MOLECULAR TEMPLATES

CLINICAL STUDY PROTOCOL

Protocol Title:		A Phase 2a Open-label Study to Investigate Safety and Tolerability (including the Maximum Tolerated Dose), Efficacy, Pharmacokinetics, Pharmacodynamics and Immunogenicity of MT-3724 in Combination with Lenalidomide in Subjects with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma	
Protocol Number:		MT-3724_NHL_003	
Compound:		MT-3724	
Study Phase:		2a	
Sponsor	**Name**	Molecular Templates, Inc.	
	Legal registered address	9301 Amberglen Blvd. Suite 100 Austin, TX 78729	
Regulatory Agency Identifier Number(s)		IND: 121918 EudraCT: Not applicable NCT: NCT03645395	
Protocol Version and Date:		**Document Version**	**Date**
		Original (version 1.0)	18 July 2018
		Version 2.0	10 December 2018
		Version 3.0	14 April 2020

-CONFIDENTIAL-

MOLECULAR TEMPLATES APPROVAL

MT-3724_NHL_003: A Phase 2a Open-label Study to Investigate Safety and Tolerability (including the Maximum Tolerated Dose), Efficacy, Pharmacokinetics, Pharmacodynamics and Immunogenicity of MT-3724 in Combination with Lenalidomide in Subjects with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

I, the undersigned, have approved version 3.0 of the clinical trial protocol with the date of 14 April 2020.

Name and Title	Signature and Date
[redacted], MD Chief Medical Officer Molecular Templates, Inc.	DocuSigned by: [redacted] FF0FAA91A60846D... 4/16/2020
[redacted], PhD Senior Director, Clinical Development Molecular Templates, Inc.	DocuSigned by: [redacted] 66B68053ACE74CE... 4/22/2020

INVESTIGATOR AGREEMENT

MT-3724_NHL_003: A Phase 2a Open-label Study to Investigate Safety and Tolerability (including the Maximum Tolerated Dose), Efficacy, Pharmacokinetics, Pharmacodynamics and Immunogenicity of MT-3724 in Combination with Lenalidomide in Subjects with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma

I have read the protocol, including all appendices, and I agree that it contains all necessary details to conduct this study as described. I will conduct this study in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me. I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by Molecular Templates, Inc. I will discuss this material with them to ensure that they are fully informed about the drug(s) and the study.

Signature: _____ Date: _____

Name (print): _____

Site Name: _____

LIST OF CONTACTS

Sponsor's Medical Representative:	[redacted], MD Chief Medical Officer Molecular Templates, Inc. Work: [redacted]
Pharmacovigilance and SAE reporting:	Managed by CRO. Refer to Study Contacts for MT-3724_NHL_003 for the most up-to-date contact details.
Clinical Operations:	[redacted] Clinical Operations Molecular Templates, Inc. Mobile: [redacted]

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Synopsis

Protocol Title:
A Phase 2a Open-label Study to Investigate Safety and Tolerability (including the maximum tolerated dose [MTD]), Efficacy, Pharmacokinetics, Pharmacodynamics and Immunogenicity of MT-3724 in Combination with Lenalidomide in Subjects with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma.

Objectives and Endpoints:

OBJECTIVES	ENDPOINTS
Primary	
Determine the safety and tolerability (including the MTD) of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-Cell NHL	Incidence of adverse events (AEs), including DLTs, inclusive of physical exam findings, laboratory abnormalities, and/or subject-reported symptoms
Secondary	
Characterize the pharmacokinetics (PK) of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-Cell NHL	PK parameters will be derived from MT-3724 serum concentration time data from all eligible subjects; parameters will be stratified by dose group.
Assess the pharmacodynamics (PD) of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-Cell NHL	B-cell count and immunophenotype data by flow cytometry
Assess the immunogenicity of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-Cell NHL	Anti-drug antibodies (ADA) Neutralizing antibodies (NAb)
Assess the tumor response to MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-Cell NHL	Objective response based on local assessment Duration of response Progression-free survival (PFS) Overall survival (OS)
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]

Overall Design:
This will be an open-label dose escalation study of MT-3724 in combination with LEN in subjects with relapsed or refractory B-Cell NHL.

The study will be conducted in two sequential parts (Part 1 and Part 2); in both parts of the study, the subject's participation in the study will comprise of 4 periods: Screening,

Treatment, Short-Term Follow-Up (STFU) and Long-Term Follow-Up (LTFU). All assessments will be identical in Parts 1 and 2.

Screening:

The screening procedures will be performed within 35 days before Day 1 of cycle 1 (C1D1), with the exception of laboratory safety and radiographic assessments which are to be done within 28 days of C1D1.

Treatment:

Each subject may be treated only in one part of the study.

Part 1 (MT-3724 Dose Escalation)

Part 1 will include MT-3724 dose escalation according to the modified 3+3 design to identify the MTD of MT-3724 in combination with standard doses of LEN.

In all dose cohorts, MT-3724 will be administered in combination with LEN at a dose of 20mg. The LEN starting dose can be decreased per investigator's discretion based on the known safety profile of LEN and subject's status.

Before each dose escalation decision, the sponsor and all investigators will review all available data in the current dose cohort. These parties must decide by consensus whether it is safe to proceed to the next planned dose level, or to another dose not pre-specified in the protocol. The details of the safety review before dose escalation decisions are described in the study manual.

Cohort management and dose escalation decisions will be based on the incidence of treatment-emergent adverse events (TEAEs) that fulfill the criteria for a DLT. See Section 3.6 for conduct of dose escalation and for dose decisions in Part 1.

MTD definition: The highest MT-3724 dose that can be given in combination with LEN so that no more than 1 of 6 subjects experiences a DLT will be declared as the MTD for MT-3724 in Part 1 of this study. At least 6 subjects must be treated at the MTD dose level of MT-3724 in combination with LEN and complete cycle 1 or experience a DLT.

The sponsor will make the decision on the MTD after consultation with all investigators.

Part 2 (MTD Expansion Cohort)

The purpose of Part 2 is to confirm the safety, efficacy and tolerability of the MTD of MT-3724 in the MTD Expansion Cohort, where MT-3724 will be given at the MTD in combination with LEN. In addition, the PK, PD, immunogenicity and tumor response at the MTD of MT-3724 in combination with LEN will be evaluated in Part 2.

Part 2 can start only after the MTD of MT-3724 in combination with LEN is declared in Part 1; however, the screening of prospective subjects for Part 2 may begin during the review of the safety data leading to the MTD decision.

End of Treatment Visit and Short-Term Follow-up phone call:

The EoT Visit will be performed at the end of the treatment period for each subject in Part 1 and Part 2. The EoT Visit should occur at the time of discontinuation, as soon as possible after the last dose of MT-3724 or LEN (within 14 days of the last dose) for all subjects, except those who withdrew consent and objected to further data collection or were lost to follow up. End of Treatment Visit assessments should be performed during the clinic visit. The EoT Visit may be performed by telephone call only if subject cannot attend a clinic visit or has started a new anticancer treatment. The EoT Visit will be followed by a STFU phone call at least 30 days (+7 days) after last dose of MT-3724 or LEN, except for subjects who withdrew consent and objected to further data collection or were lost to follow up.

Long-term Follow Up Visit:

Subjects will be followed every 3 months (±14 days) for 18 months from the last dose of MT-3724. Subjects who discontinue treatment for disease progression will be followed only for OS. Subjects who discontinue treatment for reasons other than disease progression (e.g., toxicity) will be followed for PFS and OS. Subjects with CR, PR, or SD should also be followed for radiology assessment until progressive disease, death, or start of new anticancer treatment. The LTFU Visits will be performed via a telephone call and radiology data should be obtained from medical records.

Study Treatment and Duration

MT-3724 Investigational Medical Product (IMP)

MT-3724 will be administered as intravenous (IV) infusion over 1 hour (window of 54-75 minutes).

For subjects enrolled in Cohorts 1-3, in cycles 1 and 2, MT-3724 infusion should be administered on Day 1, 3, 5, 8, 10 and 12 (±1) of each 28-day cycle.

In subsequent cohorts in cycles 1 and 2, MT-3724 infusion should be administered on Days 1, 5, 8 and 12 of each 28-day cycle. Different dosing days up to D21 may be selected at investigator's discretion.

In all cohorts, starting with cycles 3 (C≥3), MT-3724 will be administered weekly (Day 1, 8, 15 and 22) of each 28-day cycle. Different dosing days within ±2 days from Day 1, 8, 15 and 22 may be selected at the investigator's discretion.

MT-3724 doses must be administered at least 48 hours apart.

Intra-subject escalation of MT-3724 dose is not permitted in either part of this study. The guidance for treatment modification (dose interruption/delay, dose reduction or treatment discontinuation) is presented in Section 5.4.

In Part 1, the starting MT-3724 doses in each of the planned cohorts are described in Table 1.

If MT-3724 is not tolerated in any of the planned cohorts, then additional MT-3724 doses may be evaluated in the interim cohorts at the sponsor's discretion in consultation with the investigator.

In Part 2, the starting MT-3724 dose will be the MTD of MT-3724 in combination with LEN from Part 1.

Premedication:

One premedication agent from each of the following 3 therapeutic classes must be given within 60 minutes before the start of each MT-3724 infusion in cycle 1 in both parts of the study:

- Oral anti-pyretic agent (325 – 1000mg acetaminophen or equivalent)
- Intravenous H1 histamine receptor antagonist (50 – 100mg diphenhydramine or equivalent)
- Intravenous corticosteroid agent with a shorter biological half-life (125 – 1000mg methylprednisolone or equivalent)

The specific drugs in each class should be selected at investigator's discretion or according to the institutional guideline. Cases where a subject has a contraindicating medical condition that precludes pretreatment with any of the categories above should be discussed with the sponsor. Although continued pre-medication is recommended during all cycles, after cycle 1, the investigator may adjust the dosage and/or avoid using certain premedication agents during the treatment, if supported by the investigator's assessment of the risk from infusion-related reaction, anaphylaxis or other hypersensitivity events.

See Section 5.1.3 for details about the IMP properties and dosing schedule.

Lenalidomide (Revlimid®, LEN)

Lenalidomide is available as 2.5-20mg oral capsules. It is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

In both parts of the current study, subjects will self-administer LEN once daily (qd) orally (PO) with or without food on the first 21 consecutive days (D1-D21) of each 28-day cycle. Subjects will record doses taken in a subject diary.

The starting dose of LEN in each cohort in Part 1 and Part 2 will be 20mg qd. The LEN starting dose can be decreased per investigator's discretion based on the known safety profile of LEN and subject's status. For Parts 1 and 2, starting with cycle 2 (after completion of the

DLT assessment period for subjects in Part 1), the investigator may increase the LEN dose to 25mg qd, if clinically indicated, with sponsor approval.

Modification of LEN treatment in this study will be guided by the reference prescribing information, as interpreted by the investigator after consultation with the medical monitor.

If the LEN dose has been reduced due to a TEAE, the intra-subject escalation of the LEN dose is permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio after consultation with the medical monitor. In such cases, the LEN dose may be increased only up to the level before the most recent dose reduction.

Table 1: MT-3724 Dose Cohorts and Corresponding MT-3724 and LEN Dose Levels

Planned MT-3724 Dose Cohorts	Interim MT-3724 Dose Cohorts[1]	Starting MT-3724 Dose (μg/kg/dose)[2]	Starting LEN Dose (mg)[3]
1		10 TIW	20
	-1 (optional)	≤5[4] TIW	20
2		25 TIW	20
	-2 (optional)	≤17.5[4] TIW	20
3		20 TIW	20
	-3 (optional)	15[4] TIW	20
4		25 BIW	20
	-4 (optional)	<17.5[4] BIW	20
5		50 BIW	20
	-3 (optional)	≤37.5[4] BIW	20

BIW = twice weekly; LEN = lenalidomide; TIW = three times weekly

[1]To be evaluated only if warranted by the safety results in the planned cohorts

[2]The administered dose of MT-3724 will be capped at 6000μg per infusion

[3]LEN dose is once daily

[4]The actual MT-3724 doses for 'interim' cohorts will be recommended by the sponsor after consultation with the investigators.

Duration: In Part 1 and Part 2, the treatment with MT-3724 and/or LEN in this study may be continued until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal, or until study discontinuation. LEN dosing may be discontinued at investigator's discretion, after approval by the medical monitor. Treatment with MT-3724 as a monotherapy may be permitted to continue with sponsor's approval.

Number of Subjects:

Approximately 64 subjects (i.e., 24 subjects in Part 1 and approximately 40 subjects in Part 2), as well as the appropriate number of replacements (if needed), will be enrolled and treated in this study. The actual number will depend on the number of dose cohorts needed to identify the MTD of MT-3724 in combination with LEN in Part 1.

Inclusion/Exclusion criteria:

Inclusion Criteria

Subjects must meet ALL the following criteria to be eligible for the study.

1. Be adequately informed about the study and fully consent to participation as demonstrated by signing the written informed consent form before any screening procedure.
2. Be aged ≥18 years on the date of signing the informed consent form.
3. Have relapsed or refractory CD20-positive B-cell NHL that, in the investigator's opinion, could benefit from MT-3724+LEN therapy. Subjects must have proof of CD20-positive NHL, either by:
   a. Historical biopsies (obtained with diagnosis of relapsed or refractory disease), or
   b. Fresh biopsies.
   c. Bone marrow biopsy, excisional lymph node biopsy, or core biopsy of any involved organ are all acceptable methods; fine needle aspirates (FNA) are not acceptable.
4. All subtypes of B-cell NHL may be considered for Part 1 (MT-3724 Dose Escalation). Only histologically documented DLBCL (including mixed histology) may be considered for Part 2 (MTD Expansion Cohort).
5. Have received all available approved therapies for NHL, one of which should be anti-CD20-based therapy.
   a. Subjects whose prior therapy includes chimeric antigen receptor T-cell (CAR-T) therapy are eligible.
   b. Subjects who underwent stem cell transplant (SCT) >100 days for autologous SCT or >180 days for allogeneic SCT before study drug administration and exhibited a full hematological recovery (consistent with the existing inclusion criteria requirements and without PRBC or platelet transfusions within 2 weeks of C1D1) prior to relapse are eligible.
   c. Subjects who have been ineligible for approved therapies in the opinion of the investigator, or have refused such therapies, may be eligible at the investigator's discretion, upon sponsor approval.
6. Have bi-dimensionally measurable disease by Lugano Classification for NHL:
   a. >1.5 centimeter (cm) longest diameter (LDi) for lymph nodes
   b. >1.0 cm LDi for extra nodal disease
7. Have Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (Appendix 6).
8. Have adequate bone marrow function, as determined by all the following:
   a. Absolute neutrophil count (ANC) ≥1,000/mm^3 and
   b. Platelet count ≥50,000 mm^3
   c. Hemoglobin ≥8g/dL
9. Have adequate kidney function, creatinine clearance (CLcr) to be ≥50mL/min either measured or assessed by using the Cockcroft-Gault formula (Appendix 5).

a. At the investigator's discretion, the eGFR result ≤50 mL/min may be verified by measurement of CLcr based on the 24-hour urine collection. Subjects with CLcr ≥50 mL/min will be eligible irrespective of the eGFR result.

10. Have adequate hepatic function, as determined by:
    a. Total bilirubin <1.5 x upper limit normal (ULN), or direct bilirubin <1.5 x ULN for subjects with elevated total bilirubin secondary to Gilbert's Syndrome, and
    b. Aspartate aminotransferase (AST) ≤3.0 x ULN (or ≤5 x ULN if liver involvement), and
    c. Alanine aminotransferase (ALT) ≤3.0 x ULN (or ≤5 x ULN if liver involvement).
11. Have adequate coagulation, as determined by:
    a. International normalized ratio (INR) or prothrombin time (PT) ≤1.5 x ULN (unless on therapeutic anticoagulants)
    b. Activated partial thromboplastin time (aPTT) ≤1.5 x ULN (unless on therapeutic anticoagulants)
12. Albumin ≥3.0 g/dL
13. Women of reproductive potential must have a negative pregnancy test on 2 occasions during the screening period (within 10-14 days and within 24 hours before the start of treatment). Women not of reproductive potential are female subjects who are postmenopausal (>1 year since last menstrual cycle) or permanently sterilized (e.g., hysterectomy, bilateral salpingectomy).
14. Males must agree to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking LEN and for up to 4 weeks after discontinuing LEN, even if they have undergone a successful vasectomy. Male subjects taking LEN must not donate sperm.
15. Subjects of reproductive potential and their partners must agree to either to abstain continuously from heterosexual intercourse or to use 2 methods of reliable birth control simultaneously to begin 4 weeks prior to initiating treatment with LEN until 28 days after the last dose of MT-3724 or LEN. The investigator or a designated associate should advise the subject how to achieve adequate contraception. The following birth control methods may be considered: one highly effective form of contraception – tubal ligation, intrauterine device (IUD), hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy, and one additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap.
16. Subjects must have a life expectancy of >3 months from the start of treatment.

Exclusion Criteria

Subjects who meet any of the following criteria must be excluded from the study.

Medical and surgical history

1. History or current evidence of neoplastic disease that is histologically distinct from NHL, except cervical carcinoma in situ, superficial noninvasive bladder tumors, curatively

treated Stage I-II non-melanoma skin cancer. Subjects with prior, curatively treated cancer >2 years ago before the start of treatment can be enrolled..

2. Current evidence of new or growing brain or spinal metastases during screening. Subjects with known brain or spinal metastases may be eligible if they:
   a. Had radiotherapy or another appropriate therapy for the brain or spinal metastases; concurrent prophylactic treatment is allowed.
   b. Neurological symptoms must be stable and no worse than Grade 2.
   c. Have evidence of stable brain or spinal disease on computer tomography (CT) or magnetic resonance imaging (MRI) scan obtained within 4 weeks of signing the ICF and compared with prior imaging results.
   d. Do not require chronic steroid therapy (or, if applicable, have been stable on steroid dose of no more than prednisone 20mg/day or equivalent by C1D1)
3. Current evidence of Graft versus Host Disease.
4. Current evidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade >1 toxicity before the start of treatment, except for hair loss and those Grade 2 toxicities listed as permitted in other eligibility criteria.
5. Current evidence of incomplete recovery from surgery or radiotherapy before the start of treatment, or planned surgery or radiotherapy at any time during the study until the EoT Visit, except minor elective interventions deemed acceptable by the investigator.
6. Current evidence of significant (CTCAE Grade ≥2) infection or wound within 4 weeks before the start of treatment.
   a. Subjects with Grade 2 infection that has stabilized or improved with oral anti-infectives before the start of treatment may be eligible at the sponsor's discretion.
7. Current evidence of significant cardiovascular disease including, but not limited to the following conditions:
   a. Unstable angina (symptoms of angina at rest) or new-onset angina within 3 months before the start of treatment.
   b. Arterial thrombosis or pulmonary embolism within 3 months before the start of treatment.
   c. Myocardial infarction or stroke within 3 months before the start of treatment.
   d. Any of the following within 3 months before the start of treatment with MT-3724: pericarditis (any CTCAE grade), pericardial effusion (CTCAE Grade ≥2), non-malignant pleural effusion (CTCAE Grade ≥2) or malignant pleural effusion (CTCAE Grade ≥3).
   e. Congestive heart failure (New York Heart Association [NYHA] Class III or IV; Appendix 7) at Screening or left ventricular ejection fraction (LVEF) <45%, assessed by Echo or multiple-gated acquisition (MUGA) scan within 1 month before starting study treatment (inclusion of subjects with LVEF between 40%-45% should be discussed and approved by the sponsor). Echo or MUGA scan performed within 6 months before screening and at least 28 days after the last cancer therapy is acceptable provided the subject has not received any potential cardiotoxic agents since then.

f. Cardiac arrhythmia requiring anti-arrhythmic therapy at Screening. Subjects receiving digoxin, calcium channel blockers, or beta-adrenergic blockers are eligible at the investigator's discretion after consultation with medical monitor if the dose has been stable for ≥2 weeks before the start of treatment with MT-3724. Subjects with sinus arrhythmia and infrequent premature ventricular contractions are eligible at the investigator's discretion.

8. QT interval corrected according to Fridericia's formula (QTcF) >480 ms, determined as the average from three QTcF values on the triplicate electrocardiogram (ECG) obtained at Screening.
9. Current evidence of uncontrolled HIV, HBV or HCV at screening. Serology testing is not required if seronegativity is documented in the medical history, and if there are no clinical signs suggestive of HIV or hepatitis infections, or suspected exposure. The following exceptions apply for subjects with positive viral serology:
   a. Subjects with HIV and an undetectable viral load and CD4+ T-cells counts ≥350 cells/microliter may be enrolled, but must be taking appropriate opportunistic infection prophylaxis, if clinically relevant.
   b. Subjects with positive HBV serology are eligible if they have an undetectable viral load and the subject will be receive antiviral prophylaxis for potential HBV reactivation per institutional guidelines.
   c. Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is below the lower limit of detection. Concurrent antiviral HCV treatment per institutional guidelines is allowed.
10. Women who are pregnant or breastfeeding.
11. History or current evidence of hypersensitivity to any of the study drugs, or of current hypersensitivity requiring systemic steroids at doses >20 mg/day prednisone equivalent.
12. History or current evidence of any other medical or psychiatric condition or addictive disorder, or laboratory abnormality that, in the opinion of the investigator, may increase the risks associated with study participation, or require treatments that may interfere with the conduct of the study or the interpretation of study results.

Prior treatments

13. Prior treatment with MT-3724.
14. Received anti-CD20 monoclonal antibody (Mab) therapy within the following periods before the start of treatment.
   a. Rituximab (Rituxan®; RTX): 84 days; if a subject has received RTX within 37 weeks before the start of treatment, then a serum RTX level must be negative (<500 ng/mL) at screening.
   b. Obinutuzumab (Gazyva®): 184 days
   c. Ofatumumab (Arzerra®): 88 days
15. Received therapy for NHL (except the anti-CD20 Mab therapies listed above and radioimmunoconjugates) within 4 weeks before the start of treatment. Radioimmunoconjugates are excluded within 12 weeks before the start of treatment. For small molecules (MW <0.9kDa), the washout shall be 2 weeks or 5 half-lives, whichever is longer (Macielag 2012).

16. Any investigational drug treatment from 4 weeks or 5 half-lives of the agent before the start of treatment, whichever is longer, until the EoT Visit.
17. Received radiotherapy to tumor lesions that would be chosen as target lesions (measurable disease) within 4 weeks before the start of treatment, unless the lesion exhibited objective progression between the radiotherapy and Screening according to the Lugano Classification for NHL.
    a. Palliative radiotherapy to non-target lesions may be permitted at the investigator's discretion after consultation with the medical monitor. See Section 5.10 for more information on the use of radiotherapy.
18. Received any live vaccines within 4 weeks before the start of treatment, unless the investigator believes benefits outweigh risk, after approval with sponsor.
19. Require the use of systemic immune modulators during study treatment.
    a. Systemic immune modulators include but are not limited to systemic corticosteroids at doses >20 mg/day or prednisone equivalent, cyclosporine and tacrolimus. Please see Section 5.9 for more details and exceptions.

Statistical Considerations:

All subjects who receive at least one dose of MT-3724 or LEN will be included in the safety analysis set, the analysis of tumor response and PD analysis set. All safety and tolerability evaluations will be based on this analysis set.

All subjects who received at least one dose of MT-3724 or LEN and have at least one post-treatment PK and immunogenicity assessment will be included in the analysis set for the PK and immunogenicity analysis, respectively. The subjects who received only LEN will be excluded from the PK and immunogenicity analysis.

Safety Analyses

Adverse events (AEs), serious adverse events (SAEs) and medical history findings will be coded according to MedDRA dictionary and graded for severity using the CTCAE v5.0. The AEs and SAEs are treatment-emergent if they have started or worsened after the start of the first dose of MT-3724.

