MOLECULAR TEMPLATES

CLINICAL STUDY PROTOCOL

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

Protocol Number:	MT-3724_NHL_002
EudraCT no.	Not applicable
IND Number:	121918
Development Phase:	2a
Study Sponsor:	Molecular Templates, Inc. 9301 Amberglen Blvd., Suite 100 Austin, TX 78729 United States
Current Protocol Version:	Amendment 1, Version 2.0
Version Date:	14-JAN-2019
Previous Version:	Version 1.0 18-JUL-2018

-CONFIDENTIAL-

AMENDMENT 1, VERSION 2.0 (JAN 2019)

Amendment rationale:

A complete list of changes can be found in APPENDIX I. SUMMARY OF CHANGES, 14 JAN 2019, VERSION 2.0 REPLACES VERSION 1.0

[redacted]TES APPROVAL

[redacted], MD, PhD — [redacted] Date

Acting Chief Medical Officer

Molecular Templates, Inc.

[redacted]PhD. — [redacted] Date

SVP Operation

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[redacted], PharmD — [redacted] Date

Director Clinical Operations

Molecular Templates, Inc.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

As the Investigator on the study MT-3724_NHL_002, I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the Sponsor.
- Not to implement any changes to the protocol without written agreement from the Sponsor, and prior review and written approval from the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to study subjects.
- That I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by the Sponsor, including, but not limited to, the current Investigator's Brochure (IB) for MT-3724.
- That I am aware of, and will comply with, good clinical practices (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Sponsor, study drug and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: _____

Name (print): _____

Site Name: _____

LIST OF CONTACTS

Sponsor's Physician Responsible:

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Acting Chief Medical Officer
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SYNOPSIS

Title	A Phase 2a Open-label Study to Investigate Safety and Tolerability (including the MTD), Efficacy, Pharmacokinetics, Pharmacodynamics and Immunogenicity of MT-3724 in Combination with Gemcitabine and Oxaliplatin in Subjects with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma
Sponsor	Molecular Templates, Inc.
Development Phase	2a
Primary Objective	Determine the safety and tolerability [including the maximum tolerated dose (MTD)] of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell Non-Hodgkin Lymphoma (NHL)
Secondary Objectives	• Characterize the pharmacokinetics (PK) of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL • Assess the pharmacodynamics (PD) of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL • Assess the immunogenicity of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL • Assess the tumor response to MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL
Exploratory Objectives	Not applicable
Study Design	This will be an open-label dose escalation study of MT-3724 in combination with gemcitabine and oxaliplatin (GEMOX) in subjects with relapsed or refractory B-Cell NHL. Eligible subjects will be identified and treated through competitive enrollment at multiple study centers in North America and Europe.

	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 2 periods: screening and treatment. Screening Period The screening procedures should be performed up to 28 days before Day 1 C1D1. The screening procedures will be identical in Part 1 and Part 2. Treatment Period Each subject may be treated only in one part of the study. The treatment procedures will be identical in Part 1 and Part 2. Treatment with MT-3724 in combination with GEMOX will continue for two cycles of 28-days each or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal (see 4.3.1). After two cycles, the MT-3724 treatment (either alone or in combination with GEMOX) can be continued for another two 28-day cycles if supported by the investigator's assessment of the benefit-risk ratio, after consultation with sponsor and Medical Monitor. In all cycles, MT-3724 will be administered as intravenous (IV) infusion over 1 hour. In C1 and C2, MT-3724 infusion should be administered on Day 1, 3, 5, 8, 10 and 12. If MT-3724 treatment is continued to C3 and C4, then MT-3724 should be administered weekly (Day 1, 8, 15 and 22) of each 28-day cycle. MT-3724 cannot be administered between D22-D28 in C1-C2 or between D24-D28 in C3-C4. Gemcitabine (Gemzar®) 1000 mg/m2 will be administered as 30-minute IV infusion on Day 2 and Day 16 of each 28-day cycle (i.e., every 14 days). Oxaliplatin (Eloxatin®) 100 mg/m2 will be administered as 2-hour IV infusion after gemcitabine on Day 2 and Day 16 of each 28-day cycle (i.e., every 14 days). Oxaliplatin infusion will start one hour after the start of gemcitabine infusion (unless a delay is warranted at the investigator's discretion).

	Treatment with GEMOX will continue for two cycles of 28-days each or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal (see 4.3.1). After two cycles, the GEMOX treatment may be continued for another two 28-day cycles if supported by the investigator's assessment of the benefit-risk ratio, after consultation with sponsor and Medical Monitor. End of Treatment The End of Treatment (EoT) Visit will be performed at the end of the treatment period in each subject in Part 1 and Part 2. EoT Visit should occur at the time of discontinuation (except for subjects who died, withdrew consent and objected to further data collection, or were lost to follow up) or ≥ 7 days and ≤ 14 days after the last dose of MT-3724, gemcitabine or oxaliplatin for those that complete the study. The EoT Visit should be performed during the clinic visit. 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. The EoT visit will be followed by a safety follow-up (SFU) phone call at least 30 days after last dose of MT-3724 or gemcitabine or oxaliplatin. **Part 1 (MT-3724 Dose Escalation)** Part 1 will include MT-3724 dose escalation according to the modified 3+3 design to identify the maximum tolerated dose (MTD) of MT-3724 in combination with standard doses of gemcitabine and oxaliplatin. If permitted by the safety results, the MT-3724 dose escalation is planned to proceed in three sequential dose cohorts (Cohorts 1-3). In all dose cohorts, MT-3724 will be administered in combination with starting doses of gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2. The starting dose can be decreased per investigators discretion based on the known safety profile of gemcitabine and/or oxaliplatin and the patient status.

Table 1: MT-3724 Dose Cohorts and Corresponding Dose Levels of MT-3724, gemcitabine and oxaliplatin

Planned MT-3724 Dose Cohorts	Interim MT-3724 Dose Cohorts[a]	Starting MT-3724 Dose (µg/kg/dose)	Starting Gemcitabine Dose (mg/m^2)	Starting Oxaliplatin Dose (mg/m^2)
1		10	1000	100
	-1 (optional)	≤ 5[b]	1000	100
2		25	1000	100
	-2 (optional)	≤ 17.5[b]	1000	100
3		50	1000	100
	-3 (optional)	≤ 37.5[b]	1000	100

a. To be evaluated only if warranted by the safety results in the previous planned cohorts

b. 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, all investigators and Medical Monitor 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 dose-limiting toxicity (DLT). See Section 5.4. 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 GEMOX 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 GEMOX and complete C1 or experience a DLT. The maximum dose of MT-3724 that will be given in this study is 50 ug/kg/ dose (with a maximum total dose of 6000 µg), which is the MTD of MT-3724 as monotherapy. The MT-3724 dose escalation will not proceed above the 50 ug/kg/dose even if no more than 1 of 6 subjects in Cohort 3 experience a DLT. The sponsor will make the decision on the MTD after consultation with all investigators and Medical Monitor. Up to 24 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 GEMOX. Subjects in Part 1 will be enrolled through competitive enrollment at multiple study centers in North America and Europe. **Part 2 (MTD Expansion Cohort)** The purpose of Part 2 is to confirm the safety and tolerability of the MTD of MT-3724 from Part 1 in the MTD Expansion Cohort, where MT-3724 will be given at the MTD in combination with GEMOX. In addition, the PK, PD, immunogenicity and tumor response at the MTD of MT-3724 in combination with GEMOX will be more thoroughly evaluated in Part 2. Part 2 can start only after the MTD of MT-3724 in combination with GEMOX 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.

	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 study centers in North America and Europe. **Long-Term Follow Up** Subjects will be followed every 6 months for 24 months for PFS and DOR until progressive disease, death or lost to follow up.
Study Population	Eligible subjects will have histologically confirmed, relapsed or refractory B-cell NHL that, in the investigator's opinion, could benefit from MT-3724+GEMOX therapy. All subtypes of B-cell NHL may be considered for Part 1 (MT-3724 dose escalation). Only Diffuse Large B-Cell Lymphoma (DLBCL) may be considered for Part 2 (MTD Expansion Cohort).
Sample Size	Up to 64 subjects (i.e., up to 24 subjects in Part 1 and up to 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 GEMOX in Part 1.
Eligibility 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 B-cell NHL that, in the investigator's opinion, could benefit from MT-3724+GEMOX therapy. At least one histologically documented relapse of NHL, by: a. Bone marrow biopsy (FNA is not acceptable) or

	b. Excisional lymph node biopsy or c. Core biopsy of any involved organ (FNA not acceptable) d. CD20-positive histology must have been confirmed at any time during NHL disease course and documented in the medical history e. If no histology is available after any relapse the investigator can consult the medical monitor to discuss if the patient can be included 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 (expansion cohort). 5. Have received all approved therapies for NHL that are applicable for the patient in the opinion of the treating physician. a. Patients refractory to treatment are eligible. b. Patient who have progressed following CAR T-cell therapy are also eligible. 6. Have measurable disease by Lugano Classification for NHL (APPENDIX D) a. >1.5 cm longest diameter (LDi) for lymph nodes b. >1 cm LDi for extranodal disease 7. Have ECOG performance score of ≤2 (APPENDIX G). 8. Have adequate bone marrow function, as determined by: a. Absolute neutrophil count (ANC) ≥1,000/mm3 and b. Platelet count ≥50,000 mm^3 9. Have adequate kidney function, assessed by the estimated glomerular filtration rate (eGFR) ≥60 mL/min calculated by the CPK-EPI equation (APPENDIX F).

	a. At the investigator's discretion, the eGFR result <60 mL/min may be verified by measurement of creatinine clearance (CLcr) based on the 24-hour urine collection. Subjects with CLcr ≥60 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 ≤3 x ULN for subjects with Gilbert's Syndrome and b. Aspartate aminotransferase (AST) ≤3 x ULN (or ≤ 5.0 xULN if liver involvement) and c. Alanine aminotransferase (ALT) ≤3 x ULN (or ≤ 5.0 xULN if liver involvement). 11. Have adequate coagulation, as determined by: a. INR or PT ≤1.5 x ULN b. aPTT ≤1.5 x ULN 12. Have adequate serum albumin, as determined by: a. Albumin ≥ 3.0 g/dL 13. Women of reproductive potential must have a negative pregnancy test during the screening period within 72 hours before the start of treatment. Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy). 14. Subjects of reproductive potential and their partners must agree to either to abstain continuously from heterosexual intercourse or to use a reliable birth control method between signing the informed consent until 6 months following the last dose of MT-3724 or GEMOX . The investigator or a designated associate should advise the subject how to achieve adequate contraception. The following birth control methods may be considered as adequate:

	a. Condoms (male or female) with or without a spermicidal agent; b. Diaphragm or cervical cap with spermicide; c. Intrauterine device; d. Hormone-based contraception: Established use of oral, injected, or implanted hormonal methods of contraception; e. True abstinence; f. Vasectomy is an acceptable method for a male subject or male partner of a female subject. **Exclusion Criteria** Subjects who meet ANY of the following criteria will not be eligible for the study. <u>Medical and surgical history</u> 15. 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, or any other previous cancer curatively treated >2 years before the start of treatment. 16. 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 b. Have no neurological symptoms (except Grade ≤2 neuropathy)? c. Have stable brain or spinal disease on the CT or MRI scan within 1 month of enrollment and d. Do not require chronic steroid therapy

	17. History of allogeneic hematopoietic stem cell transplant within 180 days before the start of treatment. 18. Current evidence of acute or chronic Graft versus Host Disease. 19. Current evidence of CTCAE Grade >1 toxicity (except for hair loss, and those toxicities listed as permitted in other eligibility criteria) before the start of treatment. 20. Current evidence of incomplete recovery from surgery before the start of treatment, or planned surgery at any time during the study until the EoT Visit, except minor elective interventions deemed acceptable by the investigator. 21. History or current evidence of significant (CTCAE Grade ≥2) infection or wound within 4 weeks before the start of treatment. 22. History or 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 H) at screening or LVEF <45%, assessed by Echo or MUGA scan within 1 month before starting study treatment. (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). 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 if the dose has been stable for ≥2 weeks before the start of treatment. Subjects with sinus arrhythmia and infrequent premature ventricular contractions are eligible at the investigator's discretion. 23. QTcF (Fridericia) >480 ms, determined as the average from three QTcF values on the triplicate ECG obtained at screening 24. Current evidence of seropositive status for HIV, hepatitis B (positive for HBsAg or anti-HBsAg and anti-HBcAg antibodies) or hepatitis C (positive for anti-HCV antibody or HCV-RCV-RNA quantitation) at screening. a. Serology testing may be omitted at the investigator's discretion if seronegativity is documented in the medical history and there are no clinical signs suggestive of HIV or hepatitis infection. b. Subjects with positive HBV serology are eligible if quantitative PCR for plasma HBV-DNA is negative and the subject will be receiving prophylaxis for potential HBV reactivation. c. Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is negative. 25. Women who are pregnant or breastfeeding. 26. History of hypersensitivity to any of the study drugs, or current evidence of hypersensitivity requiring systemic steroids at doses >20 mg/day prednisone equivalent.

	27. 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 28. Received any amount of anti-CD20 MAb therapy within the following periods before the start of treatment a. Rituximab (Rituxan®): 84 days; if a subject received rituximab within 37 weeks before the start of treatment, then a serum rituximab level must be negative (<500 ng/mL) at screening. b. Obinutuzumab (Gazyva®): 184 days c. Ofatumumab (Arzerra®): 88 days 29. Received therapy for NHL (excluding the anti-CD20 MAbs listed above) within 4 weeks of the agent before the start of treatment. 30. 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. 31. Received radiotherapy to tumor lesion(s) that would be chosen as target lesions (measurable disease) within 4 weeks before the start of treatment, unless the lesion(s) exhibited objective progression between the radiotherapy and the screening according to the Lugano classification for NHL. a. Palliative radiotherapy to non-target lesions is allowed at the investigator's discretion. 32. Received any vaccines within 28 days of the start of treatment, or likely to require vaccines at any time from the start of treatment until 28 days after the last dose of MT-3724.

	Injectable flu vaccine (inactivated or recombinant) is permitted at the investigator's discretion. 33. Received systemic immune modulators within 2 weeks before the start of treatment. a. Systemic immune modulators include, but are not limited to, systemic corticosteroids at doses >20 mg/day of prednisone equivalent (except for premedication), cyclosporine and tacrolimus. b. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is permitted.
Treatments	<u>MT-3724 Investigational Medical Product (IMP)</u> MT-3724 will be administered as intravenous (IV) infusion over 1 hour. In C1 and C2, MT-3724 infusion should be administered on Day 1, 3, 5, 8, 10 and 12 of each 28-day cycle. If the treatment with MT-3724 is continued to Cycle 3 (C3) and Cycle 4 (C4), then MT-3724 will be administered weekly (Day 1, 8, 15 and 22) of each 28-day cycle. Different dosing days within ±2 days from scheduled weekly doses may be selected at investigator's discretion. In C1-C2, no more than two MT-3724 doses can be administered on consecutive days. If MT-3724 is administered on consecutive days, then at least 20 hours (more than five half-lives of MT-3724 in plasma) must elapse between the start of the two infusions. MT-3724 cannot be administered between D22-D28 in C1-C2 or between D24-D28 in C≥3. <u>In Part 1 (MT-3724 dose escalation)</u>, the starting MT-3724 doses in each of the planned cohorts will be: • 10 μg/kg/dose in Cohort 1 • 25 μg/kg/dose in Cohort 2 • 50 μg/kg/dose in Cohort 3

	If MT-3724 is not tolerated in any of the planned cohort, then additional MT-3724 dose may be evaluated in the interim cohorts at the sponsor's discretion in consultation with the investigator and Medical Monitor (Table 1). In Part 2 (Expansion Cohort), the starting MT-3724 dose will be the MTD (or a maximum dose of 50µg/kg) of MT-3724 from Part 1 in combination with GEMOX. The administered dose of MT-3724 for subjects will be capped at 6000 µg per infusion. Intra-subject escalation of MT-3724 dose is not permitted in this study. The guidance for treatment modification (dose interruption / delay, dose reduction or treatment discontinuation) is presented in Section 5.4. Premedication Premedication should be given within 60 minutes before the start of each MT-3724 infusion in every cycle in Part 1 and Part 2. The agents from the following 3 drug classes are recommended for premedication: • Oral anti-inflammatory agent (e.g. acetaminophen not to exceed 1000 mg PO) • H1 histamine receptor antagonist (e.g. diphenhydramine not to exceed 100 mg IV) • Corticosteroid agent (e.g. methylprednisolone not to exceed 1000 mg IV) **Note:** The specific premedication agents in each class and their doses should be selected at investigator's discretion or according to the institutional guideline. **The investigator may adjust the dosage and/or avoid using certain premedication agents during the treatment, if warranted by the investigator's assessment of the risk from infusion-related reaction or other hypersensitivity events.** See Section 5 for details about the IMP properties and dosing schedule.

