsAg negative, anti-HBc positive and detectable viral DNA (regardless of HBsAb status).

Patients who exhibit the classical vaccination profile of HBsAb positive, anti-HBc negative and HBsAg negative are eligible.

A positive hepatitis C test is defined as a positive test for hepatitis C virus antibody (anti-HCV) and a positive test for HCV RNA. Thus, patients with positive serology but negative HCV RNA test results are eligible.

Please refer to Section 10.3.7.2 for further information.

b) "known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)"

Additional information: no safety data on the use of CD19 antibodies in HIV positive patients are currently available.

c) "evidence of active, severe systemic, uncontrolled infections (e.g., tuberculosis [TB], opportunistic infections) or sepsis

Infections controlled on concurrent antimicrobial agents and/or antimicrobial prophylaxis per institutional guidelines are acceptable.

f) "a history or evidence of clinically significant cardiovascular, cerebrovascular, CNS and/or other systemic disease that would in the investigator's opinion preclude participation in the study or compromise the patient's ability to give informed consent."

Additional information: clinically significant cardiovascular, cerebrovascular, CNS and/or other systemic disease include, but are not limited to:

1) a myocardial infarction within 6 months before enrolment, uncontrolled angina pectoris, electrocardiographic evidence of acute ischaemia
2) New York Heart Association (NYHA) class II or higher congestive heart failure (see Appendix E for NYHA classification)
3) severe uncontrolled or clinically significant conduction system abnormalities (e.g. ventricular tachycardia, high-grade atrioventricular-block). Patients with stable, asymptomatic atrial fibrillation are allowed in the study provided they do not meet the other exclusion criteria
4) severe, uncontrolled cardiac disease including clinically significant pericardial disease
5) CNS lesions/cerebrovascular event(s) with clinically significant sequelae
6) CNS, meningeal or epidural malignancies (e.g., brain metastases, known meningeosis leukaemia)
7) cerebrovascular event(s) with clinically significant sequelae.

Screening for cerebrospinal fluid CNS involvement is not required but may be performed at the discretion of the investigator.

8.7 Randomisation

During Screening, each patient who signs the ICF will be allocated a unique identification number.

All patients who fulfil all inclusion criteria and who are not barred by any of the exclusion criteria will be randomly assigned to treatment comprising MOR00208 with BEN or RTX with BEN in a 1:1 ratio. Randomisation will be done through interactive response technology (IRT) before the patient receives any study medication. While all inclusion and exclusion criteria need to be reviewed again prior to randomisation, for all criteria that refer to laboratory parameters, central laboratory results obtained during the screening period will be used for determining patient eligibility for study randomisation.

Rescreening of patients who were not eligible for study enrolment will be allowed under the conditions described in Section 8.8. Patients who are rescreened will receive a new unique identification number.

Before randomisation, enrolled patients will be stratified according to the following factors:

a) Disease relapse/recurrence: early (≤12 months) versus late (>12 months) from the completion of the last treatment
b) Age ≤65 versus >65 years
c) ECOG performance status 0-1 versus 2
d) Prior systemic therapy lines ≤2 versus >2.

Randomisation during Initial Safety Evaluation: During Initial Safety Evaluation, patients will be allocated to treatment comprising MOR00208 with BEN or RTX with BEN via simple randomisation in a 1:1 ratio. The information about stratification factors will nevertheless be collected for these patients as well to be used in the analysis of the study data.

8.8 Re-screening Procedures

A patient can be re-screened at the discretion of the investigator under certain circumstances. Re-screening is restricted to one attempt per patient and can only be performed if one of the following criteria is met:

1. The patient has already consented and met all of the inclusion and none of the exclusion criteria and his or her enrolment was delayed due to an unexpected change in the patient's personal situation (e.g. family issues).
2. The patient previously failed to be eligible due to any event (e.g., planned surgery, laboratory test result) or any technical/logistic reason (e.g. screening period elapsed due to unexpected leave or absence of patient) that has been resolved.
3. The patient failed screening previously and becomes eligible for the study based on a change in the inclusion and exclusion criteria as the result of a protocol amendment.
4. The patient failed screening due to non-progressed/non-relapsed disease at the time of screening and later is clinically diagnosed as having progressed/relapsed.

Note: A patient should only be re-screened if there is a clear indication that the patient may be eligible according to the currently valid study protocol.

In these cases, if previous screening activities were discontinued and enrolment did not occur, the following procedures should be implemented:

1. The patient must sign and date a new ICF as part of the re-screening procedure
2. The eligible patient will receive a new unique identification number via the IRT
3. A new electronic case report form (eCRF) will be completed
4. The patient will be documented as re-screened in the source documents.

A re-screened patient can be enrolled, if all of the current inclusion criteria are met and none of the exclusion criteria are met.

8.9 Definition of Female of Childbearing Potential

A sexually mature female patient or a sexually mature female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

1. Age ≥50 years and naturally amenorrhoeic for ≥24 months (i.e., has not had menses at any time in the preceding 24 consecutive months). Amenorrhoea following cancer therapy does not rule out childbearing potential
2. Premature ovarian failure confirmed by a gynaecologist
3. Previous bilateral salpingo-oophorectomy, or hysterectomy
4. XY genotype, Turner syndrome, uterine agenesis.

9 TREATMENTS

9.1 Study Treatments

This is an open-label study. The combination treatment consisting of MOR00208 with BEN or RTX with BEN will be administered at specified time points at protocol-prescribed dose levels for a maximum of six cycles.

Subsequent to the completion of the Combination Treatment, patients with an ongoing response of at least PR, as per local disease response assessment, at the end of Cycle 6 will enter Antibody Monotherapy Treatment in accordance with their original treatment allocation until disease progression. Therefore, the duration of Antibody Monotherapy Treatment may vary individually. Treatment may be stopped due to disease recurrence/progression, withdrawal due to unacceptable toxicity, discontinuation for any other reason or death, whichever comes first.

In the case of disease recurrence/progression, as assessed locally, the investigator will, based on the patient`s individual risk/benefit ratio, align with the Sponsor and decide if the patient should receive "Further or Continued treatment with antibody" in accordance with the original treatment allocation (RTX 375 mg/m^2 at 28-day intervals or MOR00208 12 mg/kg at 14-day intervals) for up to 24 months in total. MOR00208 will be provided by the sponsor in the course of the trial. However, RTX in this particular clinical situation will not be provided by the sponsor and has to be prescribed by the treating physician and obtained from commercial sources. For patients receiving antibody treatment despite disease recurrence/progression, before the administration of antibodies, blood parameters (haematology, serum chemistry) should be evaluated in the local lab according to local guidelines/standards of local medical practice for the administration of mAbs. A urine pregnancy test should be performed for an FCBP. Vital signs should be measured according to local practice for the administration of mAbs.

Each investigator is responsible for ensuring that deliveries of study drugs and other study materials from the sponsor and other drugs from the appropriate suppliers are correctly received, recorded, handled and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol. The investigator may delegate these tasks to another person (according to the local laws and regulations). Drug accountability forms will be kept by each site participating in the study and will be checked during monitoring visits.

Study drug must be handled, prepared and administered as described in the Drug Handling Manual, the IB for MOR00208, and other safety-relevant documents (e.g., Summary of Product Characteristics ([SmPC] for the European Medicines Agency [EMA] or the Prescribing Information [US Food and Drug Administration (FDA)] for BEN and RTX). Please see Appendix F for additional information.

The infusion rates and times for study drugs specified in the protocol and the Drug Handling Manual are recommendations for the investigative sites' use. If required, the investigator should use clinical judgement and institutional guidelines to optimise patient safety by adjusting the rate of infusion according to the medical condition of the patient.

MOR00208 will be supplied by the sponsor. BEN and RTX will be available from commercial source. Concomitant medications will be provided by the investigative site and not by the sponsor.

9.1.1 MOR00208

MOR00208 DP (drug product) must be stored under refrigeration at 2°C to 8°C in its original package in an appropriate storage facility equipped with temperature control, accessible only to the pharmacist(s), the investigator, or a duly designated person.

MOR00208 DP is a lyophilisate supplied in single-use 20 mL glass vials. Each vial contains 200 mg of MOR00208 for reconstitution with 5 mL water for injection (WFI). Reconstitution yields 40 mg/mL MOR00208 in 25 mM sodium citrate, 200 mM trehalose and 0.02% (w/v) polysorbate 20 at pH 6.0. Each product vial is intended to deliver 200 mg of MOR00208 in 5 mL of reconstituted solution. The solution after reconstitution is colourless to slightly yellow and essentially free of foreign particles; it may contain a few white to whitish product-related particles.

For administration, MOR00208 will be diluted into a commercially available 250 mL infusion container with 0.9% (w/v) sodium chloride for injection.

The individual MOR00208 infusion will be prepared under aseptic conditions and administered at the study site, according to the directions of the sponsor, which will be provided in a Drug Handling Manual. In general, a vial of MOR00208 must be used as soon as possible after reconstitution with WFI; any solution remaining in the vial has to be discarded. After dilution for infusion, administration of MOR00208 should take place as soon as possible. Maximum allowed storage times and conditions will be detailed in the Drug Handling Manual.

MOR00208 will be administered at a dose of 12.0 mg/kg IV. Dose reductions of MOR00208 are not allowed during the course of the study.

For the first three months (Cycle 1-3) of the study, each cycle will consist of a MOR00208 infusion on Day 1, Day 8, Day 15 and Day 22 of the cycle. Additionally, a loading dose will be administered on Day 4 of Cycle 1. Thereafter (Cycle 4-until disease progression), each cycle will consist of a MOR00208 infusion on Day 1 and Day 15.

For the first infusion, the IV infusion rate should be 70 mL/h for the first 30 minutes and subsequently increased to a rate of 125 mL/h; the total infusion duration should ideally not exceed 2.5 hours. All subsequent MOR00208 infusions will be administered IV at a constant rate of 125 mL/h over a 2-hour period. MOR00208 should NOT be administered as an IV push or bolus.

Unless contraindicated the MOR00208 treatment should continue, even if the patient discontinues BEN treatment.

9.1.2 RTX

Specific information about the chemical structure, properties, formulation, storage, disposal and administration of RTX are provided in the SmPC (EMA) and Prescribing Information (US FDA).

RTX should be administered only as an IV infusion through a dedicated line and not as an IV push or bolus.

RTX will be administered at a dose of 375 mg/m^2 IV on Day 1 with a pre-planned treatment interval of at least 28 days to the subsequent RTX administration. Dose reductions of RTX are not allowed during the course of the study.

RTX will be available from commercial drug supplies (e.g. MabThera®/Rituxan®).

Unless contraindicated the RTX treatment should continue, even if the patient discontinues BEN treatment.

9.1.3 BEN

Specific information about the chemical structure, properties, formulation, storage, disposal and administration of BEN are provided in the SmPC (EMA) and Prescribing Information (US FDA).

BEN will be administered at a dose of 90 mg/m^2 on Days 2+3 of Cycle 1. BEN administration will be repeated on Days 1+2 or 2+3 of the subsequent cycles, with a pre-planned treatment interval of at least 28 days between the commencements of two succeeding cycles, according to institutional/patient/physician choice. An exception to this rule may occur in case the BEN administration scheme changes from Days 2+3 to Days 1+2, or vice versa, in subsequent cycles.

It is suggested that during Combination Treatment, BEN treatment should be aligned with the administration of mAb on Day 1 of the cycle. When applicable, BEN should be administered after the MOR00208 or RTX infusion.

BEN dose may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. In the case of early BEN discontinuation, the antibody treatment should continue unless contraindicated.

Detailed guidance on how to manage haematological and/or other toxicities is provided in Section 9.4.2. The recommended infusion time is 30 to 60 minutes. The prepared BEN solution should be administered as an IV infusion and not as an IV push or bolus.

BEN will be available from commercial drug supplies (e.g. Levact®/Treanda®).

9.2 Premedication for Study Drug Infusions

Any premedication given should be reported in the eCRF.

Premedication for RTX and BEN infusions should follow institutional guidelines and/or premedication and administration/infusions sections of the SmPC (EMA) or Prescribing Information (US FDA).

IRRs have been reported in clinical trials with MOR00208. Therefore, a recommended premedication regimen includes a histamine H_1 receptor blocker (e.g., diphenhydramine 50 mg per dose IV or equivalent), an antipyretic (e.g. acetaminophen [paracetamol] 1000 mg per dose by mouth [p.o.] or IV or equivalent) and glucocorticosteroids (e.g. methylprednisolone 80 to 120 mg per dose IV or equivalent). For the equivalent corticosteroid doses please refer to Appendix G. If required, the investigator may repeat doses of individual agents and use other agents, doses and/or formulations in accordance with institutional guidelines.

Premedication is mandated for the first three MOR00208 infusions. Premedication for patients who do not experience any IRRs to MOR00208 during the first three infusions (doses) will be optional for subsequent MOR00208 infusions at the discretion of the investigator. Otherwise, the premedication should be continued for subsequent administrations.

9.3 Patient Monitoring During Study Drug Infusions

Vital signs should be measured as outlined in Section 13.8.4. If mAb and BEN are being administered on the same day, vital signs should be recorded in eCRF for mAb infusion(s) only. All supportive measures consistent with optimal patient care should be provided throughout the study according to institutional standards.

Precautions for anaphylaxis should be observed during study drug administration. Emergency resuscitation equipment and medications should be readily available.

9.4 Criteria for Dose Modifications and Study Drug Discontinuation

9.4.1 Management of Study Drug Infusion-Related Reactions

For IRRs related to BEN and/or RTX, the investigator should follow the instructions contained in the SmPC (EMA) or Prescribing Information (US FDA) of the specific product.

IRRs will be defined according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (or higher) definition of Infusion-Related Reaction and Cytokine Release Syndrome (Table 1).

Table 1: Definition of Infusion-Related Reaction

NCI-CTCAE Version 4.0, Selection Criteria: Infusion-Related Reaction and Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (i.e. not rapidly responsive to symptomatic medication, brief interruption of infusion, or both); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening; consequences; pressor or ventilatory support indicated

Abbreviation: NSAID = nonsteroidal anti-inflammatory drug.
Please note: An acute infusion reaction may occur with an agent that causes cytokine release (e.g., monoclonal antibodies or other biological agents). Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia; Bronchospasm; Cough; Dizziness; Dyspnoea; Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia; Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating; Tachycardia; Tumour pain (onset or exacerbation of tumour pain due to treatment); Urticaria; Vomiting.

9.4.1.1 Grade 2 IRRs for patients receiving MOR00208

If a patient presents with a grade 2 IRR:

- The infusion should be stopped immediately.
- The patient should receive appropriate supportive treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) if clinically indicated.
- Once the symptoms have been resolved or reduced to grade ≤1 according to investigator assessment, the infusion can be continued at an infusion rate of 50%. If, after one hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes, as tolerated, to the baseline rate.

If a patient who developed a grade 2 IRR receives further infusions, then premedication according to the institutional guidelines should be given before all subsequent infusions.

9.4.1.2 Grade 3 IRRs for patients receiving MOR00208

If a patient presents with a grade 3 IRR:

- The infusion should be stopped immediately.
- The patient must receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) and, if necessary, further medications (i.e. epinephrine, bronchodilator).
- Only after the complete resolution of all symptoms (to grade ≤1), and after having received appropriate prophylactic medication(s) as described above, the infusion may be resumed at an infusion rate of 25%. If, after 1 hour, the patient's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50%.
- If, after the resumption of infusion, symptoms return (irrespective of grade), the infusion must be stopped immediately and the infusion tubing should be disconnected from the patient. Based on the investigator's decision the patient may receive further study drug(s), provided clinically appropriate precautions are undertaken. If the investigator decides to continue with further study drug(s) administration, then premedication according to the institutional guidelines should be given before all subsequent infusions.

9.4.1.3 Grade 4 IRRs for patients receiving MOR00208

If a patient presents with a grade 4 IRR:

- The infusion should be stopped immediately and the infusion tubing should be disconnected from the patient.
- The patient must receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) and/or methylprednisolone (or equivalent) and, if necessary, further medications (i.e. epinephrine, bronchodilator).
- The patient must not receive further infusions of the study drug that is judged by the investigator to be the cause of the IRR, but should continue treatment with the other study drug as per protocol.

9.4.2 Management of Treatment-Related Toxicities

The following information will support the management of treatment-related toxicities which may result in study drug(s) dose reduction or postponement, either at the start of a new cycle of therapy or during a cycle.

Guidance for dose postponement for BEN and dose reduction for BEN is provided in Section 9.4.2.1, guidance for dose omission/delay/postponement of MOR00208 and RTX in Section 9.4.2.2, and guidance for study drug(s) treatment discontinuation in Section 9.4.2.3. All scenarios may require the implementation of the principles of best supportive care (BSC) according to the local medical practice and the institutional guidelines.

9.4.2.1 Safety-related Criteria for BEN Treatment and BEN Treatment Postponement

Patients can begin chemotherapy with BEN only if the pre-dose local laboratory parameters measured locally remain in the ranges specified below. Furthermore, patients can receive subsequent BEN infusions if they have passed the neutrophils and platelets nadir and recovered from potential BEN-induced non-haematological toxicities as described in Table 2.

