CLINICAL STUDY PROTOCOL

L-MIND

AMENDMENT NO. 5

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

Brief Description of Study:	Open-label study to evaluate the safety and clinical efficacy of lenalidomide combined with MOR00208 in adult patients with R-R DLBCL (L-MIND)
Study Type:	Phase II
Sponsor:	MorphoSys AG
Sponsor's Address:	Semmelweisstr. 7 82152 Planegg Germany
Study Protocol Number:	MOR208C203
IND No.:	114,856
EudraCT No.:	**2014-004688-19**
Date of Protocol:	18 March 2015
Amendment No. 5:	Final v8.0, 24 February 2021

SIGNATURES

Amendment No. 5: Final v8.0, 24 February 2021

Approved/Authorised By:

Country Coordinating Investigator's Signature (in countries where required)

Signature of Principal Investigator

I have read the entire clinical study protocol. I agree that this protocol version contains all the information required to conduct this study. I agree to conduct the study as outlined in the study protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and the principles which have their origin in the Declaration of Helsinki; copies of both documents have been given to me by the sponsor. I will also ensure that co-investigator(s) and other relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines and the Declaration of Helsinki, to enable them to work in accordance with the provisions of these documents.

Investigator:

Contact Details of Key Study Personnel

Sponsor's Clinical Programme Leader	[redacted]
Sponsor's Clinical Project Manager	
Contact for Serious Adverse Events (SAEs):	
Medical Monitor (24/7 Medical Coverage)	

[redacted]

PROTOCOL SYNOPSIS

Title of Study	A Phase II, Single-Arm, Open-Label, Multicentre Study to Evaluate the Safety and Efficacy of Lenalidomide Combined with MOR00208 in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL)
Investigational Drugs	MOR00208 (an Fc-engineered, humanised, monoclonal antibody targeting the B-cell surface antigen CD19) and Lenalidomide (LEN: Revlimid®)
Protocol Number	MOR208C203
IND Number	114,856
EudraCT Number	**2014-004688-19**
Sponsor and CRO	**Sponsor:** MorphoSys AG Semmelweisstr. 7 82152 Planegg Germany [redacted]
Study Phase	Phase II
Background/Study Purpose and Rationale	Diffuse large B-cell lymphoma (DLBCL) represents approximately 40% of all non-Hodgkin lymphomas (NHLs), with a rate of incidence which continues to increase and a median age at diagnosis of 64 years. The addition of the CD20 monoclonal antibody (mAb) rituximab (RTX) to standard CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy (R-CHOP) has been shown to improve the outcome compared with CHOP alone in untreated patients with DLBCL. Despite advances in first-line treatment, 30–40% of such patients relapse. Patients progressing or relapsing after first-line treatment may be offered salvage chemotherapy followed by high-dose chemotherapy (HDC) with, if the disease is still chemosensitive, autologous stem-cell transplantation (ASCT). Several second-line combination therapies are used with variable success. However, a substantial percentage of patients will either fail to respond to salvage therapy and subsequently not be eligible for ASCT, or will progress after ASCT. Additionally, the use of HDC with stem cell support in patients with R-R DLBCL may not be appropriate for those with comorbidities or advanced age, restricting the benefit of this aggressive approach to a relatively small fraction of patients.

	R-CHOP-like regimens have become standard first-line treatment in patients with DLBCL. Those patients who have received prior RTX are less likely to respond to RTX-containing salvage treatment and therefore effective and well-tolerated new treatment modalities with manageable toxicities are needed to ameliorate prognosis in R-R DLBCL. Rational combinations of effective compounds have been shown to be active and often lead to better clinical outcomes in DLBCL than single-agent therapy. The B-lymphocyte lineage specific surface antigen CD19 is the earliest and most broadly expressed of the selective B-cell markers, and is highly expressed in the tumour cells of most patients with B-cell NHL. Because of this expression pattern, a CD19 antibody may have clinical utility as a new therapeutic approach to NHL treatment. MOR00208 is an Fc-engineered, humanised, mAb with significantly enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP) and direct cytotoxic effects (apoptosis) compared with the parental murine antibody. Monotherapy with MOR00208 has shown preliminary signs of clinical efficacy and acceptable toxicity in a phase I study in R-R chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and a phase IIa study in R-R NHL. Additionally, MOR00208 is currently being studied as single-agent therapy in a phase IIa study in R-R B-cell acute lymphoblastic leukaemia (B-ALL). Lenalidomide (LEN) belongs to a class of immunomodulating agents (immunomodulatory drugs [IMiDs®]), which have demonstrated direct tumouricidal and immunomodulatory actions. LEN has both antiproliferative and antiangiogenic activities, modulating the tumour cell microenvironment and stimulating the activity of effector cells such as cytotoxic T-cells and natural killer (NK) cells. LEN demonstrated manageable toxicity when administered as monotherapy and in combination, as well as a synergistic effect with RTX, administered alone or as a part of an immunochemotherapeutic regimen. Preclinical data suggest that the combination of LEN with MOR00208 may increase NK cell-mediated ADCC, making this combination of interest for further study in patients with R-R DLBCL. This patient population is particularly relevant for the current study as they can usually achieve a rapid and complete lymphoma regression with second-line therapy, but invariably experience relapse, which is the principal unfavourable prognostic factor. Combining two agents with probable synergistic mechanisms of action and acceptable safety profiles could potentially contribute to significantly prolonging time to progression, and possibly overall survival (OS), in this patient population. Therefore, this open label, single-arm, prospective phase II study is designed to confirm the activity of MOR00208 combined with LEN in patients with R-R DLBCL who have had at least one, but no

	more than three prior systemic regimens and who are not eligible for HDC with ASCT at the time of study entry.
Study Objectives (Key Primary and Secondary)	**PRIMARY OBJECTIVE:** To determine the activity of a combination of LEN with MOR00208 in terms of objective response rate (ORR = complete response [CR] + partial response [PR]) in adult patients with R-R DLBCL. **SECONDARY OBJECTIVES:** 1. To determine the disease control rate (DCR = CR + PR + stable disease [SD]) 2. To determine the duration of response (DoR) 3. To determine the activity of a combination of LEN with MOR00208 in terms of progression-free survival (PFS) 4. To determine the overall survival (OS) 5. To determine time to progression (TTP) 6. To determine the time to next treatment (TTNT) 7. To determine the safety of LEN combined with MOR00208 assessed according to the frequency and severity of adverse events (AEs) 8. To assess the potential immunogenicity of MOR00208 9. To assess the pharmacokinetics (PK) of MOR00208 10. To make a preliminary evaluation of ORR, DCR, DoR, PFS, OS, TTP and TTNT in patients treated with a combination of LEN plus MOR00208 in cohorts with a “low risk”, “low-intermediate”, “high-intermediate” and “high” International Prognostic Index (IPI) 11. To compare each patient’s TTP on LEN plus MOR00208 with the TTP of their most recent prior therapy 12. To correlate efficacy parameters with certain biomarkers (e.g., baseline tumour CD19 expression level, peripheral NK cell count, constitutional FcγRIIIa and FcγRIIa polymorphism status).
Study Endpoints (Key Primary and Secondary)	**PRIMARY ENDPOINT:** 1. ORR, defined as the proportion of complete and partial responders (ORR = CR + PR) **SECONDARY ENDPOINTS:** 2. **DCR**, **DoR**, **PFS**, OS, **TTP** and **TTNT** 3. Incidence and severity of AEs 4. Determination and characterisation of a potential anti-MOR00208 antibody formation 5. PK analysis of MOR00208 6. Absolute and percentage change from baseline in measurements of B-, T- and NK cell populations 7. Analysis of exploratory and diagnostic biomarkers (e.g., CD19, CD20, BCL2, and BCL6 expression, CD16 expression on NK cells, ADCC capacity), gene expression profiling for

	cell of origin subtyping and evaluation of AEs and ORR stratified by FcγRIIIa and FcγRIIa polymorphism) are planned to be investigated during the course of the study.
Design and Methodology/Patient Population	This is a single-arm, multicentre, open-label, phase II study of LEN combined with MOR00208 in adult patients with DLBCL who have relapsed after or are refractory to at least one, but no more than three prior systemic therapies and who are not candidates for HDC and ASCT, and are thus considered to have exhausted their therapeutic options for demonstrable clinical benefit. One prior therapy line must have included a CD20-targeted therapy (e.g., RTX). Histological confirmation of the diagnosis of DLBCL will be performed by a central pathologist, retrospectively after enrolment. Objective disease response assessments will be made by central radiology and clinical reviewers. Details will be provided in an imaging charter, outlining functions and processes. This study will consist of two parts, which will be performed sequentially, where the first part (safety run-in) will conclude with an evaluation of the safety data after six patients have completed the first cycle of treatment. The second part will commence pending the outcome of this evaluation. Approximately 80 patients will be enrolled in the study.
Key Inclusion/Exclusion Criteria	**INCLUSION CRITERIA:** **<u>Diagnosis/Study Population</u>** 1. Age >18 years 2. Histologically confirmed diagnosis of DLBCL not otherwise specified (NOS); T cell/histiocyte rich large B-cell lymphoma (THRLBCL); Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL), Grade 3b Follicular Lymphoma, Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification. Additionally, patients with the evidence of histological transformation to DLBCL from an earlier diagnosis of low grade lymphoma (i.e., an indolent pathology such as follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukaemia) into DLBCL with a subsequent DLBCL relapse are also eligible. 3. Fresh tumour tissue for central pathology review and correlative studies must be provided as an adjunct to participation in this study. Should it not be possible to obtain a fresh tumour tissue sample from the patient, 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) relapsed and/or refractory disease as defined in the protocol (Section 5.1.15.1.1)

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 regimens for the treatment of DLBCL and one therapy line must have included a CD20-targeted therapy (e.g., RTX)
d) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

5. Patients not considered in the opinion of the investigator eligible, or patients unwilling to undergo intensive salvage therapy including ASCT because of, but not limited to, advanced age, comorbidities, impossibility or, refusal to perform ASCT. Documentation of the reason for a patient's ineligibility must be provided in the patient's source data.

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 recent bone marrow aspiration and bone marrow biopsy)
   b) platelet count ≥90 × 10^9/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy)
   c) total serum bilirubin ≤2.5 × upper limit of normal (ULN) unless secondary to Gilbert's syndrome 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 × ULN (see exclusion criterion 5g)
   d) alanine transaminase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (AP) ≤3 × ULN or <5 × ULN in cases of documented liver involvement
   e) serum creatinine clearance must be ≥60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (Cockroft and Gault, 1976; see Appendix_A)

General Provisions

7. Females of childbearing potential (FCBP) must:
   a) not be pregnant as confirmed by a negative serum pregnancy test at screening and a medically supervised urine pregnancy test prior to starting study therapy
   b) refrain from breastfeeding and donating blood or oocytes during the course of the study and for 3 months after the last dose of study medication. Restrictions concerning

	blood donation apply as well to females who are not of childbearing potential c) agree to ongoing pregnancy testing during the course of the study, and after study therapy has ended. This applies even if the patient practices complete and continued sexual abstinence d) commit to continued abstinence from heterosexual intercourse if it is in accordance with her lifestyle (which must be reviewed on a monthly basis) or agree to use and be able to comply with the use of effective contraception without interruption during the study and for 3 months after the last dose of study medication 8. Males must use an effective barrier method of contraception without interruption, refrain from donating blood or sperm during the study participation and for 3 months after the last dose of study medication if the patient is sexually active with a FCBP 9. In the opinion of the investigator, the patients must: a) be able and willing to receive adequate prophylaxis and/or therapy for thromboembolic events b) be able to understand, give written informed consent, and comply with all study-related procedures, medication use, and evaluations c) not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative d) be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement of this. **EXCLUSION CRITERIA:** **<u>Exclusionary Diagnosis</u>** 1. Patients who have: a) any other histological type of lymphoma including primary mediastinal (thymic) large B-cell (PMBL) or Burkitt lymphoma b) primary refractory DLBCL (see Section 5.1.1 for definitions) c) a history of "double/triple hit" genetics DLBCL characterised by simultaneous detection of *MYC* with *BCL2* and/or *BCL6* translocation(s) defined by fluorescence *in situ* hybridisation. *MYC*, *BCL2*, *BCL6* testing prior to study enrolment is not required **<u>Exclusionary Previous and Current Treatment</u>** 2. 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

	b) undergone major surgery or suffered from significant traumatic injury c) received live vaccines (see Section 6.7 for details) d) required parenteral antimicrobial therapy for active, intercurrent infections 3. Patients who: a) have, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies b) were previously treated with CD19-targeted therapy or IMiDs® (e.g., thalidomide, LEN) c) have a history of hypersensitivity to compounds of similar biological or chemical composition to MOR00208, IMiDs® and/or the excipients contained in the study drug formulations d) have undergone ASCT within the period ≤ 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 allogenic stem cell transplantation f) have a history of deep venous thrombosis/embolism, threatening thromboembolism or known thrombophilia or are at high risk for a thromboembolic event in the opinion of the investigator and who are not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period g) concurrently use other anticancer or experimental treatments **<u>Exclusionary Patient's Medical History</u>** 4. Prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥5 years prior to screening. Exceptions to the ≥5 year time limit include a 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) 5. Patients with: a) positive hepatitis B and/or C serology (see Section 7.2.13.2 for details) b) known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV) c) CNS lymphoma involvement – present or past medical history

	d) history or evidence of clinically significant cardiovascular, 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 e) history or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption f) gastrointestinal abnormalities including the inability to take oral medication, requiring intravenous alimentation, or prior surgical procedure affecting absorption g) history or evidence of severe hepatic impairment (total serum bilirubin > 3mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion 6c)
Investigational Drug(s) (Name, Description)	MOR00208 and LEN (Revlimid®)
Dose, Route of Administration, Treatment Regimen	Treatment consisting of **LEN** and **MOR00208** combination will be administered up to twelve 28-day cycles at specified dose levels, as scheduled, until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first. **MOR00208 Dose:** 12 mg/kg For the first three cycles of the study, each cycle (Cycles 1-3) 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 MOR00208 will be administered on a bi-weekly (every fourteen days) basis with infusions on Days 1 and 15 of each 28-day cycle until disease progression, or unacceptable toxicity, or discontinuation for any other reason, whichever comes first. **LEN:** Patients will self-administer a starting dose of 25 mg oral LEN daily on Days 1–21 of each cycle. Treatment with LEN may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage haematologic and/or other toxicities are provided in the relevant sections of the protocol. **LEN** can be given for up to a total of 12 cycles. **MOR00208** can be administered until disease progression, or unacceptable toxicity, or discontinuation for any other reason, whichever comes first. It is up to the investigator to decide according to the individual risk/benefit ratio if the patient should continue further MOR00208 therapy in the case of disease progression.

Supply, Preparation and Administration	**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 of 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. **LEN** will be sourced from commercially available drug suppliers (Revlimid®).
Efficacy Assessments	Disease response assessments will be made according to the revised response criteria for malignant lymphoma based on the guidelines of the International Working Group (IWG, as reported by Cheson et al. (2007) and will be based on a central review (radiological + clinical) of the disease assessments. Efficacy will be evaluated in terms of ORR, DCR, DoR, PFS, OS, TTP and TTNT. Results of local disease response assessments will also be available.
Safety Assessments	The safety and tolerability of study drug treatments will be evaluated by means of AE reports (number 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.
Pharmacokinetics	The PK 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. Exploratory and diagnostic biomarkers (e.g., CD19, CD20, BCL2, BCL6), CD16 expression on NK cells, B-, T- and NK cell counts, ADCC capacity and gene expression profiling for cell of origin subtyping are planned to be investigated during the course of the study.
Statistical Methods and Data Analysis	The primary purpose of this study is to evaluate the clinical efficacy of oral LEN combined with MOR00208 administered by IV infusion in patients with R-R DLBCL. No formal statistical hypothesis testing will be performed. For the sample size determination it is assumed that the combination treatment could improve the ORR from a value of 20% (corresponding to monotherapy) to one of 35% which is achievable under combination treatment. Sample size estimation using a one-sample exact binomial test with a two-sided significance level of 5% and a power of 85% delivers a

	sample size of 73 patients. According to this scenario an observed ORR of 32% would lead to a statistically significant study outcome. Allowing for a drop-out rate of 10% the total required sample size comes to approximately 80 patients. All data will be summarised using appropriate statistics (counts/ percentages for discrete variables, mean, median, standard deviation, minimum, maximum, number of valid observations for continuous variables) for tabulation purposes. For specific variables, p-values and 95% confidence limits will be presented. Overall baseline and demographic data will be summarised using appropriate statistics. Patient disposition and status at the end of the study will be tabulated presenting the number of patients and frequencies. General medical history and history of DLBCL, including prior cancer therapies, will be tabulated using coding systems (e.g., MedDRA, WHO-DDE), where appropriate. **PRIMARY OBJECTIVE:** **Primary efficacy endpoint: Objective response rate (ORR)** The ORR will be the percentage of patients who have met the ORR definition up until progression based on the central (independent) radiological and clinical evaluations. The denominator for calculating the rate will be based upon the total number of patients in the full analysis set (FAS) population. As a sensitivity analysis, patients without any post-baseline assessment of response will be included in the denominator for ORR calculation. Number of patients being a responder and the respective rates, as well as 95% confidence limits, will be presented. **SECONDARY OBJECTIVES:** **Disease control rate (DCR)** The DCR will be evaluated like ORR. **Duration of response (DoR) and Time to next treatment (TTNT)** Response duration by the local assessment and by the central radiological + clinical assessments will be tabulated with descriptive statistics. Time to next treatment will be descriptively analysed. **Progression-free survival (PFS), overall survival (OS) and time to progression (TTP)** Kaplan-Meier methodology will be used to evaluate median survival, presenting corresponding statistical parameters and 95% confidence limits and Kaplan-Meier survival curves. **Incidence and severity of adverse events** MedDRA coded adverse events will be used to show the incidence of all AEs by specific organ class (SOC), preferred term (PT), relationship to treatment, severity and seriousness. An AE summary table will present the

	number of events, number of patients and the percentage of patients having treatment-emergent AEs (TEAEs), serious AEs, adverse drug reactions, and TEAEs that led to study discontinuation. AE frequency tables will display event and patient counts/frequency by MedDRA SOC and PT, distinguishing also by severity/toxicity, relationship to study drug, seriousness and outcome. Concomitant medications taken, starting on the day of the screening visit and through the followup- period, will be coded using appropriate coding systems and tabulated by each code system. Extent of exposure, clinical laboratory assessments, vital sign measurements, physical examination and results of ECGs will be summarised with appropriate descriptive statistics. **Immunogenicity** The absolute number and percentage of patients who develop anti-MOR00208 antibodies, and the results of semi-quantitative anti-MOR00208 antibody titre determinations of confirmed positive samples assessments, will be tabulated. **Pharmacokinetics** Appropriate PK parameters for MOR00208 will be computed based on non-compartmental data analysis and summarised using descriptive statistics. Mean concentrations will be visualised by figures. **Biomarkers** Blood and protein biomarkers which are important in the mechanism of action of, or could predict response to, the study drugs will be descriptively tabulated, presenting absolute and change to baseline values, if applicable.