Descriptive summary tables will present the number of subjects [n], mean, standard deviation, median, minimum and maximum for continuous variables and number of subjects [n] and percent for categorical variables).

Efficacy Analyses

The investigator at each site will determine the objective tumor response (OR) at each time point based on the radiologist's measurement of tumor lesions and using the five-point scale (5PS) per the Lugano Classification for Lymphoma (Cheson 2014) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (Cheson 2016) (Appendix 3). The best overall response rate (BORR) of all time points will be reported. Subjects who experience disease progression before undergoing the first tumor assessment will be added to the disease progression stratum. The best overall response rate (BORR) will

be descriptively summarized by the treatment group/cohort; the exact 95% confidence intervals will also be produced.

The OR representing clinically significant clinical benefit in this study will comprise the Lugano Score 1, 2 or 3 or the complete response (CR) or partial response (PR). All subjects achieving clinically significant clinical benefit according to both response criteria will be included in the analysis of the duration of tumor response (DOR). DOR is defined as the time from the first documented CR or PR to the actual date of disease progression or death before progression. The DOR will be descriptively summarized by the treatment group/cohort; the exact 95% confidence intervals will also be produced.

Pharmacokinetic Analyses

MT-3724 serum concentration time data from all eligible subjects will be subjected to non-compartmental analysis using the software package Phoenix WinNonlin (Certera, Princeton NJ). Pharmacokinetic parameters will be stratified by MT-3724 dose group and summary statistics will be generated. In addition, the MT-3724 serum concentration time data may be evaluated using nonlinear mixed effects modeling using Nonmem (Icon PLC, Dublin Ireland).

Immunogenicity Analyses

Data for the ADA against MT-3724 will be obtained as titer for ADA samples confirmed as a positive result, while the data for the NAb against MT-3724 will be obtained as positive or negative.

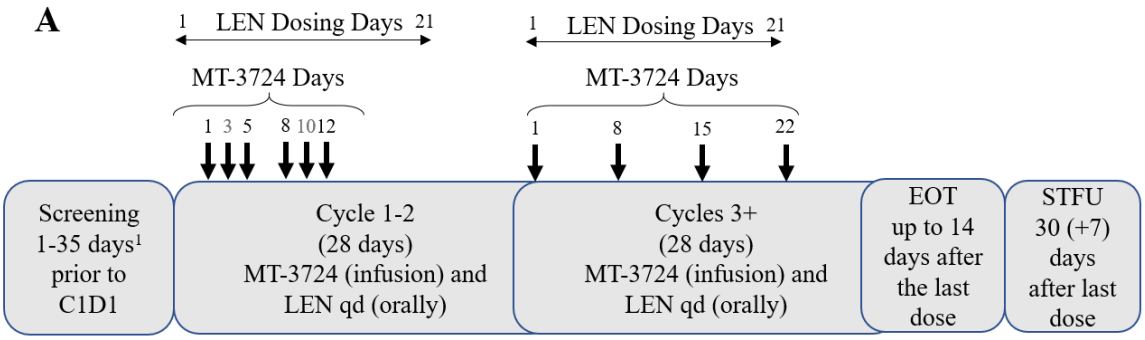
The number and percent of subjects with a detectable ADA titer, and separately with a positive NAb result, will be summarized by time point for each treatment group/cohort. The individual subject's immunogenicity results will be listed by time point for each subject by treatment group/cohort. Details of the immunogenicity analyses will be provided in a separate analysis plan for this study objective.

Pharmacodynamic Analyses

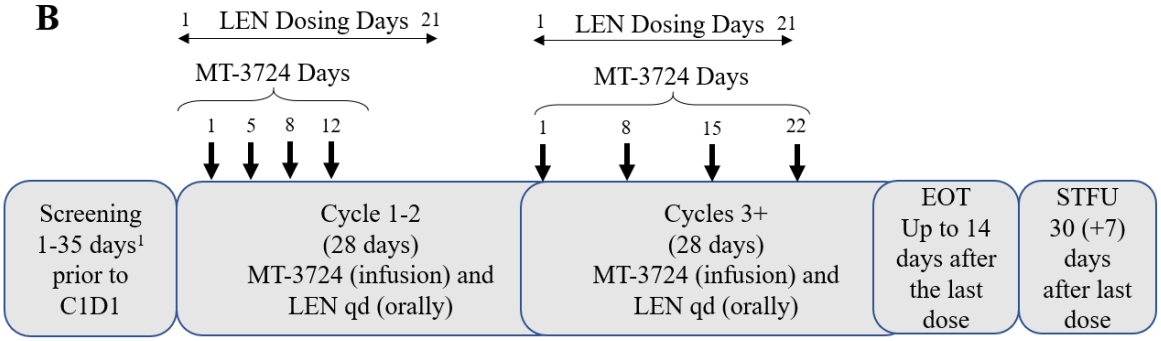
B-cell count and immunophenotype data by flow cytometry will be presented as absolute values and percentage change from pre- to post-dose time points. The summary statistics by time point and graphs of summary statistics over time will be presented by treatment group and overall.

Study Schema

Figure 1: Study Design for MT-3724_NHL_003



Procedures and schedules are the same for Parts 1 and 2



Procedures and schedules are the same for Parts 1 and 2

A) For Cohorts 1-3; B) Starting with Cohort 4.
C1D1 = cycle 1 Day 1; EoT = end of treatment; LEN = lenalidomide; qd = once daily; STFU = Short-Term Follow-Up
Long-Term Follow Up Visits should occur every 3 months (±14 days) for up to 18 months from the last dose of MT-3724.
[1]See Study Schema for timing of specific activities.

Schedule of Assessments

a. SCREENING

The schedule of assessments for the Screening period will be the same in Part 1 and Part 2. Unscheduled assessments may be performed at any time at the investigator's discretion.

Table 2: Schedule of Assessments for the Screening Period

Assessments and Procedures	Within 35 days of dosing on C1D1
Informed consent	X
Demography	X
Height, body weight and BMI	X
Medical history[1]	X
NHL disease status (at initial diagnosis and after relapse)[2]	X
NHL disease status (current)[3]	X
Prior Medications[4]	X
Prior systemic NHL therapy (including SCT)[5]	X
Prior NHL radiotherapy[6]	X
Full physical examination	X
NYHA for subjects with heart failure	X
ECOG Performance status	X
Blood pressure, heart rate, and respiratory rate[7,8]	X
Body temperature (°F/C)	X
12-lead ECG (Triplicate)[9]	X
Radiological tumor assessment (PET-CT or CT/MRI) [10]	X[11]
LVEF[12]	X
CENTRAL LABORATORY	
Serum rituximab level (if applicable)[13]	X
Hematology	X[19]
Chemistry (including eGFR[14])	X[19]
HbA1c	X[19]
Coagulation	X[19]
Thyroid function	X[19]
Beta-2 Microglobulin	X
MT-3724 Immunogenicity – (ADA/NAb)	X
B-cells and immunophenotype (flow cytometry)	X
Complement, Histamines, Cytokines, Immunoglobulins	X
Viral Serology & Virology, CD4+ T cell count [15]	X
Urinalysis (dipstick)[16]	X[19]
Pregnancy (serum or urine)[17]	X
AE reporting (new or worsening illness)[18]	X

ADA = anti-drug antibodies; C1D1 = cycle 1, day 1; CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECOG = Eastern Cooperative Group of Oncology; eGFR = estimated glomerular filtration rate; EoT = end of treatment;°F/C = degrees Fahrenheit or Celsius; FDG = fluordeoxyglucose; HbA1c = glycated hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus;

HIV = human immunodeficiency virus; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NAb = neutralizing antibodies; NHL = non-Hodgkin lymphoma; NYHA = New York Heart Association; OTC = over the counter; PET = positron-emission tomography; RNA = ribonucleic acid; r/r = relapsed or refractory; RTX = rituximab; SCT = stem cell transplant; .

[1] Illnesses that occurred at any time before the start of screening that, in the investigator's opinion, could increase the risk to subject and/or influence the study endpoints should be captured in the medical history as prior illnesses. Illnesses that are active at the time of informed consent should be captured in the medical history as concomitant illnesses.

[2] NHL disease status (at initial diagnosis and after relapse) will include the type, histology, staging (Ann Arbor Classification-Cotswold Modification), grading (low, intermediate or high)

[3] NHL disease status (current) will include the same as for the status at initial diagnosis. Please refer to Section 6.1.4 for additional information to collect.

[4] Prior medication is any medication (prescription, OTC and supplements) used within 4 weeks prior to the start of treatment. Prior therapy for NHL should be captured separately from prior medications.

[5] Prior systemic therapy for NHL (including SCT) administered at any time before the start of treatment should be documented by itemizing each regimen (line of treatment) and the individual agents within each regimen. The date of last CD20-based therapy should also be documented in the CRF.

[6] Prior radiotherapy for NHL administered at any time before the start of treatment.

[7] Blood pressure (systolic and diastolic), heart rate and respiratory rate should be measured after 5-10 minutes of quiet rest in a sitting or semi-recumbent position.

[8] When ECG and blood pressure assessments are scheduled to occur at the same time point, then the ECG should be performed first and the blood pressure/heart rate measurement may begin immediately after ECG recording (without additional 5-10 minutes' rest).

[9] Triplicate 12-lead ECG should be obtained as three standard ECGs recorded in close succession and not more than 2 minutes apart. The subject must rest quietly in supine or semi-recumbent position for 5-10 minutes before and during the procedure.

[10] A scan of all anatomic regions involved with the measurable disease by PET-CT (in subjects with FDG-avid tumor histology) or CT/MRI (in subjects with tumor histology of low or variable FDG avidity). CT of diagnostic quality should be collected for all subjects at baseline, whenever possible.

[11] Screening (baseline) radiological tumor assessments should be obtained as close to the start of treatment as possible, and within 28 days of C1D1.

[12]Done at Screening (within 1 month before starting study treatment). A pre-study LVEF assessment is acceptable if obtained within 6 months before screening and at least 28 days after the last cancer therapy provided the subject has not received any potentially cardiotoxic agents since then.

[13] It is recommended to assess RTX serum concentration prior to performing other screening procedures.

[14] Calculated by the central laboratory using the Cockcroft-Gault equation and the serum creatinine from the corresponding chemistry panel.

[15] Serology for HIV, HBV and HCV may be omitted at the investigator's discretion if seronegativity has been previously documented and there are no signs of the corresponding viral infection or suspected exposure. If applicable, serology should include anti-HIV1 and anti-HIV2 antibodies, HBsAg, anti-HBsAg and anti--HBcAg antibodies, HCV RNA quantitation and anti-HCV antibody as well as virology for HBV, HCV and HIV, when applicable. In addition, CD4+ T-cell counts should also be evaluated for subjects with HIV.

[16] Analysis of urine microsediment may be performed at the investigator's discretion by the local lab.

[17] Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours of the start of treatment. The pregnancy test performed within 24 hours of first dose is listed under C1D1.

[18] Adverse events that occur as a result of a study-related procedures during the screening period should be reported on the AE page.

[19] While screening procedures should be done within 35 days of C1D1, these should be within 28 days of C1D1

b. TREATMENT PERIOD

The schedule of assessments for the treatment period will be the same in Part 1 and Part 2. Unscheduled assessments may be performed at any time at the investigator's discretion.

Table 3: Schedule of Assessments for Treatment Period

	Treatment Period (28-day cycles)									EoT	STFU
	D1	D3	D5	D8	D10	D12	D15	D22	D23 –28		
Study treatment: cycles 1-2 for Cohorts 1-3											
Premedication for MT-3724[1]	X	X	X	X	X	X					
MT-3724	X	X	X	X	X	X					
LEN	Once daily PO on D1 - D21										
Study treatment: cycles 1-2 for subsequent cohorts											
Premedication for MT-3724[1]	X		X	X		X					
MT-3724	X		X	X		X					
LEN	Once daily PO on D1 - D21										
Study treatment: cycles 3 and beyond (applicable for all cohorts)											
Premedication for MT-3724[1]	X			X			X	X			
MT-3724	X			X			X	X			
LEN	Once daily PO on D1 - D21										
Study procedures (applicable for all cycles)											
Vital signs	X[5]									X	
Abbreviated PE	X[2]										
Full PE										X	
ECOG performance status	X[2]									X	
Body weight	X									X	
Single 12-Lead ECG (single)	X[2]									X	
LVEF[8]										X	
Radiological tumor assessment									X	X	
AE review	X										

	Treatment Period (28-day cycles)									EoT	STFU
	D1	D3	D5	D8	D10	D12	D15	D22	D23 –28		
Concomitant medication review	X										
Local lab analyses											
Urinalysis	X[2]			X[2]			X[2]			X	
Pregnancy	X			X[9]			X	X[9]		X	
Central lab analyses											
Hematology	X[2]			X[2]			X[2]			X	
Chemistry (incl. eGFR)	X[2]			X[2]			X[2]			X	
Coagulation	X[2,6]									X	
Thyroid function	X[2,6]									X	
HbA1c	X[2,6]									X	
Complement[3]	X									X	
Immunoglobulins[3]	X									X	
Histamine[3]	X									X	
Cytokines[3]	X									X	
B-cell count and immunophenotype	X[2]					X[2,10]	X[2,11]			X	
MT-3724 Immunogenicity	X[2]									X	
MT-3724 PK[7]	X	X				X				X	
Tumor tissue biopsy[4]										X	

AE = adverse events; BP = blood pressure; C = cycle; CT = computed tomography; CLS = capillary leak syndrome; CR = complete response; CRS = cytokine release syndrome; D = day in cycle; ECG = electrocardiogram; ECOG = Eastern Cooperative Group of Oncology; eGFR = estimated glomerular filtration rate; EoT = End of Treatment; ^{0}F = degrees Fahrenheit; HbA1c = glycated hemoglobin; HR = heart rate; LEN = lenalidomide; LVEF = left ventricular ejection fraction;; MRI = magnetic resonance imaging; NYHA = New York Heart Association; PE = physical examination; PET = positron-emission tomography; PK = pharmacokinetics; RR = respiratory rate; STFU = Short-Term Follow Up; TEAE = treatment-emergent AE.

[1]Premedication must be administered within 60 minutes before the start of each MT-3724 infusion in cycle 1. Premedications are encouraged in all subsequent cycles. Refer to Section 5.1.4 for more details.

[2]Up to 24 hours predose.

[3]Immunoglobulins, cytokines, complement and histamine are to be collected D1 of each cycle: predose and 3 h (±10 min) after the start of MT-3724 infusion, and at EoT. In addition, if a subject experiences a Grade ≥2 IRR, or another Grade ≥2 hypersensitivity event, Grade ≥2 CRS or Grade ≥2 CLS, the investigator should obtain serum samples for cytokines, complement and histamine as soon as possible after the TEAE onset. These samples should be marked “STAT” and shipped immediately to the central laboratory.

[4]Optional FNA biopsy at EoT for subjects in Part 2, who had consented for this procedure, exhibit PD and have accessible peripheral lymph node(s). In the absence of PET/CT, a bone marrow biopsy should be assessed to confirm CR.
[5]Collect Vital signs (BP, RR, HR, RR and body temperature) at the following times on dosing days (±10 min): predose (any time before start of infusion), 0.5, 1, 2 hours after start of infusion, C1D1: also collect 3 and 4 hours after start of infusion.
[6]Predose on Day 1 of cycle 3 and each odd cycle thereafter
[7]SeeTable 4, Pharmacokinetic sampling schedule
[8]Only done at the EoT Visit if the subject has received MT-3724 in ≥3 cycles, irrespective of the number of MT-3724 doses in each cycle.
[9]Only cycle 1
[10]Only cycles 1 and 2
[11]Cycles 3 and beyond

Table 4 Pharmacokinetic Sampling Schedule

	Time points relative to dosing								
	Predose	During infusion	After EOI						
	Within 4h prior SOI	10m before EOI	5m	0.5h	1h	2h	3h	4h	
Window			±1m	±5m	±5m	±5m	±10m	±10m	Notes
C1D1	X	X	X	X	X	X	X	X	If a MT-3724 dose is rescheduled, then the PK samples planned per protocol for that dose should be drawn on the new dosing day. For example, if Dose 3 is delayed from D5 to D7, then the PK samples planned for D5 should be drawn on D7. Unscheduled assessments may be performed at any time at the investigator's discretion. Samples for PK should be drawn from a different line than that used for MT-3724 administration.
C1D12	X	X	X	X	X	X			
CXD1	X	X	X						

C1D1 = cycle 1 Day 1; C1D12 = cycle 1 Day 12; CX = all cycles after cycle 1; EOI = end of infusion; PK = pharmacokinetics; SOI = start of infusion

1 INTRODUCTION

1.1 Non-Hodgkin lymphoma

CD20 is a B-cell specific differentiation antigen with four transmembrane domains (Kuijpers 2010). The CD20 protein plays a critical role in normal B-cell development and is expressed on 90% of B-cell NHL (Tedder 1988).

According to National Cancer Institute (NCI), the number of new NHL cases in the United States from 2010-2014 was 19.5 per 100,000 residents per year, and the number of deaths from NHL was 5.9 per 100,000 residents per year (SEER). The NCI estimates that in 2017 there would be 72,240 new NHL cases (4.3% of all cancer diagnoses) and 20,140 deaths (3.4% of all deaths) due to cancer.

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of NHL accounting for approximately 25 percent of NHL cases. In the United States, the incidence of DLBCL is approximately 7 cases per 100,000 persons per year (SEER) and varies by ethnicity, with Caucasians having higher rates than African Americans, Asians, or Native Americans.

Diffuse large B-cell lymphoma is a heterogeneous group of tumors consisting of large, transformed B cells with prominent nucleoli and basophilic cytoplasm, a diffuse growth pattern and a high (>40%) proliferation fraction. The immunophenotype of DLBCL can be confirmed by immunohistochemistry (IHC) or flow cytometry, with tumor cells generally expressing pan B cell antigens (CD19, CD20, CD22, CD79a), as well as CD45.

The prognosis for a newly diagnosed DLBCL patient depends on many host or tumor characteristics including tumor histology, tumor bulk burden and stage of tumor, participant's age and performance status. Current first line treatment for DLBCL is chemotherapy (CHOP, EPOCH, ACVBP) in combination with RTX. While 50-70% of patients are cured by current standard of care (SOC) chemotherapy (mainly R-CHOP), 30-40% of patients do not respond to R-CHOP or relapse following CR. Second line therapy with curative potential in patients with refractory or relapsed DLBCL (r/r DLBCL) is high dose chemotherapy (ICE, DHAP, GDP) + RTX followed by autologous SCT.

Before the advent of CAR-T therapy, salvage chemotherapy followed by autologous SCT was the only potentially curative therapy for patients with r/r DLBCL (Philip 1995). However, many patients do not benefit from salvage therapy because they do not respond to chemotherapy, are unfit to undergo transplants or lack caregiver support (Crump 2014; Kondo 2016); a retrospective analysis (SCHOLR-1) found that only 26% of refractory patients responded to salvage therapy, and median OS was only 6.3 months (Crump 2017).

Approved third line treatment options for DLBCL include CAR-T (Yescarta® axicabtagene ciloleucel/"axi-cel"; Tisagenlecleucel/CTL019 [Kymriah®]) and antibody drug conjugates such as polatuzumab (Polivy) in combination with RTX and bendamustine. Tafasitamab (MOR208) (formerly Xmab®5574) is an anti-CD19 mAb currently investigated in patients

with r/r DLBCL who are ineligible for autologous SCT. CAR-T trials show approximately 50% ORR and approximately 30-40% durable response rate (Neelapu 2017; Locke 2019). However, CAR-T remains difficult to access for many patients, and expensive.

1.1.1 Anti-CD20 Mab therapy for NHL

Anti-CD20 mAb therapy has become a ubiquitous component of treatment regimens for B-cell malignancies. Clinically active anti-CD20 mAbs used for the treatment of NHL can be separated into two types based on cellular effects observed on binding to CD20-expressing B-cells. Type I antibodies (RTX and ofatumumab) induce redistribution of CD20 into large lipid rafts in the plasma membrane and have strong complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) but have minimal direct antitumor effects. Type II antibodies (tositumomab and obinutuzumab) do not induce redistribution of CD20, have minimal CDC, strong ADCC and increased direct antitumor effects. Although fully humanized mAbs should be less immunogenic than the chimeric RTX, none of the more recently approved anti-CD20 antibodies appear to be clinically more effective against NHL in direct comparisons, perhaps because of patients' baseline immune status (Maloney 2012).

Of those participants with indolent NHL who relapse >6 months after initial response to RTX, only 40% will respond again when retreated with RTX (Davis 2000). The multicenter Phase 2 CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study showed that participants who had previously responded to a RTX containing treatment regimen had a worse outcome following RTX containing salvage immunochemotherapy. (Gisselbrecht 2010). Most patients across all types of NHL eventually become refractory to all anti-CD20 mAb treatments. There are several mechanisms by which this can happen, including increased mAb catabolism, initial development or post-treatment selection of malignant cells with low-levels of surface CD20 expression, resistance to mAb effector mechanisms and/or impaired immune cell function (Smith 2003). CD20 can also be removed from the B-cell surface following the molecular reorganization known as trogocytosis, which occurs during the conjugation between the Fcγ receptor on B-cells and the antigen-presenting immune cells (Beum 2011).

Further, due to their relatively large size, typically, less than 0.01% of the injected dose of an anti-CD20 mAb localizes to NHL tumors in human participants (Milenic 1991).

1.2 MT-3724

MT-3724 is a recombinant homodimeric fusion protein (theoretical molecular weight of ~110 kiloDalton), where each monomer consists of a single chain variable fragment (scFv) with affinity for human CD20 cell surface protein fused to the enzymatically active Shiga-like toxin-I A1 subunit. MT-3724 specifically binds and kills CD20-expressing malignant B-cells (Rajagopalan 2013) via a novel mechanism of action of enzymatic and permanent ribosome inactivation.

As a direct-kill immunotoxin directed against CD20, MT-3724 could achieve malignant cell lysis in refractory or relapsed NHL regardless of the biologic variations of malignant B-cells or patient's immune status. The smaller size of MT-3724 may offer an advantage over anti-CD20 mAbs enabling better tumor penetration. The scFv in MT-3724 binds to a CD20 epitope within rituximab's binding domain. While able to bind to CD20, the scFv in MT-3724 lacks an intact Fc region and does not rely on host antibody-directed cytotoxicity or CDC to induce cell death. The scFv in MT-3724 should not be adversely impacted by reduction of CD20 B-cell expression via internalization or trogocytosis. Thus, MT-3724 could avoid, mitigate or delay the emergence of resistance to anti-CD20 mAb therapy and offer potential benefit in patients with unmet medical need.

1.2.1 Clinical experience with MT-3724

The clinical development program for MT-3724 is being evaluated in 3 ongoing studies: 1 monotherapy study (MT-3724_NHL_001 [NHL_001]) and 2 combination therapy studies (MT-3724_NHL_002 [NHL_002] and MT-3724_NHL_003 [NHL_003]) with gemcitabine and oxaliplatin and LEN, respectively. Further studies of MT-3724 in other subtypes of NHL are planned.

Data from the MT-3724 monotherapy study, NHL_001, showed clinical anti-tumor activity in heavily pre-treated participants with relapsed or refractory DLBCL who had low serum level of RTX before the start of treatment.

Across all 3 studies as of 18 March 2020, CLS has been reported in 5 subjects: 2 subjects from NHL_001, 2 subjects from NHL_002, and 1 subject from NHL_003. All CLS events resolved, and the maximum severity for all events was Grade 2.

Neutropenia, acute kidney injury, capillary leak syndrome (including peripheral edema, hypotension, weight gain and hypoalbuminemia), systemic inflammatory response/cytokine release syndrome, pneumonia, and viral infection were reported as AEs related to MT-3724 and identified in the Investigator's Brochure as potential risks for participants receiving MT-3724 therapy.

