TITLE PAGE

Protocol Title:		Safety, Pharmacodynamics and Efficacy of MT-3724 for the Treatment of Patients with Relapsed or Refractory DLBCL	
Protocol Number:		MT-3724_NHL_001	
Compound:		MT-3724	
Study Phase:		1/2	
Sponsor	**Sponsor Name:**	Molecular Templates, Inc.	
	Legal Registered Address:	9301 Amberglen Boulevard Suite 100 Austin, TX 78729	
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SPONSOR SIGNATORY

MT-3724_NHL_001: Safety, Pharmacodynamics and Efficacy of MT-3724 for the Treatment of Patients with Relapsed or Refractory DLBCL

I, the undersigned, have approved version 11.0 of the clinical trial protocol with the date of 12 February 2021.

Name and Title	Signature and Date
[redacted] MD, MBA Chief Medical Officer Molecular Templates, Inc.	
[redacted], PhD Senior Director, Clinical Development Molecular Templates, Inc.	

INVESTIGATOR AGREEMENT

MT-3724_NHL_001: Safety, Pharmacodynamics and Efficacy of MT-3724 for the Treatment of Patients with Relapsed or Refractory DLBCL

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

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

_____ _____

Principal Investigator Name (printed) Signature

_____

Date

LIST OF CONTACTS

Function	Contact Information
Sponsor's Medical Representative:	[redacted] MD, MBA Chief Medical Officer Molecular Templates, Inc. Phone: [redacted]
External Medical Monitor:	Managed by CRO. Refer to the team contact list for the most up-to-date contact details.
Pharmacovigilance and SAE Reporting:	Managed by CRO. Refer to the team contact list for the most up-to-date contact details.
Clinical Operations:	[redacted], PharmD Director, Clinical Operations Molecular Templates, Inc. Phone: [redacted] [redacted], CCRA Senior Clinical Trial Manager Molecular Templates, Inc. Phone: [redacted]

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1.1 Synopsis

Protocol Title: Safety, Pharmacodynamics and Efficacy of MT-3724 for the Treatment of Patients with Relapsed or Refractory DLBCL

Study Phase: 1-2

Objectives and Endpoints (Part 3)

OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the safety of MT-3724 as monotherapy in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	• adverse events (AE) • laboratory abnormalities • vital signs
Secondary	
• To evaluate the efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL based on the overall response rate (ORR) by the Lugano Classification for Lymphoma (Cheson, 2014)	• Overall response rate is defined as the proportion of subjects with either a complete response (CR) or a partial response (PR) as determined by independent, blinded central review
• To evaluate additional measures of efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Overall response rate, defined as the proportion of subjects with either a CR or a PR as determined by investigator assessment • duration of tumor response (DOR), defined as time from initial documentation of tumor response (CR or PR) to disease progression • disease control rate (DCR), defined as proportion of subjects who have achieved CR, PR and stable disease (SD; defined as SD for 6 months or longer)
• To evaluate the pharmacokinetics (PK) of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Pharmacokinetics parameters, where calculable, include: maximum observed plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration time curve from 0 to 4 hours (AUC_{0-4}), AUC from 0 to infinity (AUC_{0-inf}), AUC from dosing to last measurable concentration (AUC_{last}), half-life ($t_{1/2}$), volume of distribution (V_z), and clearance (CL)
• To evaluate the pharmacodynamics of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• B-cell count • Immunophenotyping • Circulating immunoglobulins (IgA, IgG, IgM)
• To evaluate the immunogenicity of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• incidence of anti-drug antibodies (ADA)

OBJECTIVES	ENDPOINTS
Exploratory	
[redacted]	

Objectives and Endpoints (Part 4)

OBJECTIVES	ENDPOINTS
Primary	
• To determine the efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL based on the ORR by the Lugano Classification for Lymphoma (Cheson, 2014)	• overall response rate is defined as the proportion of subjects with either a CR or a PR as determined by independent, blinded central review
Key Secondary	
• To determine additional measures of efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Duration of tumor response, defined as time from initial documentation of tumor response (complete response [CR] or partial response [PR]) to disease progression
Secondary	
• To determine the safety of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• adverse events • laboratory abnormalities • vital signs
• To evaluate the effect of MT-3724 on the QT/QTc interval in subjects with relapsed or refractory DLBCL	• electrocardiograms (ECGs) • adverse events suggestive of cardiotoxicity
• To determine additional measures of efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• overall response rate (ORR), defined as the proportion of subjects with either a CR or a PR as determined by investigator assessment • disease control rate (DCR), defined as proportion of subjects who have achieved CR, PR and SD (defined as SD for 6 months or longer)