TABLE OF CONTENTS

Overall Table of Contents

List of Tables

(Excluding those in the appendix)

List of Figures

LIST OF ABBREVIATIONS

ABC	Activated B-cell type
ADCC	Antibodydependent- cell-mediated cytotoxicity
ADCP	Antibody-dependent cell-mediated phagocytosis
AE	Adverse event
ALC	Absolute lymphocyte count
ALL	Acute lymphoblastic leukaemia
ALT	Alanine transaminase
ANC	Absolute neutrophil count
Anti-Hbc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HCV	Hepatitis C virus antibody
AP	Alkaline phosphatase
ASCT	Autologous stem-cell transplantation
AST	Aspartate aminotransferase
B-ALL	B-cell acute lymphoblastic leukaemia
BCL-2/6	B-cell leukaemia/lymphoma protein-2/6
BEN	Bendamustine
bpm	Beats per minute (heart rate)
BSC	Best supportive care
CBC	Complete blood count
CD19	Cluster of differentiation 19
CDC	Complement-dependent cytotoxicity
CHOP	**C**yclophosphamide, **h**ydroxydaunorubicin (also referred to as doxorubicin or adriamycin), and **o**ncovin (vincristine) plus **p**rednisone or **p**rednisolone
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRF	Case report form
CRO	Contract research organisation
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHAP	Cisplatin, cytarabine, dexamethasone
DCR	Disease control rate
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DP	Drug product
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOT	End of treatment

ESHAP	Etoposide, methylprednisone, cytarabine, cisplatin
FAS	Full analysis set
FCBP	Female(s) of childbearing potential
FDG	[18]-Fluordesoxyglucose
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FL(-3)	Follicular (grade 3) lymphoma
GCB	Germinal centre B-cell
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GEP	Gene expression profiling
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practice
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCL	Hairy cell leukaemia
HCV	Hepatitis C virus
HDC	High-dose chemotherapy
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICE	Ifosfamide, carboplatin, etoposide
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IIT	Investigator initiated trial
IL-2	Interleukin-2
IMiD®	Immunomodulatory drug
IMP	Investigational medicinal product
IND	Investigational new drug
iNHL	Indolent non-Hodgkin lymphoma
IPI	International Prognostic Index
IRB	Institutional/independent review board
IRR	Infusion-related reaction
IV	Intravenous
IWG	International Working Group
LDH	Lactate dehydrogenase
LEN	Lenalidomide
mAb	Monoclonal antibody
MALT	Mucosa-associated lymphoid tissue lymphoma
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MYC	v-myc avian myelocytomatosis viral oncogene homolog
MZL	Marginal zone lymphoma

NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NOAKs	New oral anticoagulants
NOS	Not otherwise specified
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	Objective response rate (complete response + partial response)
OS	Overall survival
PD	Pharmacodynamics
PE	Physical examination
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PLL	Prolymphocytic leukaemia
PMBL	Primary mediastinal (thymic) large B-cell lymphoma
p.o.	By mouth
PPS	Per-protocol set
PR	Partial response
PR (ECG)	PR interval
PT	Preferred term
QRS	QRS interval
QT	QT interval
RBC	Red blood cell
R-CHOP	**R**ituximab plus **c**yclophosphamide, **h**ydroxydaunorubicin (also referred to as doxorubicin or adriamycin), and **o**ncovin (vincristine) plus **p**rednisone or **p**rednisolone
REAL/WHO	Revised European American Lymphoma/World Health Organization
R-EPOCH	Rituximab plus etoposide, prednisone or prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin
R-ICE	Rituximab plus ifosfamide, carboplatin, etoposide
RNA	Ribonucleic acid
rpm	Respirations per minute (respiration rate)
RR (ECG)	RR interval
R-R	Relapsed or refractory
R-R CLL/SLL	Relapsed or refractory chronic lymphocytic leukaemia/small lymphocytic lymphoma
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
SOC	System organ class
SOP	Standard operating procedure
SPC	Summary of Product Characteristics

SPD	Sum of Product Diameter
SPM	Second primary malignancy
TEAE	Treatment emergent adverse event
Th1	T (thymus) helper cell 1
TL	Transformed lymphoma
TLS	Tumour Lysis Syndrome
TFR	Tumour flare
TNM	Tumour/Node/Metastasis
TTNT	Time to next treatment
TTP	Time to progression
ULN	Upper limit of normal
US	United States
VIM	Etoposide, ifosfamide, methotrexate
VTE	Venous thromboembolic event
WBC	White blood cell
WFI	Water for injection
WHO-DDE	World Health Organization–Drug Dictionary Enhanced
β-HCG	Beta-human chorionic gonadotropin

1 INTRODUCTION

1.1 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 high-grade NHL, accounts for approximately 40% of NHLs (Armitage and Weisenbuger, 1998; Swerdlow et al., 2008) and comprises 60% of all new lymphomas in the elderly population (Thieblemont and Coiffier, 2007). The median age at the diagnosis of DLBCL is 64 years and the majority of patients present with advanced disease. There were an estimated 386,000 new cases of NHL worldwide in 2012, including 93,500 new cases in Europe and 70,400 in North America (Ferlay et al., 2014).

DLBCL is a heterogeneous disorder with two major molecular subtypes identified by gene expression profiling (GEP): germinal centre B-cell type (GCB) and activated B-cell type (ABC). The latter group is often included in non-GCB type in immunohistochemistry (IHC)-based algorithms. The ABC (non-GCB subtype) has been associated with worse outcome.

Other NHLs include mantle cell lymphoma (MCL), follicular lymphoma (FL) and other indolent NHLs (iNHL) such as marginal zone lymphoma (MZL), mucosa-associated and lymphoid tissue lymphoma (MALT).

1.2 Treatment of DLBCL

DLBCL is considered to be a chemosensitive neoplasm. Originally, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy was the standard first-line treatment. However the addition of rituximab (RTX) into CHOP-like (R-CHOP-like), anthracycline-based regimens has significantly improved the clinical results in patients with DLBCL, becoming the standard of care (Feugier et al., 2005; Habermann et al., 2006; Coiffier et al., 2002).

Nevertheless, even with the availability of R-CHOP-like treatment regimens, approximately 30–40% of patients will ultimately relapse or progress. In patients progressing or relapsing after first-line treatment the ultimate therapeutic goal is to be able to offer salvage chemotherapy such as DHAP (cisplatin, cytarabine, dexamethasone), VIM (etoposide, ifosfamide, methotrexate), ICE (ifosfamide, carboplatin, etoposide), or ESHAP (etoposide, methylprednisone, cytarabine, cisplatin), followed by high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) if the disease is still chemosensitive. HDC with ASCT is a potentially curative treatment, significantly improving disease-free survival and overall survival (OS) in patients with relapsed DLBCL (Philip et al., 1995).

However, the use of HDC with stem cell support may not be appropriate, especially for patients with comorbidities or older age, restricting the benefit of this aggressive approach to a relatively small percentage of patients. For the remaining patient population, several second-line combination therapies are used with variable success, but the median survival for patients who

have relapsed after second-line therapy is less than one year, and the median survival for those not responding to second-line therapy is less than 6 months.

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

1.3 Lenalidomide in Haematological Malignancies

Lenalidomide (LEN [Revlimid®]) belongs to the class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs®). Although the mechanism(s) of LEN activity remain(s) unclear, *in vitro* and *in vivo* preclinical studies show that IMiDs® demonstrate a variety of biological effects (Haslett et al., 2003; Galustian et al., 2009; Pan et al., 2012; Saloura and Grivas, 2010; Wiernik, 2013). Specifically, they:

- inhibit the proliferation and increase the proapoptosis of NHL cells
- costimulate CD4+ and CD8+ T-cells, thereby enhancing Th1-type cellular immunity. IMiDs® may inhibit T-regulatory cells which are known to suppress CD4+ T-cell activity in NHL
    - T-cell costimulation leads to interleukin-2 (IL-2) mediated enhanced natural killer (NK) effector function leading to enhanced tumour cell recognition and killing and increased potential for antibody dependent cell-mediated cytotoxicity (ADCC)
- inhibit regulatory T-cells that are known to suppress CD4+ and CD8+ T-cell activity in NHL
- exert antiangiogenic effects in the tumour microenvironment, and reduce endothelial cell migration.

LEN has been approved by multiple health authorities:

a. for the treatment of patients with transfusion dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndrome (MDS) associated with the cytogenetic abnormality, deletion 5q, with or without additional cytogenetic abnormalities
b. for use in combination with dexamethasone for patients with previously treated multiple myeloma (MM) based on significant antitumour activity
c. for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies including bortezomib.

LEN has also shown activity in R-R chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) (Chanan-Khan et al., 2006). Additionally, LEN is being investigated as a treatment for various oncological indications, including MM, NHL and solid tumours. Studies have also been conducted in non-oncological indications.

1.3.1 LEN as a Single Agent in Relapsed DLBCL

It has been demonstrated that LEN has single-agent activity in R-R DLBCL. Wiernik et al. (2008) evaluated the safety and efficacy of 25 mg LEN administered orally, daily, for 52 weeks, until disease progression or intolerance as monotherapy in patients with R-R aggressive NHL. The primary endpoint was ORR; secondary endpoints included duration of response (DoR), progression-free survival (PFS), and safety. Forty-nine patients with a median age of 65 years received LEN in this study. The most common histology was DLBCL, established in 53% of patients, and patients had received a median of four prior treatment regimens for NHL. The ORR was 35% including a 12% complete response (CR)/unconfirmed CR rate. Of patients with stable disease (SD) or partial response (PR) at first assessment, 25% improved with continued treatment. Estimated median DoR was 6.2 months, and median PFS was 4.0 months. The most common grade 4 adverse events (AEs) were neutropenia (8.2%) and thrombocytopenia (8.2%).

Similarly, in a phase II study of LEN in patients with R-R DLBCL, MCL, follicular grade 3 lymphoma (FL-3), or transformed lymphoma (TL) patients received oral LEN 25 mg on days 1–21 every 28 days as tolerated or until progression (Witzig et al., 2011). Two hundred and seventeen patients were enrolled and received LEN. The ORR was 35% (77/217), with 13% (29/217) of patients achieving CRs, 22% (48/217) PRs, and 21% (45/217) with SD. The ORR for DLBCL was 28% (30/108). Median PFS for all 217 patients was 3.7 months. For 77 responders, the median DoR was 10.6 months. The most common AE was myelosuppression, with grade 4 neutropenia and thrombocytopenia in 17% and 6% of patients, respectively.

Zinzani et al. (2014) have shown in a retrospective, multicentre study that LEN monotherapy is effective and safe for heavily pretreated patients with R-R NHL. The ORR in 64 evaluable patients was 42.2% and was similar among patients receiving 10, 15 or 25 mg/day LEN. ORR in patients with MCL, DLBCL and FL were 45.5%, 42.1% and 20%, respectively. Mean DoR in patients receiving any LEN dose was 10.5 months; 1-year PFS and OS rates were 50.3% and 82.6%, respectively.

Additionally it has been shown that single agent LEN was active in heavily pretreated patients with aggressive, R-R NHL subsequent to a prior ASCT (Vose et al., 2013).

1.3.2 LEN and DLBCL Subtype

A retrospective analysis of the outcomes of patients with GCB vs non-GCB DLBCL treated with LEN was performed by Hernandez-Ilizaliturri et al. (2011). Forty patients with R-R DLBCL were included (24 men; 16 women; median age, 66 years; median of four prior treatments, including RTX-containing chemotherapy). Patients were classified as having GCB (n=23) or non-GCB (n=17) DLBCL. This analysis showed that patients with R-R DLBCL with a non-GCB phenotype had a higher ORR and CR rate and longer PFS when treated with LEN than those with a GCB phenotype, despite similarities in terms of disease stage, International Prognostic Index (IPI) score, number of prior treatments, and RTX resistance.

1.3.3 LEN in Combination with RTX in R-R DLBCL

The combination of LEN with RTX has been shown to be active and well tolerated with a manageable toxicity profile in heavily pretreated patients with R-R DLBCL. Zinzani et al. (2011) conducted a phase II study in heavily pretreated, elderly patients with R-R DLBCL. The induction treatment with oral LEN (20 mg/day for 21 days of each 28-day cycle) combined with RTX followed by LEN maintenance therapy resulted in a 35% CR rate at a median follow-up of 16 months. LEN maintenance in responding patients led to continuation of their initial response. The most common AEs included neutropenia and thrombocytopenia.

Wang et al. (2013) assessed the clinical activity of oral LEN and RTX in 45 patients with R-R DLBCL (n=32), transformed large cell lymphoma (n=9) or FL-3 (n=4) who had received 1-4 prior lines of treatment. Patients were given 20 mg oral LEN on Days 1–21 of each 28-day cycle, and RTX. The ORR was 33%; median DoR was 10.2 months. Median PFS and OS were 3.7 and 10.7 months, respectively. Grade 3/4 haematological toxicities included neutropenia (53%), lymphopenia (40%), thrombocytopenia (33%), leukopenia (27%) and anaemia (18%).

Ivanov et al. (2014) analysed clinical outcomes in 17 patients with R-R DLBCL treated with LEN at a dose of 25 mg/day for 21/28 days and RTX for a maximum of 12 months. The ORR was 41.2% with 35.3% of patients achieving a CR, while the median DoR was 26.5 months at a median follow-up of 24.9 months. The estimated 24-month OS and PFS rates were 45% and 38%, respectively. The most common AEs were thrombocytopenia and neutropenia.

1.3.4 LEN in Combination with R-CHOP or R-ICE in DLBCL

A phase I study established the maximum tolerated dose (MTD) of LEN that could be combined with R-CHOP chemotherapy for adults with newly diagnosed aggressive B-cell NHL (Nowakowski et al., 2011). Eligible patients were those with newly diagnosed, untreated CD20-positive DLBCL or FL-3. Patients received oral LEN on Days 1–10 with standard dose R-CHOP administered over 21 days. All patients received pegfilgrastim on Day 2 of the cycle and aspirin prophylaxis. The LEN dose levels tested were 15, 20 and 25 mg. Twenty-four patients were enrolled. The median age was 65 (range 35–82) years and 54% (13/24) were over 60 years. Three patients received 15 mg, 3 received 20 mg and 18 received 25 mg of LEN. No dose-limiting toxicity (DLT) was found. LEN dose escalation beyond 25 mg Days 1–10 was not performed and LEN 25 mg Days 1–10 was the recommended dose for phase II studies. The incidence of grade 4 neutropenia and thrombocytopenia was 67% and 21%, respectively. The incidence of febrile neutropenia requiring hospitalisation was 4% and there were no bleeding or toxicity related deaths. There were no delays in chemotherapy due to cytopenias. The ORR was 100% with a CR rate of 77%. It was shown that the combination of LEN with the R-CHOP regimen was safe and effective for the treatment of aggressive lymphomas including DLBCL. In a subsequent phase II study, Nowakowski et al. (2015) have not only confirmed their initial observation concerning clinical efficacy, but also established that the addition of LEN to R-CHOP mitigates the negative impact of the non-GCB phenotype on patient outcome.

Additionally, studies conducted by Fondazione Italian Linfomi have shown that combining 15 mg oral LEN on Days 1–14 of 21-day cycles with standard doses of R-CHOP chemotherapy is an effective and safe treatment modality in untreated, elderly patients with DLBCL (Chiapella et al., 2013; Vitolo et al., 2014).

Feldman et al. (2014) showed that combining LEN (at doses up to 25 mg daily) with RTX in combination with ICE (R-ICE) was associated with promising clinical activity, with no additional toxicological burden, in patients with R-R DLBCL.

1.4 Overview of MOR00208

MOR00208 (synonym: XmAb®5574) is an Fc-engineered mAb that binds to the human B-cell surface antigen CD19. MOR00208 possesses significantly increased tumour cytotoxicity when compared with the parental, non-engineered, murine 4G7 CD19 antibody. The increased binding of MOR00208 to Fc gamma receptors (FcγR), due to the engineered mutations, significantly enhances *in vitro* ADCC, antibody-dependent cell-mediated phagocytosis (ADCP), and its direct cytotoxic effects (apoptosis) on the tumour cells compared with the non-engineered 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 lymphoma, CLL, hairy cell leukaemia [HCL], CD19+ chronic myeloid leukaemia [CML], 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-engineered 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 (Investigator's Brochure [IB]).

The pharmacodynamic (PD) interactions of MOR00208 in combination with two standard-of-care drugs fludarabine and bendamustine (BEN), and one investigational drug, LEN used in the treatment of patients with CLL and NHL, were investigated in a human intravenous (IV) lymphoma model in SCID mice (see 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 lenalidomide) when compared with the groups receiving MOR00208 monotherapy. The LEN xenograft study showed a clear potentiation of the efficacy benefit of MOR00208 (3 mg/kg) and LEN (100/200 mg/kg) combination therapy compared with the respective monotherapies (1.5 x increase in median lifespan).

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 IB. The findings in four preclinical studies were limited to the expected pharmacological effects of MOR00208, with no reports of unanticipated toxicity.

The four 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; and an 8-week toxicity study in which MOR00208 was administered IV every 2 weeks at a dose of 2.0, 10.0 or 50.0 mg/kg for 8 consecutive weeks with a 90-day recovery period. The aim of the latter Good Laboratory Practice (GLP)-compliant, multiple-dose toxicology study was to support the use of MOR00208 in human clinical studies. Other than the expected dose-related decreases in B-lymphocyte levels and cellularity in spleen tissues, there were no MOR00208-related changes identified in 'clinical observations', food consumption, body weight, electrocardiography, ophthalmology, urinalysis, coagulation, serum chemistry, and gross anatomic pathology at doses up to 50.0 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 of structures other than the expected mononuclear leucocytes, lymphocytes and haematopoietic precursor cells was observed.