Please refer to the latest version of the IB for comprehensive information available for MT-3724 to date.

1.3 Lenalidomide (Revlimid®, LEN)

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic and antineoplastic activity in cancer. It was structurally designed to enhance the immunomodulatory and antitumor activity of its predecessor thalidomide and is much less neurotoxic and in general well tolerated (Anderson 2005). It is approved by the FDA and EMA for the treatment of multiple myeloma (MM), mantle cell lymphoma, transfusion-dependent anemia due to myelodysplastic syndromes associated with deletion 5q abnormality, follicular lymphoma ([FL] in combination with RTX) and marginal zone lymphoma (in combination with RTX)

The most common adverse reactions are neutropenia, thrombocytopenia, anemia, pneumonia, rash and venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism). Allergic reactions including hypersensitivity, angioedema, Stevens-Johnson Syndrome, and toxic epidermal necrolysis were reported and fatal instances of tumor lysis syndrome have been reported during LEN treatment. Please see the reference prescribing information on LEN for additional details (Revlimid®).

1.3.1 Rituximab-lenalidomide (R^2) in NHL

Following demonstration of activity in MM and chronic lymphocytic leukemia (CLL), LEN has been shown to have considerable single agent clinical activity in NHL: overall response rates in subjects with aggressive NHL are 28-35% (7-12% complete response [CR]) (Witzig 2009). Lenalidomide plus RTX (R^2) has been evaluated in multiple phase II trials with variable dosing schedules and in multiple NHL subtypes (Witzig 2015).

In relapsed/refractory DLBCL or Grade 3 FL (n = 45), R^2 showed a 33% ORR (22% CR), a median DOR of 10.2 months, median PFS of 3.7 months, and median OS of 10.7 months (Wang 2013). In an Italian single-center phase II trial, 23 older participants (≥65 years) with relapsed/refractory DLBCL received LEN 20mg/day, D1-21/28 with RTX 375mg/m^2 on Days 1 and 21 for four cycles (Zinzani 2011). Participants with SD or better responses received LEN maintenance on the same dosing schedule for an additional eight cycles. At the end of induction, R^2 produced a 35% ORR and 30% CR. Of 10 participants eligible for maintenance, 8 achieved CR and a median DOR of 32 months (Zinzani 2013).

R^2 was generally well tolerated, with hematologic Adverse Event (AE) rates consistent with those for single-agent therapy. The rates of Grade 3/4 hematologic toxicity with R^2 varied across phase II studies, likely reflecting the different patient populations, NHL subtypes, and lines of therapy: neutropenia ranged from 30% to 66% and thrombocytopenia from 6% to 23% (Wang 2012; Ruan 2014; Zinani 2011; Fowler 2014). Non-hematologic toxicity, mainly Grade 1/2, also varied across studies, mostly consisting of fatigue, myalgia, rash, and infusion related reactions.

1.4 Rationale for the study design

The overall study design includes the dose escalation in the first part and the MTD expansion cohort in the second part. This design is typically used to assess the safety and efficacy of a novel anticancer agent when it is evaluated for the first time in combination with the SOC therapy.

In Part 1, the dose decisions in sequential cohorts is based on the 3+3 design guided by the incidence of DLTs. This is the most commonly used method to identify the MTD of a novel anticancer agent in clinical trials. In Part 2, the MTD expansion cohort is also the most commonly used method to confirm the MTD and gain more data about the safety and efficacy of a novel anticancer agent in a larger number of subjects.

All efficacy and safety assessments, as well as the methods used to measure them, are standard practice in clinical studies and/or clinical practice. They are widely recognized as reliable, accurate, and relevant.

Long-term follow up will be conducted to determine the impact of MT-3724 on tumor response which is part of the secondary objectives of this study.

1.5 Benefit/risk ratio

Most patients with CD20-positive B-cell NHL will eventually become resistant to available anti-CD20 therapy. The clinical unmet need is underscored in disease areas like DLBCL where the contribution or clinical benefit of anti-CD20 antibody therapies may be diminished beyond the front-line treatment setting. As a direct-kill agent targeted to CD20, where its mechanism of action is distinct from ADCC or CDC, MT-3724 could achieve malignant cell lysis in refractory or relapsed NHL regardless of the biologic variations of malignant B-cells or patient's immune status. The current study aims to address this unmet medical need by replacing RTX in the R^2 regimen with MT-3724.

In vitro MT-3724 was tested in combination with LEN to assess additive, synergistic or antagonistic cytotoxic effects on a CD20-positive cell line. A synergistic effect was observed in the combination of LEN and MT-3724 tested on CD20-positive cell line (IB). This in vitro data justifies further exploring the benefit-risk of combining MT-3724 with LEN for the treatment of NHL.

In the Phase 1 first-in-human study in NHL subjects, MT-3724 monotherapy was well tolerated up to the highest dose planned for the current study (50µg/kg/dose), and the safety profile of MT-3724 has been similar to that of RTX. MT-3724 achieved objective tumor response at the lowest dose potentially used in the current study (5µg/kg/dose).

The current study will enroll subjects with advanced progressive B-cell NHL who are not eligible for any further approved NHL therapy and/or SCT and/or refuse alternative approved therapies and/or are unlikely to achieve clinical benefit from any therapy of higher priority according to the investigator's assessment. MT-3724 has a potential to impart clinical benefit when combined with the standard doses of LEN in this population. Thus, the benefit-risk ratio in the current study is acceptable.

1.6 Guidance to the investigator

Preclinical studies and the ongoing first-in-human clinical trial MT-3724_NHL_001 have indicated several adverse events pertaining to subject safety. These adverse events should be kept in mind prior to treatment of any subject in this study as well as the precautions as indicated in the Revlimid® (lenalidomide) reference prescribing information.

The most common (≥20%) adverse events in the Parts 1 and 2 of the monotherapy study (% of subjects) were peripheral edema (63%), diarrhea, fatigue and myalgia (41% each), insomnia (30%), cough, pyrexia, and nausea (26% each), and headache, arthralgia, and hypotension (22.2% each).

DLTs in this trial were symptoms indicative of systemic inflammatory response/cytokine release syndrome (CRS) at 100µg/kg (2 subjects) and signs of CLS Grade 2 at 75µg/kg (2 subjects). All DLTs occurred in subjects who received a high total MT-3724 dose of 8500, 10730, 7208, and 11572µg/infusion.

Subjects should be closely monitored for signs of CLS/CRS.

- This includes monitoring of vital signs (body temperature, heart rate, blood pressure, and respiration rate), body weight and clinical symptoms including headache, myalgia, muscle weakness, edema, neurological and gastro-intestinal symptoms, abdominal pain and fatigue.
- Adequate monitoring of laboratory parameters of hematology, albumin, kidney, thyroid and liver function and cytokines in case of clinical symptoms indicative of CRS/CLS.

Investigators should consider supportive measures while on trial regardless of dosing or timing of dosing.

If a subject experiences Grade 2 hypotension, orthostasis, edema, or hypoalbuminemia, normal saline and/or an albumin infusion may be given, as needed.

In women, pregnancy has to be excluded before onset of treatment and highly effective contraceptive measures should be used in both men and women.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary objectives and endpoints

OBJECTIVES	ENDPOINTS
Determine the safety and tolerability (including the MTD) of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-Cell NHL	Incidence of AEs, including DLTs, inclusive of physical exam findings, laboratory abnormalities, and/or subject-reported symptoms

2.2 Secondary objectives and endpoints

OBJECTIVES	ENDPOINTS
Characterize the PK of MT-3724 in combination with LEN in subjects with relapsed or refractory B-Cell NHL	PK parameters will be derived from MT-3724 serum concentration time data from all eligible subjects; parameters will be stratified by dose group.
Assess the PD of MT-3724 in combination with LEN in subjects with relapsed or refractory B-Cell NHL	B-cell count and immunophenotype data by flow cytometry
Assess the immunogenicity of MT-3724 in combination with LEN in subjects with relapsed or refractory B-Cell NHL	ADA NAb

Assess the tumor response to MT-3724 in combination with LEN in subjects with relapsed or refractory B-Cell NHL	Objective response based on local assessment Duration of response PFS OS
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]

3 INVESTIGATIONAL PLAN

3.1 Description of overall study design and plan

This is a multi-center, open-label, multiple-dose Phase 2a, dose-escalation study of MT-3724 in combination with LEN in subjects with relapsed or refractory B-Cell NHL. Eligible subjects will be identified and treated through competitive enrollment at multiple global study centers.

There are two sequential parts to this study. Part 1 is an evaluation of doses of MT-3724 in combination with LEN in subjects with relapsed or refractory B-cell NHL, to determine the MTD; and Part 2 is an expansion of the MTD cohort to evaluate safety, tolerability, and potential efficacy in up to 40 additional subjects with DLBCL treated with MT-3724 at the MTD in combination with LEN. For LTFU, subjects from both parts of the study will be followed for 18 months from the last dose of MT-3724, see study design in Figure 1.

In both parts of the study, the subject's participation in the study will consist of 4 periods: Screening, Treatment, STFU, and LTFU.

3.2 Screening

Screening procedures will be performed within 35 days before the start of treatment on C1D1, with the exception of laboratory safety and radiographic assessments which are to be done within 28 days of C1D1. A signed written informed consent form (ICF) will be obtained before any screening procedure may begin. Screening assessments will be the same for Part 1 and Part 2.

After the investigator determines that all eligibility criteria have been fulfilled (Section 4.1 and Section 4.2.) the medical monitor will review the screening results and acknowledge that the subject may enter the treatment phase of the study.

3.3 Treatment

Each subject may be treated only in one part of the study. The treatment procedures will be identical in Part 1 and Part 2.

3.3.1 MT-3724

MT-3724 will be administered as an IV infusion over 1 hour (54 to 75 minutes).

Treatment with MT-3724 will be administered for cycles of 28 days each until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal, or until study discontinuation.

3.3.2 Lenalidomide

In both parts of the current study, subjects will self-administer LEN qd PO with or without food, around the same time each day, on the first 21 consecutive days (D1-D21) of each 28-day cycle. LEN cannot be administered between D22-D28 in any cycle.

3.4 End of Treatment Visit and Short-Term Follow-Up phone call

The EoT Visit will be performed at the end of the treatment period for each subject in Part 1 and Part 2. The EoT Visit should occur at the time of discontinuation, as soon as possible after the last dose of MT-3724 or LEN (within 14 days of last dose) for all subjects, except those who withdrew consent and objected to further data collection, or were lost to follow up.

The EoT Visit should be performed during the clinic visit. The EoT Visit may be performed by telephone call, but only if a subject cannot attend a clinic visit or has started a new anticancer treatment. In such instances, missed assessments (e.g., laboratory assessments, PE), are not considered deviations.

The STFU phone call will take place at least 30 days (+7 days) after the last dose of MT-3724 or LEN (except for subjects who withdrew consent and objected to further data collection, or were lost to follow up).

3.5 Long-Term Follow Up Visit

The LTFU Visits should occur every 3 months (±14 days) for up to 18 months from the last dose of MT-3724. Subjects who discontinue treatment for disease progression will be followed only for OS. Subjects who discontinue for reasons other than disease progression (e.g., toxicity) will be followed for PFS and OS. Subjects with CR, PR, or SD should also be followed for radiology assessment until progressive disease, death, or start of new anticancer treatment. The LTFU Visits will be performed via a telephone call to collect the information about death (if any), the NHL status (relapsed or not) and the start of any new therapy for NHL or any other investigational drug since the last study visit/phone call and radiology data should be obtained from medical records.

3.6 Part 1 (MT-3724 Dose Escalation)

Twenty-four subjects will be enrolled in Part 1; the actual number will depend on the number of dose cohorts needed to identify the MTD of MT-3724 in combination with LEN.

The first two subjects in each MT-3724 dose cohort will be enrolled in a staggered fashion, where at least 7 days elapse between D1 of the first and D1 of the second subject (the next subject(s) can be included at the same time as the second subject) to allow for adequate safety monitoring. Prospective subjects for all 3 treatment slots may be consented and screened in parallel with the treatment of previous subjects in the same cohort.

If permitted by the safety results, the MT-3724 dose escalation is planned to proceed in sequential dose cohorts. Interim MT-3724 doses may be evaluated in additional cohorts at the sponsor’s discretion in consultation with the investigator(s).

In all dose cohorts, MT-3724 will be administered in combination with a starting dose of LEN 20mg. The LEN starting dose can be decreased per investigator's discretion based on the known safety profile of LEN and subject's status.

The planned dose-escalation scheme is summarized in Table 5

Table 5: MT-3724 Dose Cohorts and Corresponding MT-3724 and LEN Dose Levels

Planned MT-3724 Dose Cohorts	Interim MT-3724 Dose Cohorts[1]	Starting MT-3724 Dose (µg/kg/dose)[2]	Starting LEN Dose (mg)[3]
1		10 TIW	20
	-1 (optional)	≤ 5[4] TIW	20
2		25 TIW	20
	-2 (optional)	≤ 17.5[4] TIW	20
3		20 TIW	20
	-3 (optional)	15[4] TIW	20
4		25 BIW	20
	-4 (optional)	< 17.5[4] BIW	20
5		50 BIW	20
	-3 (optional)	≤ 37.5[4] BIW	20

BIW = twice weekly; LEN = lenalidomide; TIW = three times weekly
[1]To be evaluated only if warranted by the safety results in the planned cohorts
[2]The administered dose of MT-3724 will be capped at 6000µg per infusion
[3]The LEN dose is once daily
[4]The actual MT-3724 doses for 'interim' cohorts will be recommended by the sponsor after consultation with the investigators and Medical Monitor.

Before each dose escalation decision, the sponsor and all available investigators will review all available data in the current dose cohort. The listed stakeholders must decide by consensus whether it is safe to proceed to the next planned dose level, or to another dose not pre-specified in the protocol. The details of the safety review before dose escalation decisions are described in the study manual.

Cohort management and dose escalation decisions (including the MTD) will be based on the incidence of TEAEs that fulfill the criteria for a DLT, as follows:

a. The first dose escalation decision in the current MT-3724 dose cohort will be made after at least 3 subjects complete cycle 1 or experience a DLT. Up to 4 subjects may be initially treated in each MT-3724 dose cohort; this aims to ensure that at least 3 evaluable subjects are available for the first dose escalation decision.
b. If none of the first 3 or 4 subjects in the current MT-3724 dose cohort experience a DLT, then dose escalation may proceed to the next planned MT-3724 dose level.
c. If 1 of the initial 3 or 4 subjects in the current MT-3724 dose cohort experiences a DLT, then this cohort will be expanded to 6 subjects. Subjects for the expanded current cohort may be enrolled simultaneously through competitive enrollment.

d. If no more than 1 of 6 subjects in the expanded current MT-3724 dose cohort experiences a DLT, then dose escalation may proceed to the next planned MT-3724 dose level.
e. If a DLT occurs in ≥2 of initial 3 or 4 subjects in the current MT-3724 dose cohort, or in ≥2 of 6 subjects in the expanded current cohort, one of the following 2 steps may be undertaken at the sponsor's discretion after consultation with the investigator(s):
   - If not previously done, up to 6 subjects may be treated at the planned MT-3724 dose level immediately below the non-tolerable dose.
   - Alternatively, up to 4 subjects may be initially treated at the 'interim' MT-3724 dose level and schedule between the non-tolerable dose level and the planned MT-3724 dose level immediately below the non-tolerable dose. The MT-3724 doses proposed for the 'interim' cohorts are listed in Table 5; however the actual MT-3724 doses and schedule for 'interim' cohorts will be recommended by the sponsor after consultation with all investigators.
f. If at least 4 subjects in the cohort have no DLTs, dose re-escalation can be attempted in up to 6 subjects at the original target dose of the previous cohort under the new schedule after consultation with the investigators and medical monitor.
g. The same principles as listed above will apply to the cohort management and dose decisions in the 'interim' MT-3724 dose cohorts.

Treatment in the expanded current MT-3724 dose cohort or the next cohort may start only after the dose decision in the current cohort has been made; however, prospective subjects may be consented and screened during the review of the safety data leading to the dose decision.

3.6.1 Subject evaluable for dose decisions

Subjects in Part 1 will be evaluable for dose decisions if they satisfy one of the following criteria:

- Have had a DLT after at least one dose of MT-3724 in cycle 1; or
- In the absence of DLT, have received at least 4 of 6 (67%) doses of MT-3724 (if 6 doses are planned) or 3 of 4 doses (75%) of MT-3724 (if 4 doses are planned) and at least 14 of 21 (67%) doses of LEN.

Subjects who are not evaluable for dose decisions will be replaced.

3.6.2 DLT Criteria

A TEAE will be declared as DLT if both of the following criteria are met:

1. The TEAE occurred after the start of infusion in cycle 1 of Part 1.
   a. If a TEAE that fulfills a DLT criterion is observed in cycle ≥2 of Part 1, then the sponsor may declare this event a DLT after consultation with the investigator(s).
2. The TEAE is at least possibly related to MT-3724, as determined by the sponsor after consultation with the investigator(s).

Note: TEAEs related to LEN will not be declared a DLT unless they exceed in severity the worst grade described or are not mentioned in the reference prescribing information. If a Grade ≥3 TEAE related to LEN is more severe than the worst grade described in the reference prescribing information or has not been reported in the reference prescribing information, then the sponsor may declare this event a DLT after consultation with the investigator(s).

The severity of TEAEs potentially fulfilling the DLT criteria will be graded according to the CTCAE v.5.0.

See Appendix 4 for the type and severity of TEAEs that may qualify as DLT.

3.6.3 MTD definition

The highest MT-3724 dose that can be given in combination with LEN so that no more than 1 of 6 subjects experiences a DLT will be declared as the MTD for MT-3724 in Part 1 of this study. At least 6 subjects must be treated at the MTD dose level of MT-3724 in combination with LEN and complete cycle 1 or experience a DLT.

The MTD decision will be made by the sponsor after consultation with all investigator.

3.6.4 MTD communication plan

The investigators and medical monitor will monitor the occurrence of TEAEs that could qualify as DLT and assess the number of subjects with DLT in real time during the conduct of Part 1. If the medical monitor becomes aware that the MTD may be declared in the current dose cohort (e.g. based on the occurrence of qualifying AE/serious adverse event [SAE] in ≥2 subjects), then they will inform the investigators that recruitment should be suspended pending the safety review meeting. The details of cohort management and safety review during Part 1 will be described in the study manual.

3.7 Part 2 (MTD Expansion Cohort)

The purpose of Part 2 is to confirm the safety and tolerability of MT-3724 in the MTD Expansion Cohort, where MT-3724 will be given at the MTD in combination with LEN. In addition, the PK, PD, immunogenicity and tumor response at the MTD of MT-3724 in combination with LEN will be more thoroughly evaluated in Part 2.

Up to 40 subjects will be enrolled in Part 2. Subjects in Part 2 may be enrolled and treated simultaneously through competitive enrollment at multiple global study centers.

Part 2 can start only after the MTD of MT-3724 in combination with LEN is declared in Part 1; however, the screening of prospective subjects for Part 2 may begin during the review of the safety data leading to the MTD decision.

See Section 4.3.2 for the principles of subject replacement in Part 2 of the study.

4 STUDY POPULATION

In addition to evaluating eligibility during the screening period, prior to first dose of MT-3724 on C1D1, the investigator must confirm there have been no changes in the subject's health that would render them medically inappropriate to begin protocol therapy.

4.1 Inclusion criteria

Subjects must meet ALL the following criteria to be eligible for the study.

1. Be adequately informed about the study and fully consent to participation as demonstrated by signing the written ICF before any screening procedure.
2. Be aged ≥18 years on the date of signing the informed consent form.
3. Have relapsed or refractory CD20-positive B-cell NHL that, in the investigator's opinion, could benefit from MT-3724+LEN therapy. Subjects must have proof of CD20-positive NHL, either by:
   a. Historical biopsies (obtained with diagnosis of relapsed or refractory disease), or
   b. Fresh biopsies.
   c. Bone marrow biopsy, excisional lymph node biopsy, and core biopsy of any involved organ are all acceptable methods; FNA are not acceptable.
4. All subtypes of B-cell NHL may be considered for Part 1 (MT-3724 Dose Escalation). Only histologically documented DLBCL (including mixed histology) may be considered for Part 2 (MTD Expansion Cohort).
5. Have received all available approved therapies for NHL, one of which should be anti-CD20-based therapy.
   a. Subjects whose prior therapy includes chimeric antigen receptor t-cell (CAR-T) cell therapy are eligible.
   b. Subjects who underwent stem cell transplant (SCT) >100 days for autologous SCT or >180 days for allogeneic SCT before study drug administration and exhibited a full hematological recovery (consistent with the existing inclusion criteria requirements and without PRBC or platelet transfusions within 2 weeks of C1D1) prior to relapse are eligible.
   c. Subjects who have been ineligible for approved therapies in the opinion of the investigator, or have refused such therapies, may be eligible at the investigator's discretion, upon sponsor approval.
6. Have bi-dimensionally measurable disease by Lugano Classification for NHL.
   a. >1.5 cm LDi for lymph nodes
   b. >1.0 cm LDi for extranodal disease
7. Have Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (Appendix 6).

8. Have adequate bone marrow function, as determined by all the following:
   a. Absolute neutrophil count (ANC) ≥1,000/mm^3
   b. Platelet count ≥50,000 mm^3
   c. Hemoglobin ≥8.0g/dL
9. Have adequate kidney function, CLcr to be ≥50 mL/min either measured or estimated using the Cockcroft-Gault formula (Appendix 5).
   a. At the investigator's discretion, the eGFR result <50 mL/min may be verified by measurement of CLcr based on the 24-hour urine collection. Subjects with CLcr ≥50 mL/min will be eligible irrespective of the eGFR result.
10. Have adequate hepatic function, as determined by:
   a. Total bilirubin <1.5 x ULN, or direct bilirubin <1.5 x ULN for subjects with elevated total bilirubin secondary to Gilbert's Syndrome, and
   b. Aspartate aminotransferase ≤3.0 x ULN (or ≤5 x ULN if liver involvement), and
   c. Alanine aminotransferase ≤3.0 x ULN (or ≤5 x ULN if liver involvement).
11. Have adequate coagulation, as determined by:
   a. International normalized ratio or PT ≤1.5 x ULN (unless on therapeutic anticoagulants)
   b. Activated partial thromoplastin time ≤1.5 x ULN (unless on therapeutic anticoagulants)
12. Albumin ≥3.0 g/dL.
13. Women of reproductive potential must have a negative pregnancy test on 2 occasions during the screening period (within 10-14 days and within 24 hours before the start of treatment). Women not of reproductive potential are female subjects who are postmenopausal (>1 year since last menstrual cycle) or permanently sterilized (e.g., hysterectomy, bilateral salpingectomy).
14. Males must agree to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking LEN and for up to 4 weeks after discontinuing LEN, even if they have undergone a successful vasectomy. Male subjects taking LEN must not donate sperm.
15. Subjects of reproductive potential and their partners must agree to either abstain continuously from heterosexual intercourse or to use 2 methods of reliable birth control simultaneously to begin 4 weeks prior to initiating treatment with LEN until 28 days after the last dose of MT-3724 or LEN. The investigator or a designated associate should advise the subject how to achieve adequate contraception. The following birth control methods may be considered: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy, and one additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap.
16. Subjects must have life expectancy of >3 months from the start of treatment.

4.2 Exclusion criteria

Subjects who meet any of the following criteria must be excluded from the study.