Table 2: Criteria Required for the Initiation of BEN Treatments

Parameter	Patient should only be dosed if:
ANC	$\geq 1000/mm^3$ (unless neutropenia is judged to be secondary to lymphoma infiltration of bone marrow). Patient may have received growth factor support.
Platelets	$\geq 75000/mm^3$ (unless thrombocytopenia is judged to be secondary to lymphoma infiltration of bone marrow). Patient may have received transfusion support in either situation.
Total bilirubin; AST; ALT	≤ 3 x ULN (unless due to Gilbert's syndrome or documented liver involvement by lymphoma)
Other clinically significant non-haematological toxicity	No active and uncontrolled infection
	Cycle 2-6: clinically relevant, non-haematological BEN-induced toxicity has diminished in severity to grade ≤ 2 or recovered to baseline level (if the condition was pre-existing)

Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BEN = bendamustine; ULN = upper limit of normal. Laboratory parameters are assessed locally.

1. If the criteria for the initiation of BEN treatment are not met, the subsequent BEN treatment is to be postponed. It is recommended that the AE grade and the haematology values are subsequently investigated at approximately 3-day intervals.

2. There must always be at least a 28-day interval between the commencement of two consecutive BEN treatment cycles (for additional information see Section 9.1.3).

3. MOR00208 or RTX may be continued (please note Section 9.4.2.2) while criteria for BEN treatment are not fulfilled. For these patients, BEN treatment will occur as soon as the criteria for re-treatment with BEN are fulfilled.

4. If based on medical judgement, the treating physician considers clinical and/or laboratory parameter changes not to be study drug-related toxicity, but to represent disease history, natural fluctuation or progression of the underlying disease, it is at the physician's discretion, in accordance with assessment of the individual risk/benefit ratio, to determine whether the new BEN treatment should be initiated (see Table 2) or BEN dose maintained (see Table 3) without meeting the criteria for subsequent cycles of chemotherapy. The decision and rationale behind the decision should be documented in the source data.

Table 3: BEN Dose Reduction Criteria

NCI CTCAE category	Severity	Dose modification
Haematologic	ANC< 1000/µl (Grade ≥3) on Day 1 of Cycles 2-6	BEN cycle initiation (Day 1) of Cycles 2 – 6 should be delayed until the ANC is ≥1000/µl and the PLTs is ≥75000/µl or cell counts return to baseline level obtained at screening respectively*. If Day 1 is delayed by more than 2 weeks, then BEN should be resumed at the next lower dose level (see Table 4). Growth factor (e.g. G-CSF) and transfusion support should be considered according to the principles of medical practice and the institutional guidelines during this and subsequent cycles.
	PLTs< 75000/µl (Grade ≥2) on Day 1 of Cycles 2-6	
	ANC< 500/µl (Grade 4) of any duration accompanied by body temperature of ≥38.3°C on a single occasion or >38°C on two occasions measured within 12 consecutive hours or >38°C maintained ≥1 hour	BEN cycle initiation (Day 1) of Cycles 2- 6 should be delayed until the ANC is ≥1000/µl without evidence of fever or infection and PLTs is ≥75000/µl*. BEN should then be resumed at the next lower dose level (see Table 4) Growth factor (e.g. G-CSF) and transfusion support should be considered according to the principles of medical practice and the institutional guidelines during this and subsequent cycles.
	ANC< 1000/µl (Grade 3) lasting ≥ 7 days	
	PLTs< 25000/µl (Grade 4) lasting ≥7 days or of any duration if accompanied by clinically significant bleeding	
	PLTs< 10000/µl at any time	
Nausea, emesis or diarrhoea in the absence of maximum prophylaxis	Grade 3	Continue BEN at the same dose, but institute the maximum prophylactic therapy, including e.g. a 5-HT_3 antagonist for nausea and emesis, and loperamide, or a comparable antidiarrhoeal agent.
	Grade 4	Withhold BEN until resolution of toxicity to Grade ≤ 2 while on maximum prophylactic therapy.

NCI CTCAE category	Severity	Dose modification
Nausea, emesis or diarrhoea in the presence of maximum prophylaxis	Grade ≥ 3	Withhold BEN until the toxicity returns to Grade ≤ 2 or baseline level if the condition was pre-existing, and restart BEN at the next lower dose (see Table 4).
All other clinically significant toxicities related to BEN	Grade ≥ 3	

Abbreviations: AEs = adverse events; ANC = absolute neutrophil count; BEN = bendamustine; G-CSF = granulocyte colony-stimulating factor; PLTs = platelets (platelet count).
*If patients have for instance a disease-related splenomegaly or marked bone marrow involvement by lymphoma as a causative factor of cytopenias at screening, treatment may continue without meeting the haematologic criteria for subsequent cycles of chemotherapy. In such cases the decision to continue BEN dosing at the current dose is at the investigator's discretion.

Principles of BEN Dose Reduction

The dose of BEN may be reduced successively from the starting dose of 90 mg/m^2 daily (Table 4). For additional information please see Section 9.1.3.

The BEN dose may only be adjusted once per cycle and by one dose level. Once a patient's BEN dose has been reduced, no dose re-escalation is permitted.

Table 4: BEN Dose Levels

Starting dose	90 mg/m^2 daily on Days 1+2 or 2+3 every at least 28 days
Dose Level - 1	60 mg/m^2 daily on Days 1+2 or 2+3 every at least 28 days
Dose Level - 2	30 mg/m^2 daily on Days 1+2 or 2+3 every at least 28 days

Patients who cannot tolerate Dose Level - 2 due to toxicities described in Table 2 and Table 3 should discontinue BEN treatment and should continue antibody therapy according to their initial treatment allocation.

9.4.2.2 Antibody Treatment Dose Omissions/Postponements

Dose reductions of MOR00208 or RTX are not allowed during the course of the study.

Treatment with MOR00208 or RTX may continue in case criteria for BEN treatment are not fulfilled (see Table 2).

In the case of clinically significant, grade 4 toxicities judged **not to be related to** RTX or MOR00208:

1. RTX doses should be postponed until toxicity diminishes in severity to ≤grade 3.

2. MOR00208 doses should be omitted until toxicity diminishes in severity to ≤grade 3. One missed MOR00208 dose should not be made up for. If the patient misses a subsequent MOR00208 dose, the second missed dose should be administered immediately after the toxicity resolves.

In the case of clinically significant grade ≥3 toxicities judged **to be related to** RTX or MOR00208:

1. RTX doses should be postponed until the toxicity diminishes in severity to grade ≤1 or returns to a baseline grade, provided the condition was pre-existing at baseline.

2. MOR00208 doses should be omitted until the toxicity diminishes in severity to grade ≤1 or returns to a baseline grade, provided the condition was pre-existing at baseline. One missed MOR00208 dose should not be made up for. If the patient misses a subsequent MOR00208 dose, the second missed dose should be administered immediately after the toxicity resolves.

If based on medical judgment, the treating physician considers a clinical AE and/or laboratory parameter change not to be a study drug-related toxicity but to represent natural fluctuation or progression of the underlying disease, then it is at the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the patient should be dosed. The decision and rationale behind the decision should be documented in the source data.

9.4.2.3 Treatment Discontinuation

If the same study drug related toxicity persists for more than 28 days, the administration of this particular study drug should be discontinued and the patient should continue to be dosed with the other study drug (i.e. the respective combination partner in that treatment arm).

If the same toxicity related to both study drugs persists for more than 28 days, then treatment with both study drugs should permanently be discontinued (see Section 9.8).

If treatment is interrupted for more than 28 days due to an AE and/or laboratory parameter change that is not a study drug-related toxicity, the administration of this particular study drug should be discontinued and the patient should continue to be dosed with the other study drug (i.e. the respective combination partner in that treatment arm).

If both study drugs are temporarily withheld for more than 28 days due to the same persisting clinical AE and/or laboratory parameter change then treatment with both study drugs should permanently be discontinued.

All scenarios may require the implementation of the principles of the BSC according to the local medical practice and the institutional guidelines. The decision and rationale behind the decision should be documented in the source data.

9.5 Prior and Concomitant Therapy

Any prior, concomitant, or procedural medications or therapy given to or taken by the patient **within 1 month prior to commencement of the study** and **up to the End of Treatment** visit **(EOT)** must be recorded in the source documents and the eCRF along with the indication, way of administration/formula and dosage. Such medications (including over-the-counter agents) must be listed on the concomitant medications form in the eCRF, with the exception of [18F] fluorodeoxyglucose (FDG) and/or CT/MRI contrast agents.

For a patient to become eligible for **"Further or Continued Antibody Treatment"** (if given despite progression of disease/relapse), an **EOT Visit** including all protocol prescribed procedures need to be performed in order to capture the event (i.e. disease progression/relapse) for the treatment to continue further. In such cases the **30-Day Safety Follow-Up** will not take place as long as antibody treatment continues further. Instead, the **30-Day Safety Follow-Up** will take place 30 days after the period of **"Further or Continued Antibody Treatment"** (if given despite progression of disease/relapse) has ended (see Section 11.2).

From the **30-Day Safety Follow-Up** visit, anticancer treatments and, in the case of an SAE/ AESI assessed as related (see Section 11.2), other relevant information, e.g. concomitant medications should be documented.

The investigator should instruct the patient not to take any additional medications (including over the- counter--products) during the study without prior consultation.

Information should be provided on any previous NHL-specific therapies since the time point of the first diagnosis of NHL. The generic or the trade name may be recorded. Patients should not receive any DLBCL specific- therapy other than study drugs (MOR00208, RTX and BEN) during Combination Treatment, during Antibody Monotherapy Treatment and during follow up for PFS.

Patients may continue the medications they were receiving at baseline. Patients may receive concomitant medications that are medically indicated as standard care for the treatment of symptoms and intercurrent illnesses. Medications to treat concomitant diseases such as diabetes, hypertension, bronchial asthma, chronic obstructive pulmonary disease etc., are allowed. Patients will also receive therapy to mitigate side effects of the study medication as clinically indicated, as well as BSC as per institutional guidelines. This may include, but is not limited to antiemetics, anti-diarrhoeals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms.

Concerning BEN and RTX, the SmPC (EMA) or Prescribing Information (US FDA) should be referred to for information on the administration of concomitant medications and potential drug-drug interactions.

9.5.1 Growth Factors and Transfusion Support

Growth factors may be prescribed at the investigator's discretion, according to the principles of medical practice and the institutional standards. Growth factors or transfusion support should not be administered during Screening solely for the purpose of improving a patient's blood values in order to meet eligibility criteria.

9.5.2 Infection Prophylaxis

Investigators should follow institutional guidelines concerning infection chemoprophylaxis for patients regarded to be at high risk for infection.

9.5.3 Anticancer Therapies

The use of concurrent antineoplastic therapies other than study drugs, including, but not limited to chemotherapies, hormonal therapy, immunotherapy, biological response modifiers, mAbs with or without conjugation, radio-isotopic therapies, and targeted small molecules are not permitted throughout Combination Treatment, Antibody Monotherapy Treatment and during follow up for PFS. Allogeneic stem cell transplantation is considered to be a protocol prohibited anticancer therapy.

Limited field radiotherapy for reducing symptoms related to tumour mass effect is allowed during Screening.

Provided all the inclusion and none of the exclusion criteria apply, at the discretion of the investigator, the intrathecal prophylaxis of CNS disease (e.g. methotrexate and cytarabine) is allowed in the course of the trial. These concomitant medications will be provided by the investigative site and not by the sponsor.

9.5.4 Systemic Glucocorticosteroids

Single-dose, topical, intranasal, inhaled corticosteroids, as well as eye drops or local injections (e.g., intra-articular) containing corticosteroids or physiologic replacement of glucocorticosteroids are permitted during study participation.

Systemic glucocorticosteroids in doses up to 20 mg/day prednisone or equivalent (i.e. equipotent corticosteroid) are permitted but only for the treatment of non-neoplastic comorbid indications (e.g., rheumatoid arthritis).

Systemic glucocorticosteroids in doses above 20 mg/day prednisone or equivalent (i.e. equipotent corticosteroid) are permitted for a limited period of time under following circumstances:

a) use as premedication
b) exacerbations of chronic non-neoplastic conditions such as chronic obstructive pulmonary disease (COPD), bronchial asthma or rheumatoid arthritis, etc.

c) severe and/or life-threatening conditions such as adrenal insufficiency, cytokine release syndrome, etc.
d) antiemetic prophylaxis for up to 24 hours
e) to manage severe DLBCL manifestations (e.g. compressive disease, rapidly progressing symptomatic adenopathy) before Cycle 1 Day 1 as per institutional standards. The glucorticosteroids dose needs to be tapered to 20 mg or less of prednisone or equivalent per day prior to study drug(s) administration on Cycle 1 Day 1. **Wherever possible, the fresh tumour tissue (Section 10.2.1) should be collected before starting the administration of glucocorticosteroids in doses above 20 mg/day (prednisone or equivalent, please refer to Appendix G).**

The glucocorticosteroid dosage and the allowable treatment period will be determined by the investigator on a case-by-case basis. The investigator should discuss the systemic usage of glucocorticosteroids in doses above 20 mg/day (prednisone or equivalent) with the medical monitor of the study prior to the implementation, whenever feasible. The specified systemic glucocorticosteroids use, if short in duration, is not likely to confound the treatment effect and efficacy analysis.

Immunosuppressive therapies other than systemic glucocorticosteroids as described are not permitted.

9.5.5 Management of Tumour Lysis Syndrome

Prevention and therapy of TLS should be conducted according to the discretion of the investigator following the principles of medical practice and the institutional guidelines. **Allopurinol should not be given on days when BEN is infused because an increased risk of Steven Johnson syndrome and toxic epidermal necrolysis (TEN) has been reported.**

9.5.6 Management of Patients with History or Previous Events of Febrile Neutropenia

Patients with a positive medical history of, or previous incidences of febrile neutropenia while on study, or those with an individual risk for febrile neutropenia >20%, should receive prophylactic granulocyte colony-stimulating factor (G-CSF) according to the principles of medical practice and the institutional guidelines.

9.5.7 Antimicrobials/Antivirals/Antifungals

Antimicrobials/antivirals/antifungals should also be administered for prophylaxis and/or for treatment according to the principles of medical practice and the institutional guidelines. Systemic antifungal coverage is generally not recommended.

9.6 Treatment Compliance

Dosing modifications due to toxicity are described in Section 9.4.2 and are not covered here.

Patients will receive MOR00208, RTX and BEN under the direct supervision of study personnel. Each administration volume or dose will be checked and the vial/outer package code and volume or dose per administration will be recorded in each patient's eCRF as well as in the source data.

A patient will be considered compliant with the protocol if the MOR00208, RTX and BEN dose administered is ≥80% to ≤120% of the assigned dosage per single infusion.

Drug accountability will be checked by the field monitor during site visits and at the completion of the study.

9.7 Overdose of Study Drugs

An overdose of MOR00208, RTX or BEN is defined as a dose exceeding the planned dose by more than 20% (for further information see Section 11.1). For exact advice on handling a BEN and/or RTX overdose please refer to SmPC (EMA) or Prescribing Information (US FDA). No specific treatment is recommended for overdose of MOR00208. Treatment remains at the discretion of the investigator.

9.8 Withdrawal from Study Treatment or Study/Site Termination

9.8.1 Withdrawal Criteria

Patients may voluntarily withdraw from the study or treatment. Patients may be discontinued from treatment at the discretion of the investigator at any time.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations at the 30-Day Safety Follow-Up visit.

If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient´s premature withdrawal from the study and record the information on the eCRF. If the reason for withdrawal is an AE, monitoring should continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF. At the discretion of the sponsor, patients may also be removed from the study, for instance in a case when it is retrospectively established that patients do not fulfil all inclusion or meet certain exclusion criteria (e.g., tumour tissue is not available for central pathology review).

It should be clearly documented in the source data, whether patients withdrew their consent and will not enter Follow-Up or if the patient withdrew their consent for study drug treatment, but will continue further participation in the study.

Examples for withdrawal criteria include but are not limited to:

- AE(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Unmanageable toxicity related to study drug(s) (including but not limited to medical events described in Sections 9.4 and 9.8.2)
- Protocol violation
- Patient withdrawal of consent
- Pregnancy or breast-feeding
- Loss to follow-up
- Inability of the patient to comply with study requirements
- Conditions requiring therapeutic intervention not permitted by the protocol
- Administrative problems
- Radiologically confirmed disease progression
- Withdrawal of a patient for any reason at the discretion of the investigator

Patients who are withdrawn for any reason must not re-enter this clinical study at any time.

For patients who are lost to follow-up at least three attempts of contact by the site should be made and documented in the source data.

9.8.2 Study or Site Termination

The investigator and the sponsor both reserve the right to terminate the study at any time at a given clinical study centre. The sponsor also reserves the right to terminate the entire study or temporarily interrupt enrolment and/or dosing of already enrolled patients for further evaluation.