1.4.1 Clinical Experience with MOR00208

1.4.1.1 Protocol No. XmAb®5574-01

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

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

A total of 27 patients were treated with MOR00208 IV in 6 dose cohorts: 0.3 mg/kg (n=1), 1.0 mg/kg (n=1), 3.0 mg/kg (n=3), 6.0 mg/kg (n=3), 9.0 mg/kg (n=3) and 12.0 mg/kg (n=16) on a weekly schedule for 8 weeks (2 cycles), with an extra dose administered on Day 4 of Cycle 1. Patients received MOR00208 via IV infusion over a period of 2 hours on Days 1, 4, 8, 15 and 22 of Cycle 1 and Days 1, 8, 15 and 22 of Cycle 2 for a total of 9 doses. Patients were evaluated at weeks 4, 8 and 12 following completion of Cycle 2 for safety and preliminary antitumour activity. Patients enrolled in the expansion phase of cohort 6 (12.0 mg/kg) received an additional

four monthly doses of MOR00208 after completing the initial two 28-day cycles of therapy, if there was no evidence of disease progression or intolerable drug-related toxicity.

All 27 enrolled patients received at least one dose of MOR00208, with 22 patients receiving all nine of the planned initial doses. Of the five patients who did not receive all nine doses, two experienced disease progression, one experienced a DLT (grade 4 neutropenia lasting at least 7 days), one was omitted from the study by the treating physician, and one completed the study but missed a dose due to an AE (grade 3 thrombocytopenia). No patients had dose reductions during the study. Five patients had at least one dose delayed due to an AE. Eighteen patients had their infusion paused at least once due to an infusion-related reaction (IRR). Eight patients were included in a maintenance cohort. One patient received only three additional infusions and the other seven patients received all four planned additional infusions.

All 27 patients treated with MOR00208 experienced treatment-emergent AEs (TEAEs) and 24 patients experienced TEAEs that were assessed by the investigator to be possibly or probably related to MOR00208. No patient deaths were reported either on study or during the 12-week follow-up phase of the study. One DLT, grade 4 neutropenia lasting at least 7 days, was observed during the study in one of 16 patients treated at the maximum-administered 12.0 mg/kg dose level. Eight treatment-emergent serious AEs (SAEs) were reported in six patients; one at the 0.3 mg/kg dose level and seven at the 12.0 mg/kg dose-level. Only two were considered to be related to the study drug: one of grade 3 febrile neutropenia in the same patient who experienced the DLT and one of grade 3 tumour lysis syndrome (TLS) in a patient receiving his first dose of study drug at 12.0 mg/kg. In the latter case, after resolution of the SAE, the patient continued to receive additional doses of MOR00208 without further complications. The six unrelated SAEs were two cases of pneumonia, sinusitis, acute otitis media and bacterial infection, all of them of grade 3 in severity and one grade 1 rash. With a data cut-off date of 28 March 2013, the most common TEAEs were IRRs in 66.7% of patients, diarrhoea, neutropenia, thrombocytopenia (29.6% of patients each), anaemia, increased alanine transaminase (ALT), hypoalbuminaemia, hypocalcaemia, insomnia and muscle spasms (22.2% of patients each) and increased aspartate aminotransferase (AST), headache, hyperglycaemia, pyrexia, rash and upper respiratory tract infection (18.5% of patients each).

Twenty seven patients were evaluable for response. Blood disease cleared in the majority of patients, with a median reduction in absolute lymphocyte count (ALC) from baseline of 90.8% and a decrease in CLL cell count. Based upon physical examination and laboratory studies alone, 18 patients (66.7%) achieved a PR, while the remaining nine (33.3%) achieved stable disease (SD). Using computed tomography (CT) criteria alongside examination and laboratory data, eight patients (29.6%) achieved a PR while an additional 16 patients (59.3%) achieved SD. Two patients had progressive disease according to CT criteria.

Considering only those 16 patients who received the 12 mg/kg dose, 12 (75%) achieved a PR according to physical examination criteria while six (37.5%) achieved a PR according to CT criteria. Patients who responded according to physical examination criteria tended to do so quickly, with 14 of 18 patients achieving a PR by the first response evaluation (Cycle 2, Day 1). Patient responses according to CT criteria were slower, with three of eight patients achieving a PR by Cycle 2 (Day 28), three by the 4-week follow-up time point, and two patients in the

expansion cohort by Cycle 5 and Cycle 7, respectively. Across all treatment groups eight (29.6%) and sixteen patients (59.3%) had a PR and SD, respectively. In the 12.0 mg/kg treatment group only, six (37.5%) and nine of 16 (56.3%) had best responses of PR and SD, respectively. The disease control rate was 88.9% (8 PR, 16 SD) across all cohorts, and 93.8% (6 PR, 9 SD) in the 12 mg/kg cohort.

At evaluation, 12 weeks post-Cycle 2 (Day 28), five patients (18.5%) had progressed according to CT criteria and eight (29.6%) according to physical examination criteria. No patient died during the observation period. PFS for all patients, including those in the extended treatment cohort, was 199 days (95% CI, 168–299) and for patients in the extended treatment cohort alone, PFS was 420 days (95% CI, 168–not reached).

The results of the first clinical study showed MOR00208 to have an acceptable safety profile as well as providing preliminary evidence of antitumour activity in patients with high-risk, heavily pretreated CLL. Although IRRs were common, they were limited to grade 1/2. Since the MTD for MOR00208 was not established, due to the occurrence of only one DLT in the 12.0 mg/kg dose cohort, this dose of MOR00208 was selected for use in subsequent clinical studies. Promising antitumour activity of MOR00208, combined with the absence of safety signal, justified movement to phase II.

Protocol MOR208C202
A Phase IIa, Single-Arm, Open-Label Study of MOR00208, a Humanised Fc-Engineered Anti-CD19 Antibody, in Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukaemia (B-ALL)
This study is completed (study was terminated prematurely due to slow recruitment after 22 out of planned 30 patients were enrolled). For details, please refer to the MOR00208 IB.

1.4.1.2 Ongoing Studies

The following studies are ongoing and indicate a positive risk-benefit ratio for the patients so far. Details of safety and efficacy data will be reported on an ongoing basis in the IB. The studies are:

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

Protocol OSU-13031
A Phase II Study of MOR00208 in combination with LEN for Patients with Relapsed or Refractory Chronic Lymphocytic Leukaemia (CLL)/Small Lymphocytic Lymphoma (SLL)/Prolymphocytic Leukaemia (PLL) or Patients with untreated CLL/SLL/PLL Investigator Initiated Trial (IIT).

Protocol MOR208C204
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).

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

1.4.2 Safety of MOR00208

MOR00208 has a novel mechanism of action that may have the potential to add to the care of patients with NHL. Based on the available data from the completed clinical study of MOR00208 (Protocol XmAb®5574-01), the preliminary data from the ongoing MOR208C201 clinical study, 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 study (e.g., by the inclusion and exclusion criteria) and by frequent monitoring of potential adverse drug reactions throughout the entire study. Based on the results of the phase I clinical study of MOR00208 in patients with CLL/SLL (Woyach et al., 2014), and the preliminary results of the MOR208C201 and MOR208202 studies, the anticipated possible risks associated with administration of MOR00208 to patients include the following AEs (incidence $\geq$ 4%) with a suspected relationship to MOR00208 treatment:

- IRRs (mostly Grade ½)
- Febrile neutropenia
- Neutropenia
- Thrombocytopenia
- Tumour lysis syndrome
- Upper respiratory tract infections
- Fatigue
- Chills
- Pyrexia
- Nausea
- Diarrhoea
- Headache
- Rash
- Aspartate aminotransferase (AST) and alanine transaminase (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. The anticipated possible risks include: B-cell depletion, ALC reduction, IRRs, TLS, neutropenia/thrombocytopenia, hepatitis B reactivation, progressive multifocal leukoencephalopathy, mucocutaneous reactions and infections.

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

2 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). Although a significant number of patients with R-R aggressive NHL can be salvaged with HDC and subsequent ASCT, the majority will succumb to the disease. Thus, the development of a more effective initial therapy in aggressive NHL is essential to improve long-term outcomes.

LEN has been shown to have significant activity in relapsed aggressive B-cell NHL either alone or in combination with immunochemotherapeutic regimens. The mechanism of action of LEN is complex and involves immune modulation, antiangiogenesis, modulation of the microenvironment and direct antitumour activity (Hasslet et al., 2003; Zhang et al., 2005).

As stated previously, the effects of MOR00208 appear to involve ADCC, ADCP, and direct cytotoxic activity (apoptosis). The B-lymphocyte lineage-specific surface antigen CD19 is the earliest and most broadly expressed of the selective B-cell markers, and is highly expressed on the malignant cells of most patients with B-cell NHL. As a consequence, it can be envisaged that a CD19 antibody may have clinical utility as a new therapeutic approach for the treatment of patients with B-cell malignancies. This hypothesis is supported by the preliminary results of ongoing clinical studies involving various CD19-targeting mAbs (Topp el al., 2012; Raufi et al., 2013; Goswami et al., 2012) and the approval of blinatumomab for the treatment of patients with Philadelphia chromosome-negative, R-R B-cell ALL.

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. It is anticipated that by using MOR00208 instead of RTX, it might be possible to partially overcome the RTX resistance in R-R NHL, improving ORRs and OS. Data from a phase I study in patients with R-R CLL/SLL (Woyach et al., 2014) and an ongoing phase IIa study in patients with R-R B-cell NHL previously treated with RTX demonstrate that MOR00208 is well-tolerated, with a potential clinical benefit in patients with R-R DLBCL (Blum et al., 2014).

MOR00208 and LEN, both as single agents and in combination show antileukaemic and antilymphoma activity *in vivo* and *in vitro*. The pattern of AEs is different. Recent data demonstrate that the modulation of immunoeffector cells by LEN enhances the NK-mediated ADCC exerted by MOR00208, increasing cancer cell killing compared with that seen with the single drugs (Awan et al., 2010). It seems justified to assume that this effect may be especially evident during chronic administration of LEN.

Since the MTD for MOR00208 was not established during the course of the previous studies the 12.0 mg/kg dose of MOR00208 was selected for use in subsequent clinical studies.

The LEN starting dose is primarily based on a review of published data and the recommendations of expert clinicians. The published studies indicate a consistent, manageable and comparable (between studies) toxicity profile for patients with DLBCL beginning treatment with LEN, 25 mg daily (Wiernik et al., 2008; Witzig et al., 2011), or a combination of 20–25 mg LEN with RTX (Zinzani et al., 2011; Wang et al., 2013; Ivanov et al., 2014) or R-CHOP (Nowakowski et al., 2011; Nowakowski et al., 2015; Vitolo et al., 2013). In the light of the available evidence, expert clinicians who were consulted thought an efficacious dose of LEN to be in the range of 20–25 mg in patients with R-R DLBCL.

As a result, MorphoSys designed MOR208C203 as an open-label, single-arm prospective phase II study investigating the safety, antitumour activity and preliminary efficacy of LEN in combination with MOR00208 in adult patients with R-R DLBCL who are not candidates for ASCT. The study will consist of two parts, which will be performed sequentially. The first part of the study (safety run-in) will conclude with an evaluation of safety data. The outcome of this evaluation will provide a recommendation for the LEN starting dose to be used in the following part of the study. The starting dose is 25 mg LEN daily on Days 1–21 of each 28-day cycle followed by a step-wise dose de-escalation if not tolerated.

In this study, several correlative analyses may be conducted; for example, biomarkers that could be predictive of response to this therapeutic combination may be assessed. These markers may be genetic in nature, cellular, or protein-based and a range of laboratory methodologies may be used for their evaluation and possible quantitation. When relevant, the markers can be evaluated in the context of PK and clinical response analyses.

3 STUDY OBJECTIVES

3.1 Primary Objective

To determine the activity of a combination of LEN with MOR00208 in terms of objective response rate (ORR = CR + PR) in adult patients with R-R DLBCL.

3.2 Secondary Objectives

1. To determine the disease control rate (DCR = CR + PR + SD)
2. To determine the duration of response (DoR)
3. To determine the activity of a combination of LEN with MOR00208 in terms of progression-free survival (PFS)
4. To determine the overall survival (OS)
5. To determine time to progression (TTP)
6. To determine the time to next treatment (TTNT)
7. To determine the safety of LEN combined with MOR00208 assessed according to the frequency and severity of adverse events (AEs)
8. To assess the potential immunogenicity of MOR00208
9. To assess the PK of MOR00208

10. To make a preliminary evaluation of ORR, DCR, DoR, PFS, OS, TTP and TTNT in patients treated with a combination of LEN plus MOR00208 in cohorts with a "low risk", "low-intermediate", "high-intermediate" and "high" International Prognostic Index (IPI) (see Appendix B)
11. To compare each patient's TTP on LEN plus MOR00208 with the TTP of their most recent prior therapy
12. To correlate efficacy parameters with certain biomarkers (e.g., baseline tumour CD19 expression level, peripheral NK cell count, constitutional FcγRIIIa and FcγRIIa polymorphism status).

4 STUDY ENDPOINTS

4.1 Primary Endpoint:

1. **ORR**, defined as the proportion of complete and partial responders (ORR = CR + PR).

4.2 Secondary Endpoints:

2. **DCR**, defined as the proportion of patients having CR or PR or stable disease (SD) (DCR = ORR + SD); **DoR**, defined as the time between the initial time point of tumour response and the first time point where a change in response is detailed (specifically, the duration of CRs or PRs until progression or relapse will be evaluated); **PFS**, defined as the time between first IMP dosing and tumour progression or death from any cause, whichever occurs first; **TTP**, defined as the time from first IMP dosing until time of progression (the only events of interest are limited to disease progression and death from lymphoma - death from other causes will not be considered in relation to the TTP evaluation); **OS**, defined as time from first IMP dosing to the date of death; time to next treatment (**TTNT**)
3. Incidence and severity of AEs
4. Determination and characterisation of a potential anti-MOR00208 antibody formation
5. PK analysis of MOR00208
6. Absolute and percentage change from baseline in measurements of B-, T- and NK cell populations
7. Analysis of exploratory and diagnostic biomarkers from blood and tumour tissue (e.g., CD19, CD20, BCL-2, and BCL-6 expression, CD16 expression on NK cells, ADCC capacity), gene expression profiling for cell of origin subtyping and evaluation of AEs and ORR stratified by FcγRIIIa and FcγRIIa polymorphism, are planned to be investigated during the course of the study.

5 INVESTIGATIONAL PLAN

5.1 Study Design

5.1.1 Protocol-specific definitions

For the purposes of this protocol, **primary refractory disease** is defined as a disease progressing in the course of the first line treatment as per International Working Group response criteria (Cheson et al., 2007), and / or, showing a response of less than a PR to first-line treatment or disease recurrence/progression within ≤ 6 months from the completion of first-line therapy.

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

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 the most recent systemic therapy.

5.1.2 Description of study design

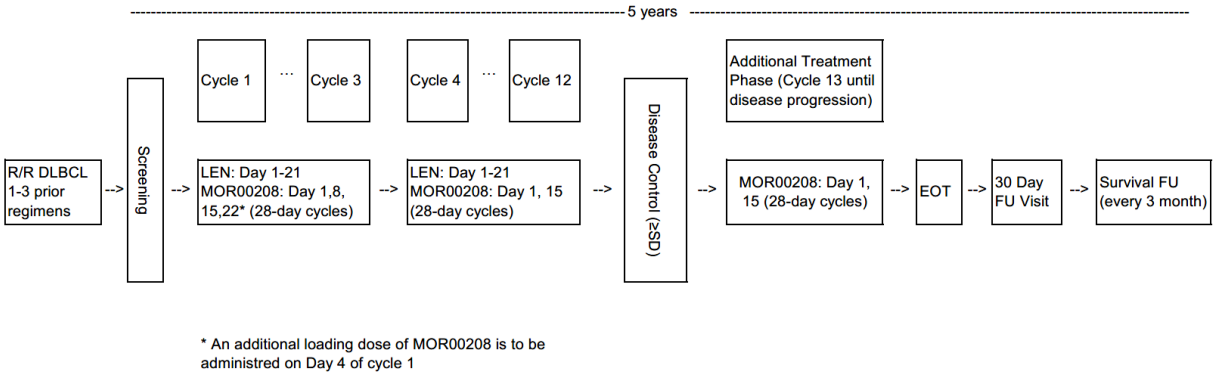
This is a single-arm, multicentre, open-label phase II, study of LEN combined with MOR00208 in adult patients with DLBCL who have relapsed after or are refractory to at least one, but no more than three previous systemic regimens administered for the treatment of their DLBCL and who are not candidates for HDC and subsequent ASCT and are thus considered to have exhausted their therapeutic options for demonstrable clinical benefit. One prior therapy line must include an anti-CD20 targeted therapy (e.g., RTX).

Patients with primary refractory DLBCL or, patients with known "double/triple hit" DLBCL genetics or those who have undergone previous allogenic stem cell transplantation are not eligible for study participation. Additionally patients with a history of ASCT ≤3 months prior to the requirement to provide signed informed consent cannot be included in the study.

This study will consist of two parts, which will be performed sequentially. During the course of the first part, six patients will be enrolled in the study and will complete the first cycle of study treatment. Once the sixth patient in the cohort has completed Cycle 1 Day 22 visit, a Safety Review Panel which consists of the sponsor, a representative of the participating investigators and two independent expert clinical haematologist will perform a clinical safety review based on the number and type of AEs occurring during the first cycle and on laboratory values (biochemistry and haematology). A LEN dose will be considered tolerated or in need of reduction after discussion of these data between the sponsor's Clinical Program Leader (or designee), the sponsor's Drug Safety Officer (or designee), a representative of the participating investigators and two expert clinical haematologists who are not participating in the study. The second part of the study will only be opened for enrolment by the sponsor following the outcome of this discussion.

Treatment consisting of **LEN** and **MOR00208** combination will be administered up to twelve 28-day cycles (Figure 1) at specified dose levels.

Figure 1 Study design



Abbreviations: EOT=end of treatment; FU=follow-up; LEN=lenalidomide; R-R DLBCL=relapsed or refractory diffuse large B-cell lymphoma; SD=stable disease.

MOR00208 dose: 12 mg/kg
For the first 3 cycles (Cycles 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 MOR00208 will be administered on a bi-weekly (every 14 days) basis with infusions on Day 1 and Day 15 of each 28-day cycle.

MOR00208 can be administered until disease progression, or unacceptable toxicity or discontinuation for any other reason, whichever comes first. It is up to the investigator to decide, according to the individual risk/benefit ratio, if the patient should continue on MOR00208 in spite of disease progression (refer to Section 7.2.3).

LEN:
Patients will self-administer a starting dose of 25 mg oral LEN daily on Days 1–21 of each cycle. Treatment with LEN may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage haematologic and/or other toxicities are provided in the respective sections of the protocol.

LEN can be given for up to 12 cycles in total.

Treatment with LEN will have to be stopped in case of disease progression, or unacceptable toxicity, or discontinuation for any other reason, whichever comes first.