Medical and surgical history

1. History or current evidence of neoplastic disease that is histologically distinct from NHL, except cervical carcinoma in situ, superficial noninvasive bladder tumors, curatively treated Stage I-II non-melanoma skin cancer. Subjects with prior, curatively treated cancer >2 years ago before the start of treatment can be enrolled.
2. Current evidence of new or growing brain or spinal metastases during screening. Subjects with known brain or spinal metastases may be eligible if they:
   a. Had radiotherapy or another appropriate therapy for the brain or spinal metastases; concurrent prophylactic treatment is allowed
   b. Neurologic symptoms must be stable and no worse than Grade 2
   c. Have evidence of stable brain or spinal disease on CT or MRI scan obtained within 4 weeks of signing the ICF and compared with prior imaging results
   d. Do not require chronic steroid therapy (or, if applicable, have been stable on steroid dose of no more than prednisone 20mg/day or equivalent by C1D1)
3. Current evidence of Graft versus Host Disease.
4. Current evidence of CTCAE Grade >1 toxicity (due to prior cancer therapy) before the start of treatment, except for hair loss and those Grade 2 toxicities listed as permitted in other eligibility criteria.
5. Current evidence of incomplete recovery from surgery or radiotherapy before the start of treatment, or planned surgery or radiotherapy at any time until the EoT Visit, except minor elective interventions deemed acceptable by the investigator.
6. Current evidence of significant (CTCAE Grade ≥2) infection or wound within 4 weeks before the start of treatment.
   a. Subjects with Grade 2 infection that has stabilized or improved with oral anti-infectives before the start of treatment may be eligible at the sponsor's discretion.
7. Current evidence of significant cardiovascular disease including, but not limited to the following conditions:
   a. Unstable angina (symptoms of angina at rest) or new-onset angina within 3 months before the start of treatment.
   b. Arterial thrombosis or pulmonary embolism within 3 months before the start of treatment.
   c. Myocardial infarction or stroke within 3 months before the start of treatment.
   d. Any of the following within 3 months before the start of treatment with MT-3724: pericarditis (any CTCAE grade), pericardial effusion (CTCAE Grade ≥2), non-malignant pleural effusion (CTCAE Grade ≥2) or malignant pleural effusion (CTCAE Grade ≥3).
   e. Congestive heart failure (NYHA Class III or IV; Appendix 7) at Screening or LVEF <45%, assessed by Echo or multiple-gated acquisition (MUGA) scan within 1 month before starting study treatment (inclusion of subjects with LVEF between 40%-45%

should be discussed and approved by the sponsor). Echo or MUGA scan performed within 6 months before screening and at least 28 days after the last cancer therapy is acceptable provided the subject has not received any potential cardiotoxic agents since then.

f. Cardiac arrhythmia requiring anti-arrhythmic therapy at screening. Subjects receiving digoxin, calcium channel blockers, or beta-adrenergic blockers are eligible at the investigator's discretion after consultation with medical monitor if the dose has been stable for ≥2 weeks before the start of treatment with MT-3724. Subjects with sinus arrhythmia and infrequent premature ventricular contractions are eligible at the investigator's discretion.

8. QTcF >480 ms, determined as the average from three QTcF values on the triplicate ECG obtained at screening.
9. Current evidence of uncontrolled human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) at screening. Serology testing is not required if seronegativity is documented in the medical history, and if there are no clinical signs suggestive of HIV or hepatitis infections, or suspected exposure. The following exceptions apply for subjects with positive viral serology:
   a. Subjects with HIV and an undetectable viral load and CD4+ T-cells counts ≥350 cells/microliter may be enrolled, but must be taking appropriate opportunistic infection prophylaxis, if clinically relevant.
   b. Subjects with positive HBV serology are eligible if they have an undetectable viral load and the subject will be receive antiviral prophylaxis for potential HBV reactivation per institutional guidelines.
   c. Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is below the limit of detection. Concurrent antiviral HCV treatment and have an undetectable viral load.
10. Women who are pregnant or breastfeeding.
11. History or current evidence of hypersensitivity to any of the study drugs, or of current hypersensitivity requiring systemic steroids at doses >20 mg/day prednisone equivalent
12. History or current evidence of any other medical or psychiatric condition or addictive disorder, or laboratory abnormality that, in the opinion of the investigator, may increase the risks associated with study participation, or require treatments that may interfere with the conduct of the study or the interpretation of study results.

Prior treatments

13. Prior treatment with MT-3724.
14. Received anti-CD20 mAb therapy within the following periods before the start of treatment:
   a. Rituximab (Rituxan®): 84 days; if a subject had received RTX within 37 weeks before the start of treatment, then a serum RTX level must be negative (<500 ng/mL) at screening.
   b. Obinutuzumab (Gazyva®): 184 days
   c. Ofatumumab (Arzerra®): 88 days

15. Received therapy for NHL (except the anti-CD20 mAb therapies and radioimmunoconjugates) within 4 weeks before the start of treatment. Radioimmunoconjugates are excluded within 12 weeks before the start of treatment. For small molecules (MW <0.9kDa), the washout shall be 2 weeks or 5 half-lives, whichever is longer (Macielag 2012).
16. Any investigational drug treatment from 4 weeks or 5 half-lives of the agent before the start of treatment, whichever is longer, until the EoT Visit.
17. Received radiotherapy to tumor lesions that would be chosen as target lesions (measurable disease) within 4 weeks before the start of treatment, unless the lesion exhibited objective progression between the radiotherapy and screening according to the Lugano Classification for NHL.
    a. Palliative radiotherapy to non-target lesions may be permitted at the investigator's discretion after consultation with the medical monitor. See Section 5.10 for more information on the use of radiotherapy.
18. Received any live vaccines within 4 weeks before the start of treatment, unless the investigator believes benefits outweigh risk, after approval with medical monitor.
19. Require the use of systemic immune modulators during study treatment
    a. Systemic immune modulators include, but are not limited to, systemic corticosteroids at doses >20 mg/day or prednisone equivalent, cyclosporine and tacrolimus. Please see Section 5.9 for more details and exceptions.

4.3 Subject withdrawal, replacement and study discontinuation

4.3.1 Subject withdrawal

Subjects **must** be withdrawn from the study at their own request or at the request of their legally acceptable representative. The subject has the right to withdraw from the study at any time for any reason, without the need to justify his/her withdrawal. The subject will not suffer any disadvantage because of the withdrawal.

Subjects **must** also be withdrawn from the treatment period if the β-human chorionic gonadotropin (β-HCG) pregnancy test indicates that they are pregnant at any time between the consent and the EoT Visit.

The subject **may** be withdrawn from the treatment period at the discretion of the investigator due to:

- safety concerns
- lack of clinical benefit (disease progression is not documented but the investigator determines that the subject requires alternative anticancer treatment)
- non-compliance with study procedures to the extent that precludes the assessment of study objectives

Discontinuation of the study drug(s) for documented disease progression is considered study completion and not as premature withdrawal from the study.

All subjects who permanently discontinue study treatment for any reason should have an EoT Visit performed and an STFU phone call as described in the Schedule of Assessments before discontinuation.

The reason for any discontinuation from the study will be documented in the subject's medical record and recorded on the appropriate case report form (CRF).

4.3.2 Subject replacement

In both parts of the study, the sponsor will determine if a subject should be replaced. All subject data collected will be analyzed in the Safety Analysis set. The additional subject(s) included to replace non-evaluable subjects will be given new unique subject IDs.

Part 1 (MT-3724 Dose Escalation)

Subjects who discontinue in cycle 1 and are not evaluable for dose decisions (Section 3.6.1) must be replaced in the current dose cohort to ensure that a sufficient number of subjects are available for dose decisions. Non-evaluable subjects may remain on treatment if supported by the investigator's assessment of the benefit-risk ratio after consultation with medical monitor.

Subjects who discontinue for any reason after cycle 1 will not be replaced.

Part 2 (MTD Expansion Cohort)

Subjects in Part 2 of the study who have insufficient safety, PD, PK or immunogenicity data in cycle 1 may be replaced at the sponsor's discretion, unless they experienced a TEAE leading to treatment modification.

4.3.3 Study discontinuation

The sponsor has the right to discontinue the study for any reason.

5 TREATMENTS

As a standard precaution for all study drugs, subjects must be treated and observed in an area with equipment/personnel for resuscitation and emergency treatments or have access to emergency facilities through an emergency call. Adequate management and treatment of infusion-related reaction, anaphylactic reaction or other hypersensitivity events according to institutional guidelines must always be assured during the treatment period.

5.1 MT-3724

MT-3724 is the investigational medicinal product (IMP) in this study.

MT-3724 is a recombinant fusion protein consisting of an scFv with affinity for human CD20 cell surface protein, fused to the enzymatically active A1 subunit of Shiga-like Toxin 1.

5.1.1 MT-3724 drug product

MT-3724 will be supplied as a sterile aqueous solution (pH 5.5) in a 2 ml vial containing 2.0ml of MT-3724 (0.5mg/ml) in a formulation buffer comprised of Sorbitol (200mM), Sodium Citrate (20mM) and Polysorbate-20 (0.1%). Vials are shipped frozen. Each vial will be labeled with the drug name, lot number, storage conditions, and US FDA-required Investigational Product statement.

MT-3724 vials must be stored in a secure facility at -20 (-10 to -25) °C until thawed for use. It is recommended to use the thawed drug to prepare the final solution for infusion within 3 hours, although MT-3724 is stable at room temperature for up to 24 hours.

During preparation of the final solution for infusion, MT-3724 is diluted in 5% dextrose in water or normal saline for IV administration. All doses should be administered over 1 hour through an IV line (54 – 75 minutes). See Pharmacy Manual for detailed instructions and worksheets regarding study drug preparation and administration.

Investigational medicinal product must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Upon receipt, the IMP should be stored according to the instructions specified on the label and in the Pharmacy Manual. Clinical supplies are to be dispensed only in accordance with the protocol. Storage conditions must be adequately monitored, and appropriate temperature logs maintained as Source data.

The investigator is responsible for the accountability of the IMP. Records of the receipt and disposition of IMP must be maintained in the trial master file at the site. Records and drug supplies must be available for inspection by the study monitor.

5.1.2 MT-3724 dose selection

The dose of MT-3724 will be calculated based on the subject's body weight (in kilograms [kg]). For MT-3724 dose calculation, the body weight will be measured before the first dose of MT-3724 in cycle 1 (baseline for all subsequent assessments). If the body weight has changed by >10% from the baseline value, this will require re-calculation of the MT-3724 dose or, according to institutional policies should they require adjustment for any change in body weight.

The total administered dose of MT-3724 will be capped at 6000 µg per infusion in all subjects in both parts of the study.

The guidance for treatment modification (dose interruption/delay, dose reduction or treatment discontinuation) is presented in Section 5.4.

Part 1 (MT-3724 dose escalation)

The planned starting dose of MT-3724 in Part 1 will depend on the cohort. Please see Table 5 for doses.

If MT-3724 is not tolerated by any subject in any planned cohort, then additional MT-3724 doses may be evaluated in the interim cohort at the sponsor's discretion in consultation with the investigator(s).
The actual MT-3724 doses in the interim cohorts will be recommended by the sponsor after consultation with the investigator(s). The actual MT-3724 dose in the interim Cohort -1 should not be <5µg/kg/dose, as this was the lowest dose evaluated in the clinic so far.

Part 2 (MTD Expansion Cohort)

The starting dose of MT-3724 in Part 2 will be the MTD of MT-3724 from Part 1.

5.1.3 MT-3724 dosing schedule

MT-3724 will be administered as an IV infusion over 1 hour (window of 54-75 minutes).

Cohort 1-3
For subjects enrolled in Cohorts 1-3, in cycles 1 and 2, MT-3724 infusion should be administered on Day 1, 3, 5, 8, 10 and 12 (±1) of each 28-day cycle.

Cohorts ≥4
In subsequent cohorts in cycles 1 and 2, MT-3724 infusion should be administered on Days 1, 5, 8 and 12 (±1) of each 28-day cycle. Different dosing days up to D21 may be selected at investigator's discretion after consultation with the medical monitor.

All Cohorts
Starting with cycle 3, MT-3724 will be administered weekly (Day 1, 8, 15 and 22) of each 28-day cycle. Different dosing days within ±2 days from Day 1, 8, 15 and 22 may be selected at investigator's discretion.

Time windows for days of MT-3724 dosing

Cycles 1-2

Any of the scheduled MT-3724 doses may be administered on different dosing days at investigator's discretion up to D21.

MT-3724 doses must be administered at least 48 hours apart.

Cycles 3 and beyond

Any of the scheduled weekly MT-3724 doses may be administered within ±2 days at investigator's discretion.

For all cycles

No more than 14 days should elapse between cycles. If more than 14 days elapse, the investigator must consult with the medical monitor before initiating the next cycle of treatment.

5.1.4 Premedication before MT-3724 infusion

One premedication agent from each of the following 3 therapeutic classes must be given within 60 minutes before the start of each MT-3724 infusion in cycle 1 in both parts of the study:

- Oral anti-pyretic agent (325 – 1000mg acetaminophen or equivalent)
- Intravenous H1 histamine receptor antagonist (50 – 100mg diphenhydramine or equivalent)
- Intravenous corticosteroid agent with a shorter biological half-life (125 – 1000mg methylprednisolone or equivalent)

The specific drugs in each class should be selected at investigator's discretion or according to the institutional guideline. Cases where a subject has a contraindicating medical condition that precludes pretreatment with any of the categories above should be discussed with the sponsor. Although continued pre-medication is recommended during all cycles, after cycle 1, the investigator may adjust the dosage and/or avoid using certain premedication agents during the treatment, if supported by the investigator's assessment of the risk from infusion-related reaction, anaphylaxis or other hypersensitivity events.

5.2 Lenalidomide (Revlimid®, LEN)

LEN is an analogue of thalidomide with immunomodulatory, antiangiogenic and antineoplastic activity in cancer.

LEN is available as 2.5-20mg oral capsules. It is available only through a restricted REMS program (REVLIMID REMS®).

This medicinal product does not require any special storage conditions.

See Section 5.4.2 for guidance about the LEN treatment modification. In addition, the modification of LEN treatment in this study should be guided by the reference prescribing information, as interpreted by the investigator.

5.2.1 Lenalidomide dose selection

The starting dose of LEN in each cohort in Part 1 and Part 2 will be 20mg qd. The LEN starting dose can be decreased per investigator's discretion based on the known safety profile of LEN and subject's status. For Parts 1 and 2, starting with cycle 2 (after completion of the DLT assessment period for Part 1), the investigator may increase the LEN dose to 25mg qd, if clinically indicated, with sponsor approval.

5.2.2 Lenalidomide dosing schedule

In both parts of the current study, subjects will self-administer LEN qd PO with or without food on the first 21 consecutive days (D1-D21) of each 28-day cycle. Subjects will be

directed to self-administer LEN at about the same time every day and record doses taken in subject diary.

Treatment with LEN in the current study will continue until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal, see Section 4.3. If pregnancy occurs during treatment, immediately discontinue the drug.

LEN dosing may be discontinued at investigator's discretion, after approval by the medical monitor. Treatment with MT-3724 as a monotherapy may be permitted to continue with sponsor's approval.

5.3 Intra-subject dose escalation

Intra-subject escalation of MT-3724 dose is not allowed in either part of the study.

If the LEN dose has been reduced due to a TEAE, the intra-subject escalation of LEN dose is permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio after consultation with the medical monitor. In such cases, LEN dose may be increased only up to the level before the most recent dose reduction. Starting with cycle 2 (after the DLT assessment period for subjects in Part 1), the dose of LEN may be increased to 25mg qd, as described in Section 5.2.1.

5.4 Treatment modification

Treatment modification due to a TEAE (dose interruption/delay, dose reduction, or permanent discontinuation) could be done in an individual subject at the investigator's discretion after consultation with the medical monitor. By convention in this study, the term 'dose interruption' will be used for the interventions during the IV infusion, and the term 'dose delay' will be used for the changes in the dosing schedule (e.g., date of the next dose) for both MT-3724 and LEN.

The severity of TEAEs requiring treatment modification will be graded according to the CTCAE v.5.0.

5.4.1 MT-3724 treatment modification

Any of the following TEAEs in any treatment cycle **may** trigger MT-3724 treatment modification, if deemed at least possibly related to MT-3724 by the investigator after consultation with the medical monitor.

- Any TEAE irrespective of the time of onset, that would otherwise fulfill the DLT criteria (Appendix 4)
- Grade ≥2 IRR, or another Grade ≥2 hypersensitivity reaction
- Any other toxicity related to MT-3724, irrespective of the type or severity or time of onset, that warrants dose modification in the opinion of the investigator after consultation with the medical monitor. This may be Grade 1 or Grade 2 toxicity that notably limits the

activities of daily life (e.g. long-lasting fatigue or anorexia), making a dose reduction necessary to ensure the subject's compliance.

The following actions are recommended after any of the above TEAEs occur.

- The investigator should notify the medical monitor about the TEAE within 24 hours of the awareness.
- The investigator should monitor the subject and if necessary, perform diagnostic procedures and therapeutic interventions.
- If a subject experiences a TEAE in cycle 1 that is related to MT-3724 and qualifies as a DLT, then the MT-3724 treatment should be discontinued, except if continued treatment is supported by the investigator's assessment of the benefit-risk ratio. In this case, the MT-3724 re-treatment should be delayed until the TEAE resolves to Grade ≤1. Further, the MT-3724 re-treatment should start at a ≥25% reduced MT-3724 dose.
- If a subject experienced a Grade ≥2 IRR, or another Grade ≥2 hypersensitivity event, Grade ≥2 CRS or Grade ≥2 CLS, the investigator should obtain serum samples for cytokines, complement and histamine as soon as possible after the TEAE onset. These samples should be marked "STAT" and shipped immediately to the laboratory.
- MT-3724 dose may be **reduced** by ≥25% at the investigator's discretion after consultation with the medical monitor. The number of dose reductions per subject is not limited, except that the reduced dose cannot be <5 μg/kg/dose (this was the lowest dose tested in the clinic so far).
- No intra-subject escalation of MT-3724 dose is permitted after previous MT-3724 dose reduction.

MT-3724 treatment should be **permanently discontinued** if a TEAE that previously led to dose interruption/delay or reduction didn't resolve to Grade ≤1 within 4 weeks after treatment modification, except if continued treatment is supported by the investigator's assessment of the benefit-risk ratio after consultation with the medical monitor.

5.4.2 Lenalidomide treatment modification

Any of the following TEAEs in any treatment cycle **<u>may</u>** trigger LEN treatment modification, if deemed at least possibly related to LEN by the investigator.

- Any TEAE that would fulfill the DLT criteria irrespective of the time of onset
- Grade ≥2 venous or arterial thrombosis or thromboembolic event
    - LEN treatment should be temporarily discontinued immediately after the onset of the thrombosis or thromboembolic event to assess the causality and clinical risk
    - If the thrombosis is confirmed as at least possibly related to LEN, the LEN treatment may be continued at the investigator's discretion after consultation with the medical monitor after the thrombosis resolves to Grade ≤1. If the treatment is continued, the LEN dose may remain the same dose or be reduced by ≥5 mg qd at the investigator's discretion.

  - If the thromboembolic event re-occurs after the LEN continuation and is confirmed as at least possibly related to LEN, then the treatment should be permanently discontinued,

- Grade ≥2 skin reactions: skin rash (acneiform or maculo-papular); angioedema or other types of hypersensitivity manifest on the skin, Stevens-Johnson Syndrome, toxic epidermal necrolysis; any other skin reaction that warrants treatment modification at the investigator's discretion
  - LEN treatment should be temporarily discontinued immediately after the onset of the skin reactions to assess the causality and clinical risk
  - If the skin reaction is confirmed as at least possibly related to LEN
    - If Grade 2 (except for Grade 2 non-blistering rash), hold LEN until toxicity resolves to Grade ≤1 and reduce LEN dose by ≥5mg qd.
    - If Grade 2 non-blistering rash, hold until toxicity resolves to ≤ Grade 1 and continue at same LEN dose or reduce LEN dose by ≥5mg qd
    - If Grade >3, the LEN treatment should be permanently discontinued

In addition, the modification of LEN treatment in this study will be guided by the reference prescribing information (REVLIMID®), as interpreted by the investigator after consultation with the medical monitor.

5.4.3 Treatment modification due to IRR or other hypersensitivity event

This guidance is applicable to any among the 2 study drugs that, in the investigator's opinion, is at least possibly related to IRR or other hypersensitivity event.

If a subject experienced a Grade ≥2 IRR or other Grade ≥2 hypersensitivity reaction, the infusion must be immediately interrupted. The following additional actions are recommended in case of a Grade ≥2 IRR:

- In case of a Grade 2 IRR or other Grade 2 hypersensitivity reaction
  - Continued treatment with the study drug causally related to IRR may be allowed at the investigator's discretion.
  - If continued treatment is indicated, then
    - it must occur after the appropriate delay (i.e., resolution of symptoms)
    - Upon restarting infusion (and for subsequent doses), if study drug is causally related to IRR, the infusion rate must be reduced by 50% (2-hour duration) preceded by appropriate anti-allergic prophylaxis (see premedication, Section 5.1.4 or the institutional guideline)
- In case of a CTCAE Grade ≥3 IRR or other Grade ≥3 hypersensitivity reaction, the study drug causally related to IRR should be permanently discontinued.

5.4.4 Treatment modification for MT-3724 and LEN due to neutropenia or thrombocytopenia

This guidance is applicable to any neutropenia and/or thrombocytopenia that, in the investigator's opinion, is at least possibly related to any of the study drugs.

If treatment modification of MT-3724 or LEN is warranted due to neutropenia or thrombocytopenia, and the continuation of treatment is appropriate at investigator's discretion after consultation with the medical monitor, then the dose of MT-3724 or LEN will be adjusted as described in Table 6.

Table 6: Dose Adjustments of MT-3724 or LEN in Response to Neutrophil and Platelet Nadir Counts

Absolute neutrophil nadir count		Platelet nadir count	MT-3724 and/or LEN dose modification [1]
>500/µl or <500/µl for <5days	and	≥25,000/µl	No change
<500/µl for ≥5 days	and/or	<25,000 for ≥7 days with or without active bleeding, OR <50,000/µl for ≥7 days with clinically significant bleeding [2]	Decrease by ≥25% or according to reference prescribing information
Febrile neutropenia [3]	and/or	<25,000/µl for ≥7 days with or without active bleeding, OR <50,000/µl for ≥7 days with clinically significant bleeding [2]	Decrease by ≥25% or according to reference prescribing information

LEN = lenalidomide

[1]MT-3724 dose reduction translates to a reduction by ≥25%, and LEN dose reduction by 1 level translates to a reduction by ≥5 mg once daily; the actual amounts for either agent will be determined by the investigator after consultation with the medical monitor.

[2]Clinically significant bleeding is that which requires platelet transfusion.

[3]Febrile neutropenia is defined as absolute neutrophil count <1000/µl and fever (a single body temperature reading of >38.3°C [101°F] or a sustained body temperature of ≥38.0°C [100.4°F] for more than one hour).

Repeated dose reductions are permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio, but not below 5 µg/kg/dose for MT-3724.

5.4.5 Treatment modification for MT-3724 and LEN due to increased AST, ALT and/or bilirubin levels

This guidance is applicable to increased serum AST, ALT and/or bilirubin levels that, in the investigator's opinion, is at least possibly related to any of the study drugs.

If treatment modification of MT-3724 or LEN is warranted due to increased AST, ALT and/or bilirubin levels, and the continuation of treatment is appropriate at investigator's

discretion after consultation with the medical monitor, then the dose of MT-3724 or LEN will be adjusted as described in Table 7.