Stopping criteria for this study will include, but are not limited to:

1. For the first 10 patients enrolled in cohort MOR00208 + BEN during the safety run-in phase:
    - Toxicities **which occur in three or more patients** (toxicity means an adverse drug reaction with a suspected causal relationship to trial medications as assessed by the investigator or the sponsor):
        - Liver: Acute hepatic failure $\geq$ Grade 4
        - Allergic reaction, anaphylaxis, cytokine release syndrome $\geq$ Grade 4
        - Any cardiac event $\geq$ Grade 4
        - ECG: QTc prolongation (Torsade de pointes) $\geq$ Grade 4
        - Gastrointestinal: Diarrhoea, nausea, vomiting $\geq$ Grade 4
        - Acute kidney injury $\geq$ Grade 4

- Multi organ failure > Grade 3
- Pulmonary haemorrhage > Grade 3
- Pneumonia ≥ Grade 4
- Sepsis ≥ Grade 4
- Tumour lysis syndrome ≥ Grade 4

- Any other unexpected, suspected adverse drug reaction of the same nature which is ≥ Grade 4 and which occurs in three or more patients.
- Haematologic toxicity which occurs in four or more patients and which has not diminished in severity to grade ≤2 or recovered to baseline level (if the condition was pre-existing) within 28 days (toxicity means an adverse drug reaction with a suspected causal relationship as assessed by the investigator or the sponsor):
  - Febrile neutropenia ≥ Grade 4
  - Neutropenia ≥ Grade 4
  - Anaemia ≥ Grade 4
  - Thrombocytopenia ≥ Grade 4

2. Thereafter for all patients enrolled in cohort MOR00208 + BEN:
   - ≥ **30% of patients** experiencing unexpected Grade ≥4 adverse drug reactions as described above.
3. Sponsor decision following the recommendation of IDMC or the outcome of the interim analysis

Should a termination of a given clinical study centre or the whole study become necessary, then adequate procedures will be arranged after careful consideration and communicated to all involved parties. In terminating a study centre, or the entire study, the sponsor and the investigators will ensure that adequate consideration is given to the protection of the patients' interests. Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and competent authorities will be notified of premature termination in accordance with applicable regulatory requirements.

10 STUDY PROCEDURES

10.1 Schedule of Visits and Procedures

Table 5 lists all scheduled assessments, and indicates with an "X" the visits at which these assessments are performed. Patients in both treatment arms are supposed to follow the same schedule of visits irrespective of treatment allocation. All data obtained from these assessments must be supported in the patient´s source documentation.

Visit scheduling calculation:

Each Visit from Cycle 1 Day 1 until and including Cycle 7 Day 1 shall be scheduled based on the date of the Cycle 1 Day 1 visit and in line with the given visit window (e.g., the Cycle 2 Day 1 visit shall be scheduled 28 days after the date of Cycle 1 Day 1±3 days; the Cycle 3 Day 1 visit shall be scheduled 56 days after the date of Cycle1 Day 1 ±3 days; Cycle 3 Day 15 shall be scheduled 70 days after the date of Cycle 1 Day 1 ±1 days, etc.).

Each Visit from Cycle7 Day 15 onwards shall be scheduled based on the date of the Cycle 7 Day 1 visit and in line with the given visit window and not based on the date of Cycle 1 Day 1.

Table 5: Schedule of Assessments

Screening and Cycles 1–3

Evaluation or Procedure	Screening	Combination Treatment																	
	Screening ≤28 Days prior to D1	Cycle 1 (28 days)							Cycle 2 (28 days)						Cycle 3 (28 days)					
Day	Screen	D1	D2	D3	D4	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D8 ±1 day	D15 ±1 day	D22 ±1 day
Informed consent	X																			
Inclusion/exclusion criteria	X	X[1]																		
Demography	X																			
Medical history	X																			
Disease staging/Ann Arbor	X																			
Disease risk assessment (IPI)	X																			
Disease progression assessment: early vs. late relapse of prior treatment line	X																			
Previous/concomitant medication	X	X	X	X	X	X	X	X	X	X	(X)	X	X	X	X	X	(X)	X	X	X
Full physical examination (Limited physical examination [L])	X	L													L					
ECOG performance status	X	X							X						X					
EORTC QLQ-C30	X	X													X					
EQ-5D-5L	X	X													X					
Body mass/height/BSA[2]	X	X							X						X					

Evaluation or Procedure	Screening	Combination Treatment																	
	Screening ≤28 Days prior to D1	Cycle 1 (28 days)							Cycle 2 (28 days)						Cycle 3 (28 days)					
Day	Screen	D1	D2	D3	D4	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D8 ±1 day	D15 ±1 day	D22 ±1 day
B-symptoms	X	X				X	X	X	X				X		X				X	
Vital signs	X	X	X	X	X	X	X	X	X	X	(X)	X	X	X	X	X	(X)	X	X	X
12-lead resting ECG	X	X[1]													X[3]					
Urinalysis	X	X							X						X					
Pregnancy test (FCBP)[4]	X	X[1]							X[1]						X[1]					
Local laboratory[5]		X	X	X	X	X	X	X	X	X	(X)	X	X	X	X	X	(X)	X	X	X
Central laboratory blood sampling	X	X[1]							X[1]						X[1]					
Hepatitis B serology	X								X[16]						X[16]					
Hepatitis C serology	X																			
B-, T- and NK cell flow cytometry (blood)		X[1]			X[1]		X[1]		X[1]											
Anti-MOR00208 antibodies[6]		X[1]													X[1]					
Optional FcγR polymorphism (mucosal cheek swab)		X																		
ADCC and CD16 assessment (blood)		X[1,23]																		
Disease response assessment (PET/CT or PET/MRI)[19]	X																			
CT or MRI scan for tumour measurement and disease response assessment[19]															X					

Evaluation or Procedure	Screening	Combination Treatment																	
	Screening ≤28 Days prior to D1	Cycle 1 (28 days)							Cycle 2 (28 days)						Cycle 3 (28 days)					
Day	Screen	D1	D2	D3	D4	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D8 ±1 day	D15 ±1 day	D22 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D8 ±1 day	D15 ±1 day	D22 ±1 day
Provide sample for central pathology review and correlative studies on tissue samples	X																			
Bone marrow aspiration & biopsy	X[7]																		X[7]	
MOR00208 administration (depending on allocation)[22]		X			X	X	X	X	X			X	X	X	X			X	X	X
RTX administration (depending on allocation)[22]		X							X						X					
BEN administration on (D1) and D2 or D2 and (D3)[22]			X	X					(X)	X	(X)				(X)	X	(X)			
SPM		X							X						X					
(S)AE assessment	X	X	X	X	X	X	X	X	X	X	(X)	X	X	X	X	X	(X)	X	X	X
PK MOR00208[6]		X[8,9]	X[9]	X[9]	X[8]		X[8]		X[8,9]				X[8]		X[8,9]				X[8]	

Cycles 4–6

Evaluation or Procedure	Combination Treatment												
	Cycle 4 (28 days)				Cycle 5 (28 days)				Cycle 6 (28 days)				
Day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D15 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D15 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D15 ±1 day	D28 ±4 days
Previous/concomitant medication	X	X	(X)	X	X	X	(X)	X	X	X	(X)	X	X
Full physical examination (Limited physical examination [L])					L								L
ECOG performance status	X				X				X				
EORTC QLQ-C30					X								
EQ-5D-5L					X								
Body mass/height/BSA[2]	X				X				X				
Vital signs	X	X	(X)	X	X	X	(X)	X	X	X	(X)	X	
B-symptoms	X			X	X			X	X			X	X
12-lead resting ECG									X[3]				
Urinalysis	X				X				X				
Pregnancy test (FCBP)[4]	X[1]				X[1]				X[1]				
Local laboratory[5]	X	X	(X)	X	X	X	(X)	X	X	X	(X)	X	
Central laboratory blood sampling	X[1]				X[1]				X[1]				
Hepatitis B serology	X[16]				X[16]				X[16]				
B-, T- and NK cell flow cytometry (blood)	X[1]			X[1]	X[1]								
Anti-MOR00208 antibodies[6]					X[1]								
Disease response assessment (CT/PET or PET/MRI)[19]													X
CT or MRI scan for tumour measurement					X								

Evaluation or Procedure	Combination Treatment												
	Cycle 4 (28 days)				Cycle 5 (28 days)				Cycle 6 (28 days)				
Day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D15 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D15 ±1 day	D1 ±3 days	D2 ±3 days	D3 ±3 days	D15 ±1 day	D28 ±4 days
and disease response assessment[19]													
Bone marrow aspiration & biopsy								X[7]					
MOR00208 administration (depending on allocation)[22]	X			X	X			X	X			X	
RTX administration (depending on allocation)[22]	X				X				X				
BEN administration[22]	(X)	X	(X)		(X)	X	(X)		(X)	X	(X)		
SPM	X				X				X				
(S)AE assessment	X	X	(X)	X	X	X	(X)	X	X	X	(X)	X	X
PK MOR00208[6]	X[1, 9]				X[1, 9]				X[1, 9]				

Antibody Monotherapy Treatment, End of Treatment Visits and Follow-Up

Evaluation or Procedure	Antibody Monotherapy Treatment (28 Days Cycles 7–until disease progression) (Cycle 7, up to 2 weeks +3 days after Cycle 6 Day 28)[15]		End of Treatment Visit (EOT; preferably within ≤30 days of last dose of study treatment)	30-Day Safety Follow-Up (FU) Visit	Follow-Up	
					FU for PFS measurement (every 3 months ±2 weeks; institution visit)	FU for OS (every 3 months ±3 weeks; by phone[18])
Days	D1 ±3 days	D15 ±1 day	Assessments can take place ±7 days of the actual visit	30 days ±2 days from last dose of study treatment	First assessments can take place within 14 days of the actual 30-Day Safety FU visit	First assessments can take place within 3 months ± 3 weeks of the EOT Visit or last FU for PFS Visit, as applicable
Previous/concomitant medication	X	X	X			
Full physical examination (Limited physical examination [L])	L[21]		X	L	L	
ECOG performance status	X		X			
EORTC QLQ-C30	X[17]		X	X	X	X[20]
EQ-5D-5L	X[17]		X	X	X	X[20]
Body mass/height/BSA[2]	X		X			
Vital signs	X	X	X			
B-symptoms	X	X	X	X	X	
12-lead resting ECG			X			
Urinalysis	X		X			
Pregnancy test (FCBP)[4]	X		X			
Local laboratory[5]	X	X				
Central laboratory blood sampling	X[1]		X			
Hepatitis B serology	X[16]		X[16]			
B-, T- and NK cell flow cytometry (blood)	X[1] (Cycle 8 only)					
Anti-MOR00208 antibodies[6]	X[1,10]		X			
CT or MRI scan for tumour measurement and disease response assessment[19]	X[12]				X[12]	

Evaluation or Procedure	Antibody Monotherapy Treatment (28 Days Cycles 7–until disease progression) (Cycle 7, up to 2 weeks +3 days after Cycle 6 Day 28)[15]		End of Treatment Visit (EOT; preferably within ≤30 days of last dose of study treatment)	30-Day Safety Follow-Up (FU) Visit	Follow-Up	
					FU for PFS measurement (every 3 months ±2 weeks; institution visit)	FU for OS (every 3 months ±3 weeks; by phone[18])
Days	D1 ±3 days	D15 ±1 day	Assessments can take place ±7 days of the actual visit	30 days ±2 days from last dose of study treatment	First assessments can take place within 14 days of the actual 30-Day Safety FU visit	First assessments can take place within 3 months ± 3 weeks of the EOT Visit or last FU for PFS Visit, as applicable
Disease response assessment (CT/PET or PET/MRI)[13, 19]			X			
Bone marrow aspiration & biopsy		X[7, 11]				
MOR00208 administration (depending on allocation)	X	X				
RTX administration (depending on allocation)	X					
SPM	X		X	X	X	
(S)AE assessment	X	X	X	X	X, only if related to study drug	
PK MOR00208[6]	X[1,10]		X			
Antineoplastic therapy after end of study drug treatment			X	X[14]	X[14]	X[14]

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; AE = adverse event; β-HCG = beta-human chorionic gonadotropin; BEN = bendamustine; BSA = body surface area; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FCBP = female of childbearing potential; FU = Follow-Up; IPI = International Prognostic Index; mAb = monoclonal antibody; MRI = magnetic resonance imaging; NK = natural killer; PET = positron emission tomography; PK = pharmacokinetics; RTX = rituximab; SAE = serious adverse event; SPM = second primary malignancy.
(X): administration of BEN on Days 1+2 or Days 2+3. Procedures indicated in brackets need to be performed on the day of BEN administration.

[1]Before study drug administration.
[2]Body height will be measured on Screening visit only. Body mass and BSA will be measured at least during the Screening visit and on Day 1 of each cycle. They will be used to calculate the study drug doses in a given cycle and on Day 1 of the succeeding cycle. On C1D1, body mass and BSA measured on that day (or up to 24 hours before study drug(s) administration) will be used to calculate the doses of the study drugs. Body mass and BSA measurement may take place pre- or post-dose, with the exception of C1D1 where they need to be measured and calculated pre-dose. For BSA calculation, the Mosteller formula should be used (see Section 10.3.2.3 and Appendix H).
[3]12-lead resting ECG performed within 3 hours post-antibody dose (see Section 10.3.4).

[4]Pregnancy tests: for FCBP: A serum pregnancy test must be performed during Screening. On C1D1, a second, medically supervised urine pregnancy test must be performed prior to the start of study drug. The results of both tests must be negative in order to receive C1D1 dosing. A β-HCG serum pregnancy test should also be performed at the EOT visit. At all other indicated time points, a urine pregnancy test for FCBP should be performed locally and the result must be negative for dosing.
[5]Sample to be collected and evaluated in the local laboratory within 24 hours prior to the administration of the study drug(s) and reviewed by study treating physician before study drug administration. The local laboratory samples will also be collected for the RTX+BEN patients, despite the fact that they may not receive study drugs at a particular visit. Under such circumstances, the sample collection time point on such visits is at the investigator's discretion.
[6]Anti-MOR00208 antibody samples and MOR00208 PK samples will be collected in the MOR00208-treatment arm only and sample collection shall be stopped after Cycle 23.
[7]See Section 10.3.9 for details. Repeat bone marrow biopsy and aspiration to confirm a CR and only in those patients who had known bone marrow involvement prior to randomisation. Bone marrow biopsy and aspiration will only be repeated if response in prior cycles was not CR.
[8]MOR00208 PK sample (to be collected in the MOR00208 treatment arm only) to be taken pre-dose and 1 hour ±10 min after the end of MOR00208 infusion.
[9]MOR00208 PK samples (to be collected in the MOR00208 treatment arm only) should optimally be collected before BEN administration (when applicable).
[10]Anti-MOR00208 antibody sample and MOR00208 PK sample will be collected pre-dose only in odd numbered Antibody Monotherapy Treatment cycles of the MOR00208 treatment arm only (i.e. treatment Cycles 7, 9, 11, etc. until and including Cycle 23). No samples to be collected after Cycle 23.
[11]Relevant for the confirmation of CR at C6D28 and during subsequent disease response assessments.
[12]With the exception of C7D1, during Antibody Monotherapy Treatment and Follow-Up for PFS, disease assessment using CT will be performed every 3 months ± 2 weeks from the previous scan until disease progression, death or study discontinuation (whichever occurs first). Disease response assessment may also include standard of care procedures to determine the disease status per Cheson 2007 criteria (e.g. confirmatory biopsy, lumbar puncture, etc for PD)
[13]In case that the patient is withdrawn from treatment before the end of Cycle 6 for reasons other than PD. CT only may be performed in lieu of PET/CT if EOT takes place within Cycle 1. PET/CT is only required at the EOT visit if it was not performed in the cycle before the end of treatment.
[14]For a patient to become eligible for **"Further or Continued Antibody Treatment"** the **30-Day Safety Follow-Up** will not take place as long as antibody treatment continues. Instead, the **30-Day Safety Follow-Up** will take place 30 days after the period of **"Further or Continued Antibody Treatment"** (if given despite progression of disease/relapse) has ended. Starting from the 30-Day Safety Follow-Up visit, anticancer treatments and SAEs/AESIs assessed as related (see Section 11.2) should be documented. For an EOT visit taking place before the end of Cycle 6, any concomitant medication needs to be recorded.
[15]For patients receiving "Further or Continued Antibody Treatment" (if given despite progression of disease/relapse) for up to 24 months in total: Before the administration of antibodies, blood parameters (haematology, serum chemistry) should be assessed in the local lab according to local guidelines/standards applicable for administration of monoclonal antibodies. A urine pregnancy test should be performed in FCBP. Vital signs should be measured prior to treatment and according to local practice applicable for the administration of monoclonal antibodies. Other procedures described in the column Antibody Monotherapy Treatment will not apply for this patient population.
[16]HBV-DNA to be re-measured only if anti-HBc was positive during screening (please see Section 10.3.7.2).
[17]EORTC QLQ-C30 and EQ-5D-5L to be administered on D1 of the odd-numbered Antibody Monotherapy Treatment cycles (e.g., C7D1, C9D1, C11D1, etc).
[18]First FU visit for OS to be performed as a clinic visit.
[19]Disease assessments and tumour measurements will be made by positron emission tomography (PET) and computed tomography (CT) or CT alone with contrast. For all patients, neck/chest/abdomen/pelvis CT is required. The CT portion of a combined [18F]fluorodeoxyglucose (FDG)-PET/CT scan should be performed with contrast and collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. If available and of acceptable quality (e.g., CT portion of PET/CT scan was performed with contrast), previously performed PET/CT examinations, in accordance with the standard of care, that were done up to 4 weeks prior to Screening may be employed. Disease response assessment may also include standard of care procedures to determine the disease status per Cheson criteria (e.g. confirmatory biopsy, lumbar puncture, etc for PD). For further details please refer to Section 10.3.8.1.
[20]In the course of FU for OS, QoL questionnaires will be applied only during the first FU for OS visit, which will be a clinic visit.
[21]During Antibody Monotherapy Treatment, a limited PE will be performed on Day 1 of Cycles 7, 10, 13, 16, etc.
[22]Premedication to be administered as outlined in Section 9.2.
[23] Data collection [redacted] was stopped as of 22-JUN-2020, because sufficient data was already collected for the exploratory purpose.