	Gemcitabine and Oxaliplatin (GEMOX) In all cohorts in Part 1 and Part 2, the starting doses of gemcitabine and oxaliplatin will be as follows: Gemcitabine 1000 mg/m^2 will be administered as 30-minute IV infusion on Day 2 and Day 16 of each 28-day cycle. Oxaliplatin 100 mg/m^2 will be administered as 2-hour IV infusion after gemcitabine on Day 2 and Day 16 of each 28-day cycle. Oxaliplatin infusion will start one hour after the start of gemcitabine infusion (unless a delay is warranted at the investigator's discretion). Modification of starting dose of gemcitabine or oxaliplatin treatments or modification during treatment will be guided by the respective reference prescribing information, as interpreted by the investigator after consultation with sponsor and Medical Monitor. If gemcitabine or oxaliplatin dose has been reduced due to a TEAE, the intra-subject escalation of the respective drug's dose is permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor. In such cases, the gemcitabine or oxaliplatin dose may be increased only up to the level before the most recent dose reduction.
Treatment Duration	Treatment with MT-3724 in combination with GEMOX will continue for 2 cycles of 28-days each or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal, or study discontinuation. If supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor, the treatment with MT-3724 in combination with GEMOX may continue for 2 additional cycles of 28-days each (up to the total of 4 cycles), or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal, or study discontinuation. If the subject exhibits SD, CR or PR after the end of Cycle 4 and the investigator determines that the benefit-risk ratio is favorable, then

	the treatment with MT-3724 may be continued after discussion with the sponsor. Continuation of GEMOX is at investigators discretion.
Withdrawal Criteria	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 if the β-HCG pregnancy test indicates that they are pregnant. The subject **may** be withdrawn from the study 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 The sponsor also has the right to discontinue the study for any reason, in which case the treatment in all subjects must be permanently discontinued. Discontinuation of the study drug(s) for documented disease progression will be considered as the study completion and not as premature withdrawal from the study.
Subject Characteristics and Safety Assessments	The subject's characteristics will include: • Demography • Height, body weight, BMI, BSA • NHL assessment (at initial diagnosis, relapse and/or current / baseline), including the NHL type, tumor histology, grading, staging (Ann Arbor-Cotswold Modification) and IPI for NHL or FLIPI (APPENDIX C). • Serum beta-2 microglobulin

	• Medical history • Prior systemic NHL therapy • Prior radiotherapy for NHL • Prior and concomitant medications (except for NHL) • Serology for rituximab level (if applicable) • Serology for HIV, HBV and HCV (if applicable) The safety assessments will include: • Adverse events: • Physical examination (PE) • Blood pressure and heart rate (HR) • Body temperature • LVEF (MUGA or Echocardiogram) • New York Heart Association (NYHA) • ECOG • 12-lead ECG • Hematology • Blood chemistry and eGFR (CPK-EPI) • HbA1c • Coagulation (PT or INR, aPTT) • Thyroid function (TSH, FT4) • Urinalysis (Dipstix); urine microsediment may be ordered at the investigator's discretion. • Cytokines • Complement, histamine • Immunoglobulins • Pregnancy test (urine or serum), if applicable

	Unscheduled assessments may be performed at any time at the investigator's discretion. Please see the Section 6. and APPENDIX A for further details.
Efficacy Assessments	Efficacy (tumor response) will be evaluated according to the revised Lugano Classification for Lymphoma (22) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (21). Positron emission tomography-computed tomography (PET-CT) should be used for response assessment in subjects with fluorodeoxyglucose (FDG)-avid tumor histology (using the 5-point scale [5PS]). Computer tomography (CT) or magnetic resonance imaging (MRI) should be used in subjects with tumor histology of low or variable FDG avidity. FDG-PET-CT or CT scan of all anatomic regions involved with the measurable disease will be performed at screening (baseline), within 7 days before the start of MT-3724 infusion on C3D1 (end of C2) and at the EoT VISIT (only if the previous tumor scan has been performed >4 weeks before the EoT VISIT). Unscheduled tumor response assessment by FDG-PET-CT (or CT / MRI, where applicable) may be ordered at the investigator's discretion. Please see Section 6 and APPENDIX A for further details.
PK Assessments	Blood samples will be collected 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, selected 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 will be collected at prespecified time points on C1-4 in Part 1 and Part 2. The PK of gemcitabine and oxaliplatin will not be assessed in this study. Please see Section 6.6 and APPENDIX A for further details.

Immunogenicity Assessments	Serial blood samples for the assessment of immunogenicity of MT-3724 [anti-drug antibody (ADA) titer and neutralizing antibody (NA)] will be collected at the prespecified time points in Part 1 and Part 2 (See Section6.8. and APPENDIX A). Unscheduled assessments may be performed at any time at the investigator's discretion.
PD Assessments	PD marker in this study will be the B-cell count and immunophenotype in peripheral blood, as determined by flow cytometry. Blood samples for the assessment of PD markers will be collected at the prespecified time points in Part 1 and Part 2 (See Section 6.9 and APPENDIX A). In Part 2 of the study an optional FNA biopsy will be obtained at EoT in patients who consented for this procedure and exhibit PD and have accessible peripheral lymph node(s). The purpose of biopsy is to assess the CD20 status of DLBCL by IHC staining of the fine needle aspirate and determine if the B-cell lymphoma cells have lost CD20 positive status. Unscheduled assessments may be performed at any time at the investigator's discretion.
Statistical Methods	All subjects who received at least one dose of MT-3724, gemcitabine or oxaliplatin will be included in the safety analysis set, which will be used for the statistical analyses of safety and efficacy data. All subjects who received at least one dose of MT-3724 and have at least one post-treatment PK and immunogenicity assessment will be included in the analysis set for the PK and immunogenicity analyses, respectively. Subjects who received only gemcitabine or oxaliplatin (haven't received MT-3724) will be excluded from the PK and immunogenicity analyses. **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 v.5.0. The AEs and SAEs are

	treatment-emergent if they have started or worsened after the first dose of MT-3724. Only TEAEs and SAEs will be summarized, while the AEs and SAEs (if any) reported before the start of treatment will be listed. 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 (20) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (21) (see APPENDIX D). 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 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 complete or partial response 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. A detailed description of analysis methods will be provided in the statistical analysis plan (SAP) to be completed before the EoT Visit in the last subject.

	PK Analyses MT 3724 serum concentration time data from all eligible subjects will be subjected to non-compartmental analysis (NCA) using the software package Phoenix WinNonlin (Certara, Princeton NJ). PK 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 anti-drug antibody (ADA) against MT-3724 will be obtained as titer for ADA samples confirmed as a positive result, while the data for the neutralizing antibodies (NA) 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 NA 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. **PD 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.

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[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
5PS	five-point scale
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALT (SGPT)	alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
ASCT	autologous stem cell transplantation
AST (SGOT)	aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BMI	body mass index
BORR	best overall response rate
BSA	body surface area
CD20	protein on B-cell surface; target for MT-3724 binding
CFR	Code of Federal Regulations
CL	clearance
CLcr	creatinine clearance
CLS	capillary leak syndrome
CRF	case report form
CR	complete remission/response
CRS	cytokine release syndrome
CRO	contract research organization
CS	clinically significant
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma

DLT	dose-limiting toxicity
DOR	duration of tumor response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	End-of-Treatment
EU	European Union
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FNA	fine needle aspiration
FT4	free thyroxin
GCP	Good Clinical Practice
GEM	Gemcitabine
H	hour
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry

IMP	investigational medicinal product
INR	international normalized ratio
IPI	international prognostic index
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	intravenous
kDa	kiloDalton
LDi	longest diameter
LVEF	left ventricular ejection fraction
LYRIC	lymphoma response to immunomodulatory therapy criteria
MAb	mononuclear antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	neutralizing antibody
NCI	National Cancer Institute
NCS	not clinically significant
NHL	Non-Hodgkin lymphoma
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	objective tumor response rate
OX	oxaliplatin
PD	‘progressive disease’ or ‘pharmacodynamic(s)’
PDNF	Protocol Deviation Notification Form
PE	physical exam
PET	positron emission tomography

pH	potential of hydrogen
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QRS	interval between Q and S wave on ECG
QT	interval between Q and T wave on ECG
QTcF	interval between Q and T wave on ECG corrected for the heart rate by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
scFv	single chain variable fragment
SD	stable disease
SFU	Safety follow-up
SOC	'system organ class' or 'standard of care'
SOP	standard operating procedure
SUSAR	suspected unexpected (related) serious adverse reaction
TEAE	treatment-emergent adverse event
TMF	Trial Master File
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

1.1. Non-Hodgkin Lymphoma (NHL)

CD20 is a B-cell specific differentiation antigen with four transmembrane domains (1). The CD20 protein plays a critical role in normal B-cell development and is expressed on 90% of B-cell Non-Hodgkin Lymphomas (NHL) (2).

According to National Cancer Institute (NCI), the number of new NHL cases in the United States between 2010 and 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 (3). The NCI estimates that in 2017 there will 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 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 (3) and varies by ethnicity, with Caucasians having higher rates than African Americans, Asians, or Native Americans.

DLBCL 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 percent) proliferation fraction. The immunophenotype of DLBCL can be confirmed by 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 subject depends on many host or tumor characteristics including tumor histology, tumor bulk burden and stage of tumor, subject's age and performance status. According to Friedberg et al. (4), one third of subjects (33%) with newly diagnosed DLBCL will be refractory to first line therapy (e.g. R-CHOP). Although 16% of all newly diagnosed will be eligible for high-dose chemotherapy followed by autologous stem-cell transplantation (HD-ASCT), only 3.3% will be cured by ASCT. Thus, approximately 30% of all newly diagnosed DLBCL subjects will have either the refractory or relapsed DLBCL and represent a population with unmet need for new therapeutic strategies to achieve or regain disease remission.

1.1.1. Anti-CD20 MAb Therapy for NHL

Anti-CD20 monoclonal antibody (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 (rituximab 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 rituximab, 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 (5).

Of those subjects with indolent NHL who relapse >6 months after initial response to rituximab, only 40% will respond again when retreated with rituximab (6). The multicenter Phase 2 CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study showed that subjects who had previously responded to a rituximab containing treatment regimen had a worse outcome following rituximab containing salvage immunochemotherapy. (7). 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 (8). It has also been shown that anti-CD20 MAbs induce internalization of CD20 by malignant cells, where the degree of internalization is higher with type I anti-CD20 MAbs (9). The internalization requires the binding of the Fc tail of the MAb to the Fcγ receptor IIb (FcγRIIb) on the malignant B cell. Differential FcγRIIb expression has been correlated with resistance to anti-CD20 therapy in different types of B-cell malignancies (10). 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 (11). 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 subjects (12).

1.2. MT-3724

MT-3724 is a recombinant homodimeric fusion protein, where each monomer consists of a single chain variable fragment (scFv) with affinity for human CD20 cell surface protein, and this fragment is fused to the enzymatically active A1 subunit of Shiga-like Toxin 1 (SLT-I A1). The theoretical molecular weight of the MT-3724 homodimer is ~ 110.4 kDa. MT-3724 has been shown to specifically bind and kill CD20-expressing malignant B-cells (13).

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 unmet medical need.

1.2.1. Clinical Experience with MT-3724

The clinical experience with MT-3724 as monotherapy is derived from the ongoing study MT-3724-NHL-001. This is a first-in-human open-label, dose escalation Phase 1 study in subjects with NHL who had relapsed after having previously responded to anti-CD20 monoclonal antibodies. MT-3724 is administered as 6 intravenous infusions over 2 hours in the first 12 days of each cycle for up to 5 cycles; Cycle 1 is 28 days and Cycles 2-5 are 21 days. As of 15JUN2018, 24 subjects with relapsed NHL have received at least one dose of MT-3724 in the study MT-3724-NHL-001; of these, 54% were female, with the mean age of 66 years (range 34-78) and ≥4 prior NHL therapies in 67% subjects. The median number of prior therapies in the study to date is 4.5 and the median age is 69.

Part 1 of this study (dose escalation according to the 3+3 design) has been completed, with the total of 21 subjects treated in the following 6 sequential dose cohorts: 5 µg/kg/dose, 10 µg/kg/dose, 20 µg/kg/dose, 50 µg/kg/dose, 100 µg/kg/dose and 75 µg/kg/dose. MT-3724 was generally well tolerated at dose levels ≤75 µg/kg/dose in Part 1. All of the 21 subjects had at least one non-serious adverse event (59 Grade≥3 events, of whom 13 were related to MT-3724), and 15 (63%) subjects had 33 serious adverse events (23 Grade ≥3 of which 4 were related). The most common adverse events in Part 1 were peripheral edema (67%), fatigue (43%), diarrhea (38%), myalgia (38%) and cough (33%). The first 2 subjects treated at 100 µg/kg/dose had one DLT each (Grade 2 pneumonia and Grade 2 ileus); in addition, one of these subjects had Grade 3 muscle weakness related to MT-3724 and multiple adverse events indicative of systemic inflammatory response in the first cycle of treatment. The Data Monitoring Committee determined that 100 µg/kg/dose is a non-tolerable dose level. None of the 19 subjects treated at dose levels ≤75 µg/kg/dose had a DLT, including the 6 subjects treated at 75 µg/kg/dose. Therefore, 75 µg/kg/dose was declared to be the MTD for MT-3724 as monotherapy in subjects with relapsed NHL in Part 1. Neutropenia, leukopenia, myalgia, pneumonia, infection, muscle weakness, acute kidney failure and vascular leak were reported as adverse events related to MT-3724 and identified in the Investigator's Brochure (16) as potential risks for subjects receiving MT-3724 therapy.

In Part 2 of this study (MTD expansion), a total of 3 subjects have received MT-3724 at 75 µg/kg/dose so far. Two had a Grade 2 capillary leak syndrome (CLS) in Cycle 1, with a typical cluster of adverse events comprising hypotension, hypoalbuminemia, weight gain due to fluid retention, headache, myalgia and arthralgia of varying levels of severity (Grade 1 to 3). All adverse events were fully reversible. The CLS occurred in obese subjects (96 and 154

kg) who received a high total MT-3724 dose of 7208 and 11572 µg/infusion, respectively); however, both events required extended dose delay and dose reduction. In light of the frequent and dose-limiting CLS, the MTD of MT-3724 was reduced to 50 µg/kg/dose and capped at the total dose of 6000 µg per infusion; the safety and efficacy of the revised MTD is being evaluated in the Part 2 of the study as of 15JUN2018.

In the first-in-human study, MT-3724 has exhibited clinical benefit at doses between 5-100µg/kg/dose in patients who had negative serum rituximab levels at baseline (<500 ng/mL). In this group, 3 of 16 patients had PR (ORR of 19%) and 5 subjects had SD (DCR 50%); 2 subjects with SD had large tumor reduction (47% and 49%) near the threshold for PR by the Cheson criteria (24). All 3 subjects with PR had DLBCL. Tumor response data were available in 10 DLBCL patients with negative serum rituximab level at baseline, so the ORR in this clinically relevant subset was 33% and the DCR was 70%. Because MT-3724 binds the same epitope as rituximab, no subjects who had positive serum level of rituximab at baseline (≥500 ng.mL) had clinical benefit in this study (16) .

In summary, MT-3724 showed clinical anti-tumor activity in heavily pre-treated subjects with relapsed B-cell NHL. The assessment of the safety and efficacy of MT-3724 at the reduced MTD of 50 µg/kg/dose is ongoing in DLBCL subjects with undetectable screening RTX level in Part 2 of the study MT-3724-NHL-001.

Please refer to the Investigator's Brochure (16) for comprehensive information available for MT-3724 to date.

1.3. Gemcitabine

Gemcitabine (Gemzar®) is a nucleoside analog anticancer agent which blocks new DNA synthesis leading to cell death. Gemcitabine is approved for the treatment of i) advanced ovarian cancer that has relapsed at least 6 months after completion of platinum- based therapy when given in combination with carboplatin, ii) first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, when given in combination with paclitaxel, iii) non-small cell lung cancer when given in combination with cisplatin and iv) pancreatic cancer as a single agent.

The most common adverse reactions (incidence ≥20%) for gemcitabine as the single agent are nausea/vomiting, anemia, neutropenia, thrombocytopenia, increase in transaminases and alkaline phosphatase, proteinuria, fever, hematuria, rash, dyspnea, and peripheral edema.

In clinical studies of gemcitabine including 979 subjects with various cancers who received gemcitabine as a single agent, no differences in the safety profile were observed between older (≥65 years) and younger subjects, except for a higher rate of Grade 3 or Grade 4 thrombocytopenia in older subjects (15). In a randomized trial in women with ovarian cancer, 175 women received gemcitabine plus carboplatin, of which 29% were ≥65 years of age. This

data set is relevant for the current study because like carboplatin, oxaliplatin is a platinum-based therapeutic agent (15). Similar anti-tumor efficacy was observed between older and younger women. There was significantly higher incidence of Grade 3 or Grade 4 neutropenia in women ≥65 years of age. The renal clearance of gemcitabine is affected by age, however there are no recommended dose adjustments based on subject's age. Please see the reference prescribing information on gemcitabine for additional details (14).

1.4. Oxaliplatin

Oxaliplatin (Eloxatin®) is a platinum-based anticancer agent that causes DNA crosslinking causing inhibition of DNA synthesis and/or repair as well as inhibition of DNA replication and transcription, leading to cell death. Oxaliplatin is approved for i) the adjuvant treatment of stage III colon cancer in combination with 5-fluorouracil /leucovorin, and ii) the treatment of advanced colorectal cancer.