OBJECTIVES	ENDPOINTS
	• progression-free survival (PFS), defined as the time from study enrollment to the earliest date of disease progression or death from any cause • overall survival (OS), defined as the time from study enrollment to death from any cause
• To determine the pharmacokinetics (PK) of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Pharmacokinetics parameters, where calculable, include: C_{max}, t_{max}, AUC_{0-4}, AUC_{0-inf}, AUC_{last}, $t_{1/2}$, V_z and CL
• To determine the pharmacodynamics of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• B-cell count • Immunophenotyping • Circulating immunoglobulins (IgA, IgG, IgM)
• To determine the immunogenicity of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• incidence of ADA
Exploratory	
[redacted]	

Overall Design:

This is an open-label, Phase 1/2, study of MT-3724.

Part 1 of the protocol included evaluating escalating doses of MT-3724 in subjects with relapsed, refractory B-cell non-Hodgkin Lymphoma (NHL) or chronic lymphocytic leukemia to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

Part 2 (implemented in version 6.0 of the protocol) included an expansion of the MTD cohort to evaluate safety, tolerability, and potential efficacy at the MTD or RP2D. Implemented in version 7.0 of the protocol, up to 40 additional subjects with diffuse large B-cell lymphoma (DLBCL) were to be treated with MT-3724 at the MTD/ RP2D (50 µg/kg/dose).

Parts 3 and 4 will be a multi-center, multinational, open-label, single-arm evaluation of MT-3724 given as monotherapy in repeat doses in subjects with relapsed or refractory DLBCL who have received 2 or more lines of prior therapy.

Part 3 will be a continuation of the expansion of the MTD cohort with the intention to verify the safety, dose and dosing schedule in up to 25 subjects.

Part 4: The goal of Part 4 is to provide sufficient evidence to test the null hypothesis that the true response rate with MT-3724 ≤ 17% vs the alternative hypothesis that the true response rate with MT-3724 ≥ 32% at the 1-sided alpha level of 0.025 with high statistical power. At least 88 evaluable subjects will be required to test the null hypothesis vs the alternative hypothesis in Part 4. If at least 23 of 88 subjects respond at the end of Part 4, then the null hypothesis is rejected in favor of the alternative hypothesis and the effectiveness of MT-3724 as monotherapy will have been proven. Under the stated null and alternative hypotheses, Part 4 carries 90.4% power at the 1-sided alpha level of < 0.025.

Eligible subjects will be identified and treated through competitive enrollment across multiple global sites.

All study procedures will be the same for Parts 3 and 4. After eligibility is assessed in the screening period (up to 35 days), subjects enter the treatment period. Each treatment cycle will be 21 days in length. Treatment will continue until death, disease progression, unacceptable toxicity, withdrawal of consent, or another reason for withdrawal, or until study discontinuation.

Treatment Beyond Progression

For subjects who have radiological, but not clinical, evidence of disease progression within 3 months of Cycle 1 Day 1 (C1D1), in lieu of discontinuation, the investigator may continue treatment at the dose they are given at the time progression is identified if s/he believes the benefit outweighs the risk and provided the conditions identified below are met.

Conditions for continued treatment:

- absence of symptoms and signs, including worsening of laboratory values, indicating unequivocal progressive disease (PD),
- no decline in Eastern Cooperative Oncology Group performance status (ECOG PS) due to PD,
- absence of tumor progression at critical anatomical sites (eg, leptomeningeal disease),
- subject's written consent to defer any standard treatment options that may exist in favor of continuing MT-3724 treatment at the time of initial progression.

Radiological assessments should be repeated in 4 to 6 weeks from the time of initial progression.

End of Treatment: upon discontinuation from treatment, all subjects should undergo the End of Treatment (EoT) Visit as soon as possible (up to 14 days) after the last dose of MT-3724 and before start of new therapy.

Short-term Safety Follow-up: The Short-term Follow-up (STFU) Visit for safety assessment should occur 30 days (± 3 days) after the last dose of MT-3724, except for subjects who

withdrew consent and objected to further data collection, started new therapy for DLBCL or started another investigational drug.