Table 7 Dose Adjustments in Response to the Worst Increase in Aspartate Aminotransferase, Alanine Aminotransferase, or Bilirubin

Worst AST and/or ALT increase		Worst bilirubin increase	MT-3724 and/or LEN dose modification
≤5 x ULN (isolated)	or	≤1.5 x ULN (isolated)	• No change in study drug Monitor subject
>5 x ULN – 8.0 x ULN (for subjects enrolled with AST/ALT <3 x ULN)	and/or	>1.5 x ULN – 5.0 x ULN	• Temporarily or permanently (see next row) discontinue study drug • Monitor subject • Continue at dose reduced by 1 dose level after abnormal values resolve to Grade ≤1 or baseline[1]
AST or ALT >8.0 x ULN for any period of time (for any subject) or AST or ALT >5x ULN for more than 2 weeks (for subjects enrolled with AST/ALT 3-5 x ULN)			• Permanently discontinue study drug
>3.0 x ULN (without findings of cholestasis defined as serum alkaline phosphatase <2×ULN)	and	> 2.0 x ULN or INR >1.5	• Permanently discontinue study drug
>3.0 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)			• Permanently discontinue study drug
		>5.0 x ULN	• Permanently discontinue study drug

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LEN = lenalidomide; ULN = upper limit normal

These are recommendations in situations where a possible relatedness of liver enzyme elevations to study drug is assumed. Further these being recommendations that cannot consider all clinical circumstances, the investigator is encouraged to contact the medical monitor to discuss alternative course of action.

[1]MT-3724 dose reduction by 1 dose level translates to an approximate reduction by ≥25%-33%, and LEN dose reduction translates to a reduction by ≥5 mg once daily; the actual amounts for either agent will be determined by the investigator after consultation with the medical monitor.

Repeated dose reductions are permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio, but not below 5 µg/kg/dose for MT-3724.

5.5 Treatment assignment

This is an open label, non-randomized study. Subjects will be assigned to MT-3724 treatment either in one of the sequential dose cohorts (Part 1) or in the MTD expansion cohort (Part 2). MT-3724 treatment assignment may occur only after the investigator declares the subject

eligible and the medical monitor reviews the screening results and acknowledge the investigator's eligibility decision.

All subjects in all cohorts will receive the same standard dose of LEN (Section 5.2).

Assignment of screening slots and treatment slots will be done on the basis of competitive enrollment (i.e. "first-come first-served"). The details will be described in the standalone Cohort Management Plan.

5.6 Blinding

Not applicable; this is an open-label study.

5.7 Treatment compliance

MT-3724

Because MT-3724 is administered IV, treatment compliance will be monitored through the eCRF and source documents (subject notes and pharmacy records) and clinical observations during study drug infusion. Actual dosing schedule vs planned dosing schedule will be used to assess compliance. Details will be provided in the standalone Pharmacy Manual.

Lenalidomide

LEN tablets will be dispensed to subjects to be taken on an out-patient basis. LEN may also be administered to subjects during clinic visits. During the study the subjects will be instructed to document intake of LEN tablets in a diary by entering the date and time of dosing as well as the administered dose. Subjects will be instructed to return all packages of used and unused LEN to the study unit. Returned LEN tablets will be counted by the study center to evaluate treatment compliance. The data from the subject diary will be transferred into the eCRF to capture any dose delays and modifications. Any discrepancies between actual and expected amount of returned study medication must be discussed with the subject at the time of the visit and any explanation must be documented in the source records.

5.8 Treatment duration

In Part 1 and Part 2, the treatment with MT-3724 and/or LEN in this study may be continued until death, progressive disease, AE requiring discontinuation or withdrawal of consent, any other reason for study discontinuation, or until study discontinuation. Thereafter, the subject will undergo the EoT Visit and STFU phone call.

5.9 Prohibited treatment

The following treatments are not permitted during the study:

- All systemic treatments for NHL.
- Radiotherapy to tumor lesions that would be chosen as target lesions (measurable disease).

- Palliative radiotherapy to non-target lesions may be permitted (Section 5.10).
- Systemic immune modulators from C1D1 until the EoT Visit, unless used for a TEAE or as pre-medication for MT-3724.
  - The immune modulators include, but are not limited to, systemic corticosteroids at doses >20mg/day or prednisone equivalent for >1 week, cyclosporine and tacrolimus.
- Vaccines: Subjects should not receive any live vaccines from 4 weeks before the start of treatment until 28 days after the last dose of MT-3724, unless the investigator believes benefits outweigh risk, after approval by the sponsor.

5.10 Permitted medication

The use of G-CSF, GM-CSF, platelet and blood transfusions and concomitant medications is permitted during the treatment phase at the investigator's discretion for management of appropriate toxicities. In particular, G-CSF is required for the treatment of Grade 3 neutropenia.

Palliative therapy such as radiotherapy (which spares at least 50% of bone marrow producing regions) to non-target lesions or intrathecal chemotherapy is allowed at the investigator's discretion after consultation with the medical monitor. Please note: palliative therapy is not allowed up to 2 weeks of C1D1 through and not during the DLT assessment period (cycle 1).

While the use of certain immunomodulators is prohibited as described in Section 5.9, the use of NSAIDs is permitted.

5.10.1 Reasons for caution

No results are available about the potential for drug-drug interactions between MT-3724 and LEN, or between MT-3724 and other drugs. Therefore, investigators should use caution when prescribing concomitant medications

6 STUDY ASSESSMENTS

Please refer to the schedule of assessments to see which assessments need to be performed at each visit (Schedule of Assessments).

Unscheduled visits may occur when indicated at the investigator's discretion. The results obtained at unscheduled visits should be entered into the eCRF (where applicable) and recorded in the source documentation.

All assessments will be performed by the investigator or medically qualified designee or other personnel at the investigating site.

6.1 General subject characteristics

6.1.1 Demographics

Information about date of birth/age, gender, race/ethnicity, detailed smoking history and alcohol history will be recorded during screening.

6.1.2 Body weight

Body weight (kg) will be measured at the following time points:

- At screening
- Pre-dose on each dosing day for MT-3724
- At the EoT Visit

The body weight measured before the start of MT-3724 dose C1D1 will be used to calculate the MT-3724 dose in all subsequent cycles. The dose must be re-calculated when the body weight has changed by >10% from the baseline value, or according to institutional policies should they require adjustment for any change in body weight.

All body weight measurements will contribute to the safety assessment. Unscheduled body weight measurements could be made for safety assessment at the investigator's discretion.

6.1.3 Height and BMI

Height in meters (m) and body mass index (BMI) will be measured at screening.

6.1.4 NHL assessment

The NHL assessment will be performed at screening by documenting the biopsy method by which the NHL histology and CD20 status has been confirmed at the initial diagnosis and at baseline.

The following information will be documented:

- NHL assessment (status at initial diagnosis):

  - NHL type (histology)
  - Staging (Ann Arbor Classification-Cotswold Modification)
  - Grading (low, intermediate, high)
- NHL assessment (status at Screening)
  - NHL type [histology and CD20+ status confirmation by historical or fresh biopsy (bone marrow, lymph node, organ) in relapse or refractory setting]
  - Date of most recent relapse
  - Staging
  - Grading at relapse
  - Grading at screening
  - Time to first relapse
  - Mutational status (e.g., MYC and/or BCL2 and/or BCL6 rearrangement/overexpression; del 9p32. TP53, MLL2 mutations)
  - Molecular subtype (GCB vs ABC)

The prognostic assessment instruments (Ann Arbor Classification with Cotswold Modification and (follicular lymphoma) International Prognostic Index) are described in Appendix 2.

6.1.5 Prior systemic therapy

Prior systemic therapy (including SCT and CAR-T) for NHL administered at any time before the start of treatment will be assessed. Each regimen (line of treatment) should be documented in sequential order of past use with the outcome of therapy. The start and stop dates of the regimen (i.e., line of treatment) should be recorded along with each individual agent given in the regimen. The date of the last CD20-based therapy should also be documented.

6.1.6 Prior radiotherapy

Prior radiotherapy for NHL administered at any time before the start of treatment will be assessed and documented at screening.

6.2 Safety assessments

Note that the AE are described in the Section 6.3, and the laboratory safety tests are described together with all laboratory tests in the Section 6.4 and Appendix 1.

6.2.1 Medical history

Medical history will be recorded at screening. This will include prior surgery, prior and concomitant illnesses and allergy history. The prior antitumor chemotherapy, radiotherapy and tumor related biopsies or surgery will be collected and documented on a separate eCRF form.

Illnesses that occurred at any time before the start of screening that, in the investigator's opinion, could increase the risk to subject and/or influence the study endpoints should be captured in the medical history as prior illnesses. Those illnesses that are active at the time of informed consent will be regarded as concomitant illnesses.

New illnesses and/or worsening of concomitant illnesses detected by verbal probes or subject's spontaneous reports between the screening and the start of treatment should be reported medical history unless they are due to study-mandated procedures, in which case they should be reported as AEs.

6.2.2 Prior and concomitant medications

Any medication (both prescription and over-the-counter [OTC] medications and supplements, and palliative treatments such as radiation or intrathecal chemotherapy, when permitted), used within 4 weeks prior to the start of treatment until the STFU Visit will be recorded in the eCRF, together with the main reason for its prescription.

The medications taken before the start of treatment on C1D1 will be regarded as prior medications (prior NHL therapy will be captured separately, Section 6.1.5). The prior medications will be captured at the following time points:

- During the screening period
- Before the start of treatment on C1D1.

The medications taken after the start of treatment on C1D1 will be regarded as concomitant medications. Concomitant medications will be captured at all visits and telephone contacts from the start of treatment until the STFU Visit.

6.2.3 Physical examination (PE)

A PE will be performed by a physician or a qualified delegate at the investigating site.

The full PE will be performed at the following time points:

- At screening
- At the EoT Visit

Abbreviated PE:

- Before MT-3724 dose on D1 of each cycle

The investigator or delegate at the site will perform the PE and evaluate the results. The PE can be captured up to 24 hours before dosing and must be done before dosing is allowed. The overall PE result will be categorized as 'normal', 'abnormal, not clinically significant (NCS)', or 'abnormal, clinically significant (CS)'. Any abnormal CS result of the PE should be followed up at the investigator's discretion and reported as an AE in the electronic CRF

(eCRF). Comments about abnormal NCS result of the PE, either overall or for individual aspects or body parts, will not be collected in the eCRF.

Complete physical examination

At a minimum, the following aspects/body parts should be assessed during the complete PE:

- General appearance
- Skin (paleness, jaundice, redness/rash, acneiform changes)
- Extremities (petechial bleedings, ulcers, signs of thrombosis), hands and feet (signs of hand-foot syndrome/palmar-plantar erythrodysesthesia)
- Ears, eyes (jaundice, inflammation), nose and throat (presence of petechial bleedings, gingival bleeding)
- Head and neck
- Lungs
- Heart
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)
- Lymph nodes
- Neurological examination to include the following assessments:
  - Oculomotor testing, pupil accommodation, double images
  - Motor system: muscle strength of arms
  - Sensory system: pain and touch sensation of thighs
  - Mental Status
  - Posture
  - Coordination: finger-to-nose and heel-to-shin test
  - Reflexes: biceps, patella and plantar (Babinski's sign) test
  - Gait: walking freely, on toes and on heels
  - Romberg test

Other aspects/body parts or organ systems may be assessed at the investigator's discretion.

Abbreviated physical examination

At a minimum, the following aspects/body parts should be assessed during the abbreviated PE:

- General appearance
- Skin (paleness, jaundice, redness/rash, acneiform changes)
- Ears, eyes (jaundice, inflammation) nose, throat (presence of petechial bleedings, gingival bleeding)
- Lungs
- Heart
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)

- Lymph nodes
- Extremities (petechial bleedings, ulcers, signs of thrombosis), hands and feet (signs of hand-foot syndrome/palmar-plantar erythrodysesthesia)
- Abbreviated neurological examination to include the following assessments:
  - Oculomotor testing, pupil accommodation, double images
  - Motor system: muscle strength of arms
  - Sensory system: pain and touch sensation of thighs
  - Mental Status (awareness of self and environment)
  - Posture
  - Coordination: finger-to-nose and heel-to-shin test

Other aspects/body parts or organ systems may be assessed at the investigator's discretion.

6.2.4 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be done at the same timepoints as physical examination, see Appendix 6.

6.2.5 New York Heart Association

NYHA classification will be performed at screening, see Appendix 7 for subjects with heart failure.

6.2.6 Vital signs

Vital signs include blood pressure (BP), heart rate (HR), respiratory rate (RR), and body temperature (°F or °C). BP and HR will be measured after 5-10 minutes of quiet rest in a sitting or semi-recumbent position using an automatic (preferred) or manual BP measuring device.

Vital signs will be assessed at the following time points:

- At screening
- Before the start of each MT-3724 infusion in each cycle;
- At 0.5h, 1h and 2h (±10 min allowed at each time point) after the start of each MT-3724 infusion in each cycle
- At 3h and 4h (±10 min allowed at each time point) after the start of MT-3724 infusion on C1D1
- At the EoT Visit

Unscheduled VS measurements may be performed at investigator's discretion in each cycle.

Any clinically-significant abnormality in VS should be investigated by repeat assessments (number and timing at investigator's discretion). The confirmed clinically significant abnormalities should be reported as AE in the eCRF.

6.2.7 Left ventricular ejection fraction

Left ventricular ejection fraction assessment should be assessed by echocardiography (ECHO). If ECHO is not available or appropriate according to the institutional standard, then multi-gated acquisition (MUGA) scan is permitted. The same modality should be used throughout the study. Left ventricular ejection fraction will be assessed at the following time points:

- At screening (within 1 month before starting study treatment)
  - A pre-study LVEF assessment is acceptable if obtained within 6 months before screening and at least 28 days after the last cancer therapy provided the subject has not received any potentially cardiotoxic agents since then.
- At the EoT Visit (only if the subject has received MT-3724 in ≥3 cycles irrespective of the number of MT-3724 doses in each cycle).

6.2.8 Electrocardiograms

Standard resting 12-lead ECG assessments will be performed after the subject had rested rest quietly for 5-10 minutes in supine or semi-recumbent position. The ECG recordings will be obtained at the following time points:

- At screening (triplicate ECG, i.e. 3 ECG recordings obtained in close succession and not more than 2 minutes apart)
- Before the start of MT-3724 infusion on D1 of each cycle (single ECG recording will be performed)
- At the EoT Visit (single ECG)

If the ECG printout is of poor quality, additional ECG(s) may be obtained at the same time point until an ECG of adequate quality is obtained. Such additional ECG(s) do not have to be reported as unscheduled assessments.

When PK, ECG and VS assessments are scheduled to occur at the same time point, the ECG and VS should be done first and in that order, with the timing of assessments based on collecting the PK sample at the protocolled time.

The investigator or delegate at the site will assess the ECG results. The three QTcF values from a triplicate ECG should be averaged to yield the QTcF value for the purpose of eligibility assessment. The derived variable will be calculated according to the formula of Fridericia using an online calculator.

The overall ECG assessment will be categorized as ‘normal’, ‘abnormal, not clinically significant (NCS)’, or ‘abnormal, clinically significant (CS)’. The overall ECG assessment by the ECG recorder and the related diagnostic comments will not be entered in the eCRF.

Any clinically significant abnormality in the ECG should be investigated by unscheduled ECG assessment(s) (number and timing at investigator's discretion). The confirmed clinically significant abnormalities should be reported as AE in the eCRF.

6.3 Adverse events

The term adverse event is defined as any untoward medical occurrence in a subject or clinical investigation in a subject administered a pharmaceutical product(s) and which does not necessarily have to have a causal relationship with this experimental treatment(s).

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All AEs that occur in enrolled subjects during the AE reporting period specified in the protocol must be recorded, regardless of the relationship of the AE to study drug.

All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented on the Medical History CRF page. Clinically significant worsening in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF page during the rest of the study. Laboratory, VS, and ECG abnormalities should also be recorded as AEs when considered clinically significant and representing a change from pre-treatment baseline.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures for preexisting, non-worsening conditions permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs. Except when the event would qualify as serious (e.g. leading to hospitalization).

Adverse events will be assessed by verbal probes and subject's spontaneous reports at screening and during every post-baseline clinic visit and telephone contact from the start of treatment until the STFU Visit. Information will be collected by trained, qualified study staff and the information will be recorded in the appropriate eCRFs. At a minimum, all relevant information regarding the AE and concomitant medication use will be captured.

All AE reports (solicited or volunteered) will be reviewed and followed by the responsible investigator and medical monitor qualified delegate for completeness, relatedness and accuracy of severity grading in order to ensure appropriate reporting practice. Cumulative AE data will be reviewed periodically by the medical monitor as well as *ad hoc* review of serious and/or severe AEs as they are reported.

Natural disease progression of the malignancy or deterioration of the subject's condition under study (including new sites of metastasis and death due to disease progression) will be recorded as part of the efficacy evaluation and should not be reported as an AE or as an SAE.

Discontinuation from the study treatment because of disease progression or deterioration of the subject's condition of the disease under study should be recorded on the Study Completion page of the eCRF as disease progression and not as an AE.

6.3.1 AE reporting period

The AE reporting period will begin on the day of the first dose of study drug until the STFU call, or until the start of new cancer therapy (unless the investigator believes the AE is related to MT-3724), whichever occurs first.

Grade ≥2 AEs related to MT-3724 and/or LEN that were ongoing at the STFU Visit should be followed by the investigator until all events have resolved to Grade ≤1.

Those AEs that occur after the first dose on C1D1 will be considered treatment-emergent.

All AEs that occur in enrolled subjects during the AE reporting period specified in the protocol must be recorded, regardless of the relationship of the AE to MT-3724 or LEN. Any serious known untoward event that occurs beyond the AE reporting period that the investigator assesses as at least possibly related to MT-3724 should also be reported to the sponsor.

For AEs of CLS, CRS/SIRS, and IRRs, individual symptoms and grade should be reported on the appropriate CRF.

6.3.2 Adverse event terminology

All AEs should be recorded in standard medical terminology rather than the subject's own words. Each AE will also be described in terms of duration, frequency, severity/intensity, association with the study medication, assessment of possible causes, actions taken, and outcome, using choices given on the eCRF.

6.3.3 Severity

Severity will be classified according to the criteria provided by CTCAE v5.0. If the AE is not listed in the CTCAE v5.0, then the highest severity level reached according to the scale in Table 8 will be assigned.

Table 8: Classification of Adverse Events by Severity

Grade	Definition
Grade 1 (mild)	An AE that is easily tolerated by the subject. It incurs only a minimum of discomfort and does not influence ordinary daily tasks.
Grade 2 (moderate)	An AE that is of sufficient severity to have a negative influence on ordinary daily tasks.
Grade 3 (severe)	An AE that effectively hinders ordinary daily tasks, often requiring intervention.
Grade 4 (life threatening or disabling)	An AE that puts the subject's life at risk.
Grade 5 (fatal)	Death related to an AE.

AE =adverse event

Every effort should be made to find the appropriate AE term and definitions of severity in the modified CTCAE v. 5.0.

Causality/Relatedness

Causality should be assessed separately for each study drug (MT-3724 and LEN) as detailed in the eCRF. If the investigator feels that the event cannot be firmly attributed to one of the study drugs, then the same assessment should be documented for each study drug. Causal relationship to protocol required procedure(s) should also be considered and reported accordingly in the eCRF.

The following should be considered when assessing causality:

- temporal associations between the agent and the event
- effect of de-challenge and/or re-challenge
- pre-existing risk factors
- a plausible mechanism
- concurrent illnesses.

The investigator will determine the causal relationship/relatedness to the study drug(s) according to the classification in Table 9.

Table 9 Classification of Adverse Events by Causality/Relationship to the Study Drug(s)

Causality/Relatedness	Definition
Definitely related	Follows a reasonable temporal sequence from drug administration, abates upon discontinuation of the drug (de-challenge), is confirmed by reappearance of the reaction on repeat exposure (re-challenge).
Probably related	Follows a reasonable temporal sequence from drug administration, abates upon discontinuation of the drug, cannot be reasonably explained by the known characteristics of the subject's clinical state.
Possibly related	Follows a reasonable temporal sequence from drug administration, could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.
Unlikely to be related	Does not follow a reasonable temporal sequence from drug administration, is readily explained by the subject's clinical state or by other modes of therapy administered to the subject.
Unrelated	The AE is definitely produced by the subject's clinical state or by other modes of therapy administered to the subject.

AE = adverse event

For all purposes of subject management, DLT assignment and treatment modification, the causality assessment of:

- "probably", "possibly" or "definitely" will be treated as "related"
- "unlikely" and "not related" will be treated as "unrelated"

6.3.4 Expected and unexpected adverse events and SUSARs

The expectedness of AEs will be determined by the sponsor according to the applicable reference document(s) and the requirements of the health authorities.

An **unexpected** AE is an AE that is not identified by type, severity grade, or frequency in the Reference Safety Information (RSI) section of the IB for MT-3724 or in the MT-3724 safety reports to the health authorities (e.g. development safety update report) and for LEN any ADR that is not described in the Revlimid® reference prescribing information.

The Safety Department of the Contract Research Organization (CRO) must report any suspected, unexpected serious adverse reaction (SUSAR) to the regulatory authorities within the required timeframes. The investigator must report any SUSARs to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) in accordance with local requirements.

6.3.5 Serious adverse events

An SAE is defined as any AE that meets one or more of the following criteria:

- The event is fatal or life-threatening.
- The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns).
- The event results in unplanned in-patient hospitalization or prolongation of an existing hospitalization.
- Is or results in a congenital abnormality or birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

An AE does not need to be severe in order to be classified as an SAE. In this protocol, the term "severe" is used to describe the intensity (severity) of a specific event according to the CTCAE v.5.0. However, the nominally severe adverse event may be of relatively minor medical significance (such as short-term severe headache or nausea). This is not the same as "serious," which is based on subject/event outcome or action criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE reporting instructions

If an SAE occurs at any time from the time of start from C1D1 until the STFU Visit (or during screening if deemed related to study-procedure), it must be reported to the Safety Department of the CRO and the medical monitor (See List of Contacts). **The investigator**

must report any SAE due to any cause, whether or not related to the study drug(s), within 24 hours of the time when s/he became aware of the event. The investigator must send a preliminary report of any such SAE to the study safety monitor via the electronic data capture (EDC) system within 24 hours or if this is not possible, via email or fax using an SAE Report Form, or at a minimum by telephone.

The event must be recorded on the electronic SAE CRF page. Preliminary reports of SAEs must be followed by detailed descriptions later, including clear copies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. All copies should be redacted to remove subjects' personal details and annotated with the subject's unique study identifiers.

Appropriate remedial measures should be taken to treat the SAE, and the response to treatment should be recorded. Subjects must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The results will be reported promptly to the sponsor.

Pregnancy reporting instructions

Pregnancy should be avoided from 4 weeks prior to first dose of LEN, during treatment, during dose interruptions and for 4 weeks following the last dose of LEN or MT-3724. Reliable contraception is specified in the exclusion criteria, see Section 4.2.

Subjects must be advised to immediately notify the investigator of pregnancy.

If pregnancy occurs during treatment in a subject, the investigator must immediately discontinue the study drugs (MT-3724 and LEN) and report the pregnancy to the Safety Department of the CRO and the medical monitor (See List of Contacts), along the same timelines as an SAE (Section 6.3.5).The subject must be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The investigator maintains the responsibility for reporting pregnancy in accordance with the Revlimid REMS program (REVLIMID REMS®).

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported. For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

Suspected Unexpected Serious Adverse Reaction

An unexpected SAE that is at least possibly related to the study drug will be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR). Please see Section 6.3.4 for the definition of the unexpected event.

The sponsor will determine if a reported SAE meets the criteria for SUSAR.

Clinical Laboratory Adverse Events

Laboratory test results will be graded according to the CTCAE v.5.0 criteria. Out of range results considered to be clinically significant should be verified by repeat testing as soon as possible. In general, a confirmed Grade 3 or Grade 4 abnormal laboratory test result will be considered to be a clinically significant AE and need to be reported as such in the eCRF, unless related to disease progression. Confirmed Grade 2 abnormal laboratory results will be assessed on a case by case basis for clinical significance based upon the subject's baseline value screening, the duration of the abnormal result, the need for and type of treatment and/or further evaluation required. Abnormal laboratory test results meeting SAE criteria will be reported as such.