The most common adverse reactions (incidence ≥40%) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. Anaphylactic reactions to oxaliplatin have been reported and may occur within minutes of administration (16). Please see the reference prescribing information on oxaliplatin for additional details (16).

1.5. R-GEMOX

R-GEMOX (rituximab 375 mg/m^2 in combination with gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2) represents one of several standard treatments for patients with relapsed or refractory DLBCL (17, 18). R-GEMOX is used to achieve maximum tumor burden cytoreduction in preparation for HD-ASCT, or as salvage (palliative) therapy in NHL subjects ineligible for HD-ASCT.

El Gnaoui et al. (17) reported on 46 subjects with R/R NHL (72% DLBCL) who received R-GEMOX (rituximab 375 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 together with oxaliplatin 100 mg/m^2 on Day 2 of a 2-week cycle) after first (26%) or second/multiple relapse (61%) or in the primary refractory setting (13%) for up to 8 cycles. After the first 4 cycles (induction), the overall response rate (ORR) was 83% with 50% of all NHL subjects and 58% of DLBCL subjects having a confirmed or unconfirmed complete response (CR/CRu). These responders continued on R-GEMOX for the second 4 cycles (consolidation), resulting in the ORR of 74%, with 72% of all NHL subjects and 73% of DLBCL subjects having a CR/CRu. R-GEMOX achieved better ORR and CR/Cru rates in rituximab-naive subjects than in those who relapsed after prior rituximab (ORR 95% vs. 73% and CR/CRu 85% vs. 65%, respectively). The subjects who were refractory to their last treatment or had a previous response for <1 year had lower ORR than those subjects who had a previous response for >1 year (53% vs. 97%, respectively). At last follow-up (median

duration of 28 months) of 38 subjects who responded, 11 had relapsed, translating to a 2-year progression free survival (PFS) of 62%. Notably, the 2-year PFS was only 37% in responders to R-GEMOX previously treated with rituximab, as compared to 81% in responders who were not previously treated with rituximab. These results are consistent with previous observations that NHL can become refractory to rituximab. R-GEMOX was generally well tolerated in this study, with Grade 3 and 4 neutropenia in 27% and 17% of cycles, respectively, Grade 3 and 4 thrombocytopenia in 19% and 4% of cycles, respectively and febrile neutropenia in 4% of cycles. There were no fatal toxicities and no Grade 3 and 4 non-hematological toxicities.

Mounier et al. (18) reported on 49 subjects with R/R DLBCL who received R-GEMOX (rituximab 375 mg/m^2 on Day 1 and gemcitabine 1000 mg/m^2 together with oxaliplatin 100 mg/m^2 on Day 2 of a 2-week cycle) for up to 8 cycles. The ORR after the first 4 cycles was 61%, with 21 (44%) subjects achieving CR/CRu and 8 (17%) a partial response (PR). These responders continued on R-GEMOX for the second 4 cycles, whereupon 18 of the 21 (86%) subjects remained in CR/CRu and 4 of 8 (50%) subjects remained in PR. The ORR at the end of consolidation treatment was 46% and the overall CR/CRu rate was 38%, with the median duration of response of 10 months. As in the Gnaoui study (17), the ORR was negatively impacted by refractory disease/relapse <1 year (18% vs. 69%) and also by prior rituximab treatment (32% vs. 71%). R-GEMOX was generally well tolerated in this study, 73% with Grade 3 and 4 neutropenia in 31% and 42% of cycles, respectively, Grade 3 and 4 thrombocytopenia in 23% and 21% of cycles, respectively and febrile neutropenia in 4% of cycles. There were no fatal toxicities; the most common non-hematological toxicities were Grade 3 or 4 infectious episodes in 22% of the cycles, while the Grade 3 neurotoxicity and Grade 3 renal toxicity were infrequent (8% and 2%, respectively).

The efficacy of R-GEMOX in NHL/DLBCL was negatively impacted by the refractory disease status or the near-term relapse (within <1 year) after the prior anti-CD20 NHL therapy, which commonly included rituximab (17, 18). The limited responsiveness to R-GEMOX in refractory or relapsed NHL/DLBCL could be driven by the acquired resistance of malignant B-cells to rituximab (see Section 1.1.1).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to determine the safety and tolerability [including the maximum tolerated dose (MTD)] of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell Non-Hodgkin Lymphoma (NHL).

2.2. Secondary Objectives

The secondary objectives of this study are to:

1. Characterize the pharmacokinetics (PK) of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL
2. Assess the pharmacodynamics (PD) of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL
3. Assess the immunogenicity of MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL
4. Assess the tumor response to MT-3724 in combination with gemcitabine and oxaliplatin in subjects with relapsed or refractory B-Cell NHL

3. INVESTIGATIONAL PLAN

3.1. Description of Overall Study Design and Plan

This will be a multi-center, open-label, dose escalation phase 2a study of MT-3724 in combination with gemcitabine and oxaliplatin (GEMOX) in subjects with relapsed or refractory B-Cell NHL. Eligible subjects will be identified and treated through competitive enrollment at multiple study centers in North America and Europe.

There are two sequential parts to this study. Part 1 is an evaluation of doses of MT-3724 in combination with GEMOX 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 GEMOX. For Long-Term Follow Up, subjects from both parts of the study will be followed for 24 months for PFS and DOR until progressive disease, death or lost to follow up.

In both parts of the study, the subject's participation in the study will comprise of 3 periods: screening, treatment and safety follow-up:

3.2. Screening Period

Screening procedures will be performed within 28 days before the start of treatment on C1D1. A signed written 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 (see Section 4.1 and Section 4.2.) the Medical Monitor on behalf of the sponsor should review the screening results and acknowledge that the subject may enter the treatment phase of the study.

3.3. Treatment Period

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 intravenous (IV) infusion over 1 hour.

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

In C1 and C2, MT-3724 infusion should be administered on Day 1, 3, 5, 8, 10 and 12. Different dosing days up to D21 may be selected at investigator's discretion. MT-3724

cannot be administered between D22-D28 in C1-C2 (or in the 7 days following the last dose of the cycle in cases where the treatment was delayed)

No more than two MT-3724 doses can be administered on consecutive days in C1-C2. If MT-3724 is administered on 2 consecutive days, then at least 20 hours (approximately five half-lives of MT-3724 in plasma) must elapse between the start of the 2 infusions.

After two cycles, the treatment with MT-3724 may be continued for another two cycles of 28 days each if supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor.

In C3-C4, MT-3724 will be administered weekly, i.e. on Day 1, 8, 15 and 22 of each 28-day cycle. Different dosing days within ±2 days from scheduled weekly doses may be selected at investigator's discretion.

MT-3724 cannot be administered between D24-D28 in C3-C4.

If the subject exhibits SD, CR or PR after the end of Cycle 4 and the investigator determines that the benefit-risk ratio is favorable, then the treatment with MT-3724 may be continued after discussion with the sponsor. Continuation of GEMOX is at investigators discretion.

3.3.2. GEMOX

Gemcitabine (Gemzar®) 1000 mg/m2 will be administered as 30-minute IV infusion on Day 2 and Day 16 of each 28-day cycle (i.e., every 14 days). Different dosing days within ±2 days from scheduled weekly doses may be selected at investigator's discretion.

Oxaliplatin (Eloxatin®) 100 mg/m^2 will be administered as 2-hour IV infusion after gemcitabine on Day 2 and Day 16 of each 28-day cycle (i.e., every 14 days). Different dosing days within ±2 days from scheduled weekly doses may be selected at investigator's discretion. Oxaliplatin infusion will start one hour after the start of gemcitabine infusion (unless a delay is warranted at the investigator's discretion) to facilitate easier compliance with the post-dose sampling schedule.

Treatment with GEMOX will continue for two cycles of 28-days each or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal, or until study discontinuation. After two cycles, the GEMOX treatment could be continued for another two cycles of 28 days each if supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor.

3.4. End of Treatment Visit and Safety Follow-up phone call

The End of Treatment (EoT) Visit will be performed at the end of the treatment period in each subject in Part 1 and Part 2. EoT VISIT should occur, at the time of discontinuation (except for subjects who died, withdrew consent and objected to further data collection, or

were lost to follow up) or ≥ 7 days and ≤ 14 days after the last dose of MT-3724, gemcitabine or oxaliplatin for those that complete the study.

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

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

3.5. Long-term Follow up Visit

Long-term Follow-up (LTFU) Visits should occur every 6 months (±14 days) for up to 24 months after the last dose of MT-3724, gemcitabine or oxaliplatin. Subjects will be followed for 24 months for PFS and DOR until progressive disease, death or lost to follow up or until progressive disease, death or loss to follow up. 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.

3.6. Part 1 (MT-3724 dose escalation)

Part 1 will include MT-3724 dose escalation according to the modified 3+3 design to identify the maximum tolerated dose (MTD) of MT-3724 in combination with standard doses of gemcitabine and oxaliplatin (GEMOX).

Up to 24 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 GEMOX.

If permitted by the safety results, the MT-3724 dose escalation is planned to proceed in three sequential dose cohorts (Cohorts 1-3). The starting MT-3724 doses will be 10 µg/kg/dose in Cohort 1, 25 µg/kg/dose in Cohort 2 and 50 µg/kg/dose in Cohort 3. Interim MT-3724 doses may be evaluated in additional cohorts at the sponsor's discretion in consultation with the investigator and Medical Monitor.

In all dose cohorts, MT-3724 will be administered in combination with gemcitabine 1000 mg/m^2 and oxaliplatin 100 mg/m^2 (Table 1).

Table 1: MT-3724 Dose Cohorts and Corresponding Dose Levels of MT-3724, gemcitabine and oxaliplatin

Planned MT-3724 Dose Cohorts	Interim MT-3724 Dose Cohortsa	Starting MT-3724 Dose (µg/kg/dose)	Starting Gemcitabine Dose (mg/m2)	Starting Oxaliplatin Dose (mg/m2)
1		10	1000	100
	-1 (optional)	≤5[b]	1000	100
2		25	1000	100
	-2 (optional)	≤17.5[b]	1000	100
3		50	1000	100
	-3 (optional)	≤37.5[b]	1000	100

a. To be evaluated only if warranted by the safety results in the planned cohorts
b. 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, all available investigators and Medical Monitor will review all available data in the current dose cohort. The sponsor, all available investigators and Medical Monitor will have a safety review meeting (teleconference) to discuss the data in the current dose cohort. All 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 relevant study manuals.

Cohort management and dose escalation decisions (including the MTD) will be based on the incidence of treatment-emergent adverse events (TEAEs) that fulfill the criteria for a dose-limiting toxicity (DLT), as follows.

- The first dose escalation decision in the current MT-3724 dose cohort will be made after at least 3 subjects complete C1 or experience a DLT. Up to 6 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.
- The first three subjects in each MT-3724 dose cohort should be treated at least one week apart, starting from the administration of MT-3724 in the previous 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 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.
- 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.
- 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.
- 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, then the dose escalation will stop, and the current MT-3724 dose level will be declared as the non-tolerable dose. In this case, one of the following 2 steps may be undertaken at the sponsor's discretion after consultation with investigator and Medical Monitor:
    - 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 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 1; however, the actual MT-3724 doses for 'interim' cohorts will be recommended by the sponsor after consultation with all investigators and Medical Monitor.
- 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 irrespective of the number of MT-3724, gemcitabine and oxaliplatin doses received in C1; or

- In the absence of DLT, have received at least 4 of 6 (83%) doses of MT-3724 and both doses of gemcitabine and oxaliplatin in C1

Subjects in the current cohort who are not evaluable for dose decisions will be replaced.

3.6.2. DLT Criteria

A treatment-emergent adverse event (TEAE) will be declared as DLT if both of the following criteria are met:

1. The TEAE occurred after the start of infusion in C1 of Part 1.
    a. If a TEAE that fulfills a DLT criterion is observed in C ≥2 of Part 1, then the sponsor may declare this event a DLT after consultation with the investigator and Medical Monitor.
2. The TEAE is at least possibly related to MT-3724 (i.e., not reasonably related to another etiology), as determined by the sponsor after consultation with investigator and Medical Monitor.

Note: If a Grade ≥3 TEAE related to gemcitabine or oxaliplatin 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 and Medical Monitor.

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

See APPENDIX E 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 GEMOX 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 GEMOX and complete C1 or experience a DLT. **The maximum dose of MT-3724 that will be given in this study is 50 ug/kg/dose with a maximum total dose of 6000 µg, which is the MTD of MT-3724 as monotherapy.** The MT-3724 dose escalation will not proceed above the 50 ug/kg/dose even if no more than 1 of 6 subjects in Cohort 3 experience a DLT.

The MTD decision will be made by the sponsor after consultation with all investigators and Medical Monitor.

3.6.4. MTD Communication Plan

The investigator, Medical Monitor and sponsor 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 and sponsor become aware that the MTD may be declared in the current dose cohort (e.g. based on the occurrence of qualifying AE/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 relevant study manuals.

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 the dose declared as MTD of MT-3724 in Part 1 would be given in combination with GEMOX. In addition, the PK, PD, immunogenicity and tumor response of MT-3724 in combination with GEMOX 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 study centers in North America and Europe.

Part 2 can start only after the MTD of MT-3724 in combination with GEMOX 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.

3.8. 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 standard of care 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. The MT-3724 dose will not exceed 50 ug/kg/dose, as this is the MTD for MT-3724 given as monotherapy. 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.

3.9. Guidance to the investigator

Preclinical studies and the ongoing first-in-man clinical trial MT-3724-NHL-001 have indicated several adverse events pertaining to patient safety. These adverse events should be kept in mind prior to treatment of any patient in this study as well as the precautions as indicated in the gemcitabine and oxaliplatin SmPC.

- The most common adverse events in the previous monotherapy study (in % of patients) were peripheral edema (62%), fatigue (46%), diarrhea (46%), myalgia (46%), insomnia (33%) nausea (29%), cough (29%), pyrexia (25%) and headache (25%).
- DLTs in this trial were symptoms indicative of systemic inflammatory response/cytokine release syndrome (CRS) at 100µg/kg (2 patients) and signs of capillary leak syndrome grade 2 at 75µg/kg (2 patients). All DLTs occurred in patients who received a high total MT-3724 dose of 8500; 10730; 7208 and 11572 µg/infusion.
- Patients should be closely monitored for signs of CLS/CRS.
    - This includes monitoring of vital signs (temperature, heart rate, blood pressure, weight and respiration rate) 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 and liver function and cytokines in case of clinical symptoms indicative of CRS/CLS.

3.10. Benefit/Risk Ratio

Most patients with CD20-positive B-cell NHL will eventually become resistant to available anti-CD20 therapy, including R-GEMOX. 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 (see Section 1.1.1). The current study aims to address this unmet medical need by replacing rituximab in the R-GEMOX regimen with MT-3724, while keeping the dose and schedule of gemcitabine and oxaliplatin the same.

In vitro, MT-3724 was tested in combination with gemcitabine or cisplatin to assess additive, synergistic or antagonistic cytotoxic effects against 4 different CD20-positive cell lines (16). In all cell lines, MT-3724 with gemcitabine yielded synergistic or predominantly synergistic effects, and MT-3724 with cisplatin yielded synergistic or predominantly synergistic effects in 2 of 4 cell lines and a mixed effect in the other 2. This in vitro data justifies further exploring the potential benefit of MT-3724 in combination with gemcitabine and oxaliplatin in the treatment of relapsed or refractory NHL/DLBCL in the Phase 2a study MT-3724-NHL-002.

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 (50 µg/kg/dose), and the safety profile of MT-3724 so far has been similar to that of rituximab in the R-GEMOX regimen. MT-3724 achieved objective tumor response at the lowest dose potentially used in the current study (5 µg/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 ASCT 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 gemcitabine and oxaliplatin in this population. Thus, the benefit-risk ratio in the current study is acceptable.

4. STUDY POPULATION

Eligible subjects will have histologically confirmed, relapsed or refractory B-cell NHL that, in the investigator's opinion, could benefit from MT-3724+GEMOX therapy.

All subtypes of B-cell NHL may be considered for Part 1 (MT-3724 dose escalation). Only DLBCL may be considered for Part 2 (MTD Expansion Cohort).