Objective disease response assessments will be made according to the revised response criteria based on the guidelines of the International Working Group (IWG) reported by Cheson et al. (2007). The data used for the primary statistical analyses will be derived from a central

independent review of the radiological + clinical disease assessments. A charter outlining the central imaging plus clinical assessment will be prepared.

Approximately 80 patients with R-R DLBCL who meet the inclusion criteria and have none of the exclusion criteria will be enrolled in the study. This study will be conducted under a United States (US) Food and Drug Administration (FDA) Investigational New Drug (IND) application.

5.2 Safety Run-in

As the combination of MOR00208 with LEN has not previously been evaluated in a clinical study, an evaluation of safety data will occur after the first 6 patients have been accrued at the starting dose level of 25 mg LEN daily and 12 mg/kg MOR00208 Days 1, 8, 15 and 22 with an additional loading dose on Day 4 of Cycle 1.

To enable the assessment of individual safety parameters by the investigators these patients will be enrolled sequentially with a 48 hours lag period between enrolment (same as start of treatment with study drugs, or Cycle 1 Day 1 Visit) of two consecutive patients. Accrual will be held until all patients have been followed for one treatment cycle. Once the sixth patient in the cohort has completed the Cycle 1 Day 22 visit, an evaluation based on the number and type of AEs occurring during the first cycle and laboratory values (biochemistry and haematology) will be performed by the sponsor's Clinical Program Leader (or designee), the sponsor's Drug Safety Officer (or designee), a representative of the participating investigators, and two expert clinical haematologists who are not participating in the study. The second part of the study will only be opened for enrolment by the sponsor following the outcome of this discussion.

The outcome of this safety run-in evaluation will provide a recommendation on the starting dose of LEN to be used in the following part of the study. Patients involved in the safety run-in will continue the study as per protocol.

5.3 Study Duration

5.3.1 Study Conduct

The study duration per patient will be at least 5 years including periods of screening (up to 28 days from signature of the Informed Consent Form (ICF), the treatment period (maximum 12 cycles for LEN + MOR00208 followed by MOR00208 monotherapy thereafter) and the survival follow-up phase. MOR00208 can be administered until disease progression as described in Section 5.1.2.

The survival follow-up phase begins with the End of Treatment (EOT) Visit (Section 7.2.2). Patients will have an on-site safety evaluation visit 30-days after last administration of study treatment (LEN + MOR208 combination or either LEN or MOR208 if one of these two drugs was discontinued earlier) (30-Day Follow-up Visit). All patients discontinued for any reason other than withdrawal of consent, or death, will be contacted every 90 days by phone from the date of the 30-Day (Safety) Follow-up Visit until end of study, or until withdrawal of consent, or death, whichever comes first.

5.3.2 End of Study

The end of the study is defined as the date of the last visit of the last patient completing 5 years study duration. If any patient is on treatment at the end of the study and MOR00208 is not yet commercially available, patients will be switched to alternative methods of supply with MOR00208, upon assessment of a clinical benefit of continued treatment by the investigator, and in accordance with the local regulatory guidance. Upon study closure, MorphoSys will notify the applicable regulatory agencies in accordance with local requirements.

5.4 Patient Selection Criteria

5.4.1 Inclusion Criteria

Patients must satisfy the following criteria to be enrolled in the study:

Diagnosis/Study Population

1. Age > 18 years
2. Histologically confirmed diagnosis of DLBCL not otherwise specified (NOS); T cell/histiocyte rich large B-cell lymphoma (THRLBCL); Epstein-Barr virus (EBV) positive DLBCL of the elderly (EBV-positive DLBCL), Grade 3b Follicular Lymphoma, Composite lymphoma with a DLBCL component with a subsequent DLBCL relapse, according to the Revised European American Lymphoma/World Health Organization (REAL/WHO) classification. Additionally, patients with the evidence of histological transformation to DLBCL from an earlier diagnosis of low grade lymphoma (i.e., an indolent pathology such as follicular lymphoma, marginal zone lymphoma, chronic lymphocytic leukaemia) into DLBCL with a subsequent DLBCL relapse are also eligible.
3. Fresh tumour tissue for central pathology review and correlative studies must be provided as an adjunct to participation in this study. Should it not be possible to obtain a fresh tumour tissue sample from the patient, 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) relapsed and/or refractory disease as defined in the protocol (Section 5.1)
   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 regimens for the treatment of DLBCL and one therapy line must have included a CD20-targeted therapy (e.g., RTX)
   d) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
5. Patients not considered in the opinion of the investigator eligible or patients unwilling to undergo intensive salvage therapy including ASCT because of, but not limited to, advanced age, co-morbidities, impossibility or, refusal to perform ASCT.

Documentation of the reason for a patient's ineligibility must be provided in the patient's source data.

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 recent bone marrow aspiration and bone marrow biopsy)
   b) platelet count $\geq 90 \times 10^9$/L (unless secondary to bone marrow involvement by DLBCL as demonstrated by recent bone marrow aspiration and bone marrow biopsy)
   c) total serum bilirubin $\leq 2.5 \times$ upper limit of normal (ULN) unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma. Patients with Gilbert's syndrome or with documented liver involvement by lymphoma may be included if their total bilirubin is $\leq 5 \times$ ULN (see exclusion criterion 5 g)
   d) ALT, AST and alkaline phosphatase (AP) $\leq 3 \times$ ULN or $< 5 \times$ ULN in cases of documented liver involvement
   e) serum creatinine clearance must be ≥ 60 mL/minute either measured or calculated using a standard Cockcroft and Gault formula (Cockroft and Gault, 1976; see Appendix A)

General Provisions

7. Females of childbearing potential (FCBP) must:
   a) not be pregnant as confirmed by a negative serum pregnancy test at screening and a medically supervised urine pregnancy test prior to starting study therapy
   b) refrain from breastfeeding and donating blood or oocytes during the course of the study and for 3 months after the last dose of study medication. Restrictions concerning blood donation apply as well to females who are not of childbearing potential
   c) agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the patients practice complete and continued sexual abstinence
   d) commit to continued abstinence from heterosexual intercourse if it is in accordance with her lifestyle (which must be reviewed on a monthly basis) or agree to use and be able to comply with the use of effective contraception without interruption during the study and for 3 months after the last dose of study medication
8. Males must use an effective barrier method of contraception without interruption, refrain from donating blood or sperm during the study participation and for 3 months after the last dose of study medication if the patient is sexually active with a FCBP
9. In the opinion of the investigator the patients must:
   a) be able and willing to receive adequate prophylaxis and/or therapy for thromboembolic events
   b) be able to understand, give written informed consent and comply with all study-related procedures, medication use, and evaluations

c) not have a history of noncompliance in relation to medical regimens or be considered potentially unreliable and/or uncooperative
d) be able to understand the reason for complying with the special conditions of the pregnancy prevention risk management plan and give written acknowledgement of this.

5.4.2 Exclusion Criteria

Exclusionary Diagnosis

1. Patients who have:
   a) any other histological type of lymphoma including primary mediastinal (thymic) large B-cell (PMBL) or Burkitt lymphoma
   b) primary refractory DLBCL (see Section 5.1.1 for definitions)
   c) a history of "double/triple hit" genetics DLBCL characterised by simultaneous detection of MYC with BCL-2 and/or BCL-6 translocation(s) defined by fluorescence *in situ* hybridisation. MYC, BCL-2, BCL-6 testing prior to study enrolment is not required

Exclusionary Previous and Current Treatment

2. Patients who have, within the 14 days prior to Day 1 dosing:
   a) not discontinued CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphomaspecific- therapy
   b) undergone major surgery or suffered from significant traumatic injury
   c) received live vaccines (see Section 6.7 for details)
   d) required parenteral antimicrobial therapy for active, intercurrent infections
3. Patients who:
   a) have, in the opinion of the investigator, not recovered sufficiently from the adverse toxic effects of prior therapies
   b) were previously treated with CD19-targeted therapy or IMiDs® (e.g., thalidomide, LEN)
   c) have a history of hypersensitivity to compounds of similar biological or chemical composition to MOR00208, IMiDs® and/or the excipients contained in the study drug formulations
   d) have undergone ASCT within the period ≤3 months prior to the signing of 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 allogenic stem cell transplantation
   f) have a history of deep venous thrombosis/embolism, threatening thromboembolism or known thrombophilia or are at a high risk for a thromboembolic event in the opinion of the investigator and who are not willing/able to take venous thromboembolic event prophylaxis during the entire treatment period
   g) concurrently use other anticancer or experimental treatments

Exclusionary Patient's Medical History

4. Prior history of malignancies other than DLBCL, unless the patient has been free of the disease for ≥5 years prior to screening. Exceptions to the ≥5 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)
5. Patients with:
   a) positive hepatitis B and/or C serology (see Section 7.2.13.2 for details)
   b) known seropositivity for or history of active viral infection with human immunodeficiency virus (HIV)
   c) CNS lymphoma involvement – present or past medical history
   d) history or evidence of clinically significant cardiovascular, 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
   e) history or evidence of rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
   f) gastrointestinal abnormalities including the inability to take oral medication, requiring intravenous alimentation, or prior surgical procedure affecting absorption
   g) history or evidence of severe hepatic impairment (total serum bilirubin > 3mg/dL), jaundice unless secondary to Gilbert's syndrome or documented liver involvement by lymphoma (see inclusion criterion 6c)

5.4.3 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 at least 50 years and naturally amenorrhoeic for at least 24 months (i.e. has not had menses at any time in the preceding 24 consecutive months). Amenorrhoea following cancer therapy or during lactation 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.

5.5 Re-screening Procedures

Patients 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:

- 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)
- the patient previously failed to be eligible due to any event (e.g., planned surgery, laboratory test result) that has been resolved
- the patient previously failed screening but has become eligible for the study based on a change in the inclusion and exclusion criteria as the result of a protocol amendment.
- the patient failed screening due to non-progressed / non-relapsed disease at the time of screening and is later clinically diagnosed as having progressed / relapsed.

A patient should only be rescreened if there is a clear indication that the patient may be eligible according to the currently valid study protocol.

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

- the patient must sign and date a new informed consent form (ICF) as part of the re-screening procedure
- the eligible patient will receive a new unique identification number via the interactive response technology
- a new electronic case report form (eCRF) should be completed
- the patient will be documented as rescreened in the source documents
- all screening procedures must be completed again.

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

6 STUDY TREATMENTS AND CONCOMITANT DRUGS

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 can 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 and/or prepared as described in the Drug Preparation Manual, the IB for MOR00208, and other safety-relevant documents (e.g., Summary of Product Characteristics (SPC) for the European Medicines Agency [EMA] or the Prescribing Information [US FDA] for LEN) (see Appendix_C).

6.1 MOR00208

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

MOR00208 DP is a yellowish 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.

MOR00208 will be administered IV at a dose of 12.0 mg/kg**.**

For the first 3 cycles (Cycles 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 MOR00208 will be administered on a bi-weekly (every 14 days) basis with infusions on Days 1 and 15 of each 28-day cycle.

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 Preparation Manual. In general, a vial of MOR00208 must be used as soon as possible after reconstitution with WFI. 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 Preparation Manual.

The preferred procedure for destruction is for all IMPs (including used, partially used, not expired unused and expired unused vials, blisters, boxes or bottles) to be returned to the Drug Depot for destruction.

In case the site is requesting formal approval for destruction of the IMP on site due to local requirements, the local destruction requirements for IMPs described in detail in the Drug Preparation Manual must be fulfilled.

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.

The infusion rate escalation schedules in this protocol and the Drug Preparation Manual are recommendations only. If required, the investigator should use clinical judgement to optimise patient safety by administering the infusion more slowly.

6.2 Lenalidomide (LEN)

Patients will self-administer a starting dose of 25 mg oral LEN daily on Days 1–21 of each cycle. Treatment with LEN may be modified in a de-escalating fashion or discontinued based upon clinical and laboratory findings. Detailed dose modification guidelines to manage haematological and/or other toxicities are provided in the respective sections of the protocol.

LEN will be obtained from a commercial source as capsules in various dose strengths for oral administration as will be outlined in the Drug Preparation Manual. If applicable, LEN will be labelled as per local regulations. Investigators must be registered through the Lenalidomide programme, as applicable in their countries (e.g., REVLIMID REMS™ programme in the US, T-register in Germany). Patients must be counselled on the reproductive risks associated with LEN, prior to enrolment and monthly, during therapy.

6.3 Treatment with Study Drugs

Treatment consisting of **LEN** and **MOR00208** combination will be administered up to twelve 28-day cycles at specified dose levels as scheduled until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first.

LEN can be given for up to 12 cycles in total. Treatment with LEN will have to be stopped after disease progression. On days when both study drugs are given together, LEN should be administered prior to MOR00208.

MOR00208 can be administered at the dose and schedule described in Section 6.1 above, until disease progression, unacceptable toxicity, or discontinuation for any other reason, whichever comes first.

It is up to the investigator to decide according to the individual risk/benefit ratio if the patient should further continue on MOR00208 in case of disease progression, after discussion with the Sponsor's Medical Monitor or designee. For patients who will be administered MOR00208 despite progression of disease / relapse, an **Unscheduled Visit** including all protocol prescribed procedures for the **EOT Visit** (except the PK sample and the anti-MOR00208 antibody sample) need to be performed in order to capture the event (i.e. disease progression/relapse) for the antibody treatment to continue further (Table 5). In such cases an **EOT Visit** will take place after these patients have finally stopped receiving the antibody. And lastly, a **Safety Follow-Up** will take place **30-Days** after last administration of MOR00208.

For patients receiving antibody treatment despite disease recurrence/progression, before the administration of MOR00208, 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 monoclonal antibodies. A urine pregnancy test should be performed for women of childbearing potential. Vital signs should be measured according to local practice for the administration of monoclonal antibodies. For this patient population only the antineoplastic therapy after the end of study drug combination treatment and AEs need to be captured in eCRF. Other procedures described in the column "MOR00208 Additional Treatment" in Table 5 will not apply for this patient population.

6.4 Pre-Medication for MOR00208 Infusions

IRRs have commonly been reported for patients with CLL or NHL treated with MOR00208.

It is suggested that the pre-medication is administered between 30 minutes and 2 hours prior to the MOR00208 infusions.

The pre-medication may include the following:

- antipyretics (e.g., acetaminophen [paracetamol] 1000 mg per dose per mouth [p.o.] or IV or equivalent)
- histamine H_1 receptor blockers (e.g., diphenhydramine 25–50 mg per dose IV or equivalent)
- histamine H_2 receptor blockers (e.g., cimetidine 300 mg p.o., ranitidine 150 mg tablet p.o. or equivalent)
- glucocorticosteroids (methylprednisolone 80–120 mg per dose IV or equivalent - please refer to Appendix_D)
- meperidine (25 mg per dose p.o. or IV) may be added as required for rigors or chills.

The investigator may repeat doses of individual agents as required and use other agents, doses and/or formulations in accordance with institutional guidelines. Equivalence for premedications includes variations to the stated dose due to the formulations available locally. Any premedication given should be reported in the eCRF.

Premedication for patients who do not experience any IRRs to MOR00208 during the first 3 infusions (doses) will be optional for subsequent infusions at the discretion of the investigator. Otherwise, the premedication should be continued for subsequent administrations.

6.5 Patient Monitoring During MOR00208 Infusion

Vital signs should be measured as outlined in Section 7.2.8. All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards.

Precautions for anaphylaxis should be observed during MOR00208 administration. Emergency resuscitation equipment and medications should be readily available. Additional supportive measures should also be available and may include, but are not limited to, epinephrine, antihistamines, corticosteroids, IV fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen (paracetamol).

6.6 Criteria for Dose Modifications and Drug Discontinuation

6.6.1 Management of MOR00208 Infusion-Related Reactions (IRRs)

IRRs will be defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0 definition of IRR 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
IRR	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

Abbreviations: IRR=infusion-related reaction; IV=intravenous; NSAIDs=non-steroidal anti-inflammatories.

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 (joint pain); Bronchospasm; Cough; Dizziness; Dyspnoea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumour pain (onset or exacerbation of tumour pain due to treatment); Urticaria (hives, welts, wheals); Vomiting

6.6.1.1 Grade 2 IRRs

If a patient presents with a grade 2 infusion reaction:

- the infusion should be stopped immediately
- the patient should receive appropriate further treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) if clinically indicated
- once the symptoms have been resolved or reduced to "mild" 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 1 or 2 IRR receives further infusions, then premedication should be given before all subsequent infusions of MOR00208.

6.6.1.2 Grade 3 IRRs

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)
- a blood sample for cytokine analysis should be obtained during the event and approximately 24 hours later
- 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 the 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 MOR00208 provided clinically appropriate precautions were undertaken. The patient may continue treatment with LEN.

6.6.1.3 Grade 4 IRRs

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 should receive appropriate treatment with an antihistamine and/or acetaminophen (paracetamol) or methylprednisolone (or equivalent) and, if necessary, further medications (i.e. epinephrine, bronchodilator)
- a blood sample for cytokine analysis should be obtained during the event and approximately 24 hours later.

The patient must not receive further MOR00208, but may continue treatment with LEN as per protocol.

6.6.2 Management of Toxicities

The next cycle of treatment may begin on the scheduled Day 1 if:

- ANC is ≥1.000/mm^3 (unless neutropenia is due to infiltration of bone marrow)
- Platelets ≥50000/mm^3 (unless thrombocytopenia is due to infiltration of bone marrow, patient may have received transfusion) and absence of active bleeding
- No serious organ or other toxicity present.

If, based on medical judgment, the treating physician considers a change in laboratory parameter or AE not to be a study drug-related toxicity, but to represent a natural fluctuation in 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.

If the above conditions are not met on Day 1 of a new cycle, the subject will be evaluated once every seven days and a new cycle will not initiated until the toxicity has resolved as described above. Specific course of action for a given toxicity occurring in the course of the treatment cycle is described below.

If treatment needs to be interrupted for ≤28 days for the same study drugs-related toxicity, the patient's treatment should continue, depending on the duration of treatment interruption, at the next protocol scheduled visit. No missed visits or doses of either drug should be made up.

If treatment with one study drug needs to be interrupted for >28 days for the same, persistent, drug-related toxicity, the study drug judged by the investigator to have caused the toxicity should be discontinued and the patient should continue to be dosed with the other study drug, as per protocol.

If treatment with both study drugs needs to be interrupted for >28 days for the same persistent study drug-related toxicity, judged by the investigator to be related to both study drugs (LEN and MOR00208), then the End of Treatment Visit will be performed and the patient will enter the follow-up phase (see Section 5.3.1).