Long-Term Follow-up: Long-term Follow-up (LTFU) Visits should occur every 3 months (± 14 days) after the last dose of MT-3724 for up to 18 months from the last dose. Subjects who discontinue the study for disease progression will be followed only for OS. Subjects who discontinue the study for toxicity, or reasons other than disease progression, will be followed for progression-free survival (PFS; as reported by investigators) and OS. Subjects with complete response (CR), partial response (PR), or stable disease (SD) should also be followed for radiology assessment until PD, death, or start of new anticancer treatment. Visits may occur by telephone contact when radiology data can be obtained from medical records.

Study Treatment:

All subjects will receive a single course of study drug via a 1 hour (54 to 75 minute window) intravenous (IV) infusion of MT-3724. Following a single AE of grade 5 capillary leak syndrome (CLS), a revised Part 3 will include 2 cohorts. For Cohort 1, the starting MT-3724 dose for each subject will be 10 µg/kg/dose for the first 2 doses and then increased to 25 µg/kg for the remaining doses of the first 21-day cycle and all doses of Cycle 2. Dosing will then continue at 25 µg/kg weekly beginning with Cycle 3. If fewer than 2/6 subjects have a dose-limiting toxicity (DLT) in Cohort 1, then the study will proceed to Cohort 2. If 2 or more subjects have a DLT in Cohort 1, the study will be stopped.

For Cohort 2, the starting MT-3724 dose in each subject will be 10 µg/kg for the first 2 doses. The dose will then be increased to 25 µg/kg for 2 doses and then the dose will be increased to 50 µg/kg for the remaining doses of the first 21-day cycle and all doses of Cycle 2. Dosing will then continue at 50 µg/kg weekly beginning with Cycle 3.

If fewer than 2/6 subjects have a DLT in Cohort 2, then the study will continue to Part 4 using the Cohort 2 dose and schedule. If 2 / 6 subjects experience a DLT in Cohort 2, the study will continue to Part 4 using the Cohort 1 dose and schedule.

For Cycle 1 and 2 doses are preferably administered on Days 1, 3, 5, 8, 10, and 12 (± 1 d). For Cycle 3 and later doses are preferably administered on Days 1, 8, and 15. All subsequent doses should be at least 20 hours apart (more than 5 half-lives of MT-3724 in serum) and must not be administered on more than 2 consecutive days; however the first 3 doses of Cycle 1 must be administered 2 days (approximately 48 hours) apart. Each subject will receive 1 dose of MT-3724 on Day 1.

The first dose of the first cycle will require approximately 5 hours in the clinic which include approximately 4 hours of post-dose safety assessments. Subsequent doses will require approximately 3 hours in the clinic which include approximately 2 hours of safety assessments post-dose (see also Section 1.3, Schedule of Activities (SoA)). All subjects will be evaluated for AEs prior to each infusion during all cycles of MT-3724 treatment. See Section 6.2 for guidance on treatment modifications.

Treatment will continue until death, disease progression, unacceptable toxicity, withdrawal of consent, or another reason for withdrawal, or until study discontinuation.

Number of Subjects:

Approximately 113 subjects with histologically confirmed, relapsed or refractory DLBCL: approximately 25 in Part 3 and approximately 88 evaluable subjects in Part 4. Additional subjects may be enrolled to ensure an adequate number of evaluable subjects in Part 4.

Inclusion criteria:

Subjects meeting ALL the following inclusion criteria will be eligible for participation in the study.

1. Subjects must be informed about the study and fully consent to participation as demonstrated by signing the written informed consent form (ICF) before any screening procedure.
2. Male and female subjects ≥ 18 years of age at the time of informed consent.
3. Subjects must have relapsed or refractory DLBCL according to the Revised European American Lymphoma/World Health Organization classification (Swerdlow, 2016). Subjects must have proof of CD20+ DLBCL, based on either:
   a. historical biopsies (obtained with diagnosis of relapsed or refractory disease), or
   b. fresh biopsies
   c. bone marrow biopsy, excisional lymph node biopsy, and core biopsy of any involved organ are all acceptable methods; Fine Needle Aspirate is not acceptable.