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 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 B-cell NHL that, in the investigator's opinion, could benefit from MT-3724+GEMOX therapy. At least one histologically documented relapse of NHL by:
    a. Bone marrow biopsy (FNA is not acceptable) or
    b. Excisional lymph node biopsy (FNA not acceptable) or
    c. Core biopsy of any involved organ
    d. CD20-positive histology must have been confirmed at any time during NHL disease course and documented in medical history.
    e. If no histology is available after any relapse the investigator can consult the medical monitor to discuss if the patient can be included.
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 (expansion cohort).
5. Have received all approved therapies for NHL that are applicable for the patient in the opinion of the treating physician.
    a. Patients refractory to treatment are eligible.
    b. Patient who have progressed following CAR T-cell therapy are also eligible.
6. Have measurable disease by Lugano Classification for NHL (APPENDIX D).
    a. >1.5 cm longest diameter (LDi) for lymph nodes
    b. >1 cm LDi for extranodal disease

7. Have ECOG performance score of ≤2 (APPENDIX G).
8. Have adequate bone marrow function, as determined by:
    a. Absolute neutrophil count (ANC) ≥1,000/mm3 (CTCAE Grade ≤2) and
    b. Platelet count ≥50,000 mm³ (CTCAE Grade ≤2)
9. Have adequate kidney function, assessed by the estimated glomerular filtration rate (eGFR) ≥60 mL/min calculated by the CPK-EPI equation (APPENDIX F).
    a. At the investigator's discretion, the eGFR result <60 mL/min may be verified by measurement of creatinine clearance (CLcr) based on the 24-hour urine collection. Subjects with CLcr ≥60 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 ≤3 x ULN for subjects with Gilbert's Syndrome and
    b. Aspartate aminotransferase (AST) ≤3 x ULN (or ≤ 5.0 xULN if liver involvement) (and
    c. Alanine aminotransferase (ALT) ≤3 x ULN (or ≤ 5.0 xULN if liver involvement)
11. Have adequate coagulation, as determined by:
    a. INR or PT ≤1.5 x ULN
    b. PTT ≤1.5 x ULN
12. Have adequate serum albumin, as determined by:
    a. Albumin ≥ 3.0 g/dL
13. Women of reproductive potential must have a negative pregnancy test during the screening period within 72 hours before the start of treatment. Women not of reproductive potential are female subjects who are postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy).
14. Subjects of reproductive potential and their partners must agree to either to abstain continuously from heterosexual intercourse or to use a reliable birth control method between signing the informed consent until 6 months following the last dose of MT-3724 or GEMOX. The investigator or a designated associate should advise the subject how to achieve adequate contraception. The following birth control methods may be considered as adequate:
    a. Condoms (male or female) with or without a spermicidal agent;
    b. Diaphragm or cervical cap with spermicide;
    c. Intrauterine device;

d. Hormone-based contraception: Established use of oral, injected, or implanted hormonal methods of contraception;

e. True abstinence;

f. Vasectomy is an acceptable method for a male subject or male partner of a female subject.

4.2. Exclusion Criteria

Subjects who meet ANY of the following criteria will not be eligible for 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, or any other previous cancer curatively treated >2 years before the start of treatment.
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
    b. Have no neurological symptoms (excluding Grade ≤2 neuropathy)
    c. Have stable brain or spinal disease on the CT or MRI scan within 1 month of enrollment and
    d. Do not require chronic steroid therapy
3. History of allogeneic hematopoietic stem cell transplant within 180 days before the start of treatment.
4. Current evidence of acute or chronic Graft versus Host Disease.
5. Current evidence of CTCAE Grade >1 toxicity (except for hair loss, and those toxicities listed as permitted in other eligibility criteria) before the start of treatment.
6. Current evidence of incomplete recovery from surgery before the start of treatment, or planned surgery at any time until the EoT Visit, except minor elective interventions deemed acceptable by the investigator.
7. History or current evidence of significant (CTCAE Grade ≥2) infection or wound within 4 weeks before the start of treatment.
8. History or 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. Pericarditis (any CTCAE grade), pericardial effusion (CTCAE Grade ≥2), non-malignant pleural effusion (CTCAE Grade ≥2) or malignant pleural effusion (CTCAE Grade ≥3) within ≤3 months before the start of treatment with MT-3724.

e. Congestive heart failure (NYHA Class III or IV) at screening or LVEF <45%, assessed by Echo or MUGA scan within 1 month before starting study treatment. (ECHO or MUGA 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 potentially cardiotoxic agents).

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 if the dose has been stable for ≥2 weeks before the start of treatment. Subjects with sinus arrhythmia and infrequent premature ventricular contractions are eligible at the investigator's discretion.

9. QTcF (Fridericia) >480 ms, determined as the average from three QTcF values on the triplicate ECG obtained at screening.

10. Current evidence of seropositive status for HIV, hepatitis B virus (positive for HBsAg or anti-HBsAg and anti-HBcAg antibodies) or hepatitis C virus (positive for anti-HCV antibody or HCV-RCV-RNA quantitation) at screening.

    a. Serology testing may be omitted at the investigator's discretion if seronegativity is documented in the medical history and there are no clinical signs suggestive of HIV or hepatitis infection.

    b. Subjects with positive HBV serology are eligible if quantitative PCR for plasma HBV-DNA is negative and the subject will be receiving prophylaxis for potential HBV reactivation.

    c. Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is negative.

11. Women who are pregnant or breastfeeding.

12. History of hypersensitivity to any of the study drugs, or current evidence of hypersensitivity requiring systemic steroids at doses >20 mg/day prednisone equivalent.
13. 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

14. Received any amount of anti-CD20 MAb therapy within the following periods before the start of treatment
    a. Rituximab (Rituxan®): 84 days; if a subject received rituximab within 37 weeks before the start of treatment, then a serum rituximab level must be negative (<500 ng/mL) at screening.
    b. Obinutuzumab (Gazyva®): 184 days
    c. Ofatumumab (Arzerra®): 88 days
15. Received therapy for NHL (other than the anti-CD20 MAbs listed above) within 4 weeks before the start of treatment.
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 lesion(s) that would be chosen as target lesions (measurable disease) within 4 weeks before the start of treatment, unless the lesion(s) exhibited objective progression between the radiotherapy and the screening according to the Lugano Classification for NHL.
    d. Palliative radiotherapy to non-target lesions is allowed at the investigator's discretion.
18. Received any vaccines within 28 days of the start of treatment, or likely to require vaccines at any time from the start of treatment until 28 days after the last dose of MT-3724. Injectable flu vaccine (inactivated or recombinant) is permitted at the investigator's discretion.
19. Received systemic immune modulators within 2 weeks before the start of treatment.
    e. Systemic immune modulators include, but are not limited to, systemic corticosteroids at doses >20 mg/day of prednisone equivalent (except for premedication), cyclosporine and tacrolimus.
    f. The use of NSAIDs is permitted.

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 if the β-HCG pregnancy test indicates that they are pregnant at any time between the consent and the EoT Visit. Subjects who are identified to have become pregnant after the EoT Visit will not be withdrawn from the Long-term Follow-up.

The subject **may** be withdrawn from the study 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.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either a screening failure (withdrawn before the start of treatment) or a dropout (withdrawn after receiving the first dose of a study drug).

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

The reason for any discontinuation from the study will be documented in the subject's medical record and recorded on the appropriate 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.

4.3.2.1. Part 1 (MT-3724 Dose Escalation)

Subjects who discontinue in C1 and are not evaluable for dose decisions (see Section 4.3.3.) must be replaced in the current dose cohort to ensure that sufficient number of subjects is

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 sponsor and Medical Monitor.

Subjects who discontinue for any reason after C1 will not be replaced.

4.3.2.2. Part 2 (MTD Expansion)

Subjects in Part 2 of the study who have insufficient safety or PK, PD or immunogenicity data in C1 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. In this case, the ongoing subjects may continue treatment for up to 4 cycles if supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor.

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 a single chain variable fragment (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 2.0 ml of MT-3724 (0.5 mg/ml or 1000 µg per vial) in a formulation buffer comprised of Sorbitol (200 mM), Sodium Citrate (20 mM) 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 (D5W) or normal saline for intravenous (IV) administration. All doses should be administered over 1 hour through an IV line (peripheral cannula or PICC catheter). See Pharmacy Manual for detailed instructions and worksheets regarding study drug preparation and administration.

Thawed vials with intact stoppers can be stored at 2 - 8°C for up to 1 month. After 1 month of storage at 2 - 8°C, unused drug vials should be destroyed by the pharmacist according to local institutional standard procedures.

The investigator is responsible for the accountability of the drug product and related supplies at the site. Records of the receipt and disposition of IMP must be maintained 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 the purpose of 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) and before the first dose of MT-3724 in Cycle 2-4. If the body weight has changed by >10% from the baseline value, this **may** require re-calculation of MT-3724 dose at investigator's discretion.

The maximum dose of MT-3724 that will be given in this study is 50 ug/kg/dose, which is the MTD of MT-3724 as monotherapy. 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 5.5.

5.1.2.1. Part 1 (MT-3724 Dose Escalation)

The starting dose of MT-3724 in Part 1 in each planned cohort will be:

1. Cohort 1: 10 µg/kg/dose
2. Cohort 2: 25 µg/kg/dose
3. Cohort 3: 50 µg/kg/dose

If MT-3724 is not tolerated in any planned cohort, then additional MT-3724 dose may be evaluated in the interim cohort at the sponsor's discretion in consultation with the investigator and Medical Monitor.

The hypothetical doses of MT-3724 in the interim cohorts are:

1. Cohort -1: 5 µg/kg/dose (if MT-3724 10 µg/kg/dose is not tolerated in Cohort 1)
2. Cohort -2: 17.5 µg/kg/dose (if MT-3724 25 µg/kg/dose is not tolerated in Cohort 2)
3. Cohort -3: 37.5 µg/kg/dose (if MT-3724 50 µg/kg/dose is not tolerated in Cohort 3)

The actual MT-3724 doses in the interim cohorts will be recommended by the sponsor after consultation with the investigators and Medical Monitor. The actual MT-3724 dose in the interim Cohort -1 should not be <5 µg/kg/dose, as this was the lowest dose evaluated in the clinic so far.

5.1.2.2. Part 2 (MTD Expansion Cohort)

The starting dose of MT-3724 in Part 2 will be the MTD (or a maximum dose of 50 µg/kg) of MT-3724 from Part 1. The total administered dose of MT-3724 for subjects will be capped at 6000 µg per infusion.

5.1.3. MT-3724 Dosing Schedule

In C1 and C2, MT-3724 should be administered as 1-hour IV infusion on Day 1, 3, 5, 8, 10 and 12 of each 28-day cycle.

MT-3724 may be continued in C3-C4 (with or without GEMOX) if supported by the investigator's assessment of the benefit-risk ratio. In C3-C4 (and subsequent cycles, if applicable), MT-3724 should be administered as 1-hour IV infusion weekly (Day 1, 8, 15 and 22 of each 28-day cycle).

MT-3724 administration on the same day as gemcitabine and oxaliplatin should be avoided, unless deemed acceptable by the investigator based on the careful assessment of all available data in the individual subject.

5.1.3.1. Time Windows for 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. However, no more than two MT-3724 doses can be administered on consecutive days.

If MT-3724 is administered on consecutive days, then at least 20 hours (approximately five half-lives of MT-3724 in plasma) must elapse between the start of the 2 infusions.

The "catch up" on missed MT-3724 doses in the current cycle is allowed at the investigator's discretion up to D21. MT-3724 should not be administered between D21-D28 in C1-C2.

Cycles 3-4 (if applicable)

Any of the scheduled weekly MT-3724 doses may be administered within ±2 days at investigator's discretion. MT-3724 should not be administered between D24-D28 in C3-C4.

5.1.4. Premedication Before MT-3724 infusion

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

- Oral anti-inflammatory agent (e.g. acetaminophen not to exceed 1000 mg PO)
- Intravenous H1 histamine receptor antagonist (e.g. diphenhydramine not to exceed 100 mg IV)
- Intravenous corticosteroid agent with a shorter biological half-life (e.g. methylprednisolone not to exceed 1000 mg IV)

The specific drugs in each class and their doses should be selected at investigator's discretion or according to the institutional guideline. 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. Gemcitabine

Gemcitabine (Gemzar®) is a nucleoside analog anticancer agent which blocks new DNA synthesis leading to cell death.

Gemcitabine drug product will be supplied by the local pharmacy at the study site. It will be prepared, administered and stored according to the reference prescribing information. Premedication is permitted at the investigator's discretion according to site protocols.

5.2.1. Gemcitabine Dose Selection

In all cohorts in Part 1 and Part 2, the starting dose of gemcitabine will be 1000 mg/m^2. This is the standard dose of gemcitabine as part of the R-GEMOX regimen in the treatment of patients with relapsed or refractory DLBCL (17,18). The gemcitabine starting dose can be decreased per investigators discretion based on the known safety profile of gemcitabine and patient status.

See Section 5.5. for guidance about the gemcitabine treatment modification. In addition, the modification of gemcitabine treatment in this study should be guided by the reference prescribing information, as interpreted by the investigator.

5.2.2. Gemcitabine Dosing Schedule

Gemcitabine will be administered as 30-minute IV infusion on Day 2 and Day 16 of each 28-day cycle (i.e., every 14 days).

5.3. Oxaliplatin

Oxaliplatin (Eloxatin®) is a platinum-based anticancer agent that causes DNA crosslinking causing inhibition of DNA synthesis and/or repair as well as inhibition of DNA replication and transcription, leading to cell death.

Oxaliplatin drug product will be supplied by the local pharmacy at the study site. It will be prepared, administered and stored according to the reference prescribing information. Premedication is permitted at the investigator's discretion according to site protocols.

5.3.1. Oxaliplatin Dose Selection

In all cohorts in Part 1 and Part 2, the starting dose of oxaliplatin will be 100 mg/m^2. This is the standard dose of oxaliplatin as part of the R-GEMOX regimen in the treatment of patients with relapsed or refractory DLBCL (17, 18). The oxaliplatin starting dose can be decreased per investigators discretion based on the known safety profile of oxaliplatin and patient status.

See Section 5.5. for guidance about the oxaliplatin treatment modification. In addition, the modification of oxaliplatin treatment in this study should be guided by the reference prescribing information, as interpreted by the investigator.

5.3.2. Oxaliplatin Dosing Schedule

Oxaliplatin will be administered as 2-hour IV infusion after gemcitabine on Day 2 and Day 16 of each 28-day cycle (i.e., every 14 days). Oxaliplatin infusion will start one hour after the start of gemcitabine infusion (unless a delay is warranted at the investigator's discretion) to facilitate easier compliance with the post-dose assessment schedule.

5.4. Intra-subject Dose Escalation

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

Intra-subject escalation of gemcitabine or oxaliplatin dose up to the most recent level is allowed in both parts of the study, if supported by the investigator's assessment of the benefit-risk ratio after consultation with the sponsor and Medical Monitor.

5.5. Treatment Modification

Treatment modification due to a TEAE (dose interruption/delay, dose reduction, or permanent discontinuation) can be done in an individual subject at the investigator's discretion after consultation with sponsor and 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).

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

5.5.1. 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 Medical Monitor and sponsor.

- Any TEAE irrespective of the time of onset that would otherwise fulfill the DLT criteria (APPENDIX E)
- 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 sponsor and 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 and sponsor 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 C1 that is related to MT-3724 and qualifies as 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 the ≥25% reduced dose of 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 central laboratory.
- MT-3724 dose may be **reduced** by ≥25% at the investigator's discretion after consultation with sponsor and Medical Monitor. The number of dose reductions per subject is not limited, except that the reduced dose cannot be <5 mcg/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 did not 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 sponsor and Medical Monitor.

5.5.2. Gemcitabine Treatment Modification

Any TEAE irrespective of the time of onset, which would otherwise fulfill the DLT criteria (APPENDIX E), **may** trigger gemcitabine (GEM) treatment modification, if deemed at least possibly related to GEM by the investigator.

In addition, the modification of GEM treatment in this study will be guided by the reference prescribing information, as interpreted by the investigator.

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

- The Investigator should notify the Medical Monitor and sponsor 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 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.
- GEM dose may be **reduced** by ≥25% at the investigator's discretion after consultation with sponsor and Medical Monitor. The number of dose reductions per subject is not limited.
- Intra-subject escalation of gemcitabine dose up to the most recent level is allowed (see Section 5.4.)

GEM treatment should be **permanently discontinued** after the onset of any of the following TEAEs in any treatment cycle, if deemed at least possibly related to GEM by the investigator after consultation with Medical Monitor and sponsor:

- Grade ≥3 dyspnea or other Grade 3 pulmonary toxicity that cannot be attributed to the underlying NHL or comorbidity
- Grade ≥3 hemolytic-uremic syndrome
- Grade ≥3 acute kidney injury (acute kidney injury (serum creatinine increase ≥2 times above baseline in the absence of dehydration or bleeding)
- Grade ≥2 capillary leak syndrome (CLS)
- Grade ≥3 posterior reversible encephalopathy syndrome

GEM treatment should also be **permanently discontinued** if any TEAE that previously led to dose interruption/delay or reduction did not 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 sponsor and Medical Monitor.

5.5.3. Oxaliplatin Treatment Modification

Any TEAE irrespective of the time of onset, which would otherwise fulfill the DLT criteria (APPENDIX E), **may** trigger oxaliplatin (OX) treatment modification, if deemed at least possibly related to OX by the investigator after consultation with Medical Monitor and sponsor.

In addition, the modification of OX treatment in this study will be guided by the reference prescribing information, as interpreted by the investigator.

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

- The Investigator should notify the Medical Monitor and sponsor 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 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.
- OX dose may be **reduced** by ≥25% at the investigator's discretion after consultation with sponsor and Medical Monitor. The number of dose reductions per subject is not limited.
- Intra-subject escalation of oxaliplatin dose up to the most recent level is allowed (see Section 5.4.).

OX dose should be **reduced** after the onset of Grade ≥2 peripheral neuropathy. Further, OX treatment should be permanently discontinued if Grade ≥2 peripheral neuropathy persists within 4 weeks after dose reduction.