6.6.2.1 Haematological and Other Toxicities

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 used as a guide for grading severity. The dose of study drug(s) for each patient will be interrupted and/or modified following toxicity as described below. Refer to Table 2 and Table 3 for instructions on dosing interruptions/modifications and Table 4 for LEN dose reduction instructions.

Guidance on managing specific toxicities is summarised in Table 2 and Table 3.

Table 2 Haematological and Other Toxicities

Grade 3/4 thrombocytopenia judged to be related to study drugs	PLTs fall to <50000/µl	Interrupt MOR00208* and LEN dosing) Follow CBC every 7 days
	PLTs return to ≥50000/µl	Provided all other criteria are fulfilled, resume dosing of MOR00208 and/or LEN. LEN should be administered at the next lower dose level (Table 4)
Grade 3/4 neutropenia judged to be related to study drugs	ANC falls to <1000/µl for at least 7 days or ANC falls to <1000/µl with an associated body temperature ≥38.5°C or ANC falls to <500/µl	Interrupt MOR00208* and LEN dosing Follow CBC every 7 days Growth factors (G-CSF) and antimicrobial prophylaxis is to be used, as per local guidelines
	ANC return to ≥1000/µl	Provided all other criteria are fulfilled, resume dosing of MOR00208 and/or LEN. LEN should be administered at the next lower dose level (Table 4)
Other clinically significant toxicities judged to be related to study drugs	Grade 3/4	Interrupt the administration of the study drug(s)* to which the toxicity is judged to be related to.
	Toxicities resolve to grade ≤2	Provided all other criteria are fulfilled, resume dosing of study drug(s). LEN should be administered at the next lower dose level (Table 4)

Abbreviations: ANC=absolute neutrophil count; CBC=complete blood count; G-CSF=granulocyte colony-stimulating factor; LEN=lenalidomide; PLT=platelets.

*If, based on medical judgment, the treating physician considers a laboratory parameter change or AE not to be a study drug-related toxicity, but to represent a natural fluctuation in 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.

Table 3 Other Toxicities Judged to be Related to LEN

Thromboembolic events	Grade 3/4	Interrupt LEN dosing Start anticoagulation as per local guidelines Continue MOR00208 treatment as per protocol
	Toxicities resolve to grade ≤2	Restart LEN at investigator's discretion (maintain dose level) Continue MOR00208 treatment as per protocol
Allergic reaction or hypersensitivity grade 3/4 (including but not limited to Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative or bullous rash, angioedema)	Grade 3/4	Discontinue LEN permanently Continue MOR00208 treatment as per protocol
Allergic reaction or hypersensitivity	Grade >2	Interrupt LEN dosing Follow at least every 7 days Continue MOR00208 treatment as per protocol
	Resolved to ≤grade 2 severity or at least the baseline value (for pre-existing conditions; at screening)	Restart LEN (next lower dose level)
Desquamating (blistering) rash ≥grade 3 or nondesquamating rash grade 4 considered to be related to LEN		Discontinue LEN permanently Continue MOR00208 treatment as per protocol
Nondesquamating rash	Grade 3/4	Interrupt LEN dosing Continue treatment with MOR00208 as per protocol
	Resolve to grade ≤1	Restart LEN at next lower dose level
Tumour flare reaction	Grade 3/4	Interrupt LEN dosing Provide symptomatic treatment as per local guidelines Continue treatment with MOR00208 as per protocol

	Resolve to grade ≤1	Restart LEN (maintain same dose level)
Tumour flare reaction	Grade 1/2	Provide symptomatic treatment as per local guidelines Continue LEN without dose modification or interrupt LEN dosing at investigator's discretion Continue treatment with MOR00208 as per protocol

Abbreviation: LEN=lenalidomide.

6.6.2.2 LEN Dose Reduction Guidelines

General rules

If LEN dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. There will be no more than one dose reduction from one cycle to the next. Once a patient's LEN dose has been reduced, no dose re-escalation is permitted.

Specific LEN dose reduction guidelines

The daily oral dose of LEN may be reduced successively by one level from the starting dose of 25 mg daily on Days 1–21 every 28 days (Table 4).

Table 4 LEN Dose Reduction Guidelines

Starting dose	**25 mg daily on Days 1–21, every 28 days**
Dose Level - 1	20 mg daily on Days 1–21, every 28 days
Dose Level - 2	15 mg daily on Days 1–21, every 28 days
Dose Level - 3	10 mg daily on Days 1–21, every 28 days
Dose Level - 4	5 mg daily on Days 1–21, every 28 days

Patients who cannot tolerate Dose Level - 4 are to be discontinued from LEN treatment in the study but should continue therapy with MOR00208 alone.

Additional information

The most up-to-date information regarding constitution, dosing and most frequent AEs related to the administration of LEN and MOR00208 are contained in the SmPC (EMA), Prescribing Information (US FDA) and the current MOR00208 IB, respectively (see Appendix_C). Dose reductions for MOR00208 are not allowed during the course of the study.

6.6.2.3 Tumour Flare with LEN

Patients in this study should be monitored for tumour flare (TFR). TFR is defined as a sudden and tender increase in the size of the disease bearing sites, including the lymph nodes, spleen and/or the liver, often accompanied by low-grade fever, non-pruritic diffuse rash and in some cases, an increase in the peripheral blood lymphocyte counts. TFR is an expected toxicity with LEN, especially in patients with a high tumour burden and may mimic disease progression. Therefore, careful monitoring and evaluation is important prior to discontinuing a study patient for progressive disease in the initial cycles of LEN therapy. There are currently no laboratory or radiological tests to help distinguish TFR from progressive disease. The distinction should be made on clinical grounds, incorporating observations such as associated physical findings, laboratory findings, and pace of disease before and after the initiation of treatment. TFR should be recorded as an AE of interest (graded using the NCI-CTCAE 4.0 criteria) and not as progressive disease.

Treatment of TFR is at the discretion of the investigator and dependent on the severity, clinical situation and institutional standards.

6.6.2.4 Tumour Lysis Syndrome

TLS results from the rapid breakdown of tumour cells and the release of their intracellular content into the circulation resulting in metabolic derangements that can lead to acute renal failure and other life-threatening complications. The onset of TLS is rapid, usually within 24-48 hours of receipt of the first dose of anticancer medication, but can also occur after the first week of treatment. Bulky disease, moderate renal insufficiency, a high number of circulating lymphoma cells and high uric acid levels (>8 mg/dL) prior to therapy, increase the likelihood of TLS. Early identification of patients at risk and the prevention of TLS development with the initiation of preventive measures as well as the careful monitoring for early signs of laboratory assessments consistent with TLS and the prompt initiation of supportive care are critical to the prevention of potentially life-threatening metabolic derangements.

Medical prophylaxis and management should be initiated according to the institutional standard of care at the investigator's discretion.

6.6.2.5 Thromboembolism

LEN increases the risk of thrombotic events in patients who are at high risk of thrombosis. High risk is defined, for example, as a history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk of a thromboembolic event and/or a known hypercoagulable state, regardless of thromboembolic history. It is recommended that patients receive adequate anticoagulation therapy according to the institutional standards and investigator's discretion. It should be tailored to the patient's individual risk/benefit profile by taking into account the individual thrombotic and bleeding risk, and the quality of compliance with venous thromboembolic event (VTE) prophylaxis. Anticoagulants may include acetylsalicylic acid (e.g., aspirin) prophylaxis, low molecular weight heparin, warfarin or new oral anticoagulants (NOAKs, e.g., dabigatran, rivaroxaban).

6.7 Prior and Concomitant Therapy

Administration and Recording of Prior and Concomitant Therapy – General Instructions

Any prior, concomitant, or procedural medications or therapy given to or taken by the patient within 1 month prior to commencement of the study (30 days prior to signing the ICF) and up to the End of Treatment Visit (EOT) must be recorded in the source documents and the eCRF along with the indication, route and dosage. Such medications (including over-the-counter medications) must be listed on the concomitant medications form in the eCRF. Starting from the EOT Visit, only anticancer treatments and, in case of an AE, other relevant concomitant medications (at the discretion of the investigator) should be entered. The investigator should instruct the patient not to take any additional medications (including over-thecounter--products) during the study without prior consultation.

For patients who will be administered MOR208 despite progression of disease / relapse, an **Unscheduled Visit** including all procedures described for EOT Visit need to be performed in order to capture the event (i.e. disease progression/relapse) for the antibody treatment to continue further.

At the EOT visit (or at the Unscheduled Visit after disease progression / relapse) as described in the above paragraph), any antineoplastic therapy after end of study drug treatment must be recorded as well.

Patients may receive concomitant medications that are medically indicated as standard care for the treatment of symptoms, AEs, and intercurrent illnesses. Medications to treat concomitant diseases like diabetes, hypertension, bronchial asthma, chronic obstructive pulmonary disease (COPD) etc., are allowed. Patients will also receive therapy to mitigate side effects of the study medication as clinically indicated, as well as best supportive care (BSC) as per institutional guidelines. This may include, but is not limited to, antiemetics, antidiarrhoeals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics, and other medications intended to treat symptoms.

Recording of Prior Lines of Anti-lymphoma Therapy

Information should be provided on any previous DLBCLspecific- therapies since the time point of the first diagnosis of DLBCL. The generic or the trade name may be recorded.
To become eligible for the MOR208C203 study the patients must have received at least one, but no more than three previous systemic therapy lines for the treatment of DLBCL and at least one therapy line must have included a CD20-targeted therapy (e.g., RTX).

Planned consolidation of responding patients, i.e. by radiotherapy or second line regimens with or without ASCT is regarded as one therapy line. Changing to a different chemotherapy regimen is regarded as a separate line of therapy, **unless** the change was caused by toxicity of the employed regimen.

Radiotherapy of the involved site (limited field radiotherapy) or radiation pre-planned to occur at the conclusion of systemic cytotoxic therapy will not be considered a separate prior line of therapy.

The administration of a mAb alone with a curative/therapeutic intent (e.g., RTX monotherapy) counts as a separate line of therapy. On the other hand the addition of a mAb to chemotherapy or mAb maintenance treatment subsequent to chemotherapy/chemoimmunotherapy regimen is considered one treatment therapy line, provided that the mAb was part of the initial treatment plan.

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

Growth Factors

Growth factors may be prescribed during the treatment and follow-up periods at the investigator's discretion, according to institutional standards. Growth factors or platelet transfusions should not be administered during the screening period solely for the purpose of improving a patient's blood values in order to meet eligibility criteria.

Infection Prophylaxis and Vaccines

Live vaccines must not be administered to patients in this study. Killed, inactivated vaccines, such as an injectable annual influenza vaccine, are permitted. Investigators should follow institutional guidelines concerning infection chemoprophylaxis for patients regarded to be at high risk for infection.

Anticancer Therapies

Patients should not have received a CD20-targeted therapy, chemotherapy, radiotherapy, investigational anticancer therapy or other lymphomaspecific- therapy within 14 days prior to Cycle 1 day 1 of the study. In addition, no radiotherapy (including limited field radiotherapy) is permitted after the baseline PET/CT scan for initial disease assessment has been performed. Other than the study drugs, patients should not receive any other DLBCLspecific- therapy during the study treatment period. The patient should not receive any investigational agent other than MOR00208 and LEN during the treatment period of the study.

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, radioisotopic therapies, stem cell transplant and targeted small molecules are not permitted during the entire treatment period (i.e., prior to disease progression during this study) of this study. After disease progression has been recorded, additional antineoplastic therapies are permitted at the discretion of the investigator and in accordance with the local guidelines and should be recorded in the eCRF.

Systemic Glucocorticosteroids

The use of systemic glucorticosteroids is generally discouraged because their potential antilymphoma activity in patients with DLBCL may confound interpretation of antitumor effects mediated by study drug treatment (MOR00208 and LEN).

However systemic corticosteroids in doses up to 20 mg/day prednisone or equivalent (i.e. equipotent corticosteroid) are permitted, provided the dosing is stable (not increased within the last month), but only for the treatment of non-neoplastic comorbid indications (e.g, rheumatoid arthritis).

- Screening:

Patients may potentially receive systemic glucorticosteroids in doses above 20 mg/day (prednisone or equivalent) to manage severe DLBCL manifestations (e.g., compressive disease, rapidly progressing symptomatic adenopathy) during Screening as per institutional standards. For these patients the glucorticosteroids treatment needs to be tapered to a total daily dosage of 20 mg or less of prednisone or its equivalent prior to study drug(s) administration on Cycle 1, Day 1.

-Cycle 1 through EOT visit:

Systemic glucocorticosteroids in doses above 20 mg/day (prednisone or equivalent) are not allowed during **Cycle 1 through EOT visit**, with the exceptions of premedication, cytokine release syndrome treatment at any time. Additionally, systemic doses above 20 mg/day (prednisone or equivalent; please refer to Appendix_D) will be allowed for antiemetic prophylaxis for up to 24 hours.

In the event a patient experiences an exacerbation of a chronic non-neoplastic condition such as chronic obstructive pulmonary disease (COPD), bronchial asthma or rheumatoid arthritis, peak doses above 20 mg/day (prednisone or equivalent) may be allowed for a limited period of time; the glucocorticosteroid dosage and the allowable treatment period will be determined by the investigator on a case-by-case basis following agreement with the medical monitor of the study. The specified systemic glucocorticosteroid use at a daily dose above 20 mg, if short in duration, is not likely to confound the treatment effect and efficacy analysis.

Similarly, patients who develop severe or life-threatening conditions that may be alleviated by systemic glucocorticosteroid (e.g., adrenal insufficiency) therapy are permitted to receive such drugs and are not required to discontinue study participation.

The investigator should aim to 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.

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

-Other Provisions on Glucocorticosteroids:

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

Concomitant Therapies that May Increase the Risk of Thrombosis

Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as oestrogen containing therapies, should be used with caution after making a careful benefit-risk assessment in patients receiving lenalidomide.

6.8 Treatment Compliance

Dosing modifications due to toxicity are described in Section 6.6.2.

Patients will receive MOR00208 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 dose administered is ≥80% to ≤120% of the assigned dosage per single infusion.

LEN is to be dispensed in 28-day cycles. Patients should return all unused or empty LEN bottles/blister packs to the site throughout the treatment period of the study, as instructed by the investigator. A patient will be considered compliant with the protocol if the LEN dose administered is ≥80% to ≤120% of the assigned dosage during a particular cycle.

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

6.9 Withdrawal from Study Treatment or Study/Site Termination

6.9.1 Withdrawal Criteria

Patients may voluntarily withdraw from the study or be discontinued from it at the discretion of the investigator at any time. An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

The investigators are encouraged to keep a patient experiencing clinical benefit in the study unless significant toxicity puts the patient at risk or repeated cases of routine noncompliance puts the study outcomes at risk.

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 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.

Following events are reasons for discontinuing a patient from the use of investigational product(s) and/or from the study:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Significant lack of co-operation or non-compliance on the side of the patient
- Pregnancy or lack of adequate contraception in FCBPs
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Unacceptable and unmanageable, in the view of either patient or physician, toxicity judged to be related to study drugs
- Occurrence of new diseases that could influence the treatment efficacy, for which the study medications are contraindicated or that are treated with a medication that is not permitted as a concomitant medication.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or somatic disease (e.g., infectious disease)
- Death
- Lost to follow up
- Major protocol violation (following discussion between the sponsor's Clinical Program Leader, Drug Safety Physician and the Investigators)
- Administrative reasons
- Termination of the study by MorphoSys or Regulatory Authorities
- Reconsideration of the risk/benefit ratio, in consensus with Ethical Committee

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

6.9.2 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, for example, if during the ongoing evaluation of the risk/benefit ratio, the sponsor decides that the risks outweigh the benefits of MOR00208 and/or LEN.

Should a termination of a given clinical study centre or the whole study become necessary, then the procedures will be arranged after review by, and consultation with, 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.

7 VISIT ASSESSMENTS AND PROCEDURES

7.1 Visit Schedule

Table 5 lists all of the assessments, and indicates with an "X" the visits at which these assessments are performed. All data obtained from these assessments must be supported in the patient´s source documentation.