   NOTE: Composite lymphoma (DLBCL and indolent histology in the same specimen) is also acceptable.
4. Subjects must have received at least 2 standard of care (SoC) regimens (including anti-CD20 antibody therapy) appropriate for DLBCL treatment.
   a. Subjects whose prior therapy includes CAR-T therapy are eligible.
   b. Subjects who underwent stem cell transplant (SCT) > 100 days for autologous SCT or > 180 days for allogeneic SCT before study drug administration.
   c. Subjects who have been ineligible for SoC DLBCL treatment(s) may be eligible at the investigator's discretion, upon sponsor approval.
5. Subjects must have at least 1 bi-dimensional tumor lesion at screening that is measurable by CT and/or magnetic resonance imaging (MRI) according to the Lugano criteria (Cheson, 2014). Bi-dimensionally measurable tumor lesion by CT and/or MRI is defined as longest diameter of > 1.5 cm for lymph nodes and > 1.0 cm for extranodal disease.
6. Subjects must have life expectancy of > 3 months from the start of treatment.
7. Subjects must have Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
8. Subjects must have met ALL the following laboratory criteria:
   a. Absolute neutrophil count ≥ 1.0×10^9/L with no myeloid growth factors (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor preparations) administered within 2 weeks of C1D1

b. Platelet count ≥ 50 × 10^9/L with no Thrombopoietin-receptor agonists agents or platelet transfusions given within 2 weeks of C1D1
c. Hemoglobin ≥ 8.0 g/dL with no erythropoietin stimulating agents or peripheral red blood cell (PRBC) transfusions within 2 weeks of C1D1
d. Creatinine clearance (CLcr) to be ≥ 50 ml/min either measured or estimated using the Cockcroft-Gault formula (Section 10.2.2.2).
e. Total bilirubin (or direct bilirubin for patients with Gilbert's disease) < 1.5 × upper limit of normal (ULN)
f. Alanine transaminase (ALT) ≤ 3.0 × ULN (or ≤ 5.0 x ULN if liver involvement).
g. Aspartate aminotransferase (AST) ≤ 3.0 × ULN (or ≤ 5.0 x ULN if liver involvement).
h. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN (unless on therapeutic anticoagulants)
i. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN (unless on therapeutic anticoagulants)

9. Have adequate serum albumin, as determined by:
   a. Albumin ≥ 3.0 g/dL
10. QT interval correction for heart rate using Fridericia's formula (QTcF) ≤ 480 ms determined as the average of 3 QTcF values from the triplicate ECG obtained at screening.
11. Women of reproductive potential must have a negative highly sensitive pregnancy test within 72 hours before the start of treatment. Women who are postmenopausal or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) may be considered as not of reproductive potential.
12. Subjects of reproductive potential must agree either to abstain continuously from heterosexual intercourse or to use a highly effective birth control method from signing the informed consent until the STFU visit for females and until 90 days after the last dose of MT-3724 for males. Refer to Section 10.4 for guidance on contraception.
13. Subject must be able to comply with all study-related procedures and medication use.

Exclusion criteria:

Subjects who meet ANY of the following criteria must be excluded:

Prior or current therapies

1. Received any amount of anti-CD20 monoclonal antibodies (mAbs) within the following periods before the start of treatment:
   a. Rituximab (Rituxan®/MabThera® or rituximab biosimilar): within 84 days (12 weeks); if a subject has received rituximab within 37 weeks before the start of treatment, then serum rituximab level must be negative (< 500 ng/mL) at screening.
   b. Obinutuzumab (Gazyva®): 184 days
   c. Ofatumumab (Arzerra®): 88 days

d. Any other anti-CD20 agents (eg, investigational agents), the washout period is 5 half-lives. The investigator must contact the medical monitor to discuss the most appropriate washout for non-approved CD20-targeting agents, where the half-life is not known.