OX treatment should be **temporarily discontinued** after the onset of pulmonary toxicity indicative of interstitial pneumonitis or pulmonary fibrosis (e.g. cough, dyspnea not attributable to the underlying NHL or comorbidity). If interstitial pneumonitis or pulmonary fibrosis are confirmed, OX treatment should be permanently discontinued.

OX treatment should also be **permanently discontinued** if any TEAE that previously led to dose interruption/delay or reduction did not 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 sponsor and Medical Monitor.

5.5.4. Treatment Modification Due to IRR or Other Hypersensitivity Event

This guidance is applicable to any among the 3 study drugs that, in the investigator's opinion, is at least possibly related to infusion-related reactions (IRR) or other hypersensitivity event.

If a subject experienced a Grade ≥2 IRR or other Grade ≥2 hypersensitivity reaction, the infusion must be immediately and permanently interrupted for that day. 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 after consultation with the sponsor and Medical Monitor

- If continued treatment is indicated, then
  - it must occur after the appropriate delay (re-treatment on the same day is not allowed)
  - it may represent the completion of the interrupted dose or the next dose per protocol.
  - for the next dose of the study drug causally related to IRR, the infusion 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.

5.5.5. Treatment Modification Due to Neutropenia or Thrombocytopenia

This guidance is applicable to any case of treatment-emergent neutropenia and/or thrombocytopenia that, in the investigator's opinion, is at least possibly related to the study drug(s).

If treatment modification of the study drug is warranted due to treatment-emergent neutropenia and/or thrombocytopenia, and the continuation of treatment is appropriate at investigator's discretion after consultation with sponsor and Medical Monitor, then the dose will be adjusted as described in Table 2.

Table 2: Dose Adjustments in Response to Neutrophil and Platelet Nadir Counts

Absolute neutrophil nadir count		**Platelet nadir count**	**MT-3724 and/or gemcitabine and/or oxaliplatin dose modification** [a]
>500/µl or <500/µl for ≤5 days	and	≥25,000/µl	No change
<500/µl for >5 days	and / or	<25,000/µl with or without active bleeding, OR <50,000/µl with clinically significant bleeding [b]	Decrease by ≥25% (MT-3724); or according to reference prescribing information (GEM and/or OX)

Febrile neutropenia [c]	and / or	<25,000/µl with or without active bleeding, OR <50,000/µl with clinically significant bleeding [b]	Decrease by ≥25% (MT-3724); or according to reference prescribing information (GEM and/or OX)

a. The actual amount(s) will be determined by the investigator after consultation with sponsor and Medical Monitor. Repeated dose reductions are permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio.

b. Clinically significant bleeding is that which requires platelet transfusion.

c. Febrile neutropenia is defined as ANC <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.

5.5.6. Treatment Modification Due to Increased AST, ALT and/or Bilirubin Levels

This guidance is applicable to any case of treatment-emergent increased serum AST, ALT and/or bilirubin levels that, in the investigator's opinion, is at least possibly related to the study drug(s).

If treatment modification of the study drug is warranted due to treatment-emergent increased AST, ALT and/or bilirubin levels, and the continuation of treatment is appropriate at investigator's discretion after consultation with sponsor and Medical Monitor, then the dose will be adjusted as described in Table 3

Table 3: Dose Adjustments in Response to the Worst Increase in AST, ALT or Bilirubin Levels

Worst AST and / or ALT increase		**Worst bilirubin increase**	**MT-3724 and/or gemcitabine and/or oxaliplatin dose modification [a]**
≤3.0 x ULN (isolated)	or	≤1.5 x ULN (isolated)	No change in treatment Monitor subject
≤3.0 x ULN	and	≤1.5 x ULN	Temporarily discontinue treatment Monitor subject May continue at same dose after abnormal values resolve to ULN

>3.0 x ULN – 5.0 x ULN	and / or	>1.5 x ULN – 3.0 x ULN	Temporarily discontinue treatment After abnormal values resolve to Grade ≤1, may continue at dose reduced by ≥25% (MT-3724) or according to reference prescribing information (GEM and/or OX)
>5.0 x ULN – 10.0 x ULN	or	>3.0 x ULN – 10.0 x ULN	Temporarily discontinue treatment May continue at dose reduced by ≥25% (MT-3724) or according to reference prescribing information after abnormal values resolve to Grade ≤1
>10.0 x ULN	or	>10.0 x ULN	Permanently discontinue

a. The actual amount(s) will be determined by the investigator after consultation with sponsor and Medical Monitor. Repeated dose reductions are permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio.

Repeated dose reductions are permitted if continued treatment is supported by the investigator's assessment of the benefit-risk ratio.

5.6. 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 in consultation with the sponsor reviews the screening results and acknowledge the investigator's eligibility decision.

All subjects in all cohorts will receive the same standard doses of gemcitabine (Section 5.2.1) and oxaliplatin (Section 5.3.1).

Assignment of screening slots and treatment slots will be done on basis of competitive enrollment (i.e. "first-come first-served"). The details will be described in a separate study manual.

5.7. Blinding

Not applicable for this open-label study.

5.8. Treatment Compliance

All study drugs will be administered by investigational site staff during the site visit.

Treatment compliance for each study drug will be monitored through the eCRF and source documents (patient notes and pharmacy records) and clinical observations during study drug infusion. Actual dose administered vs. planned dose will be used to assess compliance for each study drug. Details will be provided in the standalone Pharmacy Manual.

5.9. Treatment Duration

The following guidance for treatment duration applies to both parts of the study.

Treatment with MT-3724 in combination with GEMOX will continue for 2 cycles of 28-days each or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for subject withdrawal, or until discontinuation of the study.

If supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor, the treatment with MT-3724 in combination with GEMOX may continue for 2 additional cycles of 28-days each (up to the total of 4 cycles), or until death, disease progression, unacceptable toxicity, withdrawal of consent or another reason for withdrawal, or until discontinuation of the study.

If any of the 3 study drugs is permanently discontinued, the treatment with the remaining study drug(s) may continue for up to 4 cycles if supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor.

If the subject exhibits SD, CR or PR after the end of Cycle 4 and the investigator determines that the benefit-risk ratio is favorable, then the treatment with MT-3724 may be continued after discussion with the sponsor. Continuation of GEMOX is at investigators discretion.

5.10. Prohibited Treatment

The following treatments are not permitted during the specified periods:

- Rituximab (Rituxan®) from 84 days before the start of treatment until the EoT Visit. If a subject had received rituximab within 37 weeks before the start of treatment, then a serum rituximab level must be documented to be negative (<500 ng/mL) during the screening period
- Obinutuzumab (Gazyva®) from 184 days before the start of treatment until the EoT Visit
- Ofatumumab (Arzerra®) from 88 days before the start of treatment until the EoT Visit

- Therapy for NHL (other than the anti-CD20 MAbs listed above) from 3 weeks or 5 half-lives of the agent before the start of treatment, whichever is longer, until the EoT Visit
- 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 according to the Lugano Classification for NHL (2014) between the radiotherapy and the screening.
    - Palliative radiotherapy to non-target lesions is allowed at the investigator's discretion after consultation with the Medical Monitor and sponsor
- Systemic immune modulators from 2 weeks before the start of treatment until the EoT Visit. The immune modulators include, but are not limited to, systemic corticosteroids at doses >20 mg/day of prednisone equivalent (except for premedication), cyclosporine and tacrolimus. The use of NSAIDs is permitted
- 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
- Subjects must not have received any vaccines from 28 days before the start of treatment until 28 days after the last dose of MT-3724. The single exception to this exclusion is for the injectable flu vaccine (inactivated or recombinant), which may be administered at the investigator's discretion at any time during the above period

5.11. Permitted Medication

Except for prohibited treatments (see above), the use of any other concomitant medications is permitted during the treatment period at the investigator's discretion.

The injectable flu vaccine may be administered at the investigator's discretion from 28 days before the start of treatment until 28 days after the last dose of MT-3724, and at any time thereafter. If the investigator allows the flu vaccine, they should carefully assess if it is appropriate to administer the flu vaccine before all study-related laboratory abnormalities or AEs have resolved. The subjects treated with B-cell depleting MAbs have been shown to have impaired humoral immune responses to neo-antigens for variable periods of time following the B-cell depleting treatment.

5.11.1. Reasons for caution

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

6. STUDY ASSESSMENTS

Please refer to the schedule of assessments (APPENDIX A) for details of all assessments and procedures to be performed at each visit during the study.

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

Demographic parameters will be assessed at screening.

This will include date of birth, sex, race/ethnicity, history of smoking and alcohol consumption.

6.1.2. Body Weight

Body weight [in kilograms (kg)] will be measured at the following time points:

- At screening
- At any time before each MT-3724 infusion in each cycle.
- At the EoT Visit

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.

The body weight measured before the MT-3724 dose on Day 1 of Cycle 1 will be the baseline for all subsequent measurements. If the body weight has changed by >10% from the baseline value, this **may** require re-calculation of MT-3724 dose at investigator's discretion.

6.1.3. Height, BMI and BSA

Height [in meters (m)], body mass index (BMI) and body surface area (BSA) will be measured/calculated 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 has been last confirmed, the disease status at the initial diagnosis and the current status. The following information will be documented:

- NHL histology confirmation by biopsy (bone marrow, lymph node, organ)

- NHL assessment (status at initial diagnosis and after relapse): NHL type, histology, staging (Ann Arbor Classification-Cotswold Modification), grading (low, intermediate or high)
- NHL assessment (current status): same as for the status at initial diagnosis plus the mutational status (eg MYC and/or BCL2 and/or BCL6 rearrangement/overexpression; del 9p32. TP53, MLL2 mutations).

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

6.1.5. Prior Systemic Therapy

Prior systemic therapy for NHL (including SCT) administered at any time before the start of treatment will be assessed at screening. This should be documented by itemizing each regimen (line of treatment) and the individual agents within each regimen.

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

The following other clinical safety assessments will be performed in this study. Note that the adverse events are described in the Section 6.3, and the laboratory safety tests are described together with all laboratory tests in the Section 6.4.

6.2.1. Medical History

Medical history will be recorded at screening. This will include prior surgery, prior and concomitant medications, prior and concomitant illnesses and allergy history. The prior antitumor chemotherapy and radiotherapy will be collected as separate categories.

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 medical history and the start of treatment should be reported as pre-treatment adverse events.

6.2.2. Prior and Concomitant Medications

Any medication (either prescription and over-the-counter [OTC] medications and supplements) used within 4 weeks prior to the start of treatment until the EoT Visit will be recorded in the eCRF, together with the main reason for its prescription.

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

- At screening
- Before the start of treatment on C1D1.

The medications taken after the start of treatment will be regarded as concomitant medications. Concomitant medications will be captured at every clinic visit and telephone contact from the start of treatment until the EoT Visit

6.2.3. Physical Examination

The physical examination (PE) will be performed by a physician or a qualified delegate at the investigating site. For each element of the PE (see below), the result will be documented as normal, or abnormal, not clinically significant (NCS), or abnormal, clinically significant (CS). The pathological findings will be captured in the comment field only for the abnormal CS results.

6.2.3.1. Complete Physical Examination

The complete physical examination (PE) will be performed at the following time points:

- At screening
- At the EoT Visit

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 (awareness of self and environment)
    - 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
- ECOG performance status (APPENDIX G)
- NYHA classification (APPENDIX H)

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

The investigator or delegate at the site will perform the PE and evaluate the results. 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 AE in the 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.

6.2.3.2. Abbreviated Physical Examination

Abbreviated physical examination will be performed at the following time points:

- At any time before MT-3724 infusion on D1 of each cycle
- At any time before gemcitabine infusion on D16 of each cycle

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
- ECOG performance status (APPENDIX G)

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

6.2.4. Body Temperature

Body temperature (in Fahrenheit or Celsius) will be measured at the following time points:

- At screening
- At any time before the start of MT-3724 infusion on D1 of each cycle
- At any time before the start of gemcitabine infusion on D16 of each cycle
- At the EoT Visit

6.2.5. Blood Pressure and Heart Rate

Blood pressure and heart rate will be measured after 5-10 minutes of quiet rest in a sitting or semi-recumbent position. The use using an automatic blood pressure measuring device is recommended, but a manual device is permitted.

Blood pressure and heart rate will be assessed at the following time points:

- At screening
- At any time before the start of MT-3724 infusion in each cycle
- At 0.5h, 1h and 2h (±10 min each) after the start of 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 any time before the start of gemcitabine infusion in each cycle
- At 3 h (±10 min) after the start of oxaliplatin infusion in each cycle
- At the EoT Visit

Unscheduled blood pressure and heart rate measurements may be performed at investigator's discretion in each cycle.

When PK, ECG and blood pressure assessments are scheduled to occur at the same time point, then the PK sample collection should be performed at the protocolled time and the ECG and blood pressure / heart rate should be done in that order at least 10 minutes before or 10 minutes after the PK sampling. In this case, the blood pressure / heart rate measurement may begin immediately after ECG recording (no need for additional 5-10 minutes' rest).

Any clinically significant abnormality in the blood pressure or heart rate, as determined at the investigator's discretion, 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.

6.2.6. LVEF

The left ventricular ejection fraction (LVEF) will be measured by multigated acquisition (MUGA) scan or echocardiography. Either MUGA or echocardiography may be performed at investigator's discretion or according to institutional standards, but the method for each subject should not change during the study.

LVEF will be assessed at the following time points:

- At screening (if not available within 3 months before the start of treatment)
- At the EoT Visit (only if the subject has received MT-3724 in all 4 cycles)

6.2.7. Electrocardiograms, 12-lead ECG

Standard resting 12-lead ECG assessments will be performed after the subject had rested 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).
- At any time before the start of MT-3724 infusion on D1 of each cycle (single ECG)
- 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 blood pressure assessments are scheduled to occur at the same time point, then the PK sample collection should be performed at the protocolled time and the ECG and blood pressure / heart rate should be done in that order at least 10 minutes before or 10 minutes after the PK sampling.

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 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, vital signs 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 (AEs) 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 SFU phone call. 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 Sponsor Medical Monitor or 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 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 patient'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 because of disease progression or deterioration of the patient'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 adverse event (AE) reporting period will be from the time of signing the informed consent form until the SFU.

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

Those AEs that occur after the start of treatment 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 GEMOX. 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.

6.3.2. AE Terminology

All AE terms 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, 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 the Common Toxicity Criteria guidelines from the National Cancer Institute (CTCAE) v5.0. If the AE term chosen by the investigator is not listed in the CTCAE v.5.0, then the highest severity level on the scale in Table 4 will be assigned to the investigator's AE term.

Table 4: Classification of Adverse Events by Severity Grade (CTCAE v.5.0)

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.

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

6.3.3.1. Causality / Relationship

Causality should be assessed separately for each study drug (MT-3724, gemcitabine and oxaliplatin) as detailed in the eCRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments, then the same assessment should be documented for each study treatment. 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 and separately, the Medical Monitor on behalf of the sponsor, will determine the causal relationship / relatedness to the study drug(s) according to the classification in Table 5.

Table 5: Classification of adverse events by causality / relationship to the study drug(s)

Causal Relationship	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.
At least 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.

For all purposes of subject management, DLT assignment and treatment modification, the causality assessment of "at least probably", "possibly" or "definitely" will be treated as "related", while the causality assessment of "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 adverse event that is not identified by type, severity grade, or frequency in the Reference Safety Information (RSI) section of the Investigator's Brochure for MT-3724 or in the MT-3724 safety reports to the health authorities (e.g. DSUR) and for

gemcitabine or oxaliplatin any ADR that is not described in the respective SmPCs of each drug.

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

A serious adverse event (SAE) is 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-subject 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 patient or 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 inpatient 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. For example, an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. 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 patient/event outcome or action criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

6.3.5.1. SAE Reporting instructions

If an SAE occurs at any time from the time of signing the informed consent form until the SFU phone call, it must be reported to the CTI Safety Department and the Medical Monitor on behalf of the sponsor (contact details on page 5). **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 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 photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. All photocopies 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.

Comprehensive SAE reporting instructions will be provided in the CTI Safety Management Plan for this study.

6.3.5.2. SUSAR

An unexpected SAE that is at least possibly related to the study drug will be considered a suspected unexpected serious adverse drug reaction (SUSAR). Please see Section 6.3.2. for the definition of the unexpected event.

The sponsor will determine if a reported SAE meets the criteria for SUSAR and confirm the decision with the Medical Monitor and sponsor. The CTI Safety Department will then notify the institutional review boards (IRBs) / independent ethics committees (IECs), health authorities and ail investigators about the SUSAR according to the applicable regulations.

6.3.6. 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. 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.

6.3.7. Action Taken with Study Treatment

Any action with any of the study treatments to manage the AE should be documented using the categories as described in the eCRF completion guidelines. The study treatment action should be recorded separately for MT-3724, gemcitabine and oxaliplatin as detailed in the eCRF.

6.3.8. 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 (see APPENDIX A and APPENDIX B).