10.2 Procedures

All study-required procedures should occur as outlined in Table 5. Deviations from the timing of assessments will be considered protocol non-compliances and should be recorded in the source documents along with the reason for the excursion.

Screening begins on the date that the ICF is signed and will last for up to 28 days. In exceptional cases, the screening period may be extended at the discretion of the investigator for a total of up to 42 days due to any technical/logistic reasons (e.g., extended imaging equipment breakdown and/or servicing, delays in the delivery of central laboratory results). The reason for such extension along with an evaluation by the investigator ensuring that such extension does not pose any health risk for the patient should be documented in the patient's source data. The ICF must be signed prior to the conduct of any assessments solely for the purpose of this study. Standard of care assessments done on the day of consent (but prior to signing the ICF) do not need to be repeated solely for the purpose of screening and may be used as study data, if they and their results meet the protocol requirements.

On Cycle 1 Day 1, patient eligibility must be confirmed before drug administration.

10.2.1 Diagnostic Biopsy

Patients should be eligible and willing to undergo a biopsy or surgical excision of a lymph node and/or other pathological tissue, providing enough tumour tissue for central histological review and correlative studies, as a prerequisite for participation in this study. Should it not be possible to obtain a fresh tumour tissue sample, archival paraffin embedded tumour tissue acquired ≤3 years prior to screening for this protocol must be available for this purpose.

In addition, patients will have the option to consent for storage and use of their submitted tumour tissue for future lymphoma research.

Histological confirmation of the diagnosis of DLBCL will be performed by a central pathologist. Surgically acquired tissue samples are preferred, but core biopsies are permitted. Fine needle aspirates (FNA) will not be accepted for histological confirmation.

Central pathology review is mandatory, but retrospective in nature. An effort should be made to submit tissue sample(s) within 30 days of randomisation. Patients can be randomised prior to submission of tissue sample(s). The local pathology report indicating a DLBCL or DLBCL NOS diagnosis is acceptable for determining a patient's eligibility. On request of the investigator, the sponsor may facilitate an interaction between the investigator and the central pathologist to discuss issues connected to the initial diagnosis established locally. If the quality of the tissue sample does not allow central pathology analysis, another archival sample of the appropriate quality may be requested by the Sponsor.

In the case of discrepancies between the assessments of the local and the central pathologists, the assessment of the central pathologists will be relevant for sensitivity analyses of the primary efficacy endpoint analysis. If the DLBCL diagnosis of the local pathologist cannot be confirmed

by the central pathologists, and a patient's treatment has already commenced, the patient may remain in the study at the discretion of the treating physician.

Bone marrow biopsy and bone marrow aspiration are not considered adequate for the purpose of diagnostic biopsy in this trial (also see Section 10.3.9).

10.2.2 Demographic Data/Relevant Medical History and Current Medical Conditions/Baseline, Stage and Prognostic Classification

Demographic variables to be recorded will include: age, gender, race, body height, and body weight. Weight and height should be measured while the patient is without shoes, but dressed.

At the time of signing of the ICF, relevant medical history and current medical conditions should be recorded. The medical history of NHL should be documented in detail, including baseline symptoms as well as a detailed history of prior cancer therapies for NHL, with start and stop dates, number of therapy line(s), disease progression during or after therapy, as well as discontinuations due to intolerability or any other clinically significant illness. Any previous therapy (e.g., chemotherapy, immunotherapy, or radiation therapy) for DLBCL should be recorded in the eCRF. Also, examinations leading to the diagnosis of the latest progression of DLBCL should be documented in the patient's source documents. This may include, e.g., results of laboratory examinations, imaging results or clinical symptoms related to DLBCL. The assessment of the lymphoma should include staging. In order to reflect the patient's status at the time of enrolment, the standard staging system used for DLBCL reflecting the number of sites of involvement and their relation to the diaphragm, the existence of B-symptoms, and the presence of extranodal disease, will be documented (see Appendix I for Ann Arbor Staging).

Additionally, the disease risk assessment as per the International Prognostic Index (IPI; see Appendix J) and patient status as per ECOG performance status criteria (see Appendix K) will be recorded.

10.2.3 Quality of Life

In the course of the study, two QoL questionnaires will be used:

a) the standardised European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).
b) the EuroQol five dimensions quality of life questionnaire with 5 levels (EQ-5D-5L).

Results of the completed QoL questionnaires will be entered by the site into the eCRF.

10.3 Safety Assessments

Safety monitoring for all patients enrolled in the study will include laboratory safety assessments (e.g., haematology, blood chemistry, urinalysis and coagulation) and clinical evaluations (e.g., physical examinations, vital signs, 12-lead electrocardiogram [ECG], and monitoring of second primary malignancy [SPM] occurrence) as detailed in the Schedule of Assessments (Table 5). All AEs and SAEs should be recorded in the eCRF.

Laboratory and AE toxicities will be graded according to NCI-CTCAE, version 4.0 (or higher). Patients who experience any toxicity should be followed until the toxicity has stabilised, the toxicity has returned to the baseline level, or a new treatment has commenced.
Safety monitoring is detailed in Section 11.

10.3.1 Vital Signs

Vital signs will be measured at the time points described in the Schedule of Assessments (Table 5). If mAb and BEN are being administered on the same day, vital signs should be recorded in eCRF for mAb infusion(s) only. These assessments include body temperature, systolic and diastolic blood pressure readings (mmHg), heart rate (beats per minute [bpm]), and respiratory rate (respirations per minute [rpm]). Vital signs will be measured within 15 minutes prior to infusion, 15 ± 5 minutes after the start of infusion, and 30 ± 10 minutes after the start of infusion. After the 30-minute assessment, vital signs need to be measured once every 30 to 60 ±15 minutes during the infusion and at the end of infusion (± 20 min). The actual time of vital sign measurements should be accurately documented. If the infusion is interrupted and/or subsequently restarted, vital signs should be assessed every 60 ± 15 minutes after the first hour. During visits when study drug infusions do not take place, vital signs need to be measured only once, at all visits according to Table 5.

For the safety of the patient, in the course of Cycle 1 Day 1 (first MOR00208 infusion) and Cycle 1 Day 2 (first infusion of BEN) the patient will stay at the study site for approximately 2 hours after the end of study drug administration for the monitoring of the occurrence of acute toxicities.

The frequency or duration of monitoring may be adapted as clinically indicated, e.g., if in the opinion of the investigator, the vital sign results at the time of event onset are clinically significant. In such a case, the patient's vital sign measurements should continue to be recorded until they have returned to normal or pre-infusion levels. Subsequently, an AE should be recorded. If possible, before vital signs are measured, the patient should be resting for at least 5 minutes. The same position should be used each time vital signs are measured in a given patient, and blood pressure should be measured from the arm contralateral to the site of study drug administration. Body temperature should be measured according to normal institutional practice.

10.3.2 Physical Examination

10.3.2.1 Full Physical Examinations

A full physical examination (PE) will be performed by the Investigator or a qualified designee during Screening and at the EOT visit.

Full PE must be performed according to the best standards of local medical practice, but should include at least measurement of vital signs, palpable tumour assessment (if applicable), general appearance, skin, head, eyes, ears, nose, throat including Waldeyer lymphatic structures, lungs, breasts and axillae, cardiovascular system, back and spine, abdomen, extremities, lymph nodes, and neurological examination.

10.3.2.2 Limited Physical Examinations

Limited PEs may be focused on tumour response assessment (lymph nodes, liver, spleen, etc.) and AEs at the investigator discretion. Such limited PEs will be performed as indicated in the Schedule of Assessments (Table 5). During Antibody Monotherapy Treatment, a limited PE will be performed on Day 1 of Cycles 7, 10, 13, 16 etc.

Symptom-driven full PEs may be performed as clinically indicated at any study visit. Similarly, the investigator may extend the scope of PE at any visit if considered clinically relevant.

10.3.2.3 Body Mass, Body Surface Area (BSA) and Height Measurements

Body mass and BSA will be used to calculate the doses of MOR00208, and, RTX and BEN, respectively.

Body height will be measured on the Screening visit only.

Body mass and BSA will be measured at least during the Screening visit and on Day 1 of each cycle. These variables should be used to calculate the study drug doses in the course of a given cycle and on Day 1 of the succeeding cycle, with the exception of C1D1. On C1D1, body mass and BSA measured on that day will be used to calculate the doses of the study drugs.

Body mass and BSA measurement may take place pre- or post-dose, with the exception of C1D1 where they need to be measured and calculated pre-dose.

During the course of this study, the Mosteller's algorithm should be used for BSA calculations (see Appendix H). Provided the institutional standards require the use of another standard BSA formula, sponsor approval may be obtained on a case by case basis.

10.3.3 B-Symptoms

The protocol specific definition of B-symptoms is based on the Cotswolds Recommendations (see Appendix I).

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

- Unintentional weight loss of $\geq$ 10% within the preceding 6 months or less
- Drenching night sweats without signs of infection
- Recurrent, unexplained fever with temperatures above 38°C without signs of infection

Assessment of the presence or absence of B-symptoms will be performed at various time points as indicated in the Schedule of Assessments (see Table 5).

Medical history of B-symptoms should be documented.

10.3.4 Electrocardiogram

Standard 12-lead resting ECGs should be obtained at the various time points described in the Schedule of Assessments (Table 5). If possible, ECGs should be recorded after the patient has rested in a supine position for at least 5 minutes. Heart rate and PR, QRS, RR and QT intervals should be determined. All ECGs should be performed and interpreted locally. The investigator should evaluate the clinical significance of each value outside the reference ranges according to the nature and degree of the observed abnormality. Any new abnormal values considered to be clinically significant should be reported as AEs.

If clinically significant abnormalities are observed or artefacts are present that result in an inability to adequately interpret the results, the ECG should be repeated. An average of all intervals measured in all ECG tracings recorded at a given time point may be taken if necessary.

10.3.5 Adverse Event Monitoring

AEs should be assessed at each visit and reported as specified in Section 11. For screening failure patients, only SAEs should be recorded in the eCRF.

10.3.6 Monitoring of Second Primary Malignancies

SPMs will be monitored as events of special interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report any SPMs as Adverse Events of Special Interest (AESIs), regardless of causal relationship to the study drugs, occurring at any time, for the duration of the study, from Cycle 1, Day 1 up to and including the Follow-Up for PFS. Events of SPM are to be reported using the SAE report form and must be considered an important medical event even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and the patient's source documents.

Documentation concerning the diagnosis of the SPM must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or cytology results, X-rays, CT scans).

10.3.7 Laboratory Assessments

Detailed instructions and amounts of biological samples needed for the respective laboratory measurements will be summarised in the laboratory manual. All samples will be collected as non-fasting samples.

10.3.7.1 Laboratory Testing

Clinical laboratory parameters measured in the course of the study are listed in Table 6. Local and central laboratories will be used throughout the study.

Central laboratory results are required for determining patient eligibility for study enrolment and will be used in the analysis of the study results. During the course of the study, all scheduled central laboratory results should be reviewed as soon as possible after Day 1 of each cycle.

Patients must neither be qualified for study eligibility nor randomised based on the results of the local laboratory assessments.

It is permitted **to repeat twice the central laboratory assessment** of blood cell counts, liver enzymes, serum electrolytes concentration (sodium, potassium, calcium) and/or serum creatinine or creatinine clearance/glomerular filtration rate during Screening due to the variability of the parameters and their dependence on a multitude of factors (e.g. hydration, muscle mass). That is, provided no safety concerns arise and that such laboratory results might have been caused by a transient, medically plausible event, which resolved spontaneously or as result of a medical intervention in the meantime (e.g. dehydration, vomiting, imaging procedure with a contrast), or technical issues. This procedure and the rationale behind it must be explicitly documented in source data.

Local laboratory results will be used for treatment or clinically related decisions, or for the immediate safety needs of a study patient. Local laboratory results should be reviewed as soon as possible after their receipt and before dosing so that the administration of the investigational medicinal product may be adjusted or interrupted if necessary. **Local laboratory** assessments **may be performed up to 24 hours before administration of study drugs and may fall outside of the planned visit window**.

In order to keep the experimental conditions as similar as possible, irrespective of treatment allocation, the local laboratory samples will also be collected for the RTX+BEN patients at the respective study visits (see Table 5), despite the fact that they may not necessarily receive study drugs at a given visit. In such case the restriction that samples need to be collected and evaluated in the local laboratory and reviewed by study treating physician before study drug administration will not apply.

The signed and interpreted laboratory results (both local and central) are to be kept in the patient's source documentation. The laboratory results should be reviewed, dated and signed in a timely manner by the investigator. Any clinically significant discrepancies between local and central laboratory results will be evaluated on a case-by-case basis. All blood samples should be processed and handled according to standard laboratory procedures. The time of blood collection should be documented in the eCRF.

Any abnormal laboratory findings (identified either through local or central laboratory analysis) that constitute an AE should be reported as such and should be followed up until the outcome is known. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the patient's condition (e.g., ordering a white blood cell [WBC] differential count to help characterise a high or low WBC count, or ordering a determination of red blood cell [RBC] indices to help characterise a low haematocrit).

Table 6: Laboratory Evaluations

Evaluation	Analysis
Local laboratory (EDTA blood and serum sample)	Serum creatinine, haemoglobin, WBCs, including WBC differential[1], platelets, sodium, potassium, AST, ALT, total bilirubin
Haematology (EDTA blood)	WBC with differential count, haematocrit, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, platelet count, RBC count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils Screening: should include a peripheral blood smear Band neutrophils are only reported when a manual differential count performed and bands are present
Serum chemistry (serum sample)	ALT, total albumin, alkaline phosphatase, amylase, AST, bicarbonate, bilirubin (total), urea, total calcium, chloride, creatinine, creatinine kinase, gamma-glutamyltransferase (GGT), glucose, lactate dehydrogenase (LDH), lipase, phosphate, potassium, protein (total), sodium, uric acid, β_2-microglobulin, C-reactive protein
Coagulation parameters (sodium citrate blood)	Activated partial thromboplastin time, prothrombin time, international normalisation ratio
Ig concentrations (serum sample)	Ig concentrations (IgG, IgM, IgA)
Serology parameters (serum sample)	Hepatitis B: HBsAg, anti-HBc and HBsAbs. HBV DNA if anti-HBc positive, optional Hepatitis C: HCV antibody (HCV RNA quantification if anti-HCV positive)
Pregnancy test (serum or urine samples)	β-HCG serum or urine, females of childbearing potential only. Serum samples tested in central laboratory and urine samples tested locally
Urinalysis	Appearance, colour, urine bilirubin, glucose, haemoglobin, ketones, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated.
Genotyping* (mucosal cheek swab, optional)	FcγRIIa and FcγRIIIa polymorphism
Immunogenicity (serum sample)	Anti-MOR00208 antibodies
PK (serum sample)	MOR00208
[redacted]	

Evaluation	Analysis
B-/T-/NK cell counting (heparinised blood and EDTA blood)	Cell counts via flow cytometry
CD16 expression on peripheral NK cells (heparinised blood)	CD16 molecules expressed per cell (CD16 antibodies bound per cell) via flow cytometry
[redacted]	

* May be performed at another time point than C1D1 if it was inadvertently missed.
Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; ALT = alanine transaminase; anti-HBc = hepatitis B core antibody; anti-HCV = hepatitis C virus antibody; AST = aspartate aminotransferase; β-HCG = beta-human chorionic gonadotropin; EDTA = ethylenediaminetetraacetic acid; GGT = gamma-glutamyltransferase; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; Ig = immunoglobulin; LDH = lactate dehydrogenase; NK = natural killer; PBMCs = peripheral blood mononuclear cells; PK = pharmacokinetics; RBC = red blood cell; WBC = white blood cells.
[1]WBC differential can be automated or manual as per institutional standards. Reticulocytes (tested locally) may be determined only when clinically indicated.

Due to the exploratory nature of some assays, the sponsor may decide at any point during the study to terminate these assessments, in which case the sites will be informed accordingly.

10.3.7.2 Hepatitis Virus Serology

Patients will be examined according to the schedule in Table 5 for viral hepatitis B and C serology. Hepatitis B biomarkers include HBsAg, anti-HBc and HBsAb. Patients with a positive test for hepatitis B virus core antibody (anti-HBc) can only be included if HBV-DNA is not detected. In these patients, HBV-DNA should be assessed as outlined in Table 5.