Table 5 Schedule of Assessments

Schedule: Screening and Cycles 1–3

Evaluation or Procedure	Screening Period	Treatment Period												
	Screening ≤28 Days prior to D1	Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 (28 days)			
Day	**Screen**	**D1**	**D4**	**D8 ±1 day**	**D15 ±1 day**	**D22 ±1 day**	**D1 ±1 day**	**D8 ±1 day**	**D15 ±1 day**	**D22 ±1 day**	**D1 ±1 day**	**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													
Previous/concomitant medication	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[1]					X				X			
Body weight/height[2]		X	X	X	X	X	X	X	X	X	X	X	X	X
B-symptoms	X	X					X				X			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead resting ECG	X	X[3]			X[3]		X[3]				X[3]			
Urinalysis	X	X					X				X			
Pregnancy test (FCBP)[4]	X	X[1]		X[1]	X[1]	X[1]	X[1]				X[1]			
Pregnancy and risks counselling	X	X					X				X			
"Emergency laboratory"[5]		X	X	X	X	X	X	X	X	X	X	X	X	X
Central laboratory blood sampling [1]	X	X					X				X			
Serology Hepatitis B	X[16]						X[16]				X[16]			
Serology Hepatitis C	X													
B-, T- and NK cell flow cytometry (blood)[1]		X		X		X	X							
Anti-MOR00208 antibodies		X[1]									X[1]			
Optional FcγR polymorphism (mucosal cheek swab)		X												
ADCC and CD16 assessment (blood)		X[1]												

Evaluation or Procedure	Screening Period	Treatment Period												
	Screening ≤28 Days prior to D1	Cycle 1 (28 days)					Cycle 2 (28 days)				Cycle 3 (28 days)			
Day	**Screen**	**D1**	**D4**	**D8 ±1 day**	**D15 ±1 day**	**D22 ±1 day**	**D1 ±1 day**	**D8 ±1 day**	**D15 ±1 day**	**D22 ±1 day**	**D1 ±1 day**	**D8 ±1 day**	**D15 ±1 day**	**D22 ±1 day**
Disease and disease response assessment (CT/PET or PET/MRI)	X													
CT or MRI scan for tumour measurement and disease assessment (local)											X			
Central pathology review and correlative studies involving tissue samples	X													
Bone marrow aspiration & biopsy	X												X[7]	
MOR00208 administration		X	X	X	X	X	X	X	X	X	X	X	X	X
LEN tablets allocation		X					X				X			
(S)AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK MOR00208		X[6]	X[6]		X[6]		X[6]		X[6]		X[6]		X[6]	
Second primary malignancy		X	X	X	X	X	X	X	X	X	X	X	X	X

Schedule: Cycles 4–6

Evaluation or Procedure	Treatment Period					
	Cycle 4(28 days)		Cycle 5 (28 days)		Cycle 6 (28 days)	
Day	D1 ±2 days	D15 ±2 days	D1 ±2 days	D15 ±2 days	D1 ±2 days	D15 ±2 days
Previous/concomitant medication	X	X	X	X	X	X
Full physical examination (Limited physical examination - L)			L			
ECOG performance status	X		X		X	
Body weight/height[2]	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
B-symptoms	X		X		X	
12-lead resting ECG					X	
Urinalysis	X		X		X	
Pregnancy test (FCBP)[4]	X[1]		X[1]		X[1]	
Pregnancy and risks counselling	X		X		X	
"Emergency laboratory"[5]	X	X	X	X	X	X
Central laboratory blood sampling [1]	X		X		X	
Serology (Hepatitis B)	X[16]		X[16]		X[16]	
B-, T- and NK cell flow cytometry (blood)[1]			X			
Anti-MOR00208 antibodies			X[1]			
Disease and disease response assessment (CT/PET)						
CT or MRI scan for tumour measurement and disease assessment (local)			X			
Bone marrow aspiration & biopsy				X[7]		
MOR00208 administration	X	X	X	X	X	X
LEN tablets allocation	X		X		X	
(S)AE assessment	X	X	X	X	X	X
PK MOR00208	X[1]		X[1]		X[1]	
Second primary malignancy	X	X	X	X	X	X

Schedule: Cycles 7–12

Evaluation or Procedure	Treatment Period												
	Cycle 7 (28 days)		Cycle 8 (28 days)		Cycle 9 (28 days)		Cycle 10 (28 days)		Cycle 11 (28 days)		Cycle 12 (28 days)		
Day	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**D15 ±2 days**	**D28 ±4 days**
Previous/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
Full physical examination (Limited physical examination - L)	L						L				L		
ECOG performance status	X		X		X		X		X		X		
Body weight/height[2]	X	X	X	X	X	X	X	X	X	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		
12-lead resting ECG					X						X		
Urinalysis	X		X		X		X		X		X		
Pregnancy test (FCBP)[4]	X[1]		X[1]		X[1]		X[1]		X[1]		X[1]		
Pregnancy and risks counselling	X		X		X		X		X		X		
"Emergency laboratory"[5]	X	X	X	X	X	X	X	X	X	X	X	X	
Central laboratory blood sampling [1]	X		X		X		X		X		X		
Serology (Hepatitis B)	X[16]		X[16]		X[16]		X[16]		X[16]		X[16]		
B-, T- and NK cell flow cytometry (blood)[1]				X									
Anti-MOR00208 antibodies	X[1]				X[1]				X[1]				
Disease and disease response assessment (CT/PET)													X
CT or MRI scan for tumour measurement and disease assessment (local)	X						X						
Bone marrow aspiration & biopsy		X[7]						X[7]					X[7]
MOR00208 administration	X	X	X	X	X	X	X	X	X	X	X	X	
LEN tablets allocation	X		X		X		X		X		X		
(S)AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	
PK MOR00208	X[1]				X[1]				X[1]				
Second primary malignancy	X	X	X	X	X	X	X	X	X	X	X	X	

Schedule: Additional Treatment Period and Follow-Up Period

Evaluation or Procedure	MOR00208 Additional Treatment Phase (28 Days Cycles #13–24) (First cycle of additional treatment possible up to 2 weeks ±2 days after Cycle 12 Day 28)		MOR00208 Additional Treatment Phase[19, 20] (28 Days Cycles #25 onwards)		Unscheduled Visit (in case MOR00208 is to be administered despite disease progression)[8]	End of Treatment Visit (EOT)	30 Day Follow-up Visit	Survival Follow-up[9] (every 3 months ±2 weeks from last visit by phone)
Day	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**D15 ±2 days**		**(assessments can take place within 7 days period of the actual visit)**	**±2 days**	
Previous/concomitant medication[10]	X[17]	X[17]	X[17]	X[17]	X	X		
Full physical examination (Limited physical examination - L)	L[11, 17]		L[11, 17]		X	X	L	
ECOG performance status					X	X		
Body weight/height[2]	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X		
B-symptoms	X[17]				X	X	X	
12-lead resting ECG					X	X		
Urinalysis[18]	X[17]				X[18]	X[18]		
Pregnancy test (FCBP)[4]	X[1]		X[1]		X[18]	X[18]		
"Emergency laboratory"[5]	X	X	X	X				
Central laboratory blood sampling [1, 18]	X[17]				X[18]	X[18]		
Serology (Hepatitis B)[18]	X[16, 17]				X[16, 18]	X[16, 18]		
Anti-MOR00208 antibodies	X[1,12, 17]					X[18]		
CT or MRI scan for tumour measurement and disease	X[13, 17]		X[13, 17]					

Evaluation or Procedure	**MOR00208 Additional Treatment Phase (28 Days Cycles #13–24) (First cycle of additional treatment possible up to 2 weeks ±2 days after Cycle 12 Day 28)**		**MOR00208 Additional Treatment Phase[19, 20] (28 Days Cycles #25 onwards)**		**Unscheduled Visit (in case MOR00208 is to be administered despite disease progression)[8]**	**End of Treatment Visit (EOT)**	**30 Day Follow-up Visit**	**Survival Follow-up[9] (every 3 months ±2 weeks from last visit by phone)**
Day	**D1 ±2 days**	**D15 ±2 days**	**D1 ±2 days**	**D15 ±2 days**		**(assessments can take place within 7 days period of the actual visit)**	**±2 days**	
assessment (local)								
Disease and disease response assessment (CT/PET)			X[17, 19]		X[13, 14]	X[13, 14, 17]		
Bone marrow aspiration & biopsy		X[7, 15, 17]						
MOR00208 administration	X	X	X	X				
(S)AE assessment	X	X	X	X	X	X	X	
PK MOR00208	X[1, 12, 17]					X[18]		
Second primary malignancy	X	X	X	X	X	X	X	X
Antineoplastic therapy other than the study drug treatment[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X

Abbreviations: ADCC=antibody-dependent cell-mediated cytotoxicity; AE=adverse event; β-HCG=beta-human chorionic gonadotropin; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; FCBP=female of childbearing potential; IPI= International Prognostic Index; IV = intravenous; L= Limited physical examination; LEN=lenalidomide; MRI=magnetic resonance imaging; NK=natural killer; PET=positron emission tomography; PK=pharmacokinetics; SAE=serious adverse event.

[1]Before study drug administration.

[2]Body height will be measured at Cycle 1 Day 1 only. Body weight can be measured up to 24 hours prior to the study drug administration.

[3]12-lead resting ECG performed no later than 3 hours post-MOR00208 dose (see Section 7.2.10).

[4]Pregnancy tests: for FCBP, two pregnancy tests must be performed before enrolment; the first, a serum pregnancy test at screening within 10 to 14 days prior to the start of study drug and the second, a medically supervised urine pregnancy test within 24 hours prior to the start of study drug. The results of both tests must be negative in order to receive Cycle

1 Day 1 dosing. At all other indicated time points, a urine pregnancy test for FCBP will be performed locally and the result must be negative for dosing. A β-HCG pregnancy test should also be performed at the End of Study Visit.

[5]Sample to be collected and evaluated in the local laboratory (up to 24 hours prior to study drug administration) and reviewed by study treating physician before study drug administration.

[6]MOR00208 PK sample will be taken pre-dose and 1 hour ± 10 min after the end of MOR00208 infusion.

[7]Repeat bone marrow biopsy to confirm a CR only in those patients who had known bone marrow involvement prior to dosing (see Section 7.2.14.2 for details).

[8]For patients receiving antibody treatment despite disease progression / relapse, an **Unscheduled Visit** covering all assessments described under EOT visit should be completed (except PK sample) before the continuation of antibody therapy. These procedures, if performed within less than two weeks preceding this visit, need not be repeated. PET/CT need not be repeated if it was performed during previous treatment cycle.

[9]After 30-Day Follow-up Visit, a call will be made to the patient (or the patient's family) every 90 days for at least 5 years from Cycle 1 Day 1 to inquire about the patient's status, second primary malignancy (SPM) and information on any antineoplastic therapies utilised since discontinuation of study treatment.

[10]After disease progression has been recorded, only anticancer treatments and, in case of an AE, other relevant concomitant medications (at the discretion of the investigator) should be entered. Before and up to the End of Treatment Visit, the complete concomitant medication needs to be recorded.

[11]A limited PE (L) will be performed on Day 1 of each Cycle, every 12 weeks ±2 days from the previous PE.

[12]Anti-MOR00208 antibody sample and MOR00208 PK sample (pre-dose only) will be taken in odd numbered additional treatment cycles only (i.e. treatment Cycles 13, 15, 17, 19, 21, 23). No samples to be collected after Cycle 23.

[13]Disease assessment by CT/MRI of neck, chest, abdomen & pelvis with iv contrast during additional treatment phase; Cycles 13-24: approximately every 3 months ± 2 days from the previous scan. First assessment during this phase can be done directly 3 months after Cycle 12 D28 PET/CT assessment. Thus, this assessment is not needed at Cycle 13 Day 1, and an interval longer than ~3 months is acceptable for Cycle 16 Day 1 assessment; Cycle 25 onwards: approximately once every year ± 2 weeks from the previous scan. Images will have to be transferred to the central imaging laboratory.

[14]In case the patient is withdrawn from treatment before the end of Cycle 12 for reasons other than progression of disease. PET/CT is only required at the EOT visit if it was not performed in the cycle before the end of treatment visit.

[15]Bone marrow assessment during additional treatment phase (Cycles 13 to 24) approximately every 3 months ± 2 weeks from the previous assessment; to be performed to confirm a CR only in those patients who had known bone marrow involvement prior to dosing. Refer to Section 7.2.14.2 for further details.

[16]HBV-DNA to be measured and re-measured only if anti-HBc was positive at screening. If HBV-DNA is positive at screening, or during treatment, please see Section 7.2.13.2.

[17]Not applicable for patients who continue receiving MOR208 despite disease progression.

[18]Central laboratory tests will be performed only until Cycle 24 for each patient, as applicable. Not to be performed from Cycle 25 onwards.

[19]PET/CT Cycle 25 onwards should be performed only if deemed necessary, and not more than once per year.

[20]This treatment is planned for a total treatment duration (from Cycle 1 Day 1 onwards) of at least 5 years, including the safety follow-up visit and survival follow-up duration, as applicable.

[21]Antineoplastic therapy other than study treatment can be administered, and will be recorded in eCRF only for those patients who continue to receive MOR208 despite disease progression / relapse, and have completed an **Unscheduled Visit** covering all assessments described for the EOT visit. For further clarification please refer to Section 7.2.3.

7.2 Procedures

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

For **patients receiving antibody treatment despite disease progression / relapse**, an Unscheduled Visit covering all assessments described under EOT visit should be completed **before the continuation of antibody therapy**. 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 monoclonal antibodies. A urine pregnancy test should be performed for women of childbearing potential, prior to each infusion. Vital signs should be measured according to local practice for the administration of monoclonal antibodies. For this patient population only the **antineoplastic therapy and AEs** need to be captured in eCRF. Other procedures described in the column MOR00208 Additional Treatment will not apply for this patient population.

7.2.1 Screening followed by Enrolment (Start of IMP)

The Screening Period begins on the date the Informed Consent Form (ICF) is signed and will last for up to 28 days. The ICF must be signed prior to beginning 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 meet the protocol requirements.

During screening, it is permitted to repeat on a **single occasion** the **central laboratory assessment** of serum chemistry and haematology parameters due to the variability of the parameters and their dependence on multitude of factors (e.g., hydration, muscle mass). This 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). This procedure and the rationale behind it must be explicitly documented in source data. Such repeated assessment (once only) of the concerned parameters will not be counted as "re-screening" for that patient.

On Cycle 1 Day 1, patient eligibility must be confirmed before drug administration. Local laboratory parameters should be used for this purpose, as specified in Section 7.2.13 Laboratory Assessments.

7.2.2 End of Treatment (EOT) Visit

An end of treatment visit will have to be completed for all patients, including, but not limited to the following circumstances:

a. After disease progression / relapse, any time after start of the study treatment, provided MOR00208 will not be administered despite progression
b. After last administration of study drugs.
c. Withdrawal from study treatment as specified in Section 6.9.

If the EOT visit is after 24 cycles (i.e., Cycle 25 onwards), only the applicable laboratory tests in the local laboratory will need to be performed.

7.2.3 MOR00208 Administration Despite Disease Progression

It is up to the investigator to decide according to the individual risk/benefit ratio if the patient should continue on MOR00208 in case of disease progression, after discussion with the Sponsor's Medical Monitor. For patients who will be administered MOR00208 despite progression of disease / relapse, an **Unscheduled Visit** including all protocol prescribed procedures for the **EOT Visit** need to be performed in order to capture the event (i.e. disease progression/relapse) for the antibody treatment to continue further. These procedures, if performed within less than two weeks preceding this visit, need not be repeated. PET/CT need not be repeated if it was performed during previous treatment cycle. Note: Central laboratory tests will need to be performed only until Cycle 24 for each patient, as applicable.

Following procedures will be performed (and documented in source) for these patients **during the period** of MOR00208 administration despite disease progression (prior to each infusion):

a. Emergency Laboratory (Local Lab) evaluations consisting of haematology, serum chemistry according to local guidelines/standards of local medical practice for the administration of monoclonal antibodies.
b. A urine pregnancy test for women of childbearing potential
c. Vital signs

These patients will follow a visit schedule as mentioned under "MOR00208 Additional Treatment Phase", whereas their treatment cycle and visit numbers will be captured in a continuum with their previous applicable treatment visit, prior to disease progression. For this patient population only the antineoplastic therapy and AEs are going to be captured in eCRF. Other procedures described in the column MOR00208 Additional Treatment will not apply for this patient population.

In such cases an **EOT Visit** will take place after these patients have finally stopped receiving the antibody. At this EOT visit only anticancer therapy and AEs will be recorded. And lastly, a **Safety Follow-Up** will take place **30-Days** after last administration of MOR00208.

7.2.4 Safety Follow-up Visit

A **Safety Follow-Up** will take place **30-Days** after last administration of IMP. Following assessments will be performed and recorded in eCRF:

a. Limited physical examination

b. Adverse events including second primary malignancies

c. Antineoplastic therapy

7.2.5 Survival Follow-up

After Safety Follow-up Visit, a phone call will be made to the patient (or the patient's family) every 90 days (+ 2 weeks) for to cover a duration of up to 5 years from Cycle 1 Day 1 to inquire about the patient's status, second primary malignancy (SPM) and information on any antineoplastic therapies utilised since discontinuation of study treatment. 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.

7.2.6 Diagnostic Biopsy

Patients must be eligible and willing to undergo a biopsy of a lymph node or other pathological tissue, providing enough tumour tissue for correlative studies, as a part of participation in this study. Histological confirmation of the diagnosis of DLBCL will be performed by a central pathologist, retrospectively after enrolment. Surgically acquired tissue samples are preferred, but core biopsies are permitted. Bone marrow biopsies are not adequate for this purpose and should be performed only for disease staging.

Should it not be possible to obtain a fresh tumour tissue sample from the patient, archival paraffin embedded tumour tissue acquired $\leq$ 3 years prior to screening for this protocol must be available for this purpose.

The local pathology report indicating DLBCL diagnosis is acceptable for determining a patient's eligibility. Central pathology review is mandatory, but retrospective in nature. Tissue samples (or archival paraffin blocks, as stated above) should be submitted within 30 days of patient enrolment in the study. Patients can be enrolled prior to submission of tissue sample(s).

In case of discrepancies between the assessments of the local and the central pathologists, the one of the central pathologist prevails. If the DLBCL diagnosis of the local pathologist cannot be confirmed by the central pathologist, and a patient's treatment has already commenced, they may remain in the study.

7.2.7 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 DLBCL should be documented in detail, including baseline symptoms as well as a detailed history of prior cancer therapies for DLBCL, 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, for example, 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_E for Ann Arbor Staging).

Additionally the disease risk assessment as per IPI (see Appendix_B) and patient status as per Eastern Cooperative Oncology Group (ECOG) performance status criteria (see Appendix_F), will be recorded.

Examples of clinical significant systemic diseases, which may exclude patient participation include, but are not limited to:

a) A diagnosis of a myocardial infarction within the 6 months prior to enrolment, New York Heart Association (NYHA) class II or higher congestive heart failure, uncontrolled angina pectoris, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischaemia or significant conduction system abnormalities, in the opinion of the investigator. Patients with stable, asymptomatic atrial fibrillation are allowed in the study provided they do not meet the other cardiac exclusion criteria
b) Systemic diseases (e.g., cardiovascular, renal, hepatic) that would in the investigator's opinion preclude participation in the study or compromise the patient's ability to give informed consent
c) History or evidence of clinically significant peripheral nervous system, cerebrovascular, or CNS diseases, meningeal (e.g., meningeosis leukaemica), or epidural malignancy including brain metastasis or cerebrovascular event(s) with clinically significant sequelae. Screening for cerebrospinal fluid (CSF)/CNS involvement is not required but may be performed at the discretion of the investigator.

7.2.8 Vital Signs

Vital signs will be measured at the time points described in the Schedule of Assessments (Table 5).

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 immediately prior to infusion, 15 ± 5, 30 ± 10, and then every 60 ±15 minutes during infusion and at 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.

The frequency or the length of the monitoring period may be adapted if clinically indicated, for example 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 and an AE 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 for 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 hospital practice.

7.2.9 Physical Examination (PE)

7.2.9.1 Full PE

A full PE will be performed by the Investigator or a qualified designee during the 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 vital signs and palpable tumour assessments, general appearance, skin, head, eyes, ears, nose, throat including Waldeyer lymphatic structures, lungs, breasts and axillae (if applicable including bi-dimensional measurement of cervical, supraclavicular, axillary and inguinal lymph nodes), cardiovascular system, back and spine, abdomen (if applicable including spleen size below the costal margin), extremities, infusion site, lymph nodes, and neurological examination.

7.2.9.2 Limited PE

Limited PEs may be focused on tumour response assessment (e.g., lymph nodes, liver, spleen) and AEs per investigator discretion will be performed on Day 1 of Cycles 1, 3, 5, 7, 10 and 12. Additionally, a limited PE will be performed on the 30-Day Follow-up Visit.

During the course of the Additional Treatment Phase of the study a limited PE will be performed on Day 1 every 12 weeks ± 2 weeks.

Symptom-driven full PEs may be performed as clinically indicated at any study visit.

7.2.9.3 Body Weight and Height Measurements

Body height will be measured at Cycle 1 Day 1 only.