The following tests will be performed by the central laboratory:

- Hematology
- Chemistry (with eGFR)
- HbA1c
- Coagulation (activated partial thromboplastin time (aPTT) and either INR or PT)
- Thyroid function (TSH and FT4)
- Beta-2 microglobulin
- Serum cytokines
- Complement
- Immunoglobulins
- Histamine
- B-cell count and immunophenotype (flow cytometry)
- Immunogenicity of MT-3724; Anti-drug antibodies [anti-drug antibody (ADA) and neutralizing antibody (NA)]
- Serology for rituximab concentration (if applicable)

The following laboratory tests will be performed in the local laboratory at the site:

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

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

A standalone Laboratory Manual will provide complete instructions for the collection, handling, storage and shipment of samples for the laboratory tests.

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 should be considered as an AE and documented accordingly in the eCRF.

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
- In C1 and C2:
    - On D1 and D8 (at any time before the start of MT-3724 infusion)
    - On D16 (at any time before the start of gemcitabine infusion)
    - On D22 (at any time before the start of MT-3724 infusion)
- In C3 and C4 (if applicable):
    - On D1, D8, D15 and D22 (at any time before the start of MT-3724 infusion)
- 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.

6.4.2. eGFR

The estimated glomerular filtration rate (eGFR) will be assessed as a measure of renal function. The central laboratory will calculate eGFR using the CPK-EPI equation (APPENDIX F) (19) and the serum creatinine values from the blood chemistry assessment at the same time point.

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 creatinine clearance (CLcr) based on the 24-hour urine collection. Furthermore, if warranted by the eGFR result at any other time point, the investigator may order creatinine clearance (measured from the 24-hour urine) as unscheduled assessment.

6.4.3. Urinalysis

A standard Dipstix urinalysis will be initially performed at the following time points:

- At screening
- In C1 and C2:
    - On D1 and D8 (at any time before MT-3724 infusion)
    - On D16 (at any time before gemcitabine infusion)
    - On D22 (at any time before MT-3724 infusion)
- In C3 and C4 (if applicable):
    - On D1, D8, D15 and D22 (at any time before MT-3724 infusion)
    - On D16 (at any time before MT-3724 infusion)
- At the EoT Visit

The analysis of the urine microsediment is not part of the initial urinalysis, unless warranted as unscheduled test at the investigator's discretion.

Any clinically significant abnormality in Dipstix 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 AE in the eCRF.

6.4.4. HbA1c

Glycated hemoglobin in plasma (HbA1c) will be assessed at the following time points as a measure of glycemic control:

- At screening
- At the EoT Visit

6.4.5. Thyroid Function Assessment

The thyroid-stimulating hormone (TSH) and free thyroxine (FT4) in serum will be assessed at the following time points as a measure of thyroid function:

- At screening
- At the EoT Visit

6.4.6. Coagulation

The coagulation parameters (INR or PT, and aPTT) will be assessed at the following time points:

- At screening
- At any time before the start of MT-3724 infusion on D1 of each cycle

- At the EoT Visit

6.4.7. Cytokines, histamine, complement and Immunoglobulins

The cytokine panel, histamine, complement and immunoglobulins will be assessed at the following time points:

- At screening
- Before the start of MT-3724 infusion (±10 min) 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.

6.4.8. Beta-2 Microglobulin

A serum sample for the collection of beta-2 microglobulin will be collected at the following time points:

- At screening

6.4.9. Rituximab concentration

Serum rituximab (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 undetectable (i.e., below the lower limit of quantification for the assay of 500 ng/mL).

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). After 37 weeks, serum RTX will be assessed for exploratory purposes. The results after 37 weeks will not impact eligibility. The serology for RTX concentration should not be assessed for subjects who never received RTX.

RTX concentration in serum should be obtained prior to performing any other screening procedure, unless the investigator has determined that the subject must obtain access to anti-cancer therapy as soon as possible.

6.4.10. Serology – HIV, HBV and HCV

The serology for individual viruses **<u>may</u>** be omitted at screening at the investigator's discretion if seronegativity has been previously documented and there are no signs of the corresponding viral infection.

If applicable, viral serology assessments will include the following parameters:

Human immunodeficiency virus (HIV)

- Anti-HIV-1 antibody
- Anti-HIV-2 antibody

Hepatitis B virus (HBV)

- HBsAg
- Anti-HBsAg antibody
- Anti-HBcAg antibody

Hepatitis C Virus (HCV)

- HCV-RCV-RNA quantitation
- Anti-HCV antibody

6.4.11. 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 72 hours before the start of treatment)
- Within 72 h before the start of treatment in each cycle
- At the EoT Visit

6.5. Drug administration

Drug administration schedule and study's specific handling instructions are described in Section 5.

6.6. 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 pre-specified time points listed below.

Cycle 1

- Dose 1 (Day 1):

- Within 4 h before the start of MT-3724 infusion (SOI)
- Within 10 minutes before the end of infusion (EOI)
- At the following times after the EOI:
  - 5 minutes (±1 min)
  - 0.5 h, 1 h, 2 h (±5 min)
  - 3 h and 4 h (±10 min)

- Dose 3 (Day 5):
  - Within 4 h before the start of MT-3724 infusion (SOI)
  - Within 10 minutes before the end of infusion (EOI)
  - At the following times after the EOI:
    - 5 minutes (±1 min)
    - 2 h (±5 min)
- Dose 6 (Day 12):
  - Within 4 h before the start of MT-3724 infusion (SOI)
  - Within 10 minutes before the end of infusion (EOI)
  - At the following times after the EOI:
    - 5 minutes (±1 min)
    - 2 h (±5 min)

Cycles 2-4

- Dose 1 (Day 1):
  - Within 4 h before the start of MT-3724 infusion (SOI)
  - Within 10 minutes before the end of infusion (EOI)
  - At 5 minutes (±1 min) after the EOI

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.

The PK of gemcitabine and oxaliplatin will not be assessed in this study.

6.7. Efficacy Assessments

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

- At screening (except if an existing scan of the same lesion(s) obtained within 28 days before the start of treatment is available)
    - The investigator is encouraged to obtain the screening tumor scan as close as possible to the start of treatment, as the advanced, R/R DLBCL is commonly aggressive and grows rapidly.
- Within 7 days before the start of treatment on C3D1 (end of C2)
- Between D23 and D28 of C4 (end of C4, if applicable) and each even numbered cycle thereafter in cases where treatment was continued past C4.
- Within 7 days of the EoT Visit (**only** if the previous tumor scan has been performed >4 weeks before the EoT Visit)

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

Efficacy (tumor response) will be assessed by the scan of all anatomic regions involved with the measurable disease. Positron emission tomography-computed tomography (PET-CT) should be used in subjects with fluorodeoxyglucose (FDG)-avid tumor histology. Computed tomography (CT) or magnetic resonance imaging (MRI) should be used in subjects with tumor histology of low or variable FDG avidity.

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 (20) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (21). An overview of NHL response criteria in subjects with FDG avid NHL is presented in APPENDIX D. 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).

6.7.1. 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.

6.8. Immunogenicity Assessments

Blood samples will be collected at pre-specified time points for the assessment of immunogenicity of MT-3724 [anti-drug antibody (ADA) titer and neutralizing antibody (NA)].

The immunogenicity samples will be collected at pre-specified time points listed below.

- At screening
- Day 1 of each cycle (at any time before the start of MT-3724 infusion)
- At the EoT Visit

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

6.9. Pharmacodynamic Assessments

6.9.1. Peripheral blood

The pharmacodynamics (PD) markers in this study will be the B-cell count 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
- Day 1 in each cycle (at any time before the start of MT-3724 infusion on the dosing day)
- Day 12 of C1-C2 (at any time before the start of MT-3724 infusion on the dosing day)
- Day 15 of C3-C4 (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.

6.10. Optional Tumor Tissue Biopsy

In Part 2 of the study an optional FNA biopsy will be obtained at EoT in patients who consented for this procedure and exhibit PD and have accessible peripheral lymph node(s). The purpose of biopsy is to assess the CD20 status of DLBCL by IHC staining of the fine needle aspirate and determine if the B-cell lymphoma cells have lost CD20 positive status.

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 a FDA 21 CFR Part 11 compliant electronic case report form (eCRF), also known as the electronic data capture (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 (SAS); the SAS 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

Up to 64 subjects (i.e., up to 24 subjects in Part 1 and up to 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 GEMOX in Part 1.

This is an exploratory Phase 2a study, so the formal power calculation is not deemed necessary to justify the sample size. 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

All subjects who received at least one dose of any study drug (either MT-3724, or gemcitabine or oxaliplatin) will be included in the safety population. The safety population will be used for the primary statistical analysis of safety and efficacy endpoints.

7.4.2. Efficacy Population

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

7.4.3. PK 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 gemcitabine or oxaliplatin 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 gemcitabine or oxaliplatin but haven't received MT-3724 will be excluded from the immunogenicity analyses.

7.4.5. PD 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 gemcitabine or oxaliplatin 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.

Early withdrawals (i.e., subjects who did not complete 4 cycles of MT-3724+GEMOX) and the reason for withdrawal will be tabulated. The number and percentage of subjects who complete the study (i.e., complete 4 treatment cycles of MT-3724+GEMOX), and dropouts (i.e., subjects who withdraw consent, are discontinued from the study or die) will be tabulated. If dropouts are numerous or concentrated in specific cohort(s), safety assessments among dropouts 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 (BLQ) 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 CV (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 SAEs, presented by treatment group / cohort and overall, based on:

- The type, incidence, severity, timing, seriousness, relatedness and outcome of adverse events. In particular, the following AE categories will be evaluated:
- Incidence of DLT and TEAEs that led to treatment modification
- Recording of Infusion-related reactions (IRR), cytokine release syndrome (CRS) and capillary leak syndrome (CLS)
- Results of vital sign assessment (blood pressure, heart rate and body temperature)
- Results of ECG assessment
- Results of clinical chemistry, hematology, thyroid function, coagulation, and urinalysis tests
- Changes in physical examination
- Results of immunogenicity assessments ADA and NA
- Need for concomitant medications

All safety variables will be descriptively summarized by cohort 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

7.8.1.1. 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 SFU phone call.

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 (SOC) 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 (SOC and PT), 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 were ongoing at consent, as well as the new or worsening AEs reported between the screening medical history and the start of treatment. These AEs will be assessed by verbal probes and from medical history. The pre-treatment AEs will be listed by subject but not summarized.

7.8.1.2. 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.

7.8.1.3. Physical examination

The overall results of the physical examination ('normal', 'abnormal, not clinically significant', or 'abnormal, clinically significant') will be summarized by treatment group / cohort and listed per subject. Comments for abnormal CS results will be listed.

7.8.1.4. 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 vital signs (body temperature, systolic blood pressure, diastolic blood pressure, and heart rate) will be summarized by the descriptive statistics listed above.

ECG results [heart rate, PR, QRS, RR interval, QT, QT interval corrected according to Fridericia's formula (QTcF), and the results of the overall ECG review by the investigator or delegate] 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 (WHO) 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, and by the CT or MRI scan in subjects with low or variable FDG avidity. The investigator at each site will determine the objective tumor response rate (ORR) at each time point based on the rediologist's measurement of all evaluable lesions.

The investigator at each site will determine the objective tumor response rate (ORR) using the five-point scale (5PS) per the Lugano Classification for Lymphoma (20) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (21). An overview of LYRIC is presented in APPENDIX D (0). The best objective tumor 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 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 duration of tumor response (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 DOR will be descriptively summarized by the treatment group / cohort; the exact 95% confidence intervals will also be produced.

7.10. PK analyses

MT-3724 serum concentration time data from all eligible subjects will be subjected to non-compartmental analysis (NCA) using the software package Phoenix WinNonlin (Certera, Princeton NJ). PK 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).

7.11. Immunogenicity analyses

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 NA 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 NA 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. PD 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 immunogenicity 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. DSUR), 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 major deviation occurs, the Investigator must immediately inform the monitor, and the implications of the major deviation must be reviewed and discussed with the sponsor. Major deviations must be documented on the applicable Protocol Deviation Notification Form (PDNF), stating the date and description of the deviation as well as the action taken and the impact on the subject's safety and/or the study results. The PDNF must be kept in the trial master file at the site. Major 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 (or designee), the EU Clinical Trials Directive and the FDA Code of Federal Regulations, the guidelines of the ICH (22), and the most recent guidelines of the Declaration of Helsinki (21).

8.1.2. Independent ethics committee/Institutional Review Board

Conduct of the study must be approved by an appropriately constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Approval is required for the study protocol, Investigator's Brochure, protocol amendments, informed consent form, subject information sheets, patient diaries and other non-CRF data collection documents, and any advertising materials. No study drug will be shipped to the study site until the site has received written IRB or IEC authorization.

The investigator should inform the IRB/IECs about the study progress annually (or as required by the IRB/IEC). The CTI Safety Department (contact details on page 4) will also submit to IRB/IEC periodic reports of any reportable adverse events per ICH guidelines and local requirements.

The IRB/IEC and Competent Authorities will be notified of the end of the trial per local requirements. Where required, a summary of the study outcome will be provided to the IRB/IEC.

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 standard of care procedures or tests were performed prior to signing of the ICF but are still within 28 days 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 Administrative Changes

Changes to this protocol that would require a substantial amendment according to the EU Guidance (2010/C 82/01) will be implemented via a protocol amendment. A substantial amendment in the EU will be treated as a protocol amendment in the USA per 21 CFR 312.30(b). The sponsor, investigator(s), IRB/IEC and health authorities must approve the protocol amendment before implementation.

The requirements for approval of the substantial changes should not prevent any immediate action from being taken by the investigator or by the sponsor to preserve the safety of study subject(s).

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 TMF. 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 and/or close the site for safety or administrative reasons at any time. Should the sponsor terminate the study and/or close the site for whatever reason, all documentation and study medication pertaining to the study must be returned to the sponsor or its representative, or discarded as instructed by the sponsor or according to institutional guidelines.

8.4. Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential. These documents and/or results should not be disclosed 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 to Good Clinical Practice (GCP) and comply with all applicable federal, state, and local laws and regulations regarding the privacy of subject health information. The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the Code of Federal Regulations, EU Clinical Trials Directive, and EU Law, 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/ECs, 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 Subject Informed Consent Form and Clinical Trial Agreement. Study subjects will not be identified by their names on eCRF or any other documents and biological samples submitted to the sponsor or other parties. Each subject will be assigned an identification number to be used on any data or laboratory samples collected by the sponsor. Documents not for submission to the sponsor (e.g. the signed informed consent forms), 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. If the subject's medical records are shared with the sponsor and/or Medical Monitor (e.g. for the purpose of eligibility review), they must be redacted of all information revealing the subject's identity.

8.5. Study monitoring, Auditing and inspection

CRO personnel will monitor the conduct of this study on behalf of the sponsor. Monitoring will include personal 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 by the sponsor, its designee or by regulatory authorities. According to the GCP, 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, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in CRF 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, see 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.

The Sponsor/CRO will provide the following:

- Backup SAE Forms
- Backup Pregnancy Forms
- Infusion Bag Preparation Sheet (from Pharmacy Manual)

The Central laboratory will provide the following:

- Laboratory Report Correction Request Forms
- Laboratory Requisition Forms
- Laboratory Way Bills

A Clinical Research Associate (CRA) will perform source document verification as per the monitoring plan so 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. A Screen Procedure CRF will be provided. This will be completed beginning at the Screening Visit. It will be the only CRF for subjects who fail one or more screen procedures and never progress to receive study drug. Local laboratory data will be entered into the CRFs by trained and qualified study staff.

Monitors and auditors must have direct 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. If the source document contains a subject's address and phone number, it must be obliterated before it is included as a study document and the subject's name will be obliterated except for the first letters of the first, middle (if present), and last names.

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 Principal Investigator and signed by the Principal 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 Principal 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 or CRO acting as an agent of 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 sponsor's TMF.

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 disclosures and publications

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

By signing the study protocol, the investigator agrees to the sponsor's use of the study results for the national and global regulatory filings of the study drug for marketing approval. If necessary, the authorities will be notified of the investigator's name, address, qualifications,

and extent of involvement. The sponsor will prepare a final integrated study report covering clinical and biometric aspects of the study 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/CRO, as appropriate.