6.3.6 Action taken with study treatment

Any action with any of the study treatments to manage the AE should be documented using the categories in the eCRF completion guidelines and the study treatment action should be recorded separately for MT-3724 and LEN.

6.3.7 Outcome

The outcome of the AE should be documented as described in the eCRF completion guidelines.

6.4 Laboratory Tests

The following laboratory tests are to be performed as indicated by the Schedule of Assessment and Safety Laboratory Panel.

The following tests will be performed by the central laboratory:

- Hematology
- Chemistry (with eGFR)
- HbA1c
- Coagulation
- Thyroid function
- Beta-2 microglobulin
- Serum cytokines
- Complement
- Immunoglobulins
- Histamine
- B-cell count and immunophenotype (flow cytometry)
- Immunogenicity of MT-3724; Anti-drug antibodies (ADA and NAb titer)

- Serum RTX concentration (if applicable)

The following laboratory tests will be performed by a local laboratory:

- Urinalysis (dipstick)
- Pregnancy test (serum or urine)
- Serology/Virology for HIV, HBV and HCV (if applicable)

The same laboratory should analyze all scheduled laboratory tests throughout the study.

In the event of an unexplained clinically-significant abnormal laboratory test value, the test should be repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found. Any clinically-significant laboratory abnormality considered an AE should be recorded in the eCRF.

A standalone Laboratory Manual will provide complete instructions regarding how these samples should be collected, stored and shipped.

6.4.1 Hematology, Chemistry and Urinalysis

The hematology, chemistry (with eGFR) and urinalysis assessments will be performed at the following time points:

- At screening
- Before the MT-3724 infusion on D1, D8
- On D15 of each cycle (at any time in C1-C2 and before the MT-3724 infusion in C3 and beyond)
- At the EoT Visit

If possible, the blood for chemistry assessments should be drawn after a subject has fasted for at least 2 hours, in order to facilitate a more reliable interpretation of the serum glucose result. The compliance with this recommendation (Yes/No) will be entered in the eCRF for every chemistry assessment.

Local laboratory for chemistry and hematology should be collected to assess subject status/safety if results from central laboratory will not be available pre-dose, whenever central laboratory assessments are scheduled. See Schedule of Assessments (Study Schema) for details. These results need only be entered in the EDC if there is a clinically significant finding, related to an adverse event.

6.4.2 Estimated glomerular filtration rate

The eGFR will be assessed as a measure of renal function and will be calculated using the Cockcroft-Gault creatinine equation (Appendix 5).

The eGFR will be derived from the serum creatinine values obtained from the blood chemistry assessment at all time points listed above (Section 6.4.1).

At the investigator's discretion, the eGFR results at screening that fall outside the limit required for eligibility may be verified by the formal measurement of CLcr based on the 24-hour urine collection. Furthermore, if warranted by the eGFR result at any other time point, the investigator may order CLcr (measured from the 24-hour urine) as an unscheduled assessment.

6.4.3 Urinalysis

A standard dipstick urinalysis will be initially performed at the time points listed above (Section 6.4.1).

Any clinically-significant abnormality in the dipstick urinalysis should be investigated by repeat urinalysis coupled with the microscopic analysis of the urine sediment. The confirmed clinically significant abnormalities should be reported as per standard medical practice and reported as AE in the eCRF.

6.4.4 Glycated hemoglobin in plasma

The HbA1c will be assessed at the following time points:

- At Screening
- Before MT-3724 dose on D1 of cycle 3 and every odd cycle thereafter
- At the EoT Visit

6.4.5 Thyroid function

The thyroid function parameters (see Appendix 1) will be assessed at the following time points:

- At Screening
- Before MT-3724 dose on D1 of cycle 3 and every odd cycle thereafter
- At the EoT Visit

6.4.6 Coagulation

Coagulation will be assessed at the following time points:

- At Screening
- Before MT-3724 dose on D1 of cycle 3 and each odd cycle thereafter
- At the EoT Visit

6.4.7 Immunoglobulins

The immunoglobulins (IgG, IgA, IgM) will be assessed at the following time points:

- At screening
- Before the start of MT-3724 infusion on D1 of each cycle
- At 3h (±10 min) after the start of MT-3724 infusion on D1 of each cycle
- At the EoT Visit

6.4.8 Rituximab concentration

Serum RTX concentration must be assessed at screening if a subject had received RTX within 37 weeks before the start of treatment on C1D1. Subject will be eligible only if the serum RTX concentration is <500ng/mL. Serum RTX does not need to be re-evaluated once determined to be "negative", in cases of rescreening.

The serology for RTX concentration should not be assessed in subjects who had received RTX within 84 days before the start of treatment (automatically ineligible based on this criterion). When 37 weeks have elapsed since the last treatment with RTX, serum RTX will be assessed for exploratory purposes because these results will not impact eligibility. The serology for RTX concentration should not be assessed for subjects who never received RTX.

It is recommended to assess RTX serum concentration prior to performing other screening procedures.

6.4.9 Complement, histamine, and cytokines

Complement, histamine, and cytokines will be assessed at the following time points:

- At screening
- Before the start of MT-3724 infusion on D1 of each cycle.
- At 3 h (±10 min) after the start of MT-3724 infusion on D1 of each cycle
- At the EoT Visit

If a subject experienced a Grade ≥2 IRR, or another Grade ≥2 hypersensitivity event, Grade ≥2 CRS or Grade ≥2 CLS, the investigator should obtain serum samples for cytokines, complement and histamine as soon as possible after the TEAE onset. These samples should be marked "STAT" and shipped immediately to the central laboratory.

6.4.10 Serum beta-2 microglobulin

A blood sample for the collection of beta-2 microglobulin will be collected at Screening.

6.4.11 Serology/Virology – HIV, HBV and HCV and CD4+ T-cell counts

Viral serology and viral load assessment will be assessed at screening and will include the following parameters:

Human immunodeficiency virus

- Anti-HIV-1 antibody
- Anti-HIV-2 antibody
- HIV viral load
- CD4+ T-cell counts

Hepatitis B virus

- HBsAg
- Anti-HBsAg antibody
- Anti-HBcAg antibody
- HBV viral load

Hepatitis C Virus

- HCV-RCV-RNA quantitation
- Anti-HCV antibody
- HCV viral load

The serology for individual virus(es) may be omitted at the investigator's discretion if seronegativity has been previously documented and there are no signs of the corresponding viral infection.

6.4.12 Pregnancy test

The pregnancy test (urine or serum at the investigator's discretion) will be assessed for women of childbearing potential at the following time points:

- At screening (within 10-14 days and within 24 hours before the start of treatment)
- Within 24 hours before D1, D8, D15, D22 in cycle 1.
- Starting with cycle 2, within 24 hours before D1 and D15. If the biweekly pregnancy test is scheduled for the day of MT-3724 dosing, the result must be known before the start of treatment.
- At the EoT Visit

For pregnancy tests scheduled to occur when there is no corresponding on-site visit, the subject should use a commercial pregnancy test kit on their own and contact the site to report the test result. The site should follow up if the subject has not contacted the site to confirm that the test was done.

If the scheduled pregnancy test coincides with the dosing of MT-3724, then the result must be known before the start of MT-3724 infusion.

6.5 Pharmacokinetic assessments

Blood samples will be collected prior to, during, and at specified times following the MT-3724 infusion for determination of free MT-3724 concentrations in serum, which will be used for the assessment of the single-dose and repeat-dose PK of MT-3724. If warranted, select serum samples collected for the MT-3724 concentration may also be analyzed for any other anti-CD20 biologic agent that the subject may have received prior to enrollment.

The PK samples for the free concentration of MT-3724 will be collected at prespecified times in Table 4.

The PK of LEN will not be assessed in this study.

6.6 Efficacy assessments: Radiological Assessment of Tumor Response

The tumor response assessment should be performed at the following time points:

- At Screening:
  - The investigator is encouraged to obtain the screening tumor scan as close as possible to the start of treatment within 28 days of C1D1.
- Within 7 days before the start of treatment on C3D1 and every other cycle thereafter (i.e. Between D23 and D28 of the cycle). The original schedule needs to be maintained even if there is a delay is dosing.
- Within 7 days of the EoT Visit (**only** if the previous tumor scan has been performed >4 weeks before the EoT Visit)

The investigator and the radiologist should carefully consider if the increase from baseline in tumor size could be “pseudoprogression” due to the tumor flare induced by the study drug(s).

Unscheduled tumor response assessment by FDG-PET-CT (or CT/MRI, where applicable) may be ordered at the investigator’s discretion.

Efficacy of the study drugs (tumor response) will be assessed by the scan of all anatomic regions involved with the measurable disease. Positron emission tomography-computed tomography should be used in subjects with FDG-avid tumor histology. Computed tomography or MRI should be used in subjects with tumor histology of low or variable FDG avidity. Diagnostic quality CT should be collected for all subjects at baseline, whenever possible.

Tumor response in subjects with FDG-avid tumor histology will be determined using the 5-point scale (5PS) according to the Lugano Classification for Lymphoma (Cheson 2014) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (Cheson 2016). An overview of NHL response criteria for FDG avid and non-avid NHL is presented in Appendix 3.

The same technique (e.g. slice thickness, field of view) should be used for all scans during the study treatment period. Preferably, all scans should be interpreted by the same investigator during the study whenever possible. Scans must meet the SOC for imaging of lesions in the respective organ system(s).

6.6.1 Central review of efficacy results

If the sponsor considers it necessary at any time during the study, a third-party radiology service may perform a blinded independent central review of digital images used for the tumor response assessment by the investigators at the sites, coupled with relevant clinical data from the eCRF.

Sites should archive imaging in standard DICOM format in readiness for data transfer. All data will be transferred to a central database by the end of the study.

6.7 Immunogenicity

Blood samples will be collected at pre-specified time points for the assessment of immunogenicity of MT-3724 ADA and NAb titer.

The immunogenicity samples will be collected at prespecified time points listed below:

- At Screening
- Pre-dose on D1 in each cycle: Before the start of MT-3724 infusion
- At the EoT Visit

Please also see the Schedule of Assessments. Unscheduled assessments may be performed at any time at the investigator's discretion.

6.8 Pharmacodynamics assessments

6.8.1 Peripheral blood

The B-cell count will be the PD marker in this study and the immunophenotype in peripheral blood, as determined by flow cytometry. Serial blood samples for the assessment of PD markers will be collected at the following time points:

- At Screening
- D1 in each cycle (at any time before the start of MT-3724 infusion)
- D12 of cycles 1-2 (at any time before the start of MT-3724 infusion on the dosing day)
- D15 of cycle 3-and beyond (at any time before the start of MT-3724 infusion on the dosing day)
- At the EoT Visit

Unscheduled assessments may be performed at any time at the investigator's discretion.

6.9 Tumor tissue

Optional FNA biopsy will be collected at EoT for subjects in Part 2 who had consented for this procedure, exhibit PD and have accessible peripheral lymph node(s) at time of collection. CD20-positive status of DLBCL in the fine needle aspirate of the peripheral lymph node will be determined by IHC staining. Subjects with mediastinal or abdominal lymph nodes will not be considered for FNA biopsy.

In the absence of PET/CT, a bone marrow biopsy should be assessed to confirm CR.

6.10 Exploratory Assessments

[redacted]

7 DATA MANAGEMENT AND STATISTICAL ANALYSIS

All clinical parameters should be entered into the eCRF/EDC as soon as possible after each study visit.

The statistical analysis of the clinical data will be performed by Molecular Templates' representative. Analysis of the PK, PD and immunogenicity data may be performed separately and entered into a separate database. Data from the clinical, PK and PD databases will be integrated in the clinical study report.

All data obtained either from the eCRFs or from an external laboratory will be provided in descriptive summary tables presenting the number of subjects [n], mean, standard deviation, median, minimum and maximum for continuous variables and number of subjects [n] and percent for categorical variables.

7.1 Data handling and electronic CRF

Data will be recorded in an FDA CFR Part 11-compliant eCRF, also known as the EDC system.

Data reported on the CRF must accurately reflect the corresponding source documents, or the discrepancies must be explained. No data are to be recorded directly on the CRFs (i.e. the CRF is not to be considered as source data).

The investigator should agree to have completed source documents and eCRFs available for inspection by the monitor on behalf of the sponsor at the time of each scheduled monitoring visit. The investigator must sign the completed eCRF for each subject after the study completion.

7.2 General statistical considerations

Statistical analysis will be performed using the Statistical Analysis System®; the version used will be specified in the statistical analysis plan (SAP).

All data will be listed, and descriptive summary tables will be provided by treatment group/cohort irrespective of the study part. In addition, appropriate variables will be summarized in a separate treatment group comprising the subjects treated at the MTD of MT-3724 in Part 1 (dose escalation) and in Part 2 (expansion). These variables will be specified in the SAP.

Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum, and maximum. Where appropriate, descriptive summary statistics will be tabulated for the absolute values and changes from baseline. Graphical illustrations will be provided where appropriate. Qualitative data will be presented in the frequency tables.

The assessment obtained at the most recent time before the start of MT-3724 treatment will be the baseline for all post-baseline assessments. The value obtained before MT-3724 Dose 1 on C1D1 (if available) will serve as the baseline; if not available, then the value obtained earlier at screening will serve as the baseline.

Further details about the statistical analyses will be provided in the SAP. Any changes in the statistical methods described herein compared to the final SAP will be documented in the integrated clinical study report.

7.3 Sample size justification

Approximately 64 subjects (i.e., 24 subjects in Part 1 and approximately 40 subjects in Part 2), as well as the appropriate number of replacements (if needed), will be enrolled and treated in this study. The actual number will depend on the number of dose cohorts needed to identify the MTD of MT-3724 in combination with LEN in Part 1.

No formal power calculation and sample size justification will be performed for this descriptive non-pivotal Phase 2a study. The proposed sample size is deemed sufficient for the adequate characterization of the study objectives and would be typical of the sample sizes of exploratory Phase 1b/2a studies with novel anti-cancer agents.

7.4 Analysis sets

7.4.1 Safety population

The safety population is defined as all subjects who receive at least one dose of MT-3724 or LEN. The safety population will be used for the primary statistical analysis of safety and efficacy endpoints.

7.4.2 Efficacy analysis population

All subjects who received at least one dose of any study drug (either MT-3724 or LEN), and have the baseline tumor assessment as well as at least one post-baseline tumor assessment.

7.4.3 Pharmacokinetic population

The PK population will include all subjects who received at least one dose of MT-3724 and have at least one post-baseline PK assessment. The PK population will be used for the PK analyses.

Subjects who received only LEN but haven't received MT-3724 will be excluded from the PK analyses.

7.4.4 Immunogenicity population

All subjects who received at least one dose of MT-3724 and have at least one post-baseline immunogenicity assessment will be included in the analyses of ADA and NA. Subjects who received only LEN but haven't received MT-3724 will be excluded from the immunogenicity analyses.

7.4.5 Pharmacodynamic analysis population

All subjects who received at least one dose of MT-3724 and have at least one post-baseline PD assessment will be included in the analyses of B-cell count and immunophenotype (flow cytometry). Subjects who received only LEN but haven't received MT-3724 will be excluded from the PD analyses.

7.5 Subject disposition and termination status

The number and percentage of enrolled (signed consent), screened, screen-failed and treated subjects will be summarized by treatment group/cohort. Reasons for screen failure will be listed and reasons for treatment discontinuation will be tabulated. Safety assessments among subjects will be listed and summarized by treatment group and reason for discontinuations (grouped as due to AEs, disease progression, and other).

7.6 Handling missing data

Missing data will not be imputed in this study. For summary statistics and concentration-time profiles, all values that are below the limit of quantitation will be set to zero.

7.7 Baseline and demographic characteristics

Subject baseline characteristics; including demographics, medical history, physical examination, ECG, and vital signs will be summarized descriptively. The descriptive statistics, including n (number of observations or sample size), mean, standard deviation and/or standard error, median, range (minimum-maximum), geometric means and geometric

coefficient of variance (where applicable) for numerical variables, and frequency and percentages for categorical variables, will be presented.

7.8 Safety analyses

The primary analysis of safety will be a comprehensive evaluation of AEs and/or toxicity, presented by dose, regimen and tumor type cohort and overall, based on:

- The type, incidence, severity, timing, seriousness, and relatedness of adverse events.
- Incidence of DLT and TEAEs that led to treatment modification
- Recording of IRR, CRS and CLS
- Results of monitoring vital signs (BP, HR, RR and body temperature)
- Results of clinical chemistry, hematology, thyroid function, coagulation, and urine analysis tests
- ECG results
- Changes in physical examination
- Results of immunogenicity assessments ADA and NAb
- Need for concomitant medications

All safety analyses will be descriptively summarized based on the safety population.

AEs/SAEs will be coded and tabulated using the current version of MedDRA. Each AE will be classified by system organ class and preferred term. All AEs along with the coded terms will be listed.

7.8.1 Safety data handling

Adverse events

All AEs will be coded according to MedDRA and graded for severity using the CTCAE v.5.0.

Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) are defined as those AEs/SAEs that occurred or worsened at or after the start of the first infusion of the first study drug. The occurrence of TEAEs and TESAEs will be reported up until the STFU Visit.

Only TEAEs and TESAEs will be summarized. The incidence of TEAEs will be presented using the number and percent of subjects who experienced the AE using MedDRA (overall incidence, System Organ Class and preferred term) and the worst CTCAE grade. The incidence of the following TEAEs and drug-related TEAEs will be summarized by treatment group / cohort: Overall, TEAEs leading to dose interruption, dose delay, dose reduction, permanent discontinuation, IRR, CRS, and CLS. The TESAEs will be summarized similarly.

Individual listings of DLTs will be presented by MT-3724 dose cohort in Part 1, with the AE term, MedDRA terms, treatment cycle of onset, serious or non-serious and severity grade (CTCAE v.5.0) provided for each DLT.

The pre-treatment AEs include those AEs that occurred due to study-related procedures. These AEs will be assessed by verbal probes and from medical history. The pre-treatment AEs will be listed by subject but not summarized.

Laboratory safety tests

Laboratory results will be summarized by treatment group/cohort using absolute values and change from baseline; or presented as per-subject listings. The incidence of laboratory data outside the reference range (L, H) will be summarized in frequency tables by treatment group/cohort. Further details will be provided in the SAP.

Physical examination

The overall results of the physical examination ('normal', 'abnormal, NCS', or 'abnormal, CS') will be summarized by treatment group/cohort and listed per subject. Comments for abnormal CS results will be listed.

Other safety variables

Quantitative data for other safety variables will be summarized by the following descriptive statistics: arithmetic mean, standard deviation, median, minimum, and maximum. These summary statistics will be presented by the treatment group/cohort for the absolute values and changes from baseline. Frequency tables will be provided for qualitative data.

Results of VS (body temperature, systolic blood pressure, diastolic blood pressure, respiratory rate, and heart rate) will be summarized by the descriptive statistics listed above.

ECG results (HR, PR, QRS, RR interval, QT, QTcF, and the results of the overall ECG review by the investigator) will be summarized by the descriptive statistics listed above. Comments for abnormal CS results of the ECG will be listed.

All prior and concomitant medications will be assigned a generic name and a drug class based on the World Health Organization Dictionary. Prior and concomitant medications will be listed and summarized by treatment group/cohort and (if appropriate) by drug class.

7.9 Efficacy analyses

The statistical analysis of efficacy variables will be performed on the safety population.

Tumor assessment will be performed by the FDG-PET-CT scan in subjects with FDG-avid NHL histology along with CT or MRI to capture measurements, wherever possible, and by the CT or MRI scan in subjects with low or variable FDG avidity. The investigator at each site will determine the ORR at each time point based on the radiologist's measurement of all evaluable lesions.

The investigator at each site will determine the objective tumor response (OR) using the 5PS per the Lugano Classification for Lymphoma (Cheson 2014) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (Cheson 2016). An overview of LYRIC is presented in Appendix 3. The BORR of all time points will be reported. Subjects

who experience disease progression before undergoing the first tumor assessment will be added to the disease progression stratum. The BORR will be descriptively summarized by the treatment group/cohort; the exact 95% confidence intervals will also be produced.

The ORR representing clinically significant clinical benefit in this study will comprise the Lugano Score 1, 2 or 3, or the CR or PR. All subjects achieving clinically significant clinical benefit according to both response criteria will be included in the analysis of the DOR. DOR is defined as the time from the first documented complete or partial response to the actual date of disease progression or death before progression. The PFS will be defined as the time from the start of treatment with MT-3724 on C1D1 to the date of disease progression or death from any cause. Subjects who have not progressed or died at the time of data base lock will be censored at the date of their last tumor assessment. The DOR will be descriptively summarized by the treatment group/cohort; the exact 95% confidence intervals will also be produced.

The DCR will be defined as the percent of subjects with objective response of CR, PR or stable disease (SD, defined as SD for 6 months or longer). The DCR will be analyzed using similar methods as the ORR. Further details will be provided in the SAP.

A detailed description of analysis methods will be provided in the SAP to be completed before the EoT Visit in the last subject.

7.10 Pharmacokinetic analyses

MT-3724 serum concentration time data from all eligible subjects will be subjected to non-compartmental assessment using the software package Phoenix WinNonlin (Certera, Princeton NJ). Parameters will be stratified by dose group and summary statistics will be generated.

In addition, the concentration time data may be evaluated using nonlinear mixed effects modeling using Nonmem (Icon PLC, Dublin Ireland).

7.11 Immunogenicity analysis

Data for the ADA against MT-3724 will be obtained. The ADA titer will be determined for ADA samples confirmed as a positive result, while the data for the NAb against MT-3724 will be obtained as the positive or negative.

The number and percent of subjects with a detectable ADA titer, and separately with a positive NAb result, will be summarized by time point for each treatment group/cohort. The individual subject's immunogenicity results will be listed by time point for each subject by treatment group/cohort.

Details of the immunogenicity analyses will be provided in a separate analysis plan for this study objective.

7.12 Pharmacodynamic analyses

B-cell count and immunophenotype data by flow cytometry will be presented as absolute values and percentage change from pre- to post-dose time points. The summary statistics by time point and graphs of summary statistics over time will be presented by treatment group and overall.

Details of the PD analyses will be provided in a separate analysis plan for this study objective.

7.13 Interim analysis

No formal interim statistical analysis is planned during either part of this study. A formal interim statistical analysis may be performed only pursuant to a health authority request.

Informal (preliminary) statistical analyses may be performed at sponsor's discretion at any time during the study. These analyses would be performed without the interim data base lock for the purposes of the IB update, safety reports to the health authorities (e.g., data safety update report), meetings with health authorities or for internal decisions.

In addition, data from individual subjects and cohorts will be reviewed without formal statistical analysis on an ongoing basis during the study (e.g. to support the dose escalation decisions in Part 1).

7.14 Protocol deviations

Protocol deviations are defined as deviations from the procedures outlined in the protocol. Major protocol deviations are those deviations that could have an impact on subject's safety or on the ability to interpret the study results.

Deviations from the protocol should not occur. If a deviation occurs, the investigator must immediately inform the monitor, and the implications of the deviation must be reviewed and discussed with the sponsor. Deviations should be reported to the IRB/EC per local requirements.

The impact of the protocol deviations on data quality and integrity will be re-assessed after the completion of the study conduct (last visit by the last subject) and before the data base lock. All decisions regarding the type of deviations (major or minor) will be made prior to commencing the final analysis on the final locked database. Major protocol deviations may lead to exclusion of data from analysis. A listing of all major protocol violations will be presented in the final study report.

8 STUDY MANAGEMENT

8.1 Approval and consent

8.1.1 Regulatory guidelines

This study will be performed in accordance with the Standard Operating Procedures of the sponsor, the EU Clinical Trials Directive and the FDA CFR, the guidelines of the ICH (ICH 2016), and the most recent guidelines of the Declaration of Helsinki (World Medical Association 2013).