2. Received approved or investigational treatment for DLBCL (except anti-CD20 agents where exclusion criterion 1 applies and radioimmunoconjugates) within 4 weeks before the start of treatment. For small molecules (MW < 0.9 kiloDaltons [kDa]), the washout is 5 half-lives or at least 2 weeks. Radioimmunoconjugates are excluded within 12 weeks before the start of treatment.
3. Received radiation therapy to tumor lesions that would serve as target lesions (measurable disease) within 4 weeks before the start of treatment, unless the lesion exhibited objective progression between radiation therapy and screening according to the Lugano Classification (Cheson, 2014).
   a. Palliative radiation therapy to non-target lesions may be permitted at the investigator's discretion after consultation with the medical monitor and sponsor. See Section 6.5 for more information on permissible use of palliative radiotherapy.
4. Require the use of systemic immune modulators during study treatment:
   a. Systemic immune modulators include, but are not limited to, systemic corticosteroids at doses > 20 mg/day of prednisone equivalent, cyclosporine and tacrolimus. Please see Section 6.1.3 for more details and exceptions.
   b. The use of non-steroidal anti-inflammatory drugs (NSAIDS) is permitted.
5. Received any live vaccines within 4 weeks before the start of treatment.
6. Prior treatment with MT-3724.

Medical history

7. Current evidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1 toxicity (due to prior anticancer therapy) before the start of treatment, except for hair loss and those Grade 2 toxicities listed as permitted in other eligibility criteria.
8. Current evidence of significant (CTCAE Grade ≥ 2) infection or wound within 4 weeks before the start of treatment.
   a. Subjects with Grade 2 infection that has stabilized or improved with oral anti-infectives before the start of treatment may be eligible at the sponsor's discretion.
9. Known or suspected hypersensitivity to the study drug or excipients contained in the study drug formulation.
10. Current evidence of hypersensitivity or other underlying illness requiring systemic corticosteroids at doses > 20 mg/day prednisone equivalent.
11. Current evidence of uncontrolled human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) at screening. Serology testing is not required if seronegativity is documented in the medical history, and if there are no clinical signs suggestive of HIV or hepatitis infections, or suspected exposure. The following exceptions apply for subjects with positive viral serology:

a. Subjects with HIV and an undetectable viral load and CD4+ T-cell (CD4+) counts ≥ 350 cells/mL may be enrolled, but must be taking appropriate opportunistic infection prophylaxis, if clinically relevant.
b. Subjects with positive HBV serology are eligible if they have an undetectable viral load and the subject will receive antiviral prophylaxis for potential HBV reactivation per institutional guidelines.
c. Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is below the lower limit of detection. Concurrent antiviral HCV treatment per institutional guidelines is allowed.

12. Current evidence of incomplete recovery from surgery or radiotherapy before start of treatment, or planned surgery or radiotherapy from the start of treatment until the EoT visit, except minor elective surgery deemed acceptable by the investigator or palliative radiation therapy to non-target lesions, as described in Section 6.5.
13. History of cardiovascular, renal, hepatic or any other disease within 3 months before the start of treatment that in the investigator's opinion, 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.
14. History or current evidence of neoplastic disease that is histologically distinct from NHL, except cervical carcinoma in situ, superficial noninvasive bladder tumors, curatively treated Stage I-II non-melanoma skin cancer. Subjects with prior, curatively treated cancer > 2 years ago before the start of treatment can be enrolled.
15. Current evidence of new or growing brain or spinal metastases during screening. Subjects with known brain or spinal metastases may be eligible if they:
    a. Had radiotherapy or another appropriate therapy for the brain or spinal metastases; concurrent prophylactic treatment is allowed
    b. Neurologic symptoms must be stable and no worse than Grade 2
    c. Have evidence of stable brain or spinal disease on CT or MRI scan obtained within 4 weeks before signing the informed consent and compared with prior imaging results
    d. Do not require steroid therapy (or, if applicable, have been stable on dose of no more than prednisone 20 mg/day or equivalent by C1D1)
16. Women who are pregnant or breastfeeding.
17. History of non-adherence to the schedule of procedures or medication use.
18. Current evidence of Graft vs Host Disease
19. 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 (New York Heart Association [NYHA] Class III or IV) at screening or left ventricular ejection fraction (LVEF) ≤ 45%, assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 1 month before starting study treatment (inclusion of subjects with LVEF between 40% to 45% should be discussed with the medical monitor and approved by the sponsor). (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 since then).
f. Cardiac arrhythmia requiring anti-arrhythmic therapy at screening. Subjects receiving digoxin, calcium channel blockers, or beta-adrenergic blockers are eligible at the investigator's discretion after consultation with medical monitor and sponsor if the dose has been stable for ≥ 2 weeks before the start of treatment with MT-3724. Subjects with sinus arrhythmia and infrequent premature ventricular contractions are eligible at the investigator's discretion.