In the context of the exclusion criteria, seropositive for or active viral infection with HBV means:

a) HBsAg positive
b) HBsAg negative, anti-HBc positive and detectable viral DNA (regardless of HBsAb status).

Patients who exhibit the classical vaccination profile of HBsAb positive, anti-HBc negative and HBsAg negative are eligible.

If HBV DNA becomes detectable during treatment, patients should be prophylactically treated and followed-up for potential hepatitis B reactivation as per local medical practice or institutional guidelines for CD20 antibodies such as RTX. If the HBV DNA assay is positive, then patients can only stay in the study if they are assessed by a physician experienced in the

treatment of hepatitis B and pre-emptive treatment is initiated, if deemed appropriate, and/or according to local practice/guidelines.

Hepatitis C serology is to be done at Screening only. Hepatitis C biomarkers include hepatitis C virus antibody (anti-HCV). For patients who are positive for anti-HCV, HCV RNA should be measured.

A positive hepatitis C test is defined as a positive test for anti-HCV and a positive test for HCV RNA. Thus, patients with positive serology but negative HCV RNA test results are eligible.

10.3.7.3 Pregnancy Testing

For an FCBP, a pregnancy test will be performed at various pre- and post-treatment time points either by a urine pregnancy test or a beta-human chorionic gonadotropin (β-HCG) test of a serum sample (see Table 6). The pregnancy test assay should have a minimum sensitivity of 25 IU/mL. At Screening and the EOT visit, a β-HCG serum pregnancy test should be performed for an FCBP.

An FCBP must have two negative pregnancy tests prior to starting the study drug administration. The first pregnancy test must be performed during Screening and the second pregnancy test must be performed on Cycle 1 Day 1 prior to the start of study drug. The patient must not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Subsequent pregnancy tests will be conducted as indicated in the Schedule of Assessments, Table 5.

10.3.7.4 PK Assessments

Concentration-time profiles and PK parameters will be assessed for MOR00208 according to the schedule in Table 5. PK samples will not be collected from patients treated with RTX and concentration-time profiles or PK parameters will not be assessed for BEN or RTX. PK sample collection shall be stopped after Cycle 23.

Serum samples for PK analysis of MOR00208 will be handled and stored as specified in the laboratory manual at the study site until shipment on dry ice to an external analytical laboratory. At each sampling time point, the obtained serum sample should be split into two aliquots (one primary and one back-up sample).

10.3.7.5 Immunogenicity

Serum samples for anti-MOR00208 antibody analysis will be collected according to the schedule in Table 5. Anti-drug antibody samples will not be collected from patients treated with RTX. Serum sample collection for anti-MOR00208 antibody analysis shall be stopped after Cycle 23.

Serum samples for anti-MOR00208 antibody analysis will be handled and stored as specified in the laboratory manual at the study site until shipment on dry ice to an external analytical laboratory. At each sampling time point, the obtained serum sample should be split into three aliquots (one primary and two back-up samples).

10.3.8 Efficacy Assessments

The primary efficacy endpoint analysis will be evaluated through central review by an Independent Radiology/Clinical Review Committee (IRC) that will apply Cheson criteria (see Appendix L). The review process will be defined in the IRC Charter.

Efficacy will be evaluated in terms of PFS (primary endpoint), best ORR, DCR, DoR, OS, TTP and TTNT (secondary endpoints). For definitions, see Section 13.4.

Local assessment of efficacy response (Cheson criteria) will be required in addition to central review at the beginning of Cycle 3, Cycle 5 and at the EOT visit to determine whether the disease has progressed. Local efficacy assessment will also be performed at the end of Cycle 6 for the decision whether treatment will continue as Antibody Monotherapy Treatment from Cycles 7 onwards. Disease response assessment as indicated in Table 5 may also include standard of care procedures to determine the disease status per Cheson criteria (e.g. confirmatory biopsy, lumbar puncture, etc for PD). Data from these procedures is collected and provided to the IRC as defined in the IRC Charter.

10.3.8.1 Tumour Imaging

During the course of the study, disease and response assessments as well as tumour measurements will be performed.

Initial disease and disease response assessments will be made by positron emission tomography (PET) and computed tomography (CT) at Screening and Day 28 (±4 days) of Cycle 6 and at the EOT visit, in the cases where a patient is withdrawn from treatment before the end of Cycle 6 for reasons other than progressive disease.

The CT portion of a combined [^{18}F]fluorodeoxyglucose (FDG)-PET/CT scan should be performed with contrast and collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans.

Tumour measurements and disease response assessment will also be performed as indicated in Table 5 by CT with contrast.

Magnetic resonance imaging (MRI) may be used in lieu of CT, and PET/MRI in lieu of PET/CT for patients with contraindications to the administration of contrast agents, or due to other medical reasons, at the same time points as CT, or in addition to CT, at the discretion of the investigator (in this case, MRI may be performed as/when appropriate). The method used at baseline should be used throughout the study unless otherwise medically indicated.

If available and of acceptable quality (e.g., CT portion of PET/CT scan was performed with contrast), previously performed PET/CT examinations, in accordance with the standard of care, that were done up to 4 weeks prior to Screening may be used for a patient's baseline central radiology assessment. Additional PET/CT or CT/MRI examinations may be performed by the investigator during the course of the study, if deemed necessary (e.g., to confirm the occurrence of a CR or disease progression or to make important treatment-related decisions).

If the patient discontinues from treatment, a PET/CT scan is only required at the EOT visit if such scan was not performed in the cycle prior to the end of treatment. CT may be performed in lieu of PET/CT if the patient discontinues from treatment within Cycle 1.
The same scan modality should be used for all assessments, and all patients are required to have scans of the neck/chest/abdomen/pelvis.

If it is impossible for the patient to have their PET examination in fasted state, adequate procedures should be in place to measure and control blood glucose level.

In addition to the International Working Group 2007 (Cheson et al. 2007) evaluation components, radiologists fulfilling the roles of central reviewers will record the classification of PET/CT scans according to the 5-point scale qualitative rating and measurement of the vertical length of the spleen. These aspects of the Lugano Classification (Cheson et al. 2014) are not a direct component of the International Working Group 2007 review and are intended as supplemental information only.

10.3.9 Bone Marrow

At the Screening visit, a uni- or bilateral bone marrow biopsy and aspirate should be obtained to assess bone marrow involvement. Results from a bone marrow examination done up to 4 weeks prior to Screening are acceptable provided the patient's disease has been stable since then.

The achievement of CR in the course of MOR208C204 study must be confirmed locally, by clinical and radiologic evaluation along with bone marrow confirmation. The latter applies only in case the bone marrow was involved by lymphoma before the randomisation. If bone marrow was not involved by lymphoma before commencing the study treatment, then bone marrow confirmation biopsy and aspiration is not required. The repeated bone marrow examination is also not required for patients in whom bone marrow has already been cleared of the infiltrate at previous evaluation, i.e. their previous bone marrow response was CR.

Histological examination of the bone marrow biopsy and aspirate should be performed locally at the protocol specified time points (see Table 5).

11 SAFETY MONITORING

The patients will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period with non-leading questioning (e.g., "How do you feel?"). AEs also may be detected when they are volunteered by the patient during or between study visits or through physical examination, laboratory tests, or other assessments.

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are trained in the acute management of IRRs, cytokine release syndrome, anaphylaxis, and other emergencies, and who have access to appropriate clinical supplies, should be readily available.

All AEs should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalisation, or any other medically required intervention. Once an AE is detected, it should be followed up, and an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its seriousness, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

11.1 Definition of Adverse Events, Serious Adverse Events, Adverse Events of Special Interest

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product, which does not necessarily have a causal relationship to this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to that study drug.

AEs include any clinically significant deterioration of a patient's medical status after the signing of the ICF. Also, an increase in the frequency or intensity of a pre-existing episodic event or conditions and events resulting from protocol mandated procedures (e.g. invasive procedures) fall under the definition of AEs. In addition, overdoses (defined as exceeding the planned dose by >20%) should be recorded as AEs.

As far as possible, each AE should be evaluated to determine the following:

- Relationship to the study drug (suspected/not suspected)
- Duration (start and end date, or if continuing at end of study)
- Intensity: the intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:
    - mild: tolerable
    - moderate: interferes with normal activity
    - severe: incapacitating (causes inability to perform usual activities or work)

- Severity i.e. toxicity grade: determined according to the NCI-CTCAE version 4.0 of May 28, 2009, using the following definitions:
    - grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
    - grade 2: moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
      grade 3: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living
    - grade 4: life-threatening consequences; urgent intervention indicated
    - grade 5: death related to AE
- Outcome
- Action taken (no action taken; study drug temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication taken; non-drug therapy given; hospitalisation/prolonged hospitalisation)
- Seriousness: whether it is serious, where a SAE is defined as one that:
    - results in death
    - is life-threatening
    - requires in-patient hospitalisation or prolongation of existing hospitalisation (hospitalisation signifies that the patient was an in-patient for at least one overnight stay) unless hospitalisation is for:
        - routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to NHL
        - elective or pre-planned treatment for a pre-existing condition that is unrelated to NHL and has not worsened since signing of the informed consent
        - social reason and respite care in the absence of any deterioration in the patient's general condition
    - results in persistent or significant disability or incapacity
    - is a congenital anomaly or birth defect
    - is medically significant, i.e. defined as an event that jeopardises the patient or may require medical intervention to prevent one of the outcomes listed previously.

The term "life-threatening" refers to an event in which the patient was, in the view of the reporting investigator, at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical judgment should be exercised in deciding whether an AE is serious in other situations: important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the previous definitions should also be considered as serious.

AESIs are TLS, SPM, IRRs and allergic reactions to study drug ≥ grade 3, cytokine release syndrome and overdoses.

Unlike routine safety assessments, SAEs and AESIs are monitored continuously and have special reporting requirements (see Section 11.2).

The investigator should determine the causality (relationship to the study drug) based on his/her clinical experience and on the information given in the IB. The causal relationship of all AEs to the study drug will be judged as either suspected or not suspected. A suspected causal relationship means at least a reasonable possibility that the event is caused by the study drug. If no relationship has been provided by the investigator, the event will be considered as related to the study drug.

Information about adverse drug reactions already known about the investigational study drug can be found in the IB (MOR00208), SmPC and/or Prescribing Information (BEN, RTX), or will be communicated in the form of Investigator Notifications. This information will be included in the patient ICF and should be discussed with the patient during the study, as needed.

11.2 Adverse Event and Serious Adverse Event Recording and Reporting

All AEs (except non-serious AEs for screening failures) that occur after the provision of informed consent and up to 30 days after last drug administration will be recorded in the eCRF and in the patient's medical records, whether or not they are considered by the investigator to be related to the study drug. Thereafter, only SAEs/AESIs assessed as related to any study drug should be recorded. All AEs should be recorded using acceptable diagnoses, if possible. For screening failure patients, non-serious AEs will not be recorded in the eCRF but only in the patient's medical records.

In addition, all SAEs and AESIs will be recorded on the SAE report form. Study centres and investigators are instructed to report all SAEs and AESIs to the sponsor (or designee) within 24 hours, using the study-specific SAE report form.

Generally, the diagnosis instead of the individual symptoms should be reported as the event term. If a diagnosis has been reported as an AE, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if a febrile neutropenia is reported as an AE, there is no need to report neutrophil count decrease and fever above 38°C, or other related signs, symptoms, or laboratory values as separate AEs. However, if such events occur in isolation, and febrile neutropenia is not diagnosed, then each event should be reported as an AE.

IRRs and allergic reactions to study drugs grade 3 or higher, or cytokine release syndrome, which are AESIs in this study, should be reported as diagnosis along with their respective symptoms in one event term (e.g., 'IRR with symptoms of hives, chills and fever' for IRRs). For overdoses, the diagnosis and if applicable the accompanying symptoms caused by the overdose should be reported.

All non-serious AEs must be followed up for a final outcome. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a patient's participation in the study. All SAEs

must be followed up for a final outcome until resolution or, if resolution becomes unlikely, until stabilisation or death.

Events that are clearly caused by progression of the underlying disease (e.g. transformation to more aggressive tumour histology or B-symptoms) should not be recorded as AEs or SAEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be recorded as an AE or SAE.

Deaths that occur during the protocol-specified adverse event reporting period that are clearly attributed to progression of the underlying disease should not be recorded as SAEs. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported on the SAE report form to the Sponsor. Death should be considered an outcome and not a distinct event. The event or condition that caused the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported.

During Follow-Up for Overall Survival, the following should be reported:

- Deaths attributed to progression of the underlying disease should be reported via the eCRF.
- SAEs/AESIs the investigator becomes aware of and considers to be related to any study drug should be reported in the eCRF and on the SAE report form via fax to the CRO (see below).

Notification of initial or follow-up SAE/AESI information (by using the standard SAE form provided by the sponsor) must be sent by email or fax to the sponsor (or designee).

11.3 Pregnancies

As detailed in the Schedule of Assessments (Table 5) and Section 10.3.7.3, serum pregnancy testing will be carried out at the Screening and EOT visits. During the treatment period of the study, urine pregnancy testing will be performed locally and can be repeated if required. Any pregnancy that occurs during study participation (after signature of the informed consent form until 3, 6 or 12 months after last dose of MOR00208, BEN or RTX respectively, whichever is later) should be reported using a Clinical Trial Pregnancy Form. Likewise, if a female sexual partner of a patient participating in this trial becomes pregnant within 3, 6 or 12 months after last dose of MOR00208, BEN or RTX respectively, whichever is later, this pregnancy should be reported. (**Applicable in Republic of Korea**: any pregnancy that occurs during study participation (after signature of the informed consent form until 6 months after last dose of MOR00208, 6 months after the last dose of BEN or 12 months after the last dose of RTX) should be reported using a Clinical Trial Pregnancy Form. Likewise, if a female sexual partner of a patient participating in this trial becomes pregnant within 6 months after last dose of MOR00208, 6 months after the last dose of BEN or 12 months after the last dose of RTX, this pregnancy should be reported.)

To ensure patient safety, each pregnancy of a study patient or a female sexual partner of a study patient must also be reported within 24 hours of learning of its occurrence by email or fax to sponsor (or designee).

Study patients who become pregnant must be withdrawn from the study treatment. A male patient whose sexual partner becomes pregnant may continue study participation.

A newly diagnosed pregnancy in a patient or female sexual partner of a study patient who has received study medication is not considered an SAE unless it meets any criteria of seriousness or it is suspected that the study medication interacted with a contraceptive method and led to pregnancy.

If the pregnancy results in clinical consequences/complications in mother or child, e.g. if the child is born with a birth defect, this should be reported as an SAE of mother or child as applicable.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities or maternal and newborn complications. Every infant has to be followed up for 2 months after delivery.

12 DATA HANDLING AND ARCHIVING

12.1 Completing and Signing Case Report Forms

An eCRF will be used in this study. The investigator will be responsible for accurate and timely data entry and data clarifications in the eCRF. Data entry may be delegated to adequately trained site personnel. Any errors should be corrected within the electronic system. In the case of missing data, a reason should be given. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided. The investigator will receive a copy of their eCRF in a readable format after database lock for archiving.

12.2 Clinical Data Management

The CRO will be responsible for the processing and quality control of the data according to the CRO's standard operating procedures (SOPs). Data management will be carried out by the CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

Details for data validation and edit checks will be described in appropriate data management documents. Queries will be handled via the eCRF system. Data cleaning will continue until all queries are resolved.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1 (or higher) for AEs and medical history and the WHO Drug Dictionary Enhanced for medication.

12.3 Archiving and Filing

All study documentation at the investigator site and sponsor site will be archived in accordance with International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance and the clinical trial agreement.

13 STATISTICAL METHODS AND PLANNED ANALYSES

The data will be analysed by the sponsor and/or designee. Any data analysis carried out independently by the investigator should be submitted to Incyte Corporation before publication or presentation.

It is planned that the data from participating centres in this protocol will be combined, so that an adequate number of patients will be available for analysis.

The following analyses are planned:

- **Interim Analysis:** planned to take place after approximately 128 PFS events (based on IRC assessment) have been observed in the overall population (FAS).
  Final Analysis: planned to take place at the end of the study (for definition see Section 8.4), independent of how many IRC PFS events have been observed at that point in time. All endpoints as described in Section 7 will be analyzed.

Additional safety analyses may be performed to support interactions with regulatory authorities.

13.1 Populations for Analysis

Table 7 details the defined analysis sets.

Table 7: Analysis Sets

Analysis set	Description
Full analysis set (FAS)	All patients who were randomised to either treatment arm. Analyses using the FAS will be based upon the treatment to which each patient was randomised.
Per-protocol set (PPS)	All patients in the FAS, having at least one dose of MOR00208 or RTX, and BEN. Patients without any post-baseline assessment of DLBCL response or with specific key protocol deviations will be excluded from the PPS.
Safety analysis set (SAF)	All patients who received at least one dose of MOR00208 or RTX or BEN. Analyses using the SAF will be based on the actual treatment received.
PK analysis set (PKAS)	The PK population will include all patients who have at least one quantifiable serum MOR00208 concentration (PK parameters will be calculated as data permit.)
Immunogenicity analysis set (IAS)	All patients who were randomised and have at least one anti-MOR00208 antibody assessment.