8.1.2 Independent ethics committee/Institutional Review Board

Conduct of the study must be approved by an appropriately constituted IEC or IRB. Approval is required for the study protocol, IB, protocol amendments, informed consent forms, subject information sheets, and any advertising materials. No study drug will be shipped to the study site until written IEC or IRB authorization has been received by the sponsor or its representative.

Study progress is to be reported to the IRB/IECs annually (or as required by the committee) by the investigator or sponsor, depending on local regulatory obligations. The investigator or sponsor will also submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events per ICH guidelines and local IRB/IEC standards of practice.

The IRB/IEC and regulatory authorities will be notified of the end of the trial per local requirements. A summary of the study outcome will be provided, where required.

The investigator will be responsible for obtaining annual IRB approval or renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Molecular Templates' representative.

8.1.3 Informed consent

Before any trial activities are performed, subjects must give written consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

If local SOC procedures or tests were performed prior to signing of the ICF but are still within 35 days, unless otherwise specified (e.g. LVEF), of initiation of dosing, then those results/data can be used for the intended protocol screening procedure. If various study parameters within a given procedure are missing from the SOC procedures, then only those missing parameters need to be collected.

As part of written informed consent procedure, the principal investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The document must be in a

language understandable to the subject. The subject will have sufficient time to read the document prior to being asked if there are any questions about the study procedures. A qualified, trained member of the study team must respond to these questions, (e.g., a study staff member who has been specifically trained on the protocol). They should be informed that the subject may withdraw from the study at any time. They will receive all information that is required by the regulatory authorities and ICH guidelines.

The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject. If the subject is unable to read, oral presentation and explanation of the written ICF and information to be supplied to subjects must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (e.g., the subject's thumbprint or mark). The witness to the informed consent discussions must also sign and personally date the ICF. A copy of the ICF must be given to the subject. The original signed ICF will be retained by the investigator. Where required by local law, the person who informs the subject must be a physician.

If the ICF is obtained on the same date when screening procedures are performed, the trial file and the subject's notes must document that the ICF was signed prior to the start of any screening procedure.

The ICF and any other written information provided to subjects, or subject's legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's well-being on the study, or the amendment of the study protocol necessitates a change to the ICF content. Any revised written ICF must receive the IEC's/IRB`s approval/favorable opinion in advance of use. After the IRB/IEC approval, the investigator will inform the subject, or subject's legal representative or proxy consenter about the ICF changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. The signed revised ICF will be archived as described above for the original ICF.

8.2 Protocol amendments and other changes in study conduct

Changes to this protocol that meet the criteria of a substantial amendment in accordance with European Guidance (2010/C 82/01) require a protocol amendment that must be approved by the sponsor, the investigator(s), IRB/IEC and regulatory authorities before implementation. A substantial amendment in the EU will be treated as a protocol amendment in the USA per FDA 21 CFR 312.30(b).

The requirements for approval of the substantial changes should in no way prevent any immediate action from being taken by the investigator or by the sponsor in the interest of preserving the safety of all subjects included in the study.

Changes representing only administrative aspects of the study that meet the criteria of a non-substantial amendment in accordance with local regulatory requirements do not require formal protocol amendments or IEC/IRB approval. The IRB/IEC should be informed of each administrative change as they are implemented, and a log of such changes should be

maintained in the trial master file. The sponsor must be consulted and approve of such changes prior to their implementation.

No changes in this protocol can be made without the sponsor's written approval.

8.3 Discontinuation of the study by the sponsor

The sponsor reserves the right to discontinue the study for safety or administrative reasons at any time. Should the study be terminated, and/or the site closed for whatever reason, all documentation and study medication pertaining to the study must be returned to the sponsor or its representative.

8.4 Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential and not disclosed, in whole or in part to others, or used for any purpose other than reviewing or performing the study, without written consent of the sponsor.

The investigator agrees to conduct the study according ICH GCP and comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the EU Clinical Trials Directive or the FDA CFR. The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the EU Clinical Trials Directive, and EU Law or the FDA CFR and in a form satisfactory to the sponsor to allow for review and monitoring of the conduct of the study and to verify the accuracy of data by the sponsor, its representatives, IRBs/IECs, and regulatory authorities.

The investigator will ensure that all persons assisting in the performance of the study preserve the confidentiality of the subjects' data as set forth in the ICF and Clinical Trial Agreement. In eCRF or any other documents and biological samples submitted to the sponsor, the subjects will not be identified by their names. Each subject will be assigned an identification number to be used on any data or laboratory samples collected by the sponsor. Hence, subject name must be obliterated before a copy of the document is supplied to the sponsor. Documents not for submission to the sponsor, e.g., the signed ICFs and subject medical records, will be maintained by the investigator and made available for review and inspection as described above for as long as is required by local regulations.

8.5 Study monitoring, auditing and inspection

Contract research organization personnel may monitor the conduct of this study on behalf of the sponsor. Monitoring will include on-site visits, remote online access and telephone communication to assure that the study is conducted according to the protocol and to assess the site's compliance with GCP guidelines and other regulations. On-site or online review of eCRFs will assess the completeness and clarity, and consistency with source documents available for each subject.

The study may be audited or inspected by the sponsor or by regulatory authorities, respectively. If an audit or inspection occurs, the investigator must agree to allow direct access to required subject records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, regulatory authorities and IEC/IRBs for on-site monitoring of all appropriate study source documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality. If the Investigator is informed of an impending regulatory authority inspection, the sponsor must be notified within 24 hours of the investigator's notification by the inspecting authority.

8.6 Source data

Data will be recorded in an FDA CFR Part 11-compliant eCRF.

All data in the eCRF must reflect the corresponding source data (Section 7.1). No data are to be recorded directly on the eCRFs (i.e. the CRF is not to be considered as source data).

Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

The investigator should agree to have completed source documents and eCRFs available for inspection by the clinical monitor at the time of each scheduled monitoring visit. The investigator must sign the completed eCRF.

A Clinical Research Associate will perform source document verification as per the monitoring plan. It is critical that all information contained in the eCRF can be corroborated by the source documents/medical records that are used. Source documents may include but are not limited to all original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files and records kept at the pharmacy, at the laboratories and at technical departments involved in the clinical study) that pertain to a study subject during the course of the clinical study. Source documents may also include past and current medical and medication history, documentation of informed consent (signed ICF, including all amendments), subject study identification (e.g., subject number, protocol number), ECOG assessments, International Working Group Criteria, documentation of dosing and study procedures/evaluations, all AE records and any protocol deviations.

All data will be collected on study specific CRFs, with the exception of central laboratory data, which will be provided to the investigator on a laboratory report and submitted to the clinical database via electronic transfer from the testing laboratory. Local laboratory data will be entered into the CRFs by trained and qualified study staff.

Monitors and auditors must have access to original records (unless copies are certified as authentic copies). Source data must be legible, written concurrently with the subject visit, and no data may be obliterated.

All potentially eligible and appropriately consented study candidates will be entered into the study's electronic data base with the initiation of screening. This information will be retained for all dosed subjects as well as subjects who fail one or more screen procedures or withdraw consent following screening and never progress to receive study drug.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the eCRF. Details of eCRF completion and correction will be provided in the eCRF completion guidelines and will be explained to the investigative staff. If the investigator authorizes other persons to make entries in the eCRF, the names, positions, signatures, and initials of these persons must be supplied to the sponsor/CRO.

The eCRFs must be reviewed at regular intervals by the investigator and signed by the investigator named in the clinical study protocol at the end of the study. Any changes to the eCRF after retrieval using data clarification forms or queries must also be authorized/signed by the investigator and/or the study coordinator and/or the data entry coordinator. (Note: Study Coordinators and Data Entry Coordinators are sometimes allowed to sign Data Clarification Forms.) The sponsor will retain the final, complete electronic data base with all CRFs. The investigator will retain a copy of all CRF pages completed at their site.

8.7 Retention of records

The investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant health authority. In addition, because this may be an international study, the retention period must meet the most stringent requirements of any local health authority. The site should plan to retain study documents until directed by the sponsor that they are no longer required. The investigator should take measures to prevent accidental or premature destruction of these documents.

8.8 Subject insurance

The sponsor will obtain clinical trial insurance to cover subjects participating in the study in accordance with all applicable laws and regulations. The terms of the insurance will be kept in the study files.

8.9 Financial Disclosure

In accordance with the regulatory requirements in the involved countries Molecular Templates will request a statement attesting for any financial disclosure from all investigators and sub-investigators who participate in a clinical study (defined as those directly involved in the treatment or evaluation of research subjects). This includes the financial interests of

spouses and dependent children of the investigators. Any changes to the disclosure statement must be submitted in writing to Molecular Templates.

Disclosure is required for those financial interests other than the Clinical Study Agreement for this study.

8.10 Study disclosure and publication

The study will be posted on www.clinicaltrials.gov and other applicable public databases as required by local regulations.

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international regulatory filings and registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. A final integrated study report covering clinical and biometric aspects of the study will be prepared by the sponsor or its representative and results of the trial will be disclosed to regulatory authorities and posted on public registries, as required.

8.10.1 Publications of study results

The sponsor intends to publish the results of this study upon completion of the appropriate analyses during the study conduct and/or after the study completion. The sponsor reserves the right to name as authors members of staff at the investigational site if they have made qualifying contributions to the research. Order of authorship will generally be assigned in relation to the relative contribution of each author. Disagreements concerning authorship will be resolved by the sponsor. All authors will be required to review and agree upon the content of the draft publication prior to its submission to a peer-reviewed congress, journal or posting on the sponsor's website.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the Clinical Trial Agreement between each investigator and the sponsor, as appropriate.

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APPENDIX 1. LABORATORY PANELS

Table 10 Laboratory Assays

Hematology (central laboratory):				
WBC[1]	hemoglobin	platelet count	hematocrit	RBC and indices[2]
Chemistry (central laboratory):				
albumin	amylase	lipase	creatinine	ALT
AST	CPK	calcium	chloride	GGT
LDH	serum glucose[3]	magnesium	phosphorous	potassium
sodium	bilirubin (total and direct)	total protein	BUN	Uric acid
eGFR[4]	HbA1c	β-2 microglobulin		
Coagulation (central laboratory)				
INR or PT	aPTT			
Thyroid function (central laboratory)				
TSH	free T4			
Urinalysis macroscopic[6] (local laboratory):				
pH	specific gravity	glucose	ketones	leukocytes
nitrites	protein	occult blood		
Urinalysis microscopic [optional] (local laboratory):				
RBC	WBC	bacteria	casts	epithelial cells
mucous threads	crystals			
Urinalysis or serum (local laboratory)				
β-HCG[5]				
Immunoglobulins (central laboratory)				
IgG	IgA	IgM		
Other assessments (central laboratory)				
cytokines	complement	ADA/NAb	histamine	B-cell count
rituximab	PK (serum)	PK (CSF)		
Other assessments (local laboratory)				
Viral loads (HIV, HBV, HCV)	CD4+ T-cell counts			

β-HCG = beta human chorionic gonadotropin; ADA = anti-drug antibody; AST = aspartate aminotransferase; ALT = alanine aminotransferase; aPTT = Activated partial thromboplastin time; BUN = blood urea nitrogen; CPK = creatinine phosphokinase; CSF = cerebrospinal fluid; eGFR = Estimated glomerular filtration rate; freeT4 = Free thyroxin; GGT = gamma-glutamyl transferase; HbA1c = Glycated hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; INR = International normalized ratio; LDH = Lactate Dehydrogenase; NAb = Neutralizing antibodies; PK = pharmacokinetics; PT = Prothrombin time; RBC = Red Blood Cell; TSH = Thyroid-stimulating hormone; WBC = white blood cell.

[1]WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes) reported as percentage and absolute values

[2]Red cell indices (mean cell volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]) and distribution widths (red cell and platelet)

[3]If possible, the blood for chemistry assessments should be drawn after a subject has fasted for at least 2 hours, in order to facilitate a more reliable interpretation of the serum glucose result. The compliance with this recommendation (Yes / No) will be entered in the eCRF for every chemistry assessment.

[4]eGFR, Cockcroft-Gault calculation, see Appendix 5.

[5]β-HCG, only for women of childbearing potential

[6] Microscopic examination of sediment will be performed if the results of the urinalysis dipstick evaluation are positive at the investigator's discretion

APPENDIX 2. STAGING OF NHL

Ann Arbor Staging System with Cotswold Modification (Lister 1989)

Ann Arbor stage is determined as outlined in Table 11, for calculation of the appropriate prognostic index for disease status at initial diagnosis and at baseline. The Cotswold modification maintains this original 4-stage clinical and pathologic staging but also adds information regarding the prognostic significance of bulky disease (denoted by an X designation), regions of lymph node involvement (denoted by an E designation) and the absence or presence of symptoms (denoted by the A/B designations).

Table 11: Ann Arbor Staging System with Cotswold Modification

Stage[1]	Ann Arbor Staging System Features
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III[2]	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extra nodal site(s) beyond that designated E
Cotswold Modifications	
For all stages	
A	No B symptoms
B	Fever (>38ºC), drenching sweats, weight loss (10% body weight over 6 months)
X	A thoracic ratio of maximum transverse mass diameter greater than or equal to 33% of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level on chest radiography.
For Stages I to III	
E	Involvement of a single, extra nodal site contiguous or proximal to known nodal site

[1] The number of anatomic regions involved should be indicated by a subscript (e.g., II3).
[2] Stage III may be subdivided into: III1, with or without splenic, hilar, celiac, or portal nodes; III2, with para-aortic, iliac, mesenteric nodes.

International Prognostic Index for Aggressive Non-Hodgkin's Lymphoma (NHL Project 1993)

The International Prognostic Index (IPI) for Aggressive NHL is used to assess the prognostic score of patients at diagnosis with aggressive NHL. In this study, this index should apply to subjects who have been diagnosed with DLBCL, mantle cell lymphoma, sporadic (non-endemic, non-immune deficiency associated) Burkitt's lymphoma (BL), small noncleaved non-Burkitt's (Burkitt's–like) lymphoma (SNC-NB), DLBCL transformed FL [excluding unclassifiable, blastoid and lymphoblastic subsets], and transformed (*Helicobacter pylori* negative) mucosa-associated lymphoid tissue (or extra nodal marginal zone B-cell) lymphoma (MALTL) and, if available, should be recorded as part of the Medical History in the appropriate CRF. (n.b. Relapse-free and OS rates at 5 years are 75% for 0-1 factors; 50% for 2-3 factors and 25% for 4 - 5 factors.)

One point is assigned for each of the following risk factors:

1. Age >60 years
2. Ann Arbor Stage III or IV disease
3. Serum LDH ≥450 IU/L
4. ECOG performance status of 2, 3, or 4
5. Extra-nodal sites ≥2

Subjects will be documented to be in one of four risk groups:

Low Risk	0-1 risk factors	5-year survival of 73%
Low-intermediate risk (2 points)	2 risk factors	5-year survival of 51%
High-intermediate risk (3 points)	3 risk factors	5-year survival of 43%
High risk (4-5 points)	4-5 risk factors	5-year survival of 26%

Follicular Lymphoma International Prognostic Index (FLIPI) [Solal-Céligny 2004]

The FLIPI is used to assess the prognostic score of subjects with indolent Follicular NHL at diagnosis and, if available, should be recorded as part of the Medical History in the appropriate CRF. The FLIPI score is calculated on the basis of 5 adverse prognostic factors.

One point is assigned for each of these adverse prognostic factors:

1. Age >60 years
2. Ann Arbor Stage III or IV disease
3. Involved lymph node groups >4
4. Serum hemoglobin <12 g/dL
5. Serum LDH >450 IU/l

Subjects will be documented to be in one of three risk groups:

Low Risk	0-1 risk factors
Intermediate Risk	2 risk factors
Poor Risk	3-5 risk factors

APPENDIX 3. REVISED LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT IN LYMPHOMA WITH LYRIC MODIFICATION

Tumor response will be evaluated according to the revised Lugano Classification for Lymphoma (Table 12) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria).

Table 12: Revised Lugano Classification of Response Assessment in Lymphoma adjusted for LYRIC

Response and Site	PET-CT-Based Response	CT/MRI-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	5PS score of 1, 2, or 3[1] with or without residual mass. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesion(s)	None	None
Bone Marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5 on the 5PS (Table 13) with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node >5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesion(s)	None	None

Bone Marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesion(s)	None	None
Bone Marrow	No changes from baseline	Not applicable
Progressive Disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir: 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesion(s)	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement
LYRIC Indeterminate response (IR)[2]	Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD	>50% increase in SPD in first 12 weeks <50% increase in SPD with a. New lesion(s), or

		b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment (in the context of the lack of overall progression, a biopsy is encouraged)>50% increase in SPD in first 12 weeks <50% increase in SPD with a. New lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment (in the context of the lack of overall progression, a biopsy is encouraged)

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[1]A score of 3 in many subjects indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[2]See original paper (Cheson 2014, Cheson 2016) for more detailed information on immune related response.

Lugano 5PS range (Cheson 2014)

The 5PS ranges from a score of 1 (where no uptake is discernible in the lesion) to a score of 5 (where the uptake in the lesion is markedly increased compared to the uptake in the liver parenchyma). A single 5PS score, which represents the most FDG-avid (i.e., metabolically intense) area of disease (across all index and non-index lesions), is assigned for each PET/CT scan in the study, see Table 13.

Table 13: Modified Lugano 5-point scale (5PS)

Score	Description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased above liver at any site
5	Markedly increased uptake above liver at any site
NE	Not evaluable
X	Any areas of uptake not likely to be related to lymphoma

APPENDIX 4. DLT CRITERIA

GENERAL PRINCIPLES
A TEAE will be declared as DLT if both of the following criteria are met:

1. The TEAE occurred after the start of infusion in cycle 1 of Part 1.
    a. If a TEAE that fulfills a DLT criterion is observed in cycle ≥2 of Part 1, then the sponsor may declare this event a DLT after consultation with the investigator(s).
2. The TEAE is at least possibly related to MT-3724, as determined by the sponsor after consultation with the investigator(s).

Note: TEAEs related to LEN will not be declared a DLT unless they exceed in severity the worst grade described or are not mentioned in the reference prescribing information. If a Grade ≥3 TEAE related to LEN is more severe than the worst grade described in the reference prescribing information or has not been reported in the reference prescribing information, then the sponsor may declare this event a DLT after consultation with the investigator(s).

The severity of TEAEs potentially fulfilling the DLT criteria will be graded according to the CTCAE v.5.0.

POTENTIALLY QUALIFYING TEAEs: Any TEAE listed below may represent a DLT for MT-3724 in this study.

Hematological TEAEs

- Grade ≥3 febrile neutropenia (ANC <1000/µl and a single body temperature reading of >38.3°C (101°F) or a sustained body temperature of ≥38.0°C [100.4°F] for more than 1 hour)
- Grade 4 neutropenia (ANC <500/µl) for >5 days; if the investigator determines that G-CSF therapy for Grade 4 neutropenia is essential within ≤5 days of onset, then this AE will also qualify as DLT
- Grade 3 thrombocytopenia (<50,000/µl and ≥25,000/ µl) with clinically significant bleeding (i.e., bleeding requiring platelet transfusion)
- Grade 4 thrombocytopenia (<25,000/µl) with or without bleeding
- Grade 4 anemia

Nonhematological TEAEs

- Grade ≥2 Cytokine Release Syndrome
- Grade ≥3 Capillary Leak Syndrome
- Grade ≥3 acute kidney injury
- AST and/or ALT increase >5.0 times ULN (>8.0 times for those with liver involvement)
- AST and/or ALT increase >3.0 times ULN with concomitant increase in total bilirubin ≥2.5 times ULN
- Total bilirubin >4.0 times ULN

Note: for AST, ALT and bilirubin the investigator in consultation with the Medical Monitor and the sponsor should diligently assess if the value above either 5.0, 3.0 or 1.5 x ULN (depending on laboratory values as specified above), could be interpreted as non-DLT in light of the elevated baseline value (see CTCAE v5.0) and liver involvement.

- Grade ≥3 infusion-related reaction or other Grade ≥3 hypersensitivity reaction
- Any Grade ≥ 3 electrolyte abnormality that does not resolve, with or without intervention, to Grade <2 within 72 hours.
- Any other Grade ≥3 nonhematological toxicity **excluding** the following:
  - Nausea, vomiting, or diarrhea, if manageable with antiemetic or antidiarrheal agents within 7 days of onset
  - Fatigue lasting ≤72 hours
  - Grade 3 laboratory abnormalities, if asymptomatic and without a clear clinical correlate, as determined by the sponsor after consultation with investigator(s).
- Any other toxicity at least possibly related to MT-3724, irrespective of the type or severity, that would qualify as DLT, as determined by the sponsor after consultation with investigator, considering the severity, duration, poor response to remedial therapy and/or inadequate resolution. This may be Grade 1 or Grade 2 toxicity that notably limits the activities of daily life to the extent that makes dose reduction necessary to ensure subject's compliance (e.g., long-lasting fatigue or anorexia).

APPENDIX 5. COCKCROFT-GAULT (2009)

Creatinine clearance should be calculated using the Cockcroft-Gault Formula (Cockcroft DW 1979), which is given below:

CLcr = {((140–age) x weight) / (72 x SCr)} x 0.85 (if female)

Abbreviations/Units: CLcr (creatinine clearance) = mL/minute; Age = years; sCR (serum creatinine) = µmol/L

APPENDIX 6. ECOG PERFORMANCE STATUS

ECOG will be recorded per the investigator's assessment of subject's performance status:

Grade	Description
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 housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

APPENDIX 7. NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

The stages of heart failure will be assessed according to the NYHA functional classification system. This system relates symptoms to everyday activities and the subject's quality of life.

NYHA classification

Class	**Subject symptoms**
Class I (mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX 8. ABBREVIATIONS

Abbreviation	Definition
5PS	five-point scale
ACVBP	adriamycin, cyclophosphamide, vindesine, bleomycin and prednisone
ADA	anti-drug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
□-HCG	Beta-human chorionic gonadotropin
BIW	twice weekly
BMI	body mass index
BORR	best overall response rate
BP	blood pressure
°C	Celsius
C	cycle
C1D1	cycle 1 day 1
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CHOP	cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and prednisone
CLcr	creatinine clearance
CLS	capillary leak syndrome
Cm	centimeter
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CS	clinically significant
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Definition
DCR	disease control rate
DHAP	dexamethasone, cytosine arabinoside, cisplatin
DLBCL	diffuse large B-cell lymphoma
DLT	d-dose-limiting toxicity
DOR	duration of tumor response
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EDC	electronic data capture
EoI	end of infusion
EoT	end of treatment
EPOCH	etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin
°F	Fahrenheit
FDA	Food and Drug Administration
FDG	fluordeoxyglucose
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FNA	fine needle aspirate
GCP	Good Clinical Practice
GDP	gemcitabine, dexamethasone and cisplatin
G-CSF	granulocyte-colony stimulating factor
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
HR	heart rate
IB	Investigator’s Brochure
ICE	ifosfamide, carboplatin and etoposide
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethic Committee
Ig	immunoglobulin

Abbreviation	Definition
IHC	immunohistochemistry
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
Kg	kilogram
L	liter
LDi	longest diameter
LDH	lactic dehydrogenase
LEN	Lenalidomide
LTFU	Long-Term Follow Up
LVEF	left ventricular ejection fraction
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
Ml	milliliter
mM	millimolar
MM	multiple myeloma
mmHg	millimeter of mercury
mm^3	cubic millimeter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NAb	neutralizing antibody
NCS	not clinically significant
NHL	non-Hodgkin’s lymphoma
NSAIDS	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OR	objective tumor response
ORR	objective tumor response rate
OS	overall survival
OTC	over the counter

Abbreviation	Definition
PCR	polymerase chain reaction
PD	pharmacodynamics
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	orally
PR	partial response
PRBC	packed red blood cells
PT	prothrombin time
PTT	partial thromboplastin time
Qd	once daily
QTcF	QT interval corrected according to Fridericia's formula
R^2	lenalidomide plus rituximab
RBC	red blood cell (count)
R-CHOP	rituximab-CHOP
REMS	Risk Evaluation and Mitigation Strategy
RNA	ribonucleic acid
RR	respiratory rate
R/R	relapsed or refractory
RTX	rituximab
SAE	serious adverse event
SAP	statistical analysis plan
scFv	single chain variable fragment
SCT	stem cell transplantation
SD	stable disease
STFU	Short-Term Follow-Up
SOC	standard of care
SUSAR	suspected, unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TESAE	treatment-emergent serious adverse events
TIW	three times a week
TSH	thyroid-stimulating hormone
µg	microgram

Abbreviation	Definition
ULN	upper limit normal
WBC	white blood cell (count)

APPENDIX 9. SUMMARY OF CHANGES

Version 3.0 (14 April 2020) replaces version 2.0 (10 December 2018) and is applicable to all investigators participating in this protocol.