9. REFERENCES

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APPENDIX A. SCHEDULE OF ASSESSMENTS (SOA)

SOA FOR SCREENING PERIOD

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

Assessments and Procedures	**Within 28 days of dosing on C1D1**	**Within 72 h of dosing on C1D1**
Informed consent	X	
Demographics	X	
Height	X	
Body weight	X	X
BMI	X	
BSA	X	
Medical history[1,2]	X	
NHL disease status (at initial diagnosis and after relapse)[3]	X	
NHL disease status (current)[4]	X	
Prior Medications[5]	X	X
Prior systemic NHL therapy[6]	X	
Prior NHL radiotherapy[7]	X	
Complete physical exam (with NYHA and ECOG)	X	
Abbreviated physical exam (with ECOG)		X
Body temperature	X	X
Blood pressure and heart rate[8,10]	X	X
12-lead ECG (triplicate)[9,10]	X	
LVEF (MUGA or Echocardiogram)[11]	X	

Radiological tumor assessment (PET-CT or CT/MRI)[12,13]	X	
CENTRAL LABORATORY		
Serum rituximab level (if applicable)[14,15]	X	
Hematology	X	
Chemistry (with eGFR[16])	X	
HbA1c	X	
Coagulation (PT or INR, aPTT)	X	
Thyroid function (TSH, FT4)	X	
Beta-2 microglobulin	X	
Cytokines	X	
MT-3724 Immunogenicity (ADA/NA)	X	
B-cell count and immunophenotype (flow cytometry)	X	
Complement	X	
Histamine	X	
Immunoglobulins	X	
LOCAL LABORATORY		
Urinalysis (Dipstix)[17]	X	
Serology for HIV, HBV and HCV[18,19]	X	
Pregnancy (serum or urine)		X
Check of new or worsening illnesses[20]		X
Check of all inclusion/exclusion criteria	X	X

Abbreviations: ADA – Anti-drug antibodies; **aPTT** – Activated partial thromboplastin time; **C** – Cycle; **CT** – Computed tomography; **D** – Day in cycle; **ECG** – Electrocardiogram; **ECOG** – Eastern Cooperative Group of Oncology; **eGFR** – Estimated glomerular filtration rate; **FT4** – Free thyroxine; **HbA1c** – Glycated hemoglobin; **HBV** – Hepatitis B virus; **HCV** – Hepatitis C virus;

HIV – Human immunodeficiency virus; **INR** – International normalized ratio; **LVEF** – Left Ventricular Ejection Fraction; **NA** – Neutralizing antibodies; MRI – Magnetic resonance imaging; **MUGA** – Multigated acquisition; **NYHA** – New York Heart Association; **PET** – positron-emission tomography; **PT** – Prothrombin time; **TSH** – Thyroid-stimulating hormone.

Footnotes:

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.
2. Illnesses that are active at the time of informed consent should be captured in the medical history as concomitant illnesses.
3. 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).
4. NHL disease status (current) will include the same as for the status at initial diagnosis plus the mutational status.
5. Prior medication is any medication (either prescription and OTC) used within 4 weeks prior to the start of treatment. Prior therapy for NHL should be captured separately from prior medications.
6. Prior systemic therapy for NHL 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.
7. Prior radiotherapy for NHL administered at any time before the start of treatment.
8. Blood pressure (systolic and diastolic) and heart rate should be measured after 5-10 minutes of quiet rest in a sitting or semi-recumbent position.
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. When ECG and blood pressure assessments are scheduled to occur at the same time point, then the ECG should be performed first (occurring after 5-10 quiet rest in supine or semi-recumbent position) and the blood pressure / heart rate measurement may begin immediately after ECG recording (without additional 5-10 minutes' rest).
11. If prior LVEF is not available within 3 months before the start of treatment
12. A scan of all anatomic regions involved with the measurable disease by PET-CT (in subjects with FDG-avid tumor histology) or CT or MRI (in subjects with tumor histology of low or variable FDG avidity).
13. Screening tumor assessment may be omitted at the investigator's discretion if a scan of the same lesion(s) obtained within 28 days before the start of treatment is already available. The investigator is encouraged to obtain

the screening tumor scan as close as possible to the start of treatment, as the advanced R/R DLBCL is often aggressive and grows rapidly

14. Serum rituximab (RTX) level should be assessed in all subjects who received RTX within 37 weeks before the start of treatment.
15. Serum RTX level (where indicated) should be determined prior to performing any other screening procedure, unless the investigator has determined that the subject must obtain access to anti-cancer therapy as soon as possible.
16. Calculated by the central laboratory using CPK-EPI formula and the serum creatinine from the corresponding chemistry panel
17. Analysis of urine microsediment may be performed at the investigator's discretion.
18. 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.
19. If applicable, serology should include anti-HIV1 and anti-HIV2 antibodies, HBsAg, anti-HBsAg and anti-HBcAg antibodies, HCV-RCV-RNA quantitation and anti-HCV antibody.
20. New illnesses and/or worsening of concomitant illnesses detected by verbal probes or subject's spontaneous reports between the screening medical history and the start of treatment should be reported as pre-treatment adverse events

SOA FOR TREATMENT AND FOLLOW-UP PERIODS

The schedule of assessments for the treatment and long-term follow-up periods will be the same in Part 1 and Part 2, as outlined below. Unscheduled assessments may be performed at any time at the investigator's discretion.

Visit / Day	**Treatment Period (1 cycle = 28 Days)**												
	Day 1–Day 22										**Day 22–Day 28**	**End of Treatment (EoT) Visit**	Safety Follow-up phone call (SFU)
	1 (D1)	**2** (D2)	**3** (D3)	**4** (D5)	**5** (D8)	**6** (D10)	**7** (D12)	**8** (D15)	**9** (D16)	**10** (D22)	**11**	**12**	13
TREATMENTS IN CYCLES 1-2													
Premedication for MT-3724[1]	X		X	X	X	X	X						
MT-3724[2,3]	X		X	X	X	X	X						
Gemcitabine[4]		X							X				
Oxaliplatin[5,6]		X							X				
TREATMENTS IN CYCLES 3-4 (AND FURTHER IF APPLICABLE)[7]													
Premedication for MT-3724[1]	X				X			X		X			
MT-3724[8]	X				X			X		X			
Gemcitabine[4]		X							X				
Oxaliplatin[5,6]		X							X				
STUDY PROCEDURES IN CYCLES 1-4													

Blood pressure and heart rate[9,10,16]	X											X	
Body temperature[11]	X								X			X	
Complete PE (with NYHA and ECOG)												X	
Abbreviated PE (with ECOG)[12]	X								X				
Body weight[13.14]	X								X			X	
12-Lead ECG (single)[15,16]	X											X	
LVEF (MUGA or Echocardiography)												X	
Radiological tumor assessment (PET-CT or CT/MRI)[17,18,]											X	(X)[18]	
Concomitant medications[19]	X										X	X	X
AEs[19]	X										X	X	X
LOCAL LAB ANALYSES													
Urinalysis (Dipstix)[20]	X				X			X	X	X		X	
Pregnancy[21]	X											X	
CENTRAL LAB ANALYSES													
Hematology	X				X			X	X	X		X	
Chemistry (incl. eGFR[22])	X				X			X	X	X		X	

Coagulation (PT or INR, aPTT)	X										X	
HbA1c											X	
Thyroid function (TSH, FT4)											X	
Complement[23,24]	X										X	
Histamine[23,24]	X										X	
Immunoglobulins[23]	X										X	
Cytokines[23,24]	X										X	
B-cell count and immunophenotype (flow cytometry)[25]	X						X[26]	X[27]			X	
MT-3724 Immunogenicity (ADA/NA)[28]	X										X	
MT-3724 PK[29]	X			X			X					
FNA biopsy (optional, part 2)[30]											X	

ADA – Anti-drug antibodies; **aPTT** – Activated partial thromboplastin time; **C** – Cycle; **CT** – Computed tomography; **D** – Day in cycle; **ECG** – Electrocardiogram; **ECOG** – Eastern Cooperative Group of Oncology; **eGFR** – Estimated glomerular filtration rate; **FT4** – Free thyroxine; **HbA1c** – Glycated hemoglobin; **INR** – International normalized ratio; **LVEF** – Left Ventricular Ejection Fraction; **NA** – Neutralizing antibodies; **MRI** – Magnetic resonance imaging; **MUGA** – Multigated acquisition; **NYHA** – New York Heart Association; **PET** – positron-emission tomography; **PK** – Pharmacokinetics; **PT** – Prothrombin time; **TSH** – Thyroid-stimulating hormone.

Footnotes:
1. Premedication should be administered within 60 minutes before the start of MT-3724 infusion in each cycle in both parts of the study. See Section 5.1.4

2. In C1 and C2, MT-3724 should be administered as 1-hour IV infusion on Day 1, 3, 5, 8, 10 and 12 of each 28-day cycle. At the investigator's discretion, MT-3724 may be administered on different days up to D21. MT-3724 should not be administered between D22-D28.
3. No more than two MT-3724 doses can be administered on consecutive days. If MT-3724 is administered on 2 consecutive days in C1 and C2, then at least 20 hours must elapse between the start of the 2 infusions.
4. In all cycles, gemcitabine 1000 mg/m^2 should be administered as 30-minute IV infusion on Day 2 and Day 16 of each 28-day cycle. At the investigator's discretion, gemcitabine may be administered within ±2 days from scheduled dosing days. Gemcitabine should not be administered between D24-D28.
5. In all cycles, oxaliplatin (Eloxatin®) 100 mg/m^2 should be administered as 2-hour IV infusion after gemcitabine on Day 2 and Day 16 in each 28-day cycle. At the investigator's discretion, oxaliplatin may be administered within ±2 days from scheduled dosing days. Oxaliplatin should not be administered between D24-D28.
6. Oxaliplatin infusion will start one hour after the start of gemcitabine infusion (unless a delay is warranted at the investigator's discretion).
7. After C2, treatment with MT-3724 and/or GEMOX may be continued for another 2 (or more) cycles of 28 days each, if supported by the investigator's assessment of the benefit-risk ratio after consultation with sponsor and Medical Monitor
8. In C3 and C4 (and thereafter), MT-3724 should be administered as 1-hour IV infusion weekly, i.e. on Day 1, 8, 15 and 22 of each 28-day cycle. At the investigator's discretion, MT-3724 may be administered within ±2 days from scheduled dosing days in C3 and C4. MT-3724 should not be administered between D24-D28.
9. Blood pressure (systolic and diastolic) and heart rate should be performed at the following times on each dosing day in each cycle: at any time before the start of MT-3724 infusion; at 0.5 h, 1 h, 2 h and 3 h after the start of each MT-3724 infusion in each cycle (±10 min allowed at each time point); at any time before the start of gemcitabine infusion; at 3 h (±10 min) after the start of oxaliplatin infusion in each cycle; at the EoT Visit
10. Blood pressure and heart rate should be measured after 5-10 minutes of quiet rest in a sitting or semi-recumbent position.
11. Body temperature assessment should be performed at any time before the start of MT-3724 infusion on D1 of each cycle, at any time before the start of gemcitabine infusion on D16 of each cycle, and at the EoT Visit
12. Abbreviated physical exam. should be performed at any time before the start of MT-3724 infusion on D1 of each cycle (within 72 h before the start of MT-3724 infusion on C1D1 is allowed), and at any time before the start of gemcitabine infusion on D16 of each cycle.
13. Body weight assessment will be performed at any time before the start of MT-3724 infusion on each dosing day in each cycle, and at the EoT Visit.
14. Body weight measured before the first dose of MT-3724 in each cycle will be used to calculate all MT-3724 doses in that cycle.
15. Single 12-lead ECG should be obtained after the subject has rested quietly in supine or semi-recumbent position for 5-10 minutes before the procedure.
16. When PK, ECG and blood pressure assessments are scheduled to occur at the same time point, then the PK sample collection should be performed at the protocolled time and the ECG and blood pressure / heart rate should be done in that order at least 10 minutes before or 10 minutes after the PK sampling. In this case, the blood pressure / heart rate measurement may begin immediately after ECG recording (without additional 5-10 minutes' rest).
17. 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).
18. Radiological assessment of tumor response should be performed within 7 days before the start of treatment on C3D1 (end of C2); between D23 and D28 of C4 (and end of each even cycle thereafter, if applicable); within 7 days of the EoT Visit (only if the previous tumor scan has been performed >4 weeks before the EoT Visit).
19. Concomitant medications and treatment-emergent adverse events will be reported by verbal probes at every visit to the clinic; in addition, subject's spontaneous reports will be captured.
20. Analysis of urine microsediment may be performed at the investigator's discretion.
21. Pregnancy test (serum or urine) should be performed within 72 h before the first dose of the first study drug in each cycle and at the EoT Visit.
22. Estimated by the central laboratory using CPK-EPI equation and the serum creatinine from the corresponding chemistry panel

23. Cytokines, histamine, complement and immunoglobulins should be assessed before the start of MT-3724 infusion (±10 min) on D1 of each cycle and at 3 h after the start of MT-3724 infusion (±10 min) on D1 of each cycle.
24. 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.
25. B-cell count and immunophenotype by flow cytometry should be performed on D1 of each cycle (at any time before the start of MT-3724 infusion) and at the EoT Visit in all cycles
26. B-cell count and immunophenotype by flow cytometry should be performed on D12 of C1 and C2 only (at any time before the start of MT-3724 infusion).
27. B-cell count and immunophenotype by flow cytometry should be performed on D15 of C3 and C4 only (at any time before the start of MT-3724 infusion).
28. Immunogenicity of MT-3724 (ADA and NA) should be performed at any time before the start of MT-3724 infusion on D1 of each cycle
29. PK assessments should be made at the following time points:
    - C1D1 (MT-3724 Dose 1)
        - Within 4 h before the start of infusion (SOI)
        - Within 10 minutes before the end of infusion (EOI)
        - At the following times after the EOI: 5 minutes (±1 min); 0.5 h, 1 h, 2 h (±5 min each); 3 h and 4 h (±10 min each)

    - C1D5 (MT-3724 Dose 3)
        - Within 4 h before the SOI
        - Within 10 minutes before the EOI
        - At the following times after the EOI: 5 minutes (±1 min) and 2 h (±5 min)

    - C1D12 (MT-3724 Dose 6)
        - Within 4 h before the SOI
        - Within 10 minutes before the end of infusion (EOI)
        - At the following times after the EOI: 5 minutes (±1 min); 2 h (±5 min)

    - Day 1 of Cycles 2-4 (MT-3724 Dose 1)
        - Within 4 h before the SOI
        - Within 10 minutes before the EOI
        - At 5 minutes (±1 min) after the EOI
30. Optional FNA biopsy at EoT for patients in Part 2, who had consented for this procedure, exhibit PD and have accessible peripheral lymph node(s).

APPENDIX B. LABORATORY PANELS

Hematology (central laboratory):				
WBC[1]	hemoglobin	platelet count	hematocrit	RBC and indices[2]
Chemistry (central laboratory):				
albumin	amylase	lipase	creatinine	ALT [SGPT]
AST [SGOT]	CPK	calcium	chloride	GGT
LDH	serum glucose[3]	magnesium	phosphorous	potassium
sodium	bilirubin (total and direct)	total protein	BUN	Uric acid
eGFR[4]	β-HCG[5]	histamine	HbA1c	β-2microglobulin
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	NA	B-cell count

Abbreviations: 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; 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; NA – Neutralizing antibodies; PT – Prothrombin time; RBC – Red Blood Cell;

SGOT - serum glutamic-oxaloacetic transaminase; SGPT - serum glutamic-pyruvic transaminase; TSH – Thyroid-stimulating hormone; WBC – white blood cell.

Footnotes:

[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, CKD-EPI calculation, see APPENDIX F

[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 C. Staging of NHL

The Ann Arbor stage of NHL with Cotswolds modification (25) is determined as outlined in Table 6, 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 6 : Ann Arbor Staging System for NHL with Cotswolds Modification

Stage[a]	**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[b]	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 Ann Arbor stages	
A	No symptoms
B	Fever (>38oC), drenching sweats, weight loss (10% body weight over 6 months)
For Ann Arbor Stages I to III	
E	Involvement of a single, extra nodal site contiguous or proximal to known nodal site
X	Massive mediastinal disease has been defined by the Cotswold meeting as 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.

a. The number of anatomic regions involved should be indicated by a subscript (e.g., II_3). Staging should be identified as clinical stage (CS) or pathologic stage (PS).

b. Stage III may be subdivided into: III1, with or without splenic, hilar, celiac, or portal nodes; III, with para-aortic, iliac, mesenteric nodes.

International prognostic index for aggressive NHL

At screening, the prospective subjects will be classified in to one of the 4 risk groups according to the International Prognostic Index (IPI) for aggressive NHL (24). The classification will be determined in 2 steps, as follows.

1. One point is assigned for each of the following risk factors:
    a. Age greater than 60 years
    b. Stage III or IV disease according to the Ann Arbor staging with Cottswolds modification (25)
    c. Elevated serum LDH
    d. ECOG/Zubrod performance status of 2, 3, or 4
    e. More than 1 extranodal site
2. The sum of the points allotted correlates with the following risk groups:
    a. Low risk (0-1 points) - 5-year survival of 73%
    b. Low-intermediate risk (2 points) - 5-year survival of 51%
    c. High-intermediate risk (3 points) - 5-year survival of 43%
    d. High risk (4-5 points) - 5-year survival of 26%

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 patients 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 D. REVISED LUGANO CLASSIFICATION OF RESPONSE ASSESSMENT IN LYMPHOMA ADJUSTED FOR LYRIC

Tumor response will be evaluated according to the revised Lugano Classification for Lymphoma (20) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (21). Positron emission tomography-computed tomography (PET-CT) should be used for response assessment in subjects with fluorodeoxyglucose (FDG)-avid tumor histology (using the 5-point scale [5PS]); computer tomography (CT) or magnetic resonance imaging (MRI) is preferred in subjects with tumor histology of low or variable FDG avidity.

Overview of response criteria for FDG avid and non-avid NHL is presented in Table 7.

Table 7: 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* 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	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease

	normal tissue even if the tissue has high physiologic uptake	
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 (see Table 10) 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 or MRI, 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	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	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	Regrowth of previously resolved lesions A new node >1.5 cm in any axis

	another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	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)**	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)

Abbreviations:

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.