Body weight can be measured up to 24 hours prior to MOR00208 administration on Day 1 of each cycle. This baseline weight will be used to calculate the MOR00208 dose during the given cycle provided the weight does not deviate >±10% from baseline during the course of this cycle. In cases where the patient's body weight changes more than ± 10% from baseline, the current weight will be used to calculate the next and subsequent doses of MOR00208. Using actual body weight prior to each MOR00208 infusion is also allowed, if this is preferred by investigators.

Weight measurements should be performed at each visit and the values will need to be entered into the eCRF on the actual day of measurement.

7.2.9.4 B-Symptoms

B-symptoms are defined as any one or more of the disease-related symptoms or signs mentioned in Appendix_E.

Assessment of the presence or absence of B-symptoms will be performed at screening and on Day 1 for all cycles, as well as the End of Treatment Visit and at the 30-Day Follow-up Visit.

7.2.10 Electrocardiogram

Standard 12-lead resting ECGs will be obtained at the various time points described in the Schedule of Assessments (Table 5). ECGs will be recorded after the patient has rested in a supine position for at least 5 minutes. Heart rate, PR, QRS, RR and QT intervals will be determined. All ECGs will be performed and interpreted locally. The investigator will 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 will be repeated. An average of all intervals measured in all ECG tracings recorded at a given time point may be taken if necessary.

7.2.11 Adverse Event Monitoring

AEs will be assessed at each visit and reported as specified in Section 8.2 of the protocol.

For screening failure patients only SAEs will be recorded in the eCRF.

7.2.12 Monitoring of Second Primary Malignancies

SPMs will be monitored as events of 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 serious AEs, 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 period of up to 3 years. 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 on the diagnosis of the SPMs must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans).

7.2.13 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.

7.2.13.1 Safety and Haematology Laboratory Testing

Clinical laboratory tests will be performed according to Table 6. During the course of the study, local ("emergency") and central laboratories will be used.

Central laboratory results are required for determining patient eligibility for study enrolment and will be used in the primary statistical analysis of the study results. Note: for eligibility confirmation prior to study drug administration at Cycle 1 Day 1, local laboratory results should be used. During the course of the study, all scheduled central laboratory results should be reviewed as soon as possible after Day 1 of each cycle.

During screening, it is permitted to repeat on a **single occasion** the central laboratory assessment of serum chemistry and haematology parameters due to the variability of the parameters and their dependence on multitude of factors (e.g., hydration, muscle mass). This 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). This procedure and the rationale behind it must be explicitly documented in source data. Such repeated assessment (once only) of the concerned parameters will not be counted as "re-screening" for that patient.

Local ("emergency") laboratory results will be used for treatment or clinically related decisions, or for the immediate safety needs of a study patient. "Emergency laboratory" (local) results should be reviewed as soon as possible after their receipt and before dosing so that the administration of the investigational medicinal product (IMP) may be adjusted or interrupted if necessary.

The signed and interpreted laboratory results (both local and central) will 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 will be evaluated on a case-by-case basis. All blood samples will be processed and handled according to standard laboratory procedures. The time of blood collection should be documented in the source data.

If an abnormal laboratory value of grade 4 or an abnormal laboratory value judged to be clinically significant that was not present at baseline, is not reported as an AE, then the investigator should clearly document the rationale for not doing so in the source documentation.

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).

Central laboratory tests will be performed only until Cycle 24 for each patient, as applicable.

Table 6 Laboratory Evaluations

Evaluation	Analysis
"Emergency laboratory"[1] (EDTA blood and serum sample)	Serum creatinine, haemoglobin, WBCs, WBC differential, platelets, sodium, potassium, AST, ALT, total bilirubin
Haematology (EDTA blood)	WBC with differential count, haematocrit, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin concentration, platelet count, RBC count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils At screening: will include a peripheral blood smear Erythrocyte sedimentation rate kit from central lab will be used, however, the test as such has to be performed locally at the site.
Serum chemistry (serum sample)	ALT, total albumin, alkaline phosphatase, amylase, AST, bicarbonate, bilirubin (total), urea, total calcium, chloride, creatinine, creatinine kinase, GGT, glucose, LDH, lipase, phosphate, potassium, protein (total), sodium, uric acid, magnesium, β_2-microglobulin, C-reactive protein
Coagulation parameters (sodium citrate blood)	Activated partial thromboplastin time, prothrombin time, international normalisation ratio, immunoglobulin concentrations (IgG, IgM, IgA)
Serology parameters (serum sample)	Hepatitis B: HbsAg, anti-Hbc and anti-HBs. HBV-DNA if anti-Hbc positive (until Cycle 24), Hepatitis C: HCV antibody (HCV RNA quantification if anti-HCV-positive)
Pregnancy test (serum sample)	β-HCG serum, females of childbearing potential only
Pregnancy test (urine)	β-HCG urine, females of childbearing potential only. The pregnancy test assay should have a minimum sensitivity of 25 IU/mL (urine sticks will be provided centrally, until Cycle 24).
Urinalysis	Appearance, colour, urine bilirubin, glucose, haemoglobin, ketones, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated
Genotyping	FcγRIIa and FcγRIIIa polymorphism
CD16 expression on peripheral NK cells (heparinised blood) (exploratory assay)	CD16 expression on NK cells (Flow cytometry)
Immunogenicity (serum sample)	Anti-MOR00208 antibodies

continued

Evaluation	Analysis
Pharmacokinetics (serum sample)	MOR00208
ADCC assessment (heparinised blood) (exploratory assay)	ADCC with peripheral blood mononuclear cells (Flow cytometry)
B-/T-/NK cell counting (heparinised blood) (exploratory assay)	Cell counts (Flow Cytometry)
Analysis of exploratory biomarkers (pathology samples)	For example: CD19, CD20, BCL-2, BCL-6

Abbreviations: ADCC=antibody-dependent cell-mediated cytotoxicity; ALT=alanine transaminase; AST=aspartate aminotransferase; β-HCG=beta-human chorionic gonadotropin; EDTA=thylenediaminetetraacetic acid; GGT=gamma-glutamyltransferase; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HbsAg=hepatitis B surface antigen; LDH=lactate dehydrogenase; NK=natural killer; RBC=red blood cell; WBC=white blood cells.

[1]WBC differential can be automated or manual as per institutional standards. Reticulocytes may be determined only when clinically indicated.

7.2.13.2 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 hepatitis B surface antigen (HbsAg), total anti-hepatitis B core antibody (anti-Hbc) and hepatitis B surface antibody (anti-HBs). Patients with a positive test for anti-Hbc can only be included if hepatitis B viral DNA (HBV DNA) is not detected. **In these patients only**, HBV DNA should be assessed at various subsequent visits as outlined in Table 5. Note: Central laboratory tests will need to be performed only until Cycle 24 for each patient, as applicable.

In the context of exclusion criteria, seropositive for or active viral infection with hepatitis B virus (HBV) means:

a) HBV surface antigen positive
b) HBV surface antigen negative, HBV surface antibody positive and/or HBV core antibody positive and detectable viral DNA. Note: Subjects who are HBV surface antigen negative and viral DNA negative are eligible.
c) Patients who exhibit the classical vaccination profile of HBV surface antibody positive, HBV core antibody negative, and HBV surface antigen 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 anti-hepatitis C virus antibody (anti-HCV). For patients who are positive for anti-HCV antibody, HCV-RNA should be measured

A positive Hepatitis C test is defined as a positive test for Hepatitis C Virus (HCV) antibodies **and** a positive test for HCV RNA.

7.2.13.3 Pregnancy Testing

A pregnancy test will be performed for females of childbearing potential (FCBP) at various pre- and post-treatment time points either by urine pregnancy test or beta-human chorionic gonadotropin (β-HCG) test of a serum sample (see Table 5). The pregnancy test assay should have a minimum sensitivity of 25 IU/mL. At screening and the End of Treatment Visit, a serum β-HCG pregnancy test should be performed for FCBP.

FCBP must have two negative pregnancy tests prior to starting the study drug. The first pregnancy test must be performed within the 10–14 days prior to the start of study drug and the second pregnancy test must be performed within the 24 hours 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:

- every week for the first 28 days of the study
- every 28 days thereafter (or every 14 days if the patient has irregular periods)
- if the FCBP patient misses a period
- if the FCBP patient has unusual menstrual bleeding
- at the EOT Visit
- fourteen (14) days and 28 days (if irregular periods) and 28 days only (with regular periods) after stopping LEN.

Note: Central laboratory tests will need to be performed only until Cycle 24 for each patient, as applicable.

In addition, pregnancy and risk counselling will be conducted at the time points specified in the LEN Pregnancy Risk Minimisation Plan for Clinical Trials.

7.2.13.4 PK Assessments

Concentration-time profiles and PK parameters will be assessed for MOR00208 according to the Schedule of Assessments (Table 5). Neither samples nor concentration-time profiles or PK parameters will be assessed for LEN.

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 2 aliquots (a primary and a back-up sample).

7.2.13.5 Immunogenicity

Serum samples for anti-MOR00208 antibody analysis will be collected according to the Schedule of Assessments (Table 5).
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 2 aliquots (a primary and a back-up sample).

7.2.13.6 Other Laboratory Evaluations

A mucosal cheek swab will be used for DNA analysis of FcγRIIa and FcγRIIIa polymorphisms. The evaluation will be performed at a specified laboratory.

Genotyping is optional; it will only be performed if the patient specifically consents to this analysis. A patient can participate in the study regardless of whether they consent to undergo genotyping.

Biomarker analysis on collected tissue samples, for example CD19 and CD 20 expression assessments will be performed at a central specified laboratory.

For evaluation of the status of the patient's immune system, B-, T- and NK cells in peripheral blood will be measured frequently throughout the study (exploratory assay). The absolute and percentage changes from baseline will be evaluated.

Baseline CD16 expression on NK cells in peripheral blood will be evaluated at baseline (exploratory assay). In addition, the ADCC capacity of the patient will be assessed.

7.2.14 Efficacy Assessments

Efficacy will be evaluated in terms of ORR, DCR, DoR, PFS, OS, TTP and TTNT: For definitions see Section 10.6.

Disease response assessments will be made according to the revised response criteria based on the guidelines of the IWG reported by Cheson et al. (2007) (see Appendix_G). Response assessment made by the central radiology + clinical review at Cycle 12 Day 28 (±4 days) (and / or at the EOT visit, as applicable) will be considered for the main efficacy analysis (primary endpoint).

Local assessment of efficacy / disease response will be recorded in addition to central review at the end of Cycle 12 (for decisions concerning the additional Cycle 13 through Cycle 24 MOR00208 treatment) and at the EOT Visit (to determine whether the disease has progressed), and at additional time points specified in Table 5. Disease assessment by CT/MRI during additional treatment phase will be done as follows:

- Cycle 13 until Cycle 24: First assessment during this phase can be done after approximately 3 months + 2 days after Cycle 12 D28 PET/CT assessment. Thus, this assessment is not needed at Cycle 13 Day 1, and an interval longer than 3 months is acceptable for Cycle 16 Day 1 assessment. Thereafter, it will be repeated approximately every 3 months ± 2 days from the previous scan.
- Cycle 25 onwards: approximately once every year from the previous scan.

7.2.14.1 Tumour Imaging Assessment

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

Initial disease and disease response assessments for the primary endpoint will be made by positron emission tomography (PET)/ CT (CT should be done with IV contrast) at screening and Day 28 (±4 days) of Cycle 12 and at the EOT Visit, in the cases where a patient is withdrawn from treatment before the end of Cycle 12 for reasons other than progressive disease. PET/CT scanning during additional treatment phase (Cycle 13 onwards) with MOR00208 will be performed at the decision of the investigator, and should not be performed more than approximately once per year.

Tumour measurements and disease assessment (local) will be performed as indicated in Table 5 by CT. The CT portion of PET/CT will be acceptable in place of CT for tumour measurement and disease assessment, *only* when the CT portion is of adequate diagnostic-quality, and using adequate intravenous 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, previously performed PET/CT examinations, in accordance with the standard of care, that were done up to four weeks prior to the date of informed consent may be used for a patient's baseline central radiology assessment. Additional PET/CT or CT or MRI examinations may be performed by the investigator in the course of the study, if deemed necessary (e.g., to confirm the occurrence of a CR or to make important treatmentrelated- decisions). Whenever feasible, in such cases the investigator should seek prior approval of the sponsor for the additional imaging.

If the patient discontinues from treatment, a PET/CT scan is only required at the EOT Visit if it 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. All scans conducted during the study will be provided to a central imaging laboratory for independent radiological and clinical evaluation.

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.

7.2.14.2 Bone Marrow

At the screening visit, a uni- or bilateral bone marrow aspirate and a biopsy should be obtained to assess bone marrow involvement. Results from a bone marrow examination done within the 4 weeks prior to the date of informed consent will be acceptable if the patient's disease has been stable since then.

The achievement of CR in the course of MOR208C203 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 study entry. If bone marrow was not involved by lymphoma before commencing the study treatment, then bone marrow confirmation biopsy 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 response was CR.

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

8 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 lifethreatening-. 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 suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

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

An AE is defined as any untoward medical occurrence in a patient or clinical 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 more than 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)
- 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 noninvasive 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 inpatient hospitalisation or prolongation of existing hospitalisation (hospitalisation signifies that the patient was an inpatient 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 preplanned 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
    - hospitalisation signifies that the patient was an inpatient for at least one overnight stay
  - 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 lifethreatening- 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.

AEs of special interest are TFR, TLS, SPM, IRRs and allergic reactions to study drug ≥grade 3, cytokine release syndrome and overdoses.

Unlike routine safety assessments, SAEs and AEs of special interest are monitored continuously and have special reporting requirements (see Section 8.2).

The investigator should determine the causality (relationship to the study drugs) based on his/her clinical experience and on the information given in the IB for MOR00208 and the SmPC / Prescribing Information for lenalidomide. 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 drugs can be found in the IB for MOR00208 and the SmPC from lenalidomide, 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.

8.2 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 study 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 AEs assessed as related 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 AEs of special interest will be recorded on the SAE report form. Study centres and investigators are instructed to report all SAEs and AEs of special interest to the contract research organisation (CRO) mentioned below within 24 hours using the studyspecific- SAE report form. Preferably, the diagnosis instead of the individual symptoms should be reported. For overdoses, the diagnosis and if applicable the accompanying symptoms caused by the overdose should be reported.

If an AE has already been reported, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if a myocardial infarction is reported as an AE, there is no need to report elevated creatine phosphokinase and abnormal ECG, or other related signs,

symptoms, or laboratory values as separate AEs. However, if such events occur in isolation, and myocardial infarction is not diagnosed, then each event should be reported as an AE.

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 a study. All SAEs must be followed up for a final outcome until resolution or, if resolution becomes unlikely, until stabilisation or death. The follow-up for SAEs that are a progression of DLBCL only until the end of a patient's participation in a study is acceptable. This includes obtaining information on recovery and any sequelae and, in the case of a fatal outcome, the cause of death.

Events that are clearly caused by progression of the underlying disease (for example transformation to more aggressive histology) 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 adverse event.

Deaths that occur during the protocol-specified adverse event reporting period that are being attributed to progression of the underlying disease should not be recorded as AEs or SAEs. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported 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 survival follow-up, deaths attributed to progression of the underlying disease should be recorded in the eCRF.

Notification of initial or followup- SAE information (by using the standard SAE form provided by the sponsor) must be sent by fax to the CRO at the following numbers as appropriate:

For any safetyrelated- or protocol related questions, please use the contact numbers below (24/7 coverage):

24/7 Medical Emergency Coverage (out of office hours)	[redacted]
Medical Emergency Coverage (during Medical Monitor office hours)	

8.3 Pregnancies

As detailed in the Schedule of Assessments (Table 5) and Section 7.1, serum pregnancy testing will be carried out at the Screening, and End of Treatment Visits (performed centrally). 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 should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety, each pregnancy of a study patient or a female partner of a study patient must also be reported within 24 hours of learning of its occurrence to [redacted] by fax at the following number:

[redacted]

Female study patients who become pregnant must be withdrawn from the study treatment period (IMP is to be discontinued immediately).

A newly diagnosed pregnancy in a patient or female 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.

9 DATA HANDLING AND ARCHIVING

9.1 Completing and Signing Case Report Forms

Electronic CRFs will be used in this study. Data will be entered by trained site personnel, with reasons given for any missing data. Any errors should be corrected within the electronic system. 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.

9.2 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 18.0 or higher) for AEs and medical history and the WHO-drug dictionary enhanced for medication.

9.3 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.

10 STATISTICAL METHODS AND PLANNED ANALYSIS

10.1 Populations for Analysis

The following analysis populations will be used:

- **Full analysis set (FAS**):
  The FAS includes all patients who received at least one dose of MOR00208 and one dose of LEN. This means that both study drugs must have been applied at least once.
- **Per protocol set (PPS):**

  The PPS is the subset of all subjects in the FAS without any major protocol non-compliances. All patients in the FAS, had at least one dose of MOR00208 and one dose of LEN drug. Patients without any post-baseline assessment of DLBCL response or having major protocol deviations will be excluded from the PPS.
- **Safety analysis set (SAF):**
  All patients who received at least one dose of MOR00208 or LEN study drug.

Primary, secondary and supportive efficacy parameters will be evaluated using the FAS and PPS, while safety parameter evaluations will use the safety set (SAF), as well as for evaluations on immunogenicity and biomarkers.

The primary analysis of the primary efficacy endpoint will be based on the FAS, whereas the analysis using the PPS has a supportive function. Decisions about whether a protocol deviation is relevant for the exclusion of a patient from the PPS will be made before database closure.

10.2 Primary Endpoint

1. The primary efficacy endpoint will be ORR (ORR = CR + PR)

10.3 Secondary Endpoints

2. DCR, DoR, PFS, OS, TTP and TTNT
3. Incidence and severity of AEs
4. Determination and characterisation of a potential anti-MOR00208 antibody formation
5. PK analysis of MOR00208
6. Absolute and percentage change from baseline in measurements of B-, T- and NK cell populations
7. Analysis of exploratory and diagnostic biomarkers (e.g., CD19, CD20, BCL2, and BCL6 expression, CD16 expression on NK cells, ADCC capacity, and gene expression profiling for cell of origin subtyping and evaluation of AEs and ORR stratified by FcγRIIIa and FcγRIIa polymorphism) are planned to be investigated during the course of the study.

10.4 General Statistical Methods

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed using appropriate statistical software. 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 pharmacokinetic metrics, where additional statistics may be used.

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

The assumed overall type I error rate/significance level for the primary and secondary efficacy parameters is 5%, two-sided. Two-sided confidence limits will be evaluated at 95%, p-values from inferential tests comparing specific patient cohorts/patient subgroups will be compared to 5%.