Rationale for changes:

1. A modification of the dosing schedule has been implemented in this amendment to address the occurrence of dose-limiting toxicities in two subjects treated with MT-3724 at 25μg/kg/dose (Cohort 2). The starting dose for Cohort 3 was subsequently reduced to 20 μg/kg/dose while maintaining the 3 weekly dosing schedule for the first 2 cycles. MT-3724 will be administered at a reduced dosing frequency from twice rather than three times weekly starting with Cohort 4; the lenalidomide (LEN) schedule is unchanged.
2. The CTC Grade 2 events occurred in subjects treated at a dose lower than the MTD of 50μg/kg/dose with monotherapy. While the two trials cannot be directly compared because of confounding factors (MT-3724 in combination with LEN versus monotherapy and differences in investigator discretion vis-a-vis pre-dose medication), and since the dose-response relationship is still being evaluated, a new dosing schedule is being implemented to evaluate if dosing of MT-3724 at a reduced frequency when combined with LEN will be more tolerable while still allowing for higher doses on a μg/kg basis to maximize response potential.
3. The dose-limiting toxicity (DLT) criterion regarding capillary leak syndrome (CLS) has been updated from Grade 2 to Grade 3 based upon available safety data. Across the MT-3724 trials, to date, treatment-emergent adverse events (TEAEs) have been manageable. Capillary leak syndrome as the most common DLT did not exceed Grade 2, resolved within days in most cases, except for those dosed at 75μg/kg when resolution occurred over 2-4 weeks, and did not prevent subjects from resuming treatment.
4. Pre-dose medication requirements have been updated to clarify that subjects must receive pre-dose medications with all doses in cycle 1, rather than allowing pre-dose medications at the investigator's discretion which may reduce the incidence and/or severity of innate immune responses typically observed early in cycle 1.
5. Subjects are now required to have histologically confirmed CD20+ DLBCL obtained at the time of relapse to be eligible for this study. This is to confirm the study enrolls the appropriate patient population whose disease has the potential to respond to this therapy based upon based upon the mechanism of action of MT-3724.
6. Other changes to inclusion/exclusion criteria have been made to ensure consistency across the MT-3724 program of studies and to modify criteria which were unnecessarily stringent. These latter changes include allowing subjects with seropositive human immunodeficiency virus (HIV)/hepatitis B virus (HBV)/hepatitis C virus (HCV) the option to enroll in this study provided they have non-detectable viral loads (HIV/HBV/HCV), a minimum number of CD4+ cells (for subjects with HIV) and receive appropriate prophylactic treatments. The current safety data do not indicate a heightened risk for study subjects to have new or reactivated infectious diseases. Also, a reduced washout period (consistent with the relevant half-life for subjects whose last treatment include small molecules, as opposed to monoclonal antibodies) is implemented.

7. The protocol was modified to allow subjects continued treatment with MT-3724, rather than the prior limitation of therapy to a maximum of 12 cycles, contingent upon demonstration of continued clinical benefit and tolerability of study treatment. Given the current safety profile which includes subjects' exposure for up to 9 cycles, it is reasonable to allow subjects continued treatment with MT-3724 as long as there is a favorable risk-benefit ratio in the opinion of the investigator.
8. The screening period has been increased from 28 days to 35 days to allow for central laboratory processing of screening samples
9. The safety event collection period starting point has been updated from "signing of the informed consent" to "Cycle 1 Day 1". This was implemented to avoid collecting unrelated pre-treatment AEs; and to avoid confounding understanding of MT-3724 safety profile with toxicities from other cancer therapies. An AE/SAE during the screening period will only be collected if it is deemed related to a protocol screening procedure.
10. Respiratory rate and temperature assessments have been added to vital signs and quality of life analysis language has been added as these were inadvertently omitted from previous versions of the protocol.
11. Vast majority of changes made were to provide clarifications to existing language.

High-level summary of changes made:

	Section	Change	Rationale
1.	Global changes	Change patient to subject Changed from MT-3724 concentration in plasma to serum Sponsor and investigator are not capitalized No space between value and unit (e.g. 50µg/kg/day) No space between slash (e.g. D1/D2) Removed reference to CRO (since medical monitor is from the sponsor, have maintained only medical monitor when both sponsor and medical monitor were cited) Abbreviations updated as necessary Relocated sections of protocol for better readability (eg SOA after synopsis, TOC before synopsis)	Administrative
2.	Investigator protocol agreement	Changed to reflect prior protocol language	Consistency with previous protocol
3.	List of contacts	Updated to reflect different contacts	Administrative
4.	Amendment rationale	Added to protocol amendment	Explanatory
5.	Synopsis	Updated synopsis to reflect all the changes made to body of protocol and reformatted (matched objectives to endpoints for clarification)	Clarification and – for consistency with updated protocol
6.	Synopsis	Deleted Table (p15-18)	Redundant and information not required in synopsis
7.	Synopsis	Added “in both parts” and “either part of” for clarity in Study Treatment and Duration section	For clarity and consistency with previous protocol
8.	Section 1.1	Updated language for NHL	For clarity and consistency with previous protocol
9.	Section 1.2.1	Update clinical experience with MT-3724 based on IB v5, 2019	updating and clarification
10.	Section 2.1 Study Objectives	1 Reformatted to match objectives to endpoints 2 [redacted]	1 Administrative 2 [redacted]
11.	Figure 1	Revised Figure 1: Study Design for MT-3724_NHL-003	For clarity and consistency with changes in protocol
12.	Section 3.2 Screening	Updated screening window from 28 days to 35 days	To allow for flexibility should there be a delay in receipt of RTX results

13.	Section 3.3.1 MT-724	(1) Simplified to reduce redundancy with content in Section 5.1.3 and add period of LTFU as mention of it was previously missing; (2) removed "Every subsequent cycle should be started on D28+1, except if prevented by ongoing AEs."	(1) Clarification / administrative; (2) removed because it's not required per safety – this avoids unnecessary protocol deviations
14.	Section 3.4 End of Treatment visit and Short-Term Follow-up phone call	For EoT visit, removed "for those that complete the study" for clarification	Clarification
15.	Section 3.5 Long-term Follow up visit	Updated frequency of contact (from every 6 to every 3 months), duration (from 24 months after last dose to 18 months after first dose), and endpoints	To decrease the number of subjects lost to follow-up and increase precision with which DOR and survival will be captured
16.	Section 3.6 Part 1 (MT-3724 dose escalation)	Updated section to allow for dose re-escalation at reduced dose frequency and added evaluation criteria, clarify number of subjects in Part 1	Clarification
17.	Section 3.6.3 MTD Definition	Removed "in Cohort 3" since the dose in Cohort 3 may not be 50mcg/kg and also removed "The dose of MT-3724 that will be given in this study is 50µg/kg/dose with a maximum total dose of 6000µg, which is the MTD of MT-3724 as monotherapy. The MT-3724 dose escalation will not proceed above the 50µg/kg/dose even if no more than 1 of 6 subjects in Cohort 3 experiences a DLT"	Remove since the dose in Cohort 3 may not be 50µg/kg
18.	Section 3.7 Part 2 (MTD expansion cohort)	Removed "(or at a maximum dose of 50µg/kg)"	Clarification
19.	Section 3.8 Rationale for the study design	Updated LTFU from how and what will be collected to why it's being conducted	Clarification since this section is on rationale and not methodology. Also this section moved to 1.4
20.	Section 3.9 Guidance to the investigator	Updated most common AE from latest version of IB (v 5) and also incorporated guidance to the investigator for CLS	Update with most recent data from IB v5. Section moved to 1.6
21.	Section 3.10 Benefit/Risk Ratio	Updated to reflect MoA, in vitro and clinical data	Update with most recent data from IB v5. Section moved to 1.5
22.	Section 4 Study population	Added language that requires eligibility needs to be reconfirmed prior to C1D1	Clarification
23.	Section 4.1 inclusion criterion #3	Reorganized for clarification and added that B-cell NHL should be CD20 positive	Clarification
24.	Section 4.1 inclusion criterion #3	1. Added criterion on SCT to inclusion criterion #5 (and removed it from exclusion criteria) 2. Added that sponsor approval is required when considering enrolling patients who did not receive all available therapies for NHL 3. Added language for proof of CD20 positive NHL	1. Clarification because easier to understand hematologic recovery when worded as an inclusion criterion 2. To ensure sponsor oversight

25.	Section 4.1 inclusion criterion #5	Added criterion for eligibility regarding CAR-T and SCT	Clarification to ensure compliance and expand eligibility
26.	Section 4.1 inclusion criterion #6	Added "bi-dimensionally" for clarification and deleted reference to "Table 7"	Clarification
27.	Section 4.1 inclusion criterion #8	Added requirement on hemoglobin	To ensure adequate bone marrow function
28.	Section 4.1 Inclusion criterion #9	Updated CLcr criteria from at least 60 to at least 50 and changed method from CPK-EPI for Cockcroft-Gault	To be in alignment with data generated for MT-3724 using the Cockcroft-Gault formula with the cutoff of ≥50 mL/min.
29.	Section 4.1 inclusion criteria #10, #11	Updated for consistency across MT-3724 protocols - changed requirement for total bilirubin to be <2 instead of 1.5 (and info for subjects with Gilbert's syndrome); for AST and ALT, changed requirement from ≤3 to 2.5 and added (or ≤ 5 x ULN if liver involvement); for coagulation added that requirement is not necessary for those on therapeutic anticoagulants	Allow flexibility for subjects with liver involvement and those taking anticoagulants
30.	Section 4.1 inclusion criterion #13	Added definition for postmenopausal	Clarification
31.	Section 4.1 inclusion criterion #16	Added criteria on life-expectancy	To reduce likelihood of enrolling moribund subjects
32.	Section 4.2 exclusion criterion #1	Reworded for clarification	Clarification
33.	Section 4.2 exclusion criterion #2	Updated to add stipulation around autologous SCT and additional criteria added "b. Neurologic symptoms must be stable and no worse than Grade 2 c. Have evidence of stable brain or spinal disease on CT or MRI scan obtained within 4 weeks of signing the ICF and compared with prior imaging results d. Do not require chronic steroid therapy (or, if applicable, have been stable on steroid dose of no more than prednisone 20 mg/day or equivalent by C1D1)"	Update to allow for subjects with autologous SCT and clarify additional criteria
34.	Section 4.2 exclusion criterion #3	Relocated to inclusion criterion #5 (previously regarding SCT) and therefore all subsequent exclusion criterion were renumbered	clarification
35.	Section 4.2 exclusion criterion #4	Added "that are related to prior anti-cancer therapy"	clarification
36.	Section 4.2 exclusion criterion #5	Added "or radiotherapy"	To ensure subjects with AE from radiotherapy recovered before study enrollment
37.	Section 4.2 exclusion criterion #6	Added requirement regarding Grade 2 infection	To allow for more flexibility for subjects with Grade 2 infection with respect to eligibility
38.	Section 4.2 exclusion criterion #7e	Added option to allow for subjects with LVEF between 40-45% possible enrollment per sponsor approval	To allow for subjects with LVEF between 40-45 possibility for enrollment to trial

39.	Section 4.2 exclusion criterion #9	Updated to allow subjects with HIV/HBV/HCV to have undetectable viral load and for HIV, minimum CD4+ T-cell count of 50cells/uL, provided prophylaxis therapy for opportunistic infections given and appropriate anti-viral prophylaxis, per institutional guidelines	To allow for subjects with well controlled-HIV/HBV to participate in the trial
40.	Section 4.2 exclusion criterion #13	Added "Prior treatment with MT-3724"	To ensure subjects are naïve to MT-3724
41.	Section 4.2 exclusion criterion #15	Added requirement on washout for radioimmunoconjugates and added that for small molecules,	To ensure appropriate washout period for subjects who received radioimmunoconjugates and small molecules for NHL
42.	Section 4.2 exclusion criterion #17	Added more details regarding palliative radiation therapy	Relaxed requirement given patient population and MT-3724 MoA
43.	Section 4.2 exclusion criterion #18	Updated requirement regarding vaccinations	Relaxed requirement given patient population and MT-3724 MoA
44.	Section 4.2 exclusion criterion #19	Updated requirement regarding steroid use	Relaxed requirement given patient population and MT-3724 MoA
45.	Section 4.3.1 Subject withdrawal	Updated from "discontinued from study" to "discontinued from treatment period"	in order to make it clear that it's expected the subject will remain in follow-up
46.	Section 4.3.1 Subject withdrawal	Deleted paragraph defining withdrawn subjects as either screen failures or dropouts	Clarification
47.	Section 4.3.3 Study discontinuation	Removed last sentence	Clarification
48.	Section 5.1.1., 5.1.2, 5.1.3 MT-3724 dosing schedule	1 Updated to add window (including that doses must be administered at least 48 hours apart in cycles 1 and 2) 2 Updated to add new dosing schedule 3 Added maximum break permitted between cycles (14 days) 4 Removed mention of max dose administration will be 50mcg/kg	1 To allow for flexibility, and to ensure adequate time between dosing for tolerability, based on the DLTs that occurred in cohort 2. 2 To reduce the probability of DLTs in the first 2 cycles and broaden the therapeutic window. 3 To ensure subjects are not off treatment for extended duration 4 Removed max dose because of dosing schedule differences between this amendment and the monotherapy dose escalation study
49.	Section 5.2 Lenalidomide	Changed Lenalidomide will be "supplied" to "available"	Clarification
50.	Section 5.1.1 MT-3724 Drug Product	Changed handling requirements	Clarification for compliance
51.	Section 5.1.2 MT-3724 dose selection	Changed "may" to "will" regarding requirement for body weight adjustment for MT-3724 dose Revised dosing guidance to Table 1 Updated dosing schedules for Cohorts greater than 3 Added "MT-3724 must be administered at least 48 hours apart"	Clarification for safety, compliance

52.	Section 5.1.4 Premedication	Changed “should” to “must”	Clarification for safety
53.	Section 5.2.1 Len dose	For Parts 1 and 2, starting with cycle 2 (after completion of the DLT assessment period for Part 1), the investigator may increase the LEN dose to 25mg qd, if clinically indicated, with sponsor approval.	Clarification of dosing of LEN
54.	Section 5.2.2 Lenalidomide dosing selection	Section added to state starting dose of LEN and language regarding increasing LEN dose to 25mg	Clarification for investigator
55.	Section 5.2.3	Removed reference to “up to 6 additional cycles” Added language regarding monotherapy with MT-3724	Removed since treatment is permitted beyond cycle 6 Clarification for discontinuation of LEN
56.	Section 5.3 Intra-subject dose escalation	Starting with cycle 2 (after the DLT assessment period for subjects in Part 1), the dose of LEN may be increased to 25 mg qd, as described in Section 5.2.1	Clarification of LEN dosing
57.	Section 5.4.5 Treatment modification for MT-3724 and LEN due to increased AST, ALT and/or bilirubin levels	Updated table 3 in section 5.4.5	Updated table to better reflect possible clinical scenarios
58.	Section 5.8 Treatment duration	Updated duration from up to 12 cycles to allowing treatment until disease progression withdrawal of consent or any other reason	To allow for extended treatment in subjects who benefit
59.	Section 5.9 Prohibited Treatments	Updated radiotherapy to be allowed during screening, relaxed vaccination prohibitions, steroid use, vaccines, and added washout for radioimmunoconjugates	Relaxed requirement given patient population and MT-3724 MoA
60.	Section 5.10 Permitted medication	Added clarification that palliative therapy is allowed, Also added requirement for use of G-CSF for G3 neutropenia. Also added caution statement in 5.10.1	clarification
61.	Section 6.1.2 body weight	Added clarification that recalculation of study drug dose based on body weight changes can also be per institutional policy	Clarification
62.	Section 6.1.4 NHL assessment	Added additional criteria for NHL assessment	clarification
63.	Section 6.1.5 Prior systemic therapy	Includes CAR-T and clarification of recordation	clarification
64.	Section 6.2.3 Physical Examination	Change that physical exam can be done from up to 72 hours to up to 24 hours before dosing	To unify that predose assessments can be done up to 24 hours predose
65.	Section 6.2.2. Prior and concomitant medications	Changed from “at screening” to “during the screening period” to clarify that meds are to be collected during the screening period and not just at the screening visit	Clarification

66.	Section 6.2.3 Physical Exam	(1) Changed from up to 72 hours before to up to 24 hours before dosing; (2) removed repeated information	(1) To unify with other predose assessments that can be done up to 24 hours predose; (2) administrative
67.	Section 6.2.3.1	Changed heading to remove "including ECOG and NYHA" since these two topics are covered elsewhere	Administrative
68.	Section 6.2.5 New York Heart Association	Added clarification that NYHA need only be assessed for subjects with heart failure	Clarification
69.	Section 6.2.6 Vital signs	(1) Added respiratory rate and body temperature whenever BP and HR are assessed (and thereby removed separate section on vital signs (previously section 6.2.7), therefore section numbers were updated) (2) And changed order of assessments	(1) Inadvertently left-off RR and body temperature (2) To allow more flexibility with site procedures
70.	Section 6.2.7 Left ventricular ejection fraction	Updating requirements	Clarification
71.	Section 6.2.8 Electrocardiograms	Added language that when assessments are due at the same time; the order is ECG and VS first then PK	To allow for more flexibility with site procedures
72.	Section 6.3.1 AE reporting period	(1) Updated AE reporting to start at start of treatment, unless related to study screening procedure, and until STFU or start of new cancer therapy, (2) added that symptoms of CLS/CRS/SIRS/IRR should be reported in CRF on separate eCRF pages	(1) To avoid collection of AEs that are not due to MT-3724 treatment, (2) administrative to add guidance for reporting expectations
73.	Section 6.3.5 Serious Adverse Events	Removed erroneous example of SAE which stated that hospitalization for diagnostic procedure should be reported as SAE	Administrative
74.	Section 6.4 Laboratory tests	(1) Added Virology; for local labs, (2) removed "at the site"	(1) Added virology in order to capture data confirming viral load is undetectable for subjects with HBV/HIV; (2) administrative
75.	Section 6.4.2 eGFR	Revised calculation to Cockcroft-Gault	Consistency with previous protocol
76.	Section 6.4.1 Hematology, Chemistry, Urinalysis	a) Added that local labs should be done to evaluate status if needed; b) Added that that these will be collected with continued dosing (replaced C3-C6 with cycle 3 and beyond); c) Updated that eGFR will be assessed by Cockcroft-Gault rather than CPK-EPI	a) Clarification b) To provide flexibility in obtaining pre-dose assessments c) To address continuation of assessments given allowance of continued dosing d) Updated for consistency throughout MT-3724 program
77.	Section 6.4.4 HbA1c	Updated frequency to assess at every odd cycle after cycle 3 to account for continued dosing	Clarification to assess for HbA1c to account for continued dosing
78.	Section 6.4.5. Thyroid function	Updated frequency to assess at every odd cycle after cycle 3 to account for continued dosing	Clarification to assess for thyroid to account for continued dosing

79.	Section 6.4.6 Coagulation	Updated frequency to assess at every odd cycle after cycle 3 to account for continued dosing	Clarification to assess for coagulation to account for continued dosing
80.	Section 6.4.10 Rituximab concentration	Added language that RTX doesn't need to be re-evaluated once deemed "negative" in cases of re-screening	Clarification
81.	Section 6.4.11 Serology/Virology	Added Virology for HBV and HIV and CD4+ T-cell counts for HIV	Added for consistency with updated exclusion criterion
82.	Section 6.4.12 Pregnancy test	Updated language regarding at-home pregnancy tests "For pregnancy tests scheduled to occur when there is no corresponding on-site visit, the subject should use a commercial pregnancy test kit on their own and contact the site to report the test result."	Clarification: previous text only referred to at-home pregnancy testing for cycle 1, while this is also expected to occur for cycle 2.
83.	Section 6.5 Drug Administration	Deleted because it's redundant with section 5	Administrative
84.	Section 6.5 Pharmacokinetic assessments	Added PK timepoint in Table 3	Clarification
85.	Section 6.6. Efficacy Assessment: Radiological Assessment of Tumor Response	1. Updated to conduct efficacy assessment at every other cycle 2. added that CT is encouraged at baseline for everyone 3. updated title to include "radiological assessment" 4. Added that the original schedule needs to be maintained even if there is a delay is dosing	1. To provide guidance on continuation of efficacy assessment given continued dosing 2. To obtain accurate measurements of tumor lesions for all subjects at baseline 3. Administrative 4. Clarification
86.	Section 6.8.1 Peripheral blood	Update from change "C3-C6" to "cycle 3 and beyond"	To provide guidance on continuation of peripheral blood collection for pharmacodynamics given continued dosing
87.	Section 6.9 Tumor Tissue	Add, "Subjects may also have a biopsy to confirm CR, in the absence of PET/CT scans."	Clarification – part of Lugano criteria, added explicitly to protocol to clarify
88.	Section 6.10 Exploratory assessments	[redacted]	[redacted]
89.	Section 7.5 Subject disposition and termination status	Removed language around tabulation of subjects and dropouts	Clarification
90.	Section 7.9 Efficacy analysis	Updated to add PFS and DCR definitions; and that CT/MRI to be done even for subjects with FDG-avid lymphoma	Clarification
91.	Section 7.14 Protocol deviations	Updated language to remove language that was not applicable per Molecular Templates SOPs	Administrative
92.	Section 8.1.3 Informed consent	Updated timing of screening from 28 days predose to 35 days predose, with the exception of safety labs and radiographic assessments which are to be done within 28 days of dosing	Administrative/consistency
93.	Section 8.5 Study monitoring, auditing and inspection	Changed "personal" to "on-site"	Administrative

94.	Section 8.6 Source Data	(1) removed “direct access”; (2) removed requirement of redaction of materials reviewed on-site; (3) removed reference to screen procedure CRF (4) removed mention of specific documents being provided	(1) to allow for remove monitoring; (2) to reflect current monitoring practices; (3) removed as not part of this study (administrative); (4) administrative
95.	References	Updated IB reference to current version (v5 2019) and new references added	Update with most recent version
96.	Appendix 1 SOA for screening	(1) Added virology for HBV/HIV; (2) removed reference to visits in Table 7 header; (3) Table 8 added for PK timepoints	(1) Added for consistency with updated exclusion criterion; (2) administrative (3) clarification
97.	Appendix 2	Virology added, PK (serum and CSF for MT-3724 measurement) added	Clarification
98.	Appendix 4	Updated table to match Cheson 2014 publication	Administrative
99.	Appendix 5	(1) Updated grade of CLS from Grade 2 to Grade 3 for DLT; deleted information that is repeated in section 3.6.2; (2) corrected definition for febrile neutropenia (per CTCAE v5)	(1) CLS G2 does not constitute a major medical management challenge, and has thus far not stopped subjects from continuing treatment with study drug; (2) administrative