Footnotes:

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in 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), GI 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., GI 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).

** See original paper (Cheson BD. et al. J Clin Oncol 2014; 32: 3059-3067) for more detailed information on immune related response.

Lugano 5PS scale (21)

The Lugano 5-point scale (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) see Table 8. 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.

Table 8: 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 E. DOSE LIMITING TOXICITY CRITERIA

General Principles

A treatment-emergent adverse event (TEAE) will be declared as DLT if both of the following criteria are met:

1. The TEAE occurred after the start of infusion in C1 of Part 1.
    a. If a TEAE that fulfills a DLT criterion is observed in C ≥2 of Part 1, then the sponsor may declare this event a DLT after consultation with the investigator and Medical Monitor.
2. TEAE is at least possibly related to MT-3724 (i.e., not reasonably related to another etiology), as determined by the sponsor after consultation with investigator and Medical Monitor.

Note: If a Grade ≥3 TEAE related to gemcitabine or oxaliplatin is more severe than the worst grade described in the reference prescribing information, or hasn't been reported in the reference prescribing information, then the sponsor may declare this event a DLT after consultation with the investigator and Medical Monitor.

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

TEAEs potentially qualifying as DLT

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

Non-hematological TEAEs

- Grade ≥2 Cytokine Release Syndrome
- Grade ≥2 Capillary Leak Syndrome

- Grade ≥2 acute kidney injury (serum creatinine increase ≥2 times above baseline in the absence of dehydration or bleeding)
- AST and / or ALT increase >5.0 times ULN (CTCAE Grade ≥3)
- AST and / or ALT increase >3.0 times ULN (CTCAE Grade ≥2) with concomitant increase in total bilirubin >1.5 times ULN (CTCAE Grade ≥2)
- Total bilirubin >3.0 times ULN (CTCAE Grade ≥3)
- 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. The exception is allowed for isolated Grade 3 or 4 electrolyte abnormalities without a clinical correlate that don't 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 Medical Monitor and investigator.
- 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 and Medical Monitor, 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 F. CKD-EPI Creatinine Equation (2009)

Expressed as a single equation:

$$\mathbf{eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [if\ female] \times 1.159\ [if\ Black]}$$

Abbreviations / Units

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2

SCr (standardized serum creatinine) = mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males)

min = indicates the minimum of SCr/κ or 1

max = indicates the maximum of SCr/κ or 1

age = years

Assays

Creatinine is assayed using methods that are traceable to IDMS assigned NIST certified reference materials. To learn more, go to nkdep.nih.gov.

Clinical Use

Recommended method for estimating GFR in adults.

Designed for use with laboratory creatinine values that are standardized to IDMS.

Estimates GFR from serum creatinine, age, sex, and race.

More accurate than the MDRD Study equation, particularly in people with higher levels of GFR.

Based on the same four variables as the MDRD Study equation, but uses a 2-slope “spline” to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex and race.

Some clinical laboratories are still reporting GFR estimates using the MDRD Study equation. The National Kidney Foundation has recommended that clinical laboratories should begin using the CKD-EPI equation to report estimated GFR in adults.

Developed in 2009 by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI 2009].

APPENDIX G. ECOG PERFORMANCE STATUS

The ECOG performance status (22) will be assessed as part of the complete and abbreviated physical examinations during the screening, treatment and long-term follow-up periods (see Section 6.2.3 and APPENDIX A).

The criteria for the assessment of the ECOG performance status (22) are presented in Table 9

Table 9: ECOG Performance Status

Grade	ECOG performance status scale
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light house work, office work)
2	Ambulatory and capable of all 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	Dead

ECOG = Eastern Cooperative Oncology Group

APPENDIX H. NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

The status of heart function will be assessed according to the NYHA classification (23) as part of the complete physical examination at screening and the EoT Visit (see Section 6.2.3 and APPENDIX A).

The NYHA classes are presented in Table 10.

Table 10: NYHA Function Classification

NYHA class	Symptoms
I	No symptoms and no limitation in ordinary physical activity (e.g., shortness of breath when walking or climbing stairs)
II	Mild symptoms (mild shortness of breath and / or angina) and slight limitation during ordinary activity
III	Marked limitation in activity because of symptoms, even during less-than-ordinary activity, e.g., walking short distances (20 - 100 m); comfortable only at rest
IV	Severe limitations; experiences symptoms even while at rest; mostly bedbound patients

NYHA = New York Heart Association

APPENDIX I. Summary Of Changes

List of Changes and Rationale: Amendment 1.0

	Topic	Change	Rationale
1.	Protocol Title	Removed "CD20" from protocol title	To be in alignment with study population description
2.	Protocol Version	Changed from Version 1.0 to Amendment 1, Version 2.0	To account for the amendment
3.	Signature Page/List of Contacts	Changed medical representative name	To account for change in MTEM study management
4.	Objectives/Study Design	Removed "CD20" from protocol title	To be in alignment with study population description
5.	End of Treatment Visit	EoT VISIT should occur ~~≥ 14 days and ≤ 21 days after the last dose of MT-3724, gemcitabine or oxaliplatin, whichever is last~~, at the time of discontinuation (except for subjects who died, withdrew consent and objected to further data collection, or were lost to follow up).) or ≥ 7 days and ≤ 14 days after the last dose of MT-3724, gemcitabine or oxaliplatin for those that complete the study.	Edits to clarify when visit takes place

6.	Safety Follow-Up	Changed the safety follow-up (SFU) phone call: ~~approximately~~ at least 30 days after last dose of MT-3724 or GEMOX	To stipulate that a minimum of 30 days must elapse before the follow-up
7.	Gemcitabine and Oxaliplatin Dose	Changed from requiring a fixed starting and ongoing doses of gemcitabine and oxaliplatin to add allowance for the doses to be decreased per investigators discretion based prescribing information and patient status.	To allow flexibility for the dosing based on investigator and site practices
8.	Long-Term Follow Up	Revised to add subjects will be followed for 24 months for PFS and DOR until progressive disease, death or lost to follow up.	Long-term follow up has been revised to clarify information to be collected.
9.	Patient Population	Reference to CD20-positive histology removed in the description of the patient population and throughout the document and added as inclusion criterion 3.d.	Inclusion criterion 3.d. provides a more detailed description of the requirement for CD20 histology.
10.	Inclusion Criteria	Criterion 3: Changed 3. Have ~~histologically confirmed~~, relapsed or refractory ~~CD20-positive~~ B-cell NHL that, in the investigator's opinion, could benefit from MT-3724 + GEMOX therapy. ~~NHL histology must be determined at any time after the most recent~~ At least one histologically documented relapse of NHL by: a. Bone marrow biopsy (FNA not acceptable) or	Changes made to allow more flexibility in timing of required histology and allowance of mixed DLBCL histology in Part 2

		b. Excisional lymph node biopsy (FNA or ~~other procedure~~ not acceptable) or c. Core biopsy of any involved organ ~~(FNA not acceptable)~~ d. CD20-positive histology must have been confirmed at any time during NHL disease course and documented in medical history. e. If no histology is available after any relapse the investigator can consult the medical monitor to discuss if the patient can be included.	
11.	Inclusion Criteria	Inclusion criterion 4 Added "mixed histology" in the description of NHL subtypes	To clarify that DLBCL mixed histology will be accepted in Part 2 of the study
12.	Inclusion Criteria	Removed IPI and Ann Arbor staging requirements	Since the patient population is relapsed/refractory, prognostic scoring is not needed
13.	Inclusion Criteria	Removed CTCAE grading	redundant
14.	Inclusion Criteria	Inclusion Criterion 8: Changed calculation to be used for kidney function from Cockcroft and Gault's to CPK-EPI	The updated formula is SOC
15.	Inclusion Criteria	Inclusion Criterion 9b and c:	To include patients with liver involvement

		Added allowance for ≤ 5.0 x ULN if liver involvement	
16.	Inclusion Criteria	Inclusion Criterion 11 added: 12. Have adequate serum albumin, as determined by: a. Albumin ≥ 3.0 g/dL	For added safety
17.	Exclusion Criteria	8e. added additional detail to criterion for congestive heart failure: e. Congestive heart failure (NYHA Class III or IV;APPENDIX H) at screening or LVEF <45%, assessed by Echo or MUGA scan within 1 month before starting study treatment. (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).	For greater flexibility in assessing heart failure
18.	Exclusion Criteria	Prior Treatments: 10 – added b. and c. b. Subjects with positive HBV serology are eligible if quantitative PCR for plasma HBV-DNA is negative and the subject will be receiving prophylaxis for potential HBV reactivation.	To provide additional detail on viral test results and related actions

		c. Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is negative.	
19.	Exclusion Criteria	Prior Treatments: 14 Reduced the required rituximab washout from 110 days to 84 days and reduced the required testing period from 365 days to 37 weeks. Note: All enrolled subjects will be tested for serum rituximab, but only the result out to 37 wks will be used for exclusion.	Updated based on most recent MTEM clinical data
20.	Exclusion Criteria	Prior Treatments: 15. Received therapy for NHL (excluding the anti-CD20 MAbs listed above) ~~or any investigational treatment~~ within ~~3~~ 4 weeks ~~or 5 half-lives~~ of the agent before the start of treatment, ~~whichever is longer~~.	Added exclusion 16 for any investigational treatments
21.	Exclusion Criteria	Prior Treatments: Added criterion 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."	To exclude patients that may be on other investigation treatments not already listed
22.	Exclusion Criteria	Exclusion Criterion 17	For added clarity

		Added "according to Lugano Classification for NHL"	
23.	Exclusion Criteria	Exclusion Criterion 18 Removed the need for consultation with medical monitor	Not required
24.	Treatments	Oxaliplatin 100 mg/m^2 will be administered as 2-hour IV infusion after gemcitabine on Day 2 and Day 16 of each 28-day cycle. Oxaliplatin infusion will start ~~exactly~~ one hour after the start of gemcitabine infusion (unless a delay is warranted at the investigator's discretion).	To allow for reasonable flexibility in timing of dosing
25.	Treatment Duration (section 5.9)	Added: "If the subject exhibits SD, CR or PR after the end of Cycle 4 and the investigator determines that the benefit-risk ratio is favorable, then the treatment with MT-3724 may be continued after discussion with the sponsor. Continuation of GEMOX is at investigators discretion."	To allow for continued dosing with up to 6 additional cycles of MT-3724 for subjects who respond
26.	Clinical Experience (section 1.2.1)	Removed "Hypertension" and added updated clinical data	To be in alignment with updated IB
27.	MTD Definition (section 3.6.3)	Added "with a maximum total dose of 6000 µg" to the MTD definition	To further clarify the definition

28.	MTD Communication Plan (section 3.6.4)	Added "If the Medical Monitor and sponsor become aware that the MTD may be declared in the current dose cohort (e.g. based on the occurrence of qualifying AE/SAE in ≥2 subjects), then they will inform the investigators that recruitment should be suspended pending the safety review meeting."	To provide additional detail within the protocol
29.	Guidance to the Investigator	Section 3.9 Guidance to the Investigator added	For safety guidance in alignment with updated IB
30.	Treatments (Section 5)	Removed the requirement for assisted ventilation in the treatment area and added requirement to have access to emergency facilities through an emergency call.	To allow some flexibility with the requirements for treatment areas
31.	Table 2 & Table 3: Dose Adjustments	Changed from Dose-level decreases to % decreases and adjusted the number of days to trigger a dose adjustment. Added statement allowing for repeated dose reductions.	More accurate and consistent
32.	Prohibited Medication (section 5.10)	Reduced the required rituximab washout from 110 days to 84 days and reduced the required testing period from 365 days to 37 weeks. Note: All enrolled subjects will be tested for serum rituximab, but only the result out to 37 wks will be used for exclusion.	Updated based on most recent MTEM clinical data

33.	Prohibited Medication (section 5.10)	Added: "Subjects must not have received any vaccines from 28 days before the start of treatment until 28 days after the last dose of MT-3724. The single exception to this exclusion is for the injectable flu vaccine (inactivated or recombinant), which may be administered at the investigator's discretion at any time during the above period"	To be in alignment with inclusion/exclusion criteria
34.	Permitted Medication (section 5.11)	Added: "The injectable flu vaccine may be administered at the investigator's discretion from 28 days before the start of treatment until 28 days after the last dose of MT-3724, and at any time thereafter. If the investigator allows the flu vaccine, they should carefully assess if it is appropriate to administer the flu vaccine before all study-related laboratory abnormalities or AEs have resolved. The subjects treated with B-cell depleting MAbs have been shown to have impaired humoral immune responses to neo-antigens for variable periods of time following the B-cell depleting treatment."	To be in alignment with inclusion/exclusion criteria
35.	Study Assessments (section 6.1.2)	Removed: "Body weight measurement before the first dose of MT-3724 in each cycle will be used to calculate all MT-3724 doses in that cycle"	More accurate description of how body weight is to be used for dose calculation is provided below in the same section.

36.	Study Assessments (section 6.1.4)	Added the collection of available data on mutational status at screening	To further characterize the assessment of NHL at screening
37.	Study Assessments - Complete physical examination (section 6.2.3.1)	Removed requirement for eye examination/fundoscopy	Not standard of care and not required for this study
38.	Study Assessments – Blood Pressure/Heart Rate (section 6.2.5)	Removed the 3hr assessment after start of MT-3724 infusion in each cycle. Added 3h and 4h assessment after start of MT-3724 infusion on C1D1.	Lessen burned on subjects since a 3h assessment for each cycle would require >2h additional time after every infusion. Instead, added additional assessments only on C1D1 – where there is already an extended visit due to PK sampling.
39.	Adverse Events (section 6.3)	Re-worded	For simplification and clarification of reporting
40.	Adverse Events (section 6.3)	Added “Natural disease progression of the malignancy or deterioration of the patient’s condition under study (including new sites of metastasis and death due to disease progression) will be recorded as part of the	To provide clarity on how certain events should be characterized and reported

		efficacy evaluation and should not be reported as an AE or as an SAE. Discontinuation from the study because of disease progression or deterioration of the patient'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."	
41.	Action Taken with Study Treatment (section 6.3.7) and Outcome (section 6.3.8)	Removed list of specific categories and changed to refer to eCRF guidelines for specifics on selections for documentation	For simplification
42.	Laboratory Tests (section 6.4)	Added Histamine, Immunogenicity of MT-3724; Anti-drug antibodies [anti-drug antibody (ADA) and neutralizing antibody (NA)]	
43.	Laboratory Tests (section 6.4.7)	Added histamine	
44.	Glucose Testing	Change from Plasma to Serum	To be in better alignment with lab practices

45.	Laboratory Testing beta-2 microglobulin (section 6.4.8)	Removed all samples taken after screening	Not needed for the study
46.	Rituximab concentration (section 6.4.9)	Clarified washout period, testing period for eligibility and that testing is to be performed on all eligible subjects such that all enrolled subjects will be tested for serum rituximab, but only the result out to 37 wks will be used for exclusion.	Updated based on most recent MTEM clinical data and so that additional data can be collected for exploratory purposes after week 37.
47.	Pharmacokinetic assessments (section 6.6)	Added: "The PK of gemcitabine and oxaliplatin will not be assessed in this study.	These tests are not needed for the study
48.	Efficacy assessments (section 6.7)	Between D23 and D28 of C4 (end of C4, if applicable) and each even numbered cycle thereafter in cases where treatment was continued past C4.	
49.	Efficacy assessments (section 6.7)	Added "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	To clarify scanning technique for consistency

		whenever possible. Scans must meet the SOC for imaging of lesions in the respective organ system(s).”	
50.	Pharmacodynamic Assessments (section 6.10)	Added: In Part 2 of the study an optional FNA biopsy will be obtained at EoT in patients who consented for this procedure and exhibit PD and have accessible peripheral lymph node(s). The purpose of biopsy is to assess the CD20 status of DLBCL by IHC staining of the fine needle aspirate and determine if the B-cell lymphoma cells have lost CD20 positive status.	The optional biopsy was added to collect additional, exploratory data to determine CD20-positive status in subjects that progressed
51.	Data Management and Statistical Analysis (section 7)	Re-worded	For simplification and clarification
52.	Efficacy Population (section 7.4.2)	Added: All subjects who received at least one dose of any study drug (either MT-3724 or gemcitabine or oxaliplatin) and have the baseline tumor assessment as well as at least one post-baseline tumor assessment.	To define efficacy population

53.	Safety Analyses (section 7.8)	Added thyroid function and changes in physical exam	To align with assessments taken
54.	Informed Consent (section 8.1.3)	Re-worded	For better clarity
55.	Study monitoring, Auditing and inspection (section 8.5)	Added 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.	Standard practice for regulatory compliance
56.	Source Data (section 8.6) and Financial Disclosure (section 8.9)	Added entire sections	Standard practices for regulatory compliance

57.	APPENDIX C (formerly Appendix 3)	Added Follicular Lymphoma International Prognostic Index (FLIPI)	For the assessment of follicular lymphoma in Part 1
58.	APPENDIX F (formerly Appendix 6)	Changed from Cockcroft-Gault to CKD-EPI	To be in alignment with eligibility criterion for kidney function