Missing values will not be substituted by estimated values. All statistical evaluations will be based on valid cases except for procedures described for calculating response rates or in case of censoring within the Kaplan-Meier methodology. In the case of incomplete start or stop dates of AEs or concomitant medication appropriate conservative imputation methods will be specified in the Statistical Analysis Plan (SAP).

Baseline values will be defined as the last pre-administration observation used for calculating post-administration changes from baseline.

All data obtained and entered into the database will be provided in separate data listings showing individual patient values. A SAP detailing the statistical analyses and possible deviations from the protocol will be prepared before hard lock of database.

10.5 Patient Disposition

An overview table will be provided for all patients and will include the number of patients enrolled, the number of patients in each analysis population set, the number of completers and the number of withdrawals and the reasons for withdrawal. Compliance parameters for drug administration will be tabulated.

Demographic information will be summarised using descriptive statistics or counts and percentages.

General medical histories and DLBCLspecific- medical histories will be summarised by counts and percentages using appropriate classification codes. Concomitant medications will be recorded and tabulated with counts/percentages showing the number of medications/percentage used in each medication class.

10.6 Analysis of Efficacy Data

10.6.1 **Primary Efficacy Endpoint ORR**

Local and independent response evaluations (progressive disease, SD, PR and CR) will be tabulated with counts/percentages for each visit available. Missing response evaluations will be taken into account, with patients with missing responses included in the denominator for calculating the rates).

Objective response is defined as being when a patient is classified as having a CR or PR after DLBCL evaluation using the IWG treatment response criteria for malignant lymphoma (Cheson et al., 2007; see Appendix_G).

The ORR, for the primary efficacy endpoint, is defined as the proportion of patients with a CR or PR (ORR = CR + PR) up until disease progression, based on central radiological + clinical evaluations.

The denominator for calculating the rate will be based upon the total number of patients in the FAS population. As a sensitivity analysis, patients without any post-baseline assessment of response will be included in the denominator for ORR calculation. The number of responding patients and respective rates as well as the 95% confidence limits will be presented.

The SAP will specify further sensitivity and supportive analyses, as well as possible evaluation of further response parameters (e.g., best response).

10.6.2 Secondary Endpoints

10.6.2.1 Disease Control Rate (DCR)

The DCR is defined as CR + PR + SD (i.e. ORR + SD) and will be evaluated as for ORR.

10.6.2.2 Duration of Response (DoR) and Time to Next Treatment (TTNT)

DoR is defined as the time interval between the initial time point of tumour response (CR or PR whichever status is recorded first) and the first date that recurrence of progressive disease is documented. Response duration by the local and central assessment will be tabulated with descriptive statistics.

Disease progression is defined as the first occurrence of progressive disease according to the revised response criteria (Cheson et al., 2007) as assessed by central radiology / clinical readers.

TTNT is defined as the time from study entry (= first dosing) to the institution of next therapy for any reason including disease progression, treatment toxicity and patient preference. TTNT will be descriptively analysed.

10.6.2.3 Time to Event Variables: Progression-Free Survival (PFS), Overall Survival (OS), and Time to Progression (TTP)

PFS is defined as the time elapsed between study entry (= first dosing) and lymphoma progression or death from any cause, whichever occurs first. Patients not experiencing a lymphoma progression or death from any cause will be censored at the last available tumour assessment. The same holds true for patients who are lost-to-follow-up.

OS is defined as time from study entry (= first dosing) until the date of death from any cause. Patients who are alive but have dropped out early will be censored at the time of the last available study visit assessment.

TTP is defined as the time from study entry (= first dosing) until documented lymphoma progression or death as a result of lymphoma. The events of interest are only disease progression and death from lymphoma. Death from other causes will not be taken into account (will be censored) in the TTP evaluation. Patients not experiencing progressive disease will be censored at the last NHL assessment. Deaths 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 time of the last NHL assessment.

Kaplan-Meier methodology will be used to evaluate median survival, presenting corresponding statistical parameters and Kaplan-Meier survival curves. Further analyses concerning influence of IPI and GC/non-GC B-cells will be specified in the SAP.

TTP will be compared to the TTP of the patients' most recent therapy by tabulating descriptive statistics (including 95% confidence limits).

For the purposes of the protocol the day of enrolment is defined as the date of the first treatment (study entry).

The SAP will provide further details on how to evaluate the influence of IPI and GC/non-GC B-cells on ORR, DCR, PFS, OS, DoR, TTP and TTNT. Analyses will apply Kaplan-Meier methods using these parameters as factors, as well as stratifying analyses results by these factors or including these factors in appropriate multivariate models (e.g., analysis of variance [ANOVA]).

The analysis of incidence and severity of AEs has been described below.

10.6.2.4 Immunogenicity Analysis

The absolute number and percentage of patients, who develop anti-MOR00208 antibodies, and the results of semi-quantitative anti-MOR00208 antibody titre determinations of confirmed positive sample assessments will be tabulated. Further details will be specified in the SAP.

10.6.2.5 Pharmacokinetic Analysis

Appropriate PK parameters for MOR00208, with a focus on, but not limited to, accumulation ratios, will be computed based on non-compartmental data analysis and summarised using descriptive statistics. Mean concentrations (on original and on log-linear scale) will be visualised in figures. Further details of the PK analysis will be specified in the SAP.

10.6.2.6 Biomarkers

Blood and protein biomarkers which are important in the mechanism of action of, or could predict response to, the study drugs will be descriptively tabulated, presenting absolute and change to baseline values, if applicable.

For example:

a. FcγRIIa and FcγRIIIa genotyping results will be descriptively tabulated, whereas ORR and selective AEs tabulations will be split by these factors

b. Flow cytometry results of CD16 expression on NK cells will be descriptively tabulated, as well as ADCC results.

10.7 Analysis of Safety Data

10.7.1 Adverse Events

MedDRA (version 18.0 or higher) coded AEs will be used to show the incidence of all AEs by SOC, PT, relationship to treatment, severity and seriousness.
An AE summary table will present the number of events, number of patients and the percentage of patients having TEAEs, SAEs, and TEAEs that led to study discontinuation.

AE frequency tables will display event and patient counts by MedDRA, SOC and PT for each treatment arm. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity/toxicity, TEAEs by relationship to study drug, SAEs, drug-related TEAEs and TEAEs that led to study discontinuation.

10.7.2 Clinical Laboratory Evaluations

The analysis of laboratory parameters for each treatment arm will be presented separated into blood parameters (e.g., haematology, serum chemistry, coagulation, serology for hepatitis B and C) urine parameters (e.g., urinalysis) and serum pregnancy test.

Descriptive summaries of actual (absolute) values and selected change-from-baseline values for continuous laboratory parameters of interest will be presented. Investigator assessments of the clinical relevance of each laboratory parameter will be analysed by frequency tabulations.

The assessment of categorical urinalysis variables will be tabulated by time point, results for example of hepatitis B and C serology and pregnancy test results will be summarised using counts/percentages. Further details (e.g., tabulation of shifts, special analyses with respect to NCI CTC grading) will be detailed in the SAP.

10.7.3 Physical Examination, Vital Signs and Electrocardiogram (12-lead ECG)

Complete and limited PE results will be summarised by body system and tabulated as counts/percentages. New and worsening abnormal physical examination findings during the study will be entered as AEs and analysed within the AE tables in detail. Descriptive summaries of vital sign parameters will be calculated. Summary ECG assessments will be tabulated by time point using frequency tabulations. Results of the 12-lead ECG (PR, QRS, QT, RR interval values) will be flagged to show whether a value is below or above the normal limit and summary statistics will be provided for ECG parameters.

10.8 Sample Size Determination

Approximately 80 patients with R-R DLBCL who meet the inclusion criteria and have none of the exclusion criteria will be randomly enrolled into the study. The study will be performed with an interim stop for the evaluation of the safety of the LEN dosage. No adjustment of sample size

or adaptation of efficacy evaluations will be made at this point. As the primary purpose of this study is to evaluate the clinical efficacy of 25 mg daily oral LEN combined with 12 mg/kg MOR00208 administered by IV infusion in patients with R-R DLBCL, no formal statistical hypothesis testing will be performed.

For the determination of a suitable sample size, it is assumed that the combination treatment could improve the ORR from a value of 20% (under monotherapy) to 35% (under combination therapy). Applying an exact binomial test with a two-sided significance level of 5% and a power of 85% the estimated sample size is 73 patients (calculation performed by nQuery Advisor® 7.0). According to this scenario an observed ORR of 32% would lead to a statistically significant study outcome. Assuming a drop-out rate of 10%, a total sample size of about 80 patients is estimated.

The sample size determination has been conducted using various possible monotherapy and combination effect ORR rates and various power assumptions. Literature evaluation of study results concerning the ORR rates of LEN or comparable products (as mono- or combination-therapy) as well as former study results for MOR00208 were used to justify assumptions on response rates (Witzig et al., 2011; Wang et al., 2013).

10.9 Safety Run-In

The study will consist of two parts, which will be performed sequentially. The first part of the study (safety run-in) will conclude with an interim safety review after the first 6 patients have been accrued (see Section 5.1). This interim safety assessment will evaluate the number and type of AEs occurring during the first cycle, as well as the laboratory values (e.g., biochemistry and haematology) and other relevant safety data as necessary, with a view to providing a recommendation on the LEN dose to be used in the study, going forward.

The second part of the study will only be authorised to open for enrolment following the outcome of this evaluation. If, during the second part of the study, the safety profile of the combination is satisfactory, study patient accrual will continue until the full goal of approximately 80 patients is achieved.

11 SPECIAL REQUIREMENTS AND PROCEDURES

11.1 Charters

A charter outlining the central independent assessment (radiological and clinical) and review processes will be made available.

11.2 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.

11.3 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, MorphoSys 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 of a written amendment, 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
- MorphoSys will provide full details of the above procedures, either verbally, in writing, or both.

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.

The ICF must be signed, with name and date noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

11.4 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.

MorphoSys 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.

11.5 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 Department, 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.

11.6 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.

11.7 Publication Policy

Any presentation or publication of data from this study will be intended as a joint publication by the investigator(s)/appropriate study site personnel and appropriate sponsor personnel. Authorship will follow the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals 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 sites. 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 MorphoSys AG 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.

12 REFERENCES

Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol. 1998;16:2780-95.

Awan FT, Lapalombella R, Trotta R, et al. CD19 targeting of chronic lymphocytic leukemia with a novel Fc-domain-engineered monoclonal antibody. Blood. 2010;115(6):1204-13.

Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. Science. 2008;321:974–7.

Blum KA, Maddocks K, Nagy Z, et al. A Phase IIa, Open-Label, Multicenter Study of Single-Agent MOR00208, an Fc-Optimized Anti-CD19 Antibody, in Patients with Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma. Abstract 3089 56th ASH Annual Meeting & Exposition December 6-9, 2014; San Francisco, CA, USA.

Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol. 2006;24:5343-9.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.

Chiappella A, Tucci A, Castellino A, et al. Lenalidomide plus cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab is safe and effective in untreated, elderly patients with diffuse large B-cell lymphoma: a phase I study by the Fondazione Italiana Linfomi. Haematologica. 2013;98(11):1732-8.

Cockcroft DW, Gault MH. Prediction of creatine clearance from serum creatine. Nephron. 1976;16(1):31-41.

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235-42.

Feldman T, Mato AR, Chow KF, et al. Addition of lenalidomide to rituximab, ifosfamide, carboplatin, etoposide (RICER) in first-relapse/primary refractory diffuse large B-cell lymphoma. Br J Haematol. 2014;166:77-83.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2014;123:1917-23.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23:4117-26.

Galustian C, Dalgleish A. Lenalidomide: a novel anticancer drug with multiple modalities. Expert Opin Pharmacother. 2009;10:125-33.

Ginaldi L, De Martinis M, Matutes E, et al. Levels of expression of CD19 and CD20 in chronic B cell leukaemias. J Clin Pathol. 1998;51(5):364-9.

Goswami T, Forero A, Hamadani M, et al. Phase I/II study of MEDI-551, a humanized monoclonal antibody targeting CD19, in subjects with relapsed or refractory advanced B-cell malignancies. J Clin Oncol. 2012;30(suppl):8065.

Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24:3121-7.

Hallek M, Cheson BD, Catovsky D, et al. International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111:5446-56.

Haslett PA, Hanekom WA, Muller G, Kaplan G. Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8+ T cells in vitro. J Infect Dis. 2003;187:946-55.

Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype. Cancer. 2011;117:5058-66.

Ivanov V, Coso D, Chetaille B, et al. Efficacy and safety of lenalinomide combined with rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma. Leuk Lymphoma. 2014;55:2508-13.

Juweid ME, Stroobants S, Hoekstra OS, et al. Imaging Subcommittee of International Harmonization Project in Lymphoma. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol. 2007; 25:571-78.

Matlawska-Wasowska K, Ward E, Stevens S, et al. Macrophage and NK-mediated killing of precursor-B acute lymphoblastic leukemia cells targeted with a-fucosylated anti-CD19 humanized antibodies. Leukemia. 2013;27:1263-74.

Nowakowski GS, LaPlant B, Habermann TM, et al. Lenalidomide can be safely combined with R-CHOP (R2CHOP) in the initial chemotherapy for aggressive B-cell lymphomas: phase I study. Leukemia. 2011;25:1877-81.
Nowakowski GS, LaPlant B, Macon WR, et al. Lenalidomide Combined With R-CHOP Overcomes Negative Prognostic Impact of Non-Germinal Center B-Cell Phenotype in Newly Diagnosed Diffuse Large B-Cell Lymphoma: A Phase II Study. J Clin Oncol. 2015;33(3):251-7.

Olejniczak SH, Stewart CC, Donohue K, Czuczman MS. A quantitative exploration of surface antigen expression in common B-cell malignancies using flow cytometry: Immunol Invest. 2006;35(1):93-114.

Pan B, Lentzsch S. The application and biology of immunomodulatory drugs (IMiDs) in cancer. Pharmacol Ther. 2012;136:56-68.

Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7:379-91.

Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333:1540-5.

Raufi A, Ebrahim AS, Al-Katib A. Targeting CD19 in B-cell lymphoma: emerging role of SAR3419. Cancer Manag Res. 2013;5:225-33.

Ribrag V, Dupuis J, Tilly H, et al. A dose-escalation study of SAR3419, an anti-CD19 antibody maytansinoid conjugate, administered by intravenous infusion once weekly in patients with relapsed/refractory B-cell non-Hodgkin lymphoma. Clin Cancer Res. 2014;20:213-20.

Saloura V, Grivas PD. Lenalidomide: a synthetic compound with an evolving role in cancer management. Hematology. 2010;15:318-31.

Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol. 2005;23:5027-33.

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.

Thieblemont C, Coiffier B. Lymphoma in older patients. J Clin Oncol. 2007;25:1916-23.

Topp MS, Gökbuget N, Zugmaier G, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood. 2012;120:5185-7.

Viardot A, Goebeler M, Noppeney R et al. Blinatumomab Monotherapy Shows Efficacy in Patients with Relapsed Diffuse Large B Cell Lymphoma. ASH Annu Meet Abstr. 2011;118:1637.

Vitolo U, Chiappella A, Franceschetti S, et al. Lenalidomide plus R-CHOP21 in elderly patients with untreated diffuse large B-cell lymphoma: results of the REAL07 open-label, multicentre, phase 2 trial. Lancet Oncol. 2014;15:730-7.

Vose JM, Habermann TM, Czuczman MS, et al. Single-agent lenalidomide is active in patients with relapsed or refractory aggressive non-Hodgkin lymphoma who received prior stem cell transplantation. Br J Haematol. 2013;162:639-47.

Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia. 2013;27:1902-9.

Wiernik PH. Lenalidomide in lymphomas and chronic lymphocytic leukemia. Expert Opin Pharmacother. 2013;14:475-88.

Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2008;26:4952-7.

Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011;22:1622-7.

Woyach JA, Awan F, Flinn IW, et al. A Phase I Trial of the Fc Engineered CD19 Antibody XmAb®5574 (MOR00208) Demonstrates Safety and Preliminary Efficacy in Relapsed Chronic Lymphocytic Leukemia. Blood. 2014;124(24):3553-60.

Younes A, Kim S, Romaguera J, et al. Phase I multidose-escalation study of the anti-CD19 maytansinoid immunoconjugate SAR3419 administered by intravenous infusion every 3 weeks to patients with relapsed/refractory B-cell lymphoma. J Clin Oncol. 2012; 30: 2776-82.

Zhang H, Vakil V, Braunstein M, et al. Circulating endothelial progenitor cells in multiple myeloma: implications and significance. Blood. 2005;105:3286-9.

Zinzani PL, Pellegrini C, Gandolfi L, et al. Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 2 trial. Clin Lymphoma Myeloma Leuk. 2011;11:462-6.

Zinzani PL, Rigacci L, Cox MC, et al. Lenalidomide monotherapy in heavily pretreated patients with non-Hodgkin lymphoma: an Italian observational multicenter retrospective study in daily clinical practice. Leuk Lymphoma. 2014 (doi: 10.3109/10428194.2014.964702).

13 APPENDICES

Appendix A:

Cockcroft-Gault Formula:

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

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.

Appendix B:

International Prognostic Index (IPI):

- age older than 60
- lactate dehydrogenase level higher than normal
- ECOG performance status score of 2 or greater (see Appendix_F)
- stage III or IV disease
- more than one involved extranodal disease site

The International Prognostic Index (IPI) gives one point for each of the above characteristics, for a total score ranging from zero to five correlating with the following risk groups:

- low risk: 0–1 points
- low-intermediate risk: 2 points
- high-intermediate risk: 3 points
- high risk: 4–5 points

Appendix C:

Information on Investigational and Registered Products

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

Appendix D:

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

Appendix E:

Ann Arbor Staging* - Cotswolds Recommendations**

(Sources: *Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res. 1971; 31:1860-61. **Lister TA, Crowther D, Sutcliffe SB, et al. 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. 1989; 7:1630-36, [Erratum; J Clin Oncol. 1990; 8:1602])

Stage I: involvement of a single lymphatic region (I), or localised involvement of a single extralymphatic 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 extralymphatic 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 extralymphatic organ or site (IIIE), or by involvement of the spleen (IIIS).

Stage IV: Diffuse or disseminated involvement of one or more extralymphatic 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.

Appendix F:

ECOG Performance Status

Grade	Performance status
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

Publication: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

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

Appendix G:

Response Criteria

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

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 but criteria for progressive disease not met	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		

Relapsed disease or progressive disease	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; CT=computed tomography; FDG=[^{18}F]fluorodeoxyglucose; PET=positron emission tomography; PR=partial response; SD=stable disease; SPD=sum of the product of the diameters.