Abbreviations: BEN = bendamustine; PK = pharmacokinetics; RTX = rituximab.

13.2 General Statistical Methods

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software version 9.3 or higher.

Continuous, quantitative variable summaries will include the number of patients (N) (with non-missing values/valid cases), mean, standard deviation, minimum, 25th quartile, median, 75th quartile and maximum, except for PK metrics, where additional statistics may be used.

Categorical, qualitative variable summaries will include the frequency and percentage of patients/entries in the particular category.

Definition of baseline value: the last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline.

All data obtained via the eCRF and entered into the database will be provided in separate data listings showing individual patient values. The planning and reporting of statistical analyses will be carried out as described in the CRO's SOPs. A Statistical Analysis Plan (SAP) detailing the statistical analyses will be prepared and signed off before the database lock.

13.3 Patient Disposition, Baseline and Treatment Characteristics

The number of patients screened, randomised, and included in each analysis population will be summarised. In addition, the number of patients that discontinue treatment during the Combination Treatment or the Antibody Monotherapy Treatment or Follow-Up will be summarised, along with reasons for discontinuation.

The number of patients completing Combination Treatment (1/2/3/4/5/6 cycles), and the number of patients included in Antibody Monotherapy Treatment (cycles >7) and Follow-Up will be summarised and listed.

Demographic information will be summarised for the full analysis set (FAS) and safety analysis set (SAF) populations using descriptive statistics. Demographic information will also be summarised for the NKCC-low subgroup. Gender and race will be summarised by counts and percentages.

Medical history will be summarised by counts and percentages using MedDRA system organ class (SOC) and preferred term classifications. Concomitant medications will be recorded and coded using the WHO Drug Dictionary Enhanced and grouped by Anatomical Therapeutic Chemical (ATC) classes. Tabulations with counts/percentages will show the number of medications/percentage used in each class.

The NHL-specific medical history will be summarised for the duration of disease since initial diagnosis, number of previous therapies (therapy lines), type of previous therapy, and best response following previous NHL-specific therapy. Disease staging and disease risk assessment will be evaluated by frequency tabulations as well.

13.4 Analysis of Efficacy Data

In this study two co-primary endpoints (PFS in FAS and PFS in NKCC-low subgroup) and two key secondary endpoints (ORR and OS) in the FAS or NKCC-low subgroup will be tested with inferential statistics.

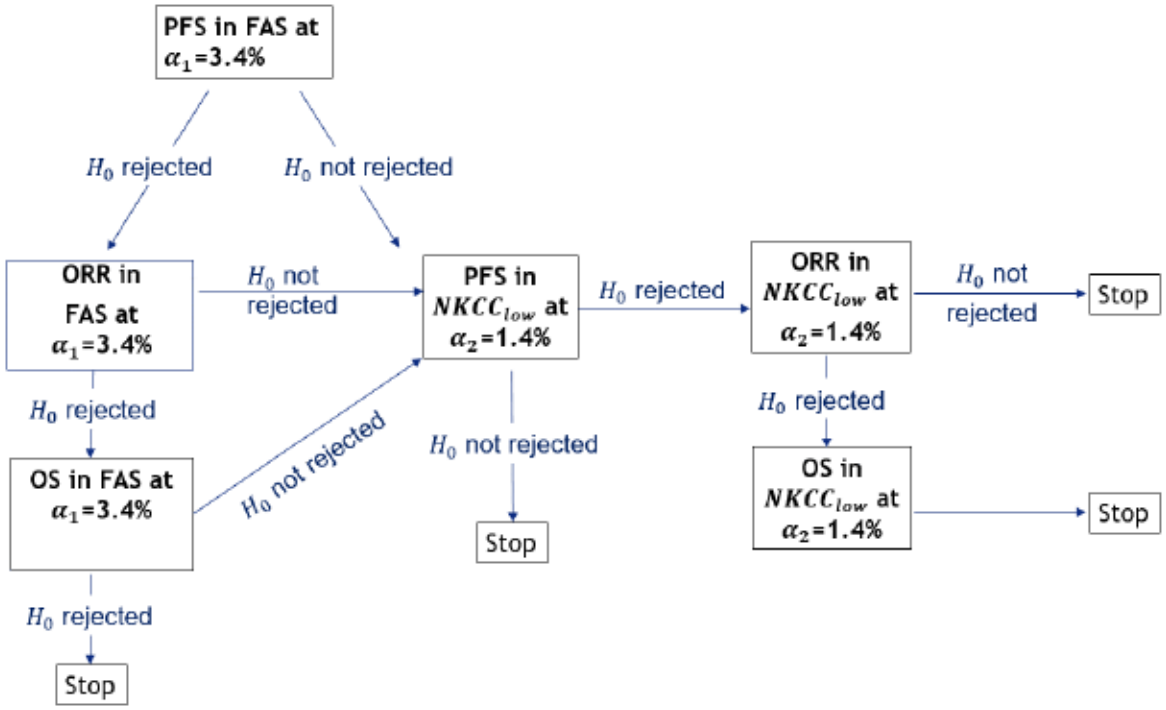
The following scheme will be followed to test the co-primary endpoints and the secondary endpoints:

1) For confirmatory hypothesis testing at the final analysis, the p-values of the statistical tests for the primary and key secondary endpoint will be combined from stage I (information up to the interim analysis) and stage II (information between the interim analysis and final analysis) of the study using the inverse normal method for the overall population (FAS) and the NKCC-low subgroup. This procedure preserves the overall (experiment-wise) type I error rate of $\alpha = 0.05$ (two-sided) (Wassmer 2006).

   The pre-specified weights to be used for combining the p-values from the two stages should satisfy the condition that the sum of the square of the weights add up to 1. The square of the weight at stage I will be equal to 0.4 and at stage II will be equal to 0.6.

2) The total Type I error in this study consisting of 4.8% will be distributed over the two co-primary endpoints and the key secondary endpoints according to the following scheme:

α_2^* is such that study wise Type I error rate is maintained at 4.8%



The alpha (two-sided) to be spent for the two co-primary endpoints will depend on the outcome of simulations demonstrating type I error control for either of the two scenarios:

a) Conservatively allocating alpha following a strict Bonferroni-type split of 3.4% for the overall population (FAS) and a maximum of 1.4% for NKCC-low. Wassmer (2011) and Sugitani et al. (2016), could demonstrate that combining inverse normal method and Bonferroni type partition of alpha into multiple hypothesis conserves the total study wise Type I error rate in the strong sense.

b) Alpha allocated to the NKCC-low subgroup depending on the correlation between the overall population (FAS) and the NKCC-low subgroup (Spiessens and Debois 2010). The correlation depends on the proportion of PFS events observed in the NKCC-low subgroup versus the total number of PFS events observed in the overall population (FAS). For example, if the NKCC-low subgroup contains 50% (or 55%) of the events observed in the overall population (FAS), alpha will be a maximum of 2.2% (or 2.3%) for the NKCC-low subgroup and 3.4% for the overall population (FAS).

3) If the primary endpoint is met for the overall population (FAS), the secondary endpoints will be hierarchically tested for the overall population (FAS) with the alpha that was provided for FAS (i.e., 3.4%). If any key-secondary endpoint is not met in the FAS, the co-primary endpoint of PFS and the key-secondary endpoints will be tested following the same hierarchical plan in the NKCC-low subgroup at the allocated alpha.

4) If the primary endpoint is not met for the FAS , but is met in the NKCC-low subgroup, the secondary endpoints will be hierarchically tested for the NKCC-low subgroup depending on the outcome of the simulations mentioned previously, that is

   a) with the alpha that was allocated to the NKCC-low subgroup with the conservative Bonferroni-type split (2a), or

   b) the alpha allocated for each key secondary endpoint will be the minimum of the alpha (2b)
      i. that was allocated to the NKCC-low subgroup and
      ii. the alpha that will be calculated considering correlation of the given endpoint between the NKCC-low subgroup and the overall population (FAS).

      For the key-secondary endpoints correlation will be calculated according to the following:
      - For ORR: based on the proportion of patients in NKCC-low vs FAS
      - For OS: based on the proportion of events in NKCC-low vs FAS

      The adequacy of the combined use of the
      - inverse normal method for the adaptive design
      - alpha spending for the two co-primary endpoints (as stated above)
      - hierarchical testing procedure of secondary endpoints in the NKCC-low subgroup

   in respect to the type I error control will be proven by simulations and reported in the SAP, which will be finalized prior to the interim analysis. The alpha to be allocated to the

NKCC-low subgroup will depend on the result of these simulations and will be decided following the conservative approach of adequately controlling the study-wise type I error rate of 4.8%.

13.4.1 Assessment of Efficacy Variables: Co-Primary Endpoints

The primary efficacy endpoint will be PFS, defined as the time elapsed between randomisation and IRC-assessed time of tumour progression or death from any cause. The date of progression will be deemed to be the first date when progressive disease was diagnosed. Patients with no disease progression as of the analysis cut-off date will be censored at the date of the last tumour assessment.

Patients lost to follow-up will be censored at the last available tumour assessment. Patients with no post-baseline assessment will be censored at the time of randomisation.

Patients who receive non-study anticancer treatment before disease progression, or patients with clinical but not radiological evidence of progression will be censored at the date of the last evaluable tumour assessment. Additional censoring details will be outlined in the SAP.

The final analysis will be performed on the FAS and the NKCC-low subgroup of the FAS, the latter defined as patients having 100 or less NK cells per µl blood at baseline.

Patients to be included in the NKCC-low subgroup must have an evaluable baseline NKCC value.

PFS will be compared between treatment groups in the FAS population and NKCC-low subgroup using the stratified log-rank test. The estimate of the hazard ratios (HRs) and corresponding 95% confidence interval (CI) will be provided using a Cox proportional hazards (CPH) model including treatment and the stratification factors (disease relapse/recurrence: ≤12 months versus >12 months from last treatment, ECOG performance status: 0-1 versus 2, age≤ 65 years versus >65 years and the number of previous systemic therapy lines ≤2 versus >2). The stratification factors will be defined as per their randomisation assignment. PFS for each arm and analysis population will be summarised using the Kaplan-Meier method.

Various supportive analyses may be performed using the FAS and NKCC-low subgroup (unless otherwise noted):

1. The primary efficacy endpoint analysis as outlined above will be conducted using the PPS.
2. An unstratified log-rank test will be calculated, and a CPH model fit, with only treatment in the model.
3. Multivariate analysis will be performed including the stratification factors, bone marrow involvement, and the following set of potential prognostic/predictive factors: race, GCB versus non-GCB DLBCL, IPI, prior ASCT, number of prior therapy lines:

a) A step-wise selection process will be used to identify a final subset of factors to be included. Once the subset is established, then treatment will be added to the model to assess its effect.
b) An exploratory analysis of treatment by factor interactions using the CPH model will be carried out. Further details will be provided within the SAP.

4. Analyses will be done for the subgroups of the stratification factors and bone marrow involvement, as well as any other prognostic factors identified in the above multivariate analysis. The HR and 95% CI will be presented for each subgroup.

Various sensitivity analyses regarding missing data will be performed using the FAS and NKCC-low subgroup:

1. Patients lost to follow-up, but having an available death date, will be included in the time-to-event analysis as an event. This will account for a possible imbalance in deaths, which could bias the PFS measurement by overestimating the PFS in the treatment arm with less documented follow-up.
2. Interval censoring will be applied. Different considerations for interval censoring will be considered with details specified in the SAP.
3. An analysis will be done as per the primary efficacy endpoint analysis but with central reader baseline diagnosis results. This is to ascertain that local and central reader differences do not affect the results.
4. The method of multiple imputation may be applied to account for NKCC values missing at baseline. This will be implemented in case of more than 10% missing baseline NKCC values.
5. Cox PH Model to estimate the HR in FAS and NKCC-low subgroup may include the additional cofactor of NKCC-low baseline status in the model.
6. To account for a possible imbalance between treatment arms in the NKCC-low subgroup, balancing of covariates via Propensity Score weighting method (Li et al. 2018) may be applied.

Further types of analyses on PFS may be specified in the SAP.

13.4.2 Analyses of the Secondary Efficacy Endpoints

Hierarchical testing will be employed for key secondary endpoints, with the primary endpoint PFS serving as a gatekeeper. The Type I error rate will be adjusted accordingly to support labelling claims for key secondary endpoints.

Specifically, the following procedures will be implemented to maintain the overall Type I error rate across the primary and two key secondary endpoints of the study at an adjusted two-sided significance level alpha for the final analysis (for details see Section 13.11.1).

The primary efficacy endpoint analysis will serve as the gatekeeper for the key secondary endpoint analyses, i.e., the primary efficacy hypothesis must be rejected at the two-sided adjusted significance level alpha before the efficacy hypotheses for the secondary efficacy

endpoints can be tested. The key secondary endpoints will be the following (in the order of descending importance):

- Key secondary 1: best ORR
- Key secondary 2: OS

If the primary hypothesis is rejected, the two key secondary endpoints will be sequentially tested at the two-sided adjusted significance level alpha in the order listed above. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be mentioned for the remaining secondary endpoints. Analyses and p-values will be reported for all the efficacy endpoints, including the primary endpoint, the key secondary endpoints, and all other secondary endpoints listed in Section 7.2.

Note that if the primary endpoint is met for the overall (FAS) population, the secondary endpoints will be hierarchically tested for the FAS population with the alpha that was provided for FAS.

If the primary endpoint is not met for the FAS population, but is met in the NKCC-low subgroup, then the secondary endpoints will be hierarchically tested for the NKCC-low subgroup with the alpha that was provided for the NKCC-low subgroup (see Section 13.4.1), taking into account the correlation between the subgroup and the overall population (FAS) with regards to the secondary endpoint considered. .

If the primary endpoint is not met in the overall population [redacted], there will not be any alpha left to carry over for the secondary endpoints. In this situation, analysis of the secondary endpoints will be performed for the [redacted] as exploratory analyses. The p-values will be presented for illustrative purposes only.

13.4.2.1 Best Objective Response Rate

Objective response is defined when a patient is classified as having a CR or PR after DLBCL evaluation using the International Working Group response criteria for malignant lymphoma (Cheson et al. (2007); see Appendix L).

For each visit available, the number (counts and percentages) of patients in each of the following categories will be presented in a table: progressive disease, SD, PR, CR and objective response (CR or PR). Tabulation will show missing response evaluations as well, including these patients in the denominator for calculating the rates. DLBCL response assessments of local and IRC evaluations will be tabulated.

The best ORR is defined as the proportion of patients with CR or PR (see Section 6.2).

The denominator for calculating the rates/percentages will be based upon the total number of patients in the FAS population (and in the NKCC-low subgroup of the FAS). Patients with no post-baseline assessment of response will be included as nonresponders. Response rates will be

evaluated using the local and the central evaluation of the IRC. For the IRC evaluations the best ORR for each treatment arm will be the rate of patients who met the objective response definition up until the last available tumour assessment. The number of patients classified as responders and the respective rates as well as 95% CIs (Clopper-Pearson) will be presented. The best ORRs will also be compared between treatments using the Cochran-Mantel-Haenszel test stratified by randomisation strata.

Best response will be determined with respect to all response evaluations given until last available tumour assessment. Best response rates will be descriptively tabulated as the best ORR, distinguishing between the local and the central radiological evaluation.

The best ORRs may also be explored within further subgroups other than NKCC-low. Details will be provided within the SAP.

13.4.2.2 Duration of Response

DoR is defined as the time elapsed between the initial time point of tumour response (CR or PR) and the time of documented tumour progression. Response duration will be tabulated for results given by the local assessment as well as by the central assessments of the IRC. Descriptive analysis will be done for DOR among patients who responded in each arm for the overall population and for the NKCC-low subgroup.

13.4.2.3 Disease Control Rate

DCR is defined as having a response of CR, PR or SD (DCR = ORR + SD). The DCR will be evaluated as for the best ORR.

13.4.2.4 Time to Progression

TTP is defined as the time from randomisation until documented DLBCL progression or death as a result of lymphoma. The event of interest is only disease progression and death from lymphoma; death from other causes will not be considered in relation to the TTP evaluation.

Patients not experiencing disease progression will be censored at the last available DLBCL assessment. Patients dying from other causes will be censored at the time of death. Early drop-outs without any documented date of progression will be censored at the last available DLBCL assessment.

TTP will be analysed using the same event analysis sets as for the primary efficacy endpoint analysis of PFS. Statistics to be reported and graphical visualisations will be the same as for the primary efficacy parameter.

TTP on-study will be compared with the TTP on each patient's most recent prior therapy via tabulated descriptive statistics. Additionally, TTP on the patient's most recent prior therapy will be tested as a factor in a CPH model with stratification factors and bone marrow involvement to determine if this significantly influences the TTP of patients under study treatment.

13.4.2.5 Overall Survival

OS is defined as the time from randomisation to the date of death. Patients who are alive or who drop out early will be censored at the last available study visit assessment. Analysis strategies will follow those applied for the primary efficacy parameter.

13.4.2.6 Time to Next Treatment

TTNT is defined as the time from randomisation to the time of institution of next therapy for any reason including disease progression, treatment toxicity and patient preference. TTNT will be summarised by treatment group and presented using Kaplan-Meier curves. TTNT will also be analysed in a similar manner to the primary efficacy endpoint analysis using a stratified log-rank test and a CPH model. Sensitivity analyses may be performed and would be outlined in the SAP.

13.5 Quality of Life Questionnaires EORTC QLQ-C30 and EQ-5D-5L

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These includes five **functional scales** (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), three **symptom scales** (fatigue, nausea and vomiting, pain), a **global health status/QoL scale** and six **single items** (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high or healthy level of functioning, a high score for the global health status represents a high quality of life, but a high score for a symptom scale or symptom item represents a high level of symptomatology and functional impairment.

The EQ-5D-5L questionnaire comprises a descriptive system and a visual analogue scale (VAS). The EQ-5D-5L contains five questions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Respondents could choose one of the five levels to describe their health state on the day of survey. These five levels include “no problem”, “slight problems”, “moderate problems” and “severe problems” in all five dimensions, and “unable” in mobility, self-care and usual activities or “extreme problems” in pain/discomfort and anxiety/depression. The health of the respondent is indicated by a tick or a cross in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent’s health state. EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single index value.

A vertical, hash-marked visual analogue scale (EQ-VAS) is anchored by 0 (the worst imaginable health state) at the bottom and 100 (the best imaginable health state) on the top for respondents to rate their overall health. A cross in the EQ-5D-5L VAS scale indicates how the respondent health is today and then the number is transcribed in a box.

Scoring of each scale will be calculated, following the respective manuals. The baseline assessment is the last available assessment before first infusion of study medication. Descriptive statistics for each of the scores will be tabulated. Also, changes from baseline for each score, and

numbers of patients with improvement and deterioration will be summarised by visit. Further detail will be provided in the SAP.

13.6 Immunogenicity Analysis

One of the secondary objectives will be to evaluate the potential immunogenicity of MOR00208 in the immunogenicity analysis set (IAS). The analysis will show both the absolute number and percentage of patients who develop anti-MOR00208 antibodies. Results of semi-quantitative anti-MOR00208 antibody titre determinations of confirmed positive samples will be tabulated, as well as the number and percentage of patients having positive assessments. Confirmed positive anti-MOR00208 antibody samples will be characterised with respect to neutralising capacity in a neutralising antibody (NAb) assay.

13.7 Pharmacokinetic Analysis

One of the secondary objectives will be to investigate the PK profile of MOR00208 using the PK analysis set (PKAS). PK parameters for MOR00208 will be computed based on non-compartmental data analysis and summarised using descriptive statistics (such as n, mean, geometric mean, standard deviation, coefficient of variation, median, minimum and maximum). Mean concentrations (on original and on log-linear scale) of MOR00208 will be visualised in figures. Further details of PK analysis will be specified in the SAP.

In addition, a population PK analysis of MOR00208 will be conducted. The planned meta-analysis will encompass PK data from MOR208C204 and other clinical trials with MOR00208. The analysis will provide an understanding of the population PK of MOR00208 and determine the influence of intrinsic and extrinsic factors (such as but not limited to age, gender, race, level of hepatic or renal function and presence of anti-drug antibodies) that may influence PK variability. Details of the intended population PK analysis will be described in a separate population PK protocol and the results will be described in a separate population PK study report.

13.8 Analysis of Safety Data

13.8.1 Adverse Events

One of the secondary endpoints is the evaluation of the frequency, incidence, and severity of AEs.

AEs will be coded according to MedDRA SOC and preferred terms. Incidence and frequency of all AEs will be summarised by SOC, preferred term, relationship to treatment, severity and seriousness.

An AE summary table will be presented showing the number of events, number of patients and the percentage of patients having:

- Treatment-emergent adverse events (TEAEs)
- SAEs
- Drug-related TEAEs (split by BEN-, MOR00208- and RTX-related and overall)
- Drug-related TEAEs in each severity/toxicity grading (according to NCI-CTCAE)
- TEAEs that led to study discontinuation
- IRRs by grade.

In addition, the incidence rate of AEs in each of the above-mentioned categories will be presented with 95% CIs based on the number of patients and the number of AEs.

The number of AEs, in relation to the number and percentage of patients with one or more TEAEs, will be summarised by MedDRA SOC and preferred term for each treatment arm. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity/toxicity, and TEAEs by relationship to study drugs, SAEs, drug-related TEAEs and TEAEs that led to study discontinuation.

The sponsor will describe AESIs, in addition to those reported as SAEs. AESI tabulations will be analogous to the tabulation of TEAEs.

13.8.2 Clinical Laboratory Evaluations

The analysis of central laboratory parameters for each treatment arm will be presented, separated into blood parameters (e.g., haematology, serum chemistry, coagulation) and urine parameters (urinalysis). All data collected in the course of the study will be listed.

Descriptive summaries of actual (absolute) values and change-from-baseline values will be presented, e.g., for haematology and serum chemistry for the SAF by visit.

Each abnormal value measured in the central laboratory will be flagged to show whether it is a value below or above the reference range. For the assessment of laboratory variables, the investigator will need to judge their clinical significance.
The assessment of the clinical relevance of central laboratory variables will be tabulated by time point for each clinical laboratory analyte using frequency tabulations. Additionally, for each laboratory parameter, shifts in assessments from baseline to selected post-administration time points will be presented. Further details will be provided in the SAP.

If NCI-CTCAE grades are available for a clinical laboratory analyte, they will be derived according to NCI-CTCAE, Version 4.0 (or higher), and used to present additional frequency and shift tables based on NCI-CTCAE grades.

The assessment of categorical urinalysis variables will be tabulated by time point for each urine parameter for the SAF (frequency tables). Additionally, for each of these, urine parameter shifts

in assessments from baseline to selected post-administration time points will be presented (shift tables).

Central laboratory values that are outside the reference range will also be flagged in the data listings, along with the corresponding reference ranges.

13.8.3 Physical Examination

Baseline PEs will be summarised by body system. New and worsening abnormal PE findings during the study will be entered as AEs and analysed within the AE tables.

13.8.4 Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs. These summaries will be presented for the SAF at all time points. Each abnormal value will be flagged to show whether it is a value below or above the normal limit.

13.8.5 Electrocardiograms (12-lead ECG)

Summary ECG assessment (categories: 'normal'; 'abnormal, clinically significant'; 'abnormal, not clinically significant') will be tabulated by time point using frequency tabulations.

Each result of the 12-lead ECG (PR, QRS, RR and QT interval values) will be flagged to show whether it is a value below or above the normal limit.

Summary statistics for all time points will be displayed for QT and both QTc correction methods. The Bazett's correction method (Bazett 1920) for QTc will be applied as follows:

Bazett's Correction (QTcB) $$QTcB = \frac{QT_{msec}}{\sqrt{RR}}$$

The Fridericia correction method (Fridericia 1920) for QTc will be applied as follows:

Fridericia's Correction (QTcF) $$QTcF = \frac{QT_{msec}}{\sqrt[3]{RR}}$$

Where relative rate (RR) = 60/heart rate

Also, the number and percentage of patients with QTc values above the normal limit (>450 ms, >480 ms, >500 ms) and the number and percentage of patients who experienced a change ≥30 ms or a change ≥60 ms will be presented by time point.

13.9 Biomarkers

13.10 Other Data

All other data as documented in the eCRF will be listed and/or tabulated using descriptive statistics or counts/percentages, depending on the nature of data.

13.11 Sample Size Determination

Approximately 330 patients with R-R DLBCL who meet the inclusion criteria and have none of the exclusion criteria will be randomised into one of the two parallel treatment groups in a ratio of 1:1. The study will be performed according to a two-stage, group-sequential, adaptive design with a possible sample size adjustment after a planned interim analysis with a check for futility.

The two-stage, group-sequential, adaptive design with one interim analysis and a single primary endpoint was evaluated by simulations to investigate the appropriateness of this approach for the study objectives, at the time of the original study design. Details of these simulations will be given in the SAP. Prior to the interim analysis, the study design was modified to incorporate one additional co-primary endpoint (based on the NKCC-low subgroup). Further simulations were conducted and details of these will also be provided in the SAP.

13.11.1 Parameters and Results of Sample Size Determination

Study sample size estimations and assumptions based on the original study design (i.e., with a single primary endpoint) are summarised in Table 8. The primary objective of the study is to detect a statistically significant difference in PFS for the experimental treatment arm relative to the comparator arm. At the time of the original study design, it was assumed that the median PFS in the MOR00208 with BEN group would equal 7.0 months versus 4.9 months in the comparator standard treatment RTX with BEN group (HR of 0.70), based on literature data (Ohmachi et al. 2013, Vacirca et al. 2014). A two-stage, group-sequential, adaptive design with one interim analysis was planned. Testing of the null hypothesis at the final analysis would be based on the inverse normal method applying O'Brien-Fleming boundary (O'Brien and Fleming 1979,

Wassmer 2006). This procedure preserves the overall (experiment-wise) type I error rate of $\alpha = 0.05$ in a strong sense for data-driven changes in design after interim analysis of survival trials.

Based on the original study design and assumptions, a total number of 256 PFS events are required based on a HR of 0.70 with 80% power at final analysis, using a two-sided log-rank test at an alpha level of 4.8% and a 1:1 randomisation ratio between the two treatment groups. Based on 18 months of enrolment and a 12-month Follow-Up, 286 evaluable patients need to be enrolled. Applying a 13% drop-out rate would result in a total number of patients of approximately 330.

Table 8: Assumptions for Sample Size Estimation (original study design and assumptions)

Parameter for sample size estimation	
MOR00208 with BEN treatment arm: median PFS	7.0 months
RTX with BEN treatment arm: median PFS	4.9 months
Hazard ratio (experimental/comparator)	0.70
Overall significance level (overall type I error rate of α)	5.0%
Adjusted significance level at interim analysis (O'Brien-Fleming)	0.52%
Adjusted significance level at final analysis (O'Brien-Fleming)	4.8%
Power	80%
Enrolment duration (months)	18
Follow-up duration (months)	12
Accrual rate	About 17 patients/month
Events required	256
Evaluable patients to be enrolled	286
Overall patient number (including 13% drop-out)	**330**

With proposed introduction of co-primary endpoint in NKCC-low subgroup, and a split of total alpha of 4.8% in the overall (FAS) population and the NKCC-low subgroup, there will be a change in the power of the two-sided log rank test if the total number of overall (FAS) PFS events is kept unchanged at 256. The table below presents the assumptions and the power as a consequence of alpha-splitting and introduction of the co-primary endpoint:

Table 9: Power Calculation for Overall Population and the NKCC-low Subgroup (as a consequence of alpha splitting) under different scenarios

Overall Population Assumption	N= 330			N=450		
	Median PFS = 7m vs. 4.9m			Median PFS = 7m vs. 4.9m		
	Hazard ratio = 0.7			Hazard ratio = 0.7		
	Events = 256			Events =369		
	Alpha = 3.4%			Alpha = 3.4%		
	Power = 77%			Power = 90%		
Possible Scenarios for NKCC-low Subgroup						
Overall Population Sample Size	N= 330			N=450		
NKCC-low Sample Size	132 (40%)	148 (45%)	165 (50%)	180 (40%)	202 (45%)	225 (50%)
Median PFS (months)	5 vs. 3	5 vs. 3	5 vs. 3	5 vs. 3	5 vs. 3	5 vs. 3
Hazard Ratio	0.6	0.6	0.6	0.6	0.6	0.6
Events	109	123	137	154	171	191
Alpha (two-sided)	1.4%	1.4%	1.4%	1.4%	1.4%	1.4%
Power	0.58	0.65	0.70	0.76	0.81	0.86
Proportion of total events	0.43	0.48	0.54	0.42	0.46	0.52
Alpha adjusted (two-sided)*	2.0%	2.2%	2.3%	2.0%	2.1%	2.2%
Power adjusted	0.63	0.71	0.76	0.8	0.85	0.89

* Assuming correlation between the subgroup and the overall population (Spiessens and Debois 2010).

As outlined in Section 13.12, at the time of the interim analysis, the IDMC will have the option of recommending an increase in sample size to 450 patients. The statistical details for a sample size increase to 450 patients, based on the revised study design (i.e., with two co-primary endpoints and alpha spending) are summarized in the SAP.

In addition to PFS, OS is considered an important endpoint to inform both efficacy and safety. Table 10 below provides details on the operating characteristics for OS at the time of Final Analysis:

Table 10: Operating Characteristics for OS at the Final Analysis

Sample Size Considerations	Details
Sample Size	450
Median OS in control arm (RTX with BEN)	Full population: 10 months NKCC-low subgroup: 7 months
Median OS in experimental arm (MOR00208 with BEN)	Full population: 14.3 months NKCC-low subgroup: 11.7 months
Assumed OS HR	Full population: 0.7 NKCC-low subgroup: 0.6
Test	2-sided stratified log-rank test
Global significance level	two-sided 5%
Expected OS events[1]	Full population: 338[1] NKCC-low subgroup: 135[2]
Local two-sided significance level	Full population: 3.4% NKCC-low subgroup: 1.4%
Power at the time of Final Analysis	Full population: 88% NKCC-low subgroup: 70%

[1] These numbers are based on the assumption that Final Analysis will occur when approximately 75% of patients have died but using local significance levels as stated in Figure 9-1 of the SAP.
[2] Assuming 40% of all patients belong to the NKCC-low subgroup.

In connection with the above, Table 11 provides the power calculations for OS given the different number of possible OS events in the FAS and the NKCC-low subgroup:

Table 11: Power Analyses for OS

Full population			NKCC-low subgroup		
Number of OS events	**Information fraction**	**Power**	**Number of OS events**	**Information fraction**	**Power**
250	91%	76%	100	61%	54%
275	**100%**	**80%**	125	76%	66%
300	109%	84%	136 (projected for Final Analysis)	82%	70%
325	118%	87%	150	91%	75%
340 (projected for Final Analysis)	120%	88%	**165**	**100%**	**80%**
350	127%	89%	175	106%	83%

*at two-sided alpha of 3.4% for the FAS, and 1.4% for the NKCC-low subgroup. The calculations are based on following assumptions: median OS for BR in FAS: 10 months, true hazard ratio of 0.7; median OS for BR in NKCC-low: 7 months, true hazard ratio of 0.6.

The information fraction in the above table refers to the number of OS events that might be observed compared to the calculated benchmark number of OS events at 80% power.

13.12 Interim Analysis

The interim analysis is planned after the observation of 50% of the required events, i.e., after 128 PFS events. The HR will be calculated and three outcomes will be possible based on the interim result. The study may be stopped due to futility, the study may continue with the minimum planned number of 330 patients (256 PFS events), or the sample size may be increased to 450 patients (to obtain 369 PFS events). Early stopping for efficacy is not allowed.

The possible scenarios of combination of observed PFS hazard ratios (MOR00208 plus BEN versus RTX plus BEN) in the FAS and NKCC-low subgroup and potential IDMC recommendations based on them are summarized in Table 12.

Table 12: IDMC Decision Guide Based on Results of the Interim Analysis (non-binding)

Scenario	Observed PFS hazard ratio at interim analysis (experimental vs comparator arm)		IDMC recommendation
	Overall population	NKCC-low subgroup	
1	≤0.75	≤0.65	Continue trial without sample size modification (SS = 330), if both conditions are met.
2	>0.85	>0.75	Stop for futility, if both conditions are met.
3	All other scenarios		Increase sample size to 450

In addition, the IDMC will recommend to continue or not continue the development of a companion diagnostic. Guidance for IDMC recommendations will be provided in the IDMC charter.

For confirmatory hypothesis testing at the final analysis, the inverse normal method of combining the p-values will be used. This procedure preserves the overall (experiment-wise) type I error rate of $\alpha = 0.05$ (two-sided).

13.13 Procedures for Missing, Unused, and Spurious Data

Missing values will not be substituted by estimated values but will be treated as missing in the statistical evaluation. All data from all patients randomised in the study will be included in all listings, plots, summary tables, and statistical analyses with respect to the analysis populations assigned to the various objectives.

13.14 Rules for Excluding Patients from Analysis

All dosed patients will be included in the analyses unless not otherwise specified (e.g., with respect to the different analysis population definitions).

13.15 Procedures for Reporting Deviations from Original Statistical Plan

Details of the analyses to be performed on data from this study will be provided in a separate SAP. Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final clinical study report.

14 SPECIAL REQUIREMENTS AND PROCEDURES

14.1 Independent Data Monitoring Committee (IDMC)

The design of the study specifies the establishment of an IDMC according to the ICH E9 guideline and in line with the recommendations of the US FDA Guidance on "*Establishment and Operation of Clinical Trial Data Monitoring Committees*" (March 2006). The IDMC will be responsible for periodically monitoring study enrolment statistics, compliance, and efficacy and safety data from the ongoing trial and for alerting the sponsor of possible concerns related to the conduct of the trial.

The sponsor will appoint the IDMC prior to the randomisation of the first patient into the study.

As the combination of MOR00208 and BEN will be systematically evaluated for the first time in a setting of a clinical trial, IDMC review will be mandated during Initial Safety Evaluation (Phase II of the trial) to conclude whether the combination treatments are safe (see Figure 1).

In the course of Initial Safety Evaluation, the first three patients in both investigational arms (MOR00208+BEN and RTX+BEN) will be dosed sequentially with a 48-hour lag period between the enrolments of two consecutive patients (counted from C1D4).

After completion of the first treatment week (C1D8) by the third consecutive patient in each arm (approximately 6 patients in total) the safety data will be reviewed by the IDMC.

Following a positive recommendation of the IDMC, seven additional patients in each arm may be dosed in parallel (approximately 14 patients in total). An additional IDMC review will take place after the last of 10 patients in each arm (approximately 20 patients in total) have completed C3D1 visit in their respective treatment allocation arm (complete Initial Safety Evaluation).

The exact number of patients eligible for evaluation depends on the treatment allocation within the randomisation blocks. Furthermore, for every patient who withdraws or discontinues in the course of Initial Safety Evaluation before having received study drug on Cycle 3 Day 1, a new patient may be randomised. For a schematic presentation of the study outline, see Figure 1 and Figure 2.

Should the IDMC maintain their initial recommendation that the combination treatments are safe, the trial may proceed further with recruitment (Phase III of the trial). Subsequent IDMC meetings will be called for as outlined in the IDMC Charter throughout the entire trial. Recruitment will continue seamlessly between meetings unless specifically requested by IDMC.

Each IDMC review will encompass the number, frequency, severity and type of AEs, as well as clinical laboratory biochemistry and haematology parameters and other relevant safety data. The IDMC will also advise the sponsor whether the trial design requires modifications or has met the pre-defined trial stopping rules.

In addition, the IDMC will be entrusted to conduct the trial's planned interim analysis as a confidential process. Although the trial will be conducted in an open-label fashion, where investigators and patients are aware of individual treatment assignment and outcome at their site, the results of the comparative interim analysis (treatment arm versus comparator arm) will only be available to IDMC members. This fulfils the need of restricting the analysis conduct and the disclosure of the interim analysis results to only a limited and predetermined number of people for the purpose of maintaining the integrity of the trial. The IDMC will operate under a Charter that describes the composition, roles and responsibilities of the committee and identifies the members and the contact persons relevant to the trial. All other persons involved in the trial conduct will remain blinded to the interim analysis results until the regular end of the trial has been reached, or until the trial has been stopped earlier (due to futility, or by decision of the sponsor).

The IDMC will be advisory to the sponsor. The sponsor will be responsible for reviewing the IDMC recommendations, to decide whether to continue or terminate the trial due to futility, and to determine whether any amendment to the protocol or changes in study conduct are required.

The information about further study conduct after the interim analysis will be used for a possible amendment of the existing trial protocol or as needed by the regulatory authorities.

If the sponsor decides to stop the trial due to futility, disclosure of the results will be performed as usual following the defined principles at a final analysis. If the sponsor decides to continue the trial or to continue the trial with modifications, the interim results will be kept confidential. Investigators will only be informed about the decision to continue/to continue with modifications/or to discontinue the trial.

14.2 Independent Radiology/Clinical Review Committee (IRC)

The primary endpoint, PFS, will be evaluated through central review by the IRC. The process will be defined in details in the text of the IRC Charter.

For radiology assessment, two primary reviewers (Radiology Reviewers 1 and 2) will independently review each patient's scans according to the International Working Group 2007 response criteria (Cheson et al. 2007). Adjudication will be required if Radiology Reviewers 1 and 2 disagree on the outcomes, namely Date of Progression, Best Response, and/or Date of Initial Response. In order to resolve discrepancies, Reviewer 3 (Adjudicator) will independently evaluate the case in question. Reviewer 3 will have simultaneous access to all images and previous assessments (i.e., images, image overlays, time point evaluations, and summary findings from both primary reviewers). Reviewer identity will be fully blinded. Reviewer names will not be added to the information provided for adjudication, and furthermore, the order in which their findings are presented will be randomised across cases to prevent conditioned bias.

Reviewer 3 will choose the assessment that he or she considers to represent the more correct assessment of the outcomes in the following order of precedence: Date of Progression, Best Response, and Date of Initial Response.

Following radiology review, the final radiology assessments and patient clinical data will be presented to the clinical oncologist who will determine the final outcome for each patient based on review of both imaging and clinical data.

The outcome of this review is either the PFS date or a censoring date, which is the date of last follow-up without evidence of disease progression for all patients submitted for review.

14.3 Protocol Amendments and Other Changes in Study Conduct

Any changes to the protocol will be made in the form of an amendment.

Changes to the conduct of the study are not permitted. Any unforeseen changes in the study conduct will be recorded in the clinical study report.

14.4 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, Incyte Corporation will obtain favourable opinion/approval from the appropriate regulatory bodies/local health authorities (in accordance with local regulations) and the IRB/IEC to conduct the study in accordance with ICH GCP and applicable country-specific regulatory requirements.

No substantial changes to the final approved protocol will be initiated without the IRB's/IEC's prior written approval or favourable opinion and approval by the regulatory bodies/local health authorities, except when necessary to eliminate immediate hazards to the patients or when the change involves only logistics or administration.

This clinical study was designed and shall be conducted and reported in accordance with the protocol, with ICH E6 GCP guidelines, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki, including, but not limited to:

- IRB/IEC review and favourable opinion/approval of the study protocol and any subsequent amendments
- Patient informed consent
- Investigator reporting requirements.

The investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study that is relevant to the patient's decision to participate.

Informed consent must be given by the patient before the patient is exposed to any study-related procedure, including screening tests for eligibility.

14.5 Quality Control (Study Monitoring)

Study monitoring will be performed in accordance with ICH E6 GCP guidelines, the sponsor's and CRO's SOPs, the sponsor's and CRO's written instructions, the protocol, and all applicable laws and regulations.

The sponsor's monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and the sponsor's requirements.

Incyte Corporation and the CRO will monitor the study to ensure that the:

- Data are authentic, accurate, and complete
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agree to allow the monitor direct access to all source data documents.

14.6 Quality Assurance

According to ICH E6 GCP guidelines, the sponsor or regulatory authorities may audit the investigational sites. The sponsor's Quality Assurance Unit and/or their authorised representative(s), independent of the Clinical Operations and Clinical Development Departments, are responsible for auditing the study. The investigator must accept such audits by the sponsor's Quality Assurance Unit and/or their authorised representative(s) and ensure access to all source data/documents.

The investigator must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP guidelines. If informed that a regulatory inspection will take place, the investigator must inform the sponsor without delay.

14.7 Insurance

This study is covered under the sponsor's Liability Insurance Policy covering damage to patients according to applicable legal requirements. A copy of the Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage will be provided to the investigator as required by Regulatory Authorities, IRBs or IECs.

The investigator must inform the patients accordingly and must also point out that the patients are allowed to undergo other medical treatment (except in an emergency) only with the investigator's prior approval or to receive additional medication only with the investigator's prior approval.

14.8 Publication Policy

Any presentation or publication of data from this study will be intended as a joint publication by the investigator(s)/appropriate study centre personnel and appropriate sponsor personnel. Authorship will follow the International Committee of Medical Journal Editors *Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals* (http://www.icmje.org/recommendations/) and will be defined prior to the first publication.

For multicentre studies, it is mandatory that the first publication be based on data from all centres, and that the data are analysed and submitted as stipulated in the protocol by a statistician assigned by the sponsor.

Thus, no investigator or institution may publish any results of the study conducted at their site, before such a first multicentre publication is made which covers the data from all centres. The authors have the final responsibility for the decision to submit their manuscript and shall be given full access to the data resulting from the study.

The coordinating investigator and/or authors shall coordinate any intended publication of study results with the sponsor, to enable the sponsor to ensure that results are presented in a responsible and coherent manner.

The sponsor reserves the right to review all manuscripts and abstracts at least 60 days before their submission for publication or presentation. This is not intended to restrict or hinder publication or presentation, but is to allow the sponsor to protect the confidentiality of information and to provide comments that may not yet be available to the investigator.

At the sponsor's request, any confidential information (other than study results) will be deleted and all reasonable comments made by the sponsor will be incorporated prior to the submission for publication or presentation. In the rare event that such publication would affect the patentability of any invention to which the sponsor has rights, the sponsor has the right to request an additional delay to the proposed publication of no more than 90 days so as to allow the sponsor to protect its intellectual property rights.

The results of the study may be used by Incyte Corporation for the purposes of national and international registration, publication, and information for medical professionals. If necessary, the authorities will be notified of the investigators' names, addresses, qualifications, and extent of involvement.

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16 APPENDICES

16.1 Appendix A: Cockcroft-Gault Formula

Cockcroft-Gault Equation:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

This formula presumes weight to be measured in kilograms and creatinine to be measured in mg/dL.

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

Source: Cockcroft and Gault (1976). Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1) 31-41.

16.2 Appendix B: Highly Effective Contraception

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Source: Clinical Trial Facilitation Group (CTFG) (15 September 2014). Recommendations related to contraception and pregnancy testing in clinical trials.

NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not highly effective methods of contraception.

16.3 Appendix C: Overview of published data on NKCC as a prognostic factor in DLBCL and FL

Publication (study name)	Study type Number of patients	Patient population	Treatment	NKCC cut-off (cells/µL)	Treatment effect based on NKCC (NKCC-low vs. NKCC-high comparison*)
Klanova et al. (2017) (GOYA)	Prospective, randomized phase III n=1287	Newly diagnosed DLBCL	R-CHOP vs obinutuzumab-CHOP	100	Univariate Analysis - PFS HR (95% CI): 1.36 (1.07-1.72) *Inverse: 0.74 (0.58-0.93)* p=0.01
Klanova et al. (2017) (GALLIUM)	Prospective, randomized phase III n=1064	Previously untreated FL	R-chemo vs obinutuzumab - chemo	100	Univariate Analysis: PFS HR (95%CI): 1.57 (1.10-2.25) *Inverse:0.64 (0.44-0.9)* p=0.01
Kim et al. (2014)	Retrospective n=72	Newly diagnosed DLBCL	R-CHOP	100	Univariate analysis: PFS HR (95% CI): 6.03 (1.79-13.55) *Inverse: 0.17 (0.07-0.56)* p<0.001
Plonquet et al. (2007) (LNH98B3)	Prospective randomized phase II (after ASCT) n=136	Newly diagnosed DLBCL	ASCT followed by randomization to RTX or no RTX	80	Univariate analysis EFS HR (95% CI): 1.85 (1.14-3) *Inverse:0.54 (0.33-0.88)* $p = 0.01$
He et al. (2016)	Retrospective n=114	Previously untreated FL	RTX-containing therapy	100	Univariate analysis: PFS HR (95%CI) Univariate analysis: PFS HR (95% CI) 3.49 (1.6-7.63) *Inverse: 0.29 (0.13-0.62)* p=0.002

Publication (study name)	Study type Number of patients	Patient population	Treatment	NKCC cut-off (cells/µL)	Treatment effect based on NKCC (NKCC-low vs. NKCC-high comparison*)
Shafer et al. (2013)	Retrospective n=75	Newly diagnosed FL	Radiotherapy (11 patients) and/or single agent or RTX-containing regimens, or observation (n=35)	150	Multivariate analysis: OS HR (95% CI) 6.73 (0.76–59) *Inverse: 0.15 (0.017-1.3)* *p=0.08*
Jurczak et al. (2018) and MorphoSys/Incyte data on file (MOR208C201)	Prospective phase II (n=31)	R-R DLBCL	MOR00208 monotherapy	100	Univariate analysis PFS HR (95% CI) 0.24 (0.09, 0.70)
	Prospective phase II (n=31)	R-R iNHL, (pooled FL & other iNHL patients)			Univariate analysis PFS HR (95% CI) 0.39 (0.12, 1.25)

* Note that in randomized studies, hazard ratios shown in this column are for the NKCC-low versus the NKCC-high subgroup using pooled data from both treatment arms

ASCT: autologous stem cell transplant; CI: confidence intervals; DLBCL: diffuse large B cell lymphoma; EFS: event-free survival; FL: follicular lymphoma; FLIPI: follicular lymphoma International Prognostic Index; HR: hazard ratio; NKCC: natural killer cell count; OS: overall survival; PFS: progression-free survival; R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; R-R: relapsed/refractory; RTX: rituximab

16.4 Appendix D: Karnofsky Performance Status Scale

Definition of Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Source: Karnofsky and Burchena (1949). The Clinical Evaluation of Chemotherapeutic Agents in Cancer. In: MacLeod CM (ed). Evaluation of Chemotherapeutic Agents. New York: Columbia University Press; 1949: 196.

16.5 Appendix E: New York Heart Association Functional Classification

Criteria for NYHA Functional Classification	
NYHA Class	**Criteria**
I	No symptoms and no limitation in ordinary physical activity; shortness of breath when walking, stair climbing, etc.
II	Mild symptoms (mild shortness of breath and/or angina pain) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g. walking short distances, approximately >20–100 meters); comfortable only at rest
IV	Severe limitations; patient experiences symptoms even while at rest, mostly bedbound
Abbreviation: NYHA, New York Heart Association	

16.6 Appendix F: Information on Investigational and Registered Products

The Investigator's Brochure for MOR00208, and Summary of Product Characteristics (EMA) or Prescribing Information (US FDA) for RTX and BEN, will be supplied to the study sites.

16.7 Appendix G: Equivalent Doses for Corticosteroids

Equivalent doses for corticosteroids			
Name (INN)	**Example**	**Equivalent doses for 80 – 100 – 120 mg methylprednisolone**	**Potency**
Hydrocortisone	Hydrocortone®	400 – 500 – 600 mg	1
Prednisone	Decortin®	100 – 125 – 150 mg	4
Prednisolone	Decortin® H	100 – 125 – 150 mg	4
Methylprednisolone	Urbason®	80 – 100 – 120 mg	5
Dexamethasone	Fortecortin®	14 – 16 – 20 mg	30

16.8 Appendix H: Body Surface Area (BSA) Calculation

The algorithm to be used in this study is:

(Source: Mosteller RD., Simplified calculation of body-surface area. N Engl J Med, 317:1098, 1987)

BSA should be determined using the appropriate following calculation:

$$BSA = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

OR

$$BSA = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

16.9 Appendix I: Ann Arbor Staging - Cotswolds Recommendations

Stage I: involvement of a single lymphatic region (I), or localised involvement of a single extra lymphatic organ or site (IE).

Stage II: involvement of two or more lymphatic regions on the same side of diaphragm (II) or localised involvement of an extra lymphatic organ or site and one or more lymph node regions the same side of diaphragm (IIE).

Stage III: involvement of two or more lymphatic regions on both sides of diaphragm (III) which may also be accompanied either by localised involvement of an extra lymphatic organ or site (IIIE), or by involvement of the spleen (IIIS).

Stage IV: Diffuse or disseminated involvement of one or more extra lymphatic organs or tissue, with or without associated lymph node involvement.
Bone marrow or liver involvement will always be considered as stage IV.

Criteria for B-symptoms
The presence of: (a) unintentional weight loss of more than 10% within the previous 6 months and/or (b) fevers of greater than 100.5° F or 38.0° C for at least 3 consecutive days without other evidence of infection and/or (c) drenching night sweats without evidence of infection, is denoted by the suffix letter 'B'. 'A' indicates the absence of these symptoms.

Sources:

Ann Arbor Staging
Carbone et al. (1971). Report of the committee on Hodgkin's disease staging classification. Cancer Res;31:1860-61.

Cotswolds Recommendations
Lister et al. (1989). Staging for Hodgkin's disease. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol;7:1630-36 [Erratum; J Clin Oncol. 1990;8:1602].

16.10 Appendix J: International Prognostic Index (IPI)

One point is assigned for each of the following characteristics:

- Age older than 60
- Lactate dehydrogenase level higher than normal
- ECOG performance status score of 2 or greater (see Appendix K)
- Stage III or IV disease
- More than one involved extranodal disease site

The total score ranges from zero to five, corresponding to the following risk groups:

- Low risk: 0–1 points
- Low-intermediate risk: 2 points
- High-intermediate risk: 3 points
- High risk: 4–5 points.

Source: International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993). A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329(14):987-94.

16.11 Appendix K: ECOG Performance Status

ECOG Performance Status Grades	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al. (1982). Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

Credit: The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

16.12 Appendix L: Response Criteria

The response criteria in this study are those defined in the table below. All of them are based on the International Working Group response criteria (Cheson et al. 2007).

Definition of Response Criteria				
Response	**Definition**	**Nodal masses**	**Spleen, liver**	**Bone marrow**
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variable FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size on CT a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) Variable FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		

Definition of Response Criteria				
Response	**Definition**	**Nodal masses**	**Spleen, liver**	**Bone marrow**
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
Abbreviations: CR = complete response; FDG = [^{18}F]fluorodeoxyglucose; PET = positron emission tomography; CT = computed tomography; PR = partial response; SPD = sum of the product of the diameters; SD = stable disease; PD = progressive disease.				

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