Statistical Methods:

Detailed methodology for summary and statistical analyses of the data collected in Parts 3 and 4 this study will be documented in a statistical analysis plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment and documented in the clinical study report.

Clinical Endpoints

Categorical variables will be summarized using counts and percentages, while continuous variables will be summarized using the mean, median, standard deviation, minimum, maximum, and number of observations. The frequency of AEs will be tabulated. Baseline, end-of-study, and change from baseline clinical laboratories, vital signs, ECG and imaging data will be summarized. Descriptive statistics will be computed for safety parameters as appropriate. Further statistical evaluations may be applied for select endpoints, if warranted.

Efficacy Endpoints

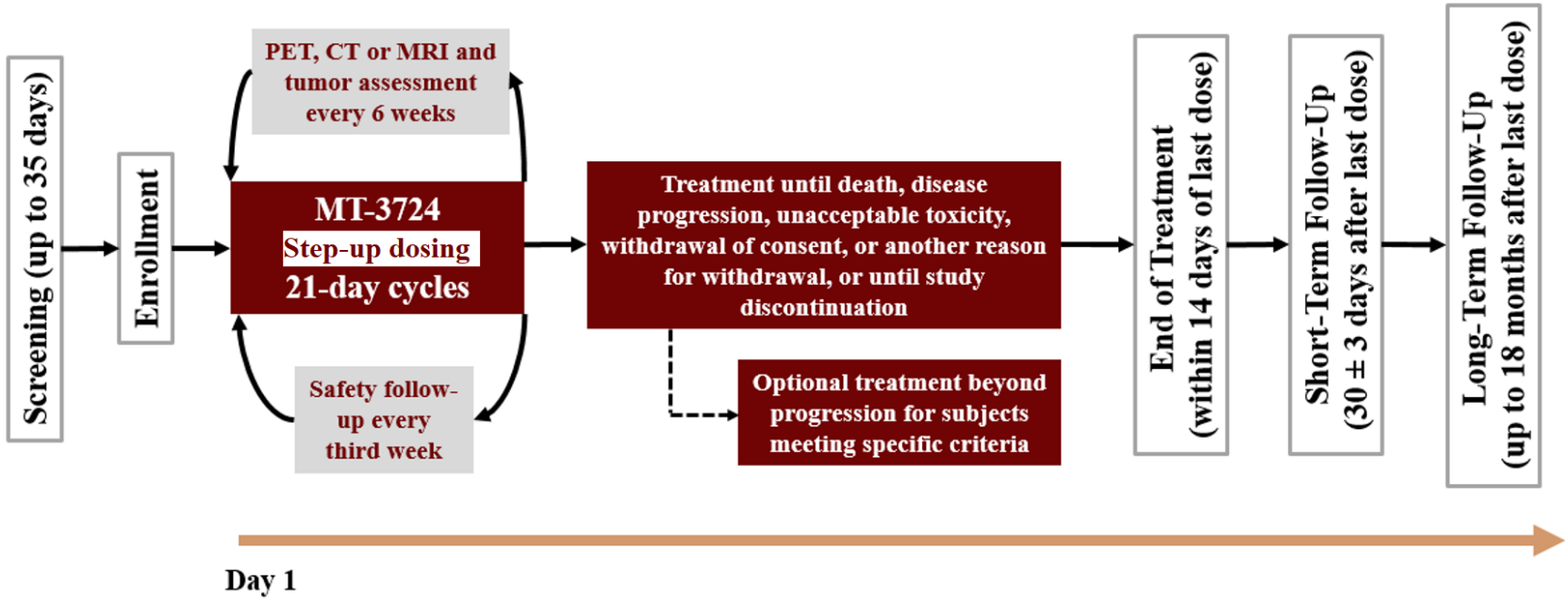
Tumor response and disease progression will be evaluated by the independent central review (ICR) for the Part 4 primary endpoint and the Part 3 secondary endpoint; and by the investigator for secondary efficacy endpoints (Parts 3 and 4) according to the Lugano Classification for Lymphoma (Cheson, 2014).

All subjects who receive at least 1 dose of study medication will be included in the full analysis set (FAS) for the efficacy analysis.

The efficacy analysis will include the ORR, DOR, and DCR at the Final Study Assessment Visit. Subjects who have not progressed at the time of analysis will be censored at the date of their last tumor assessment. Progression-free survival and OS will also be presented using Kaplan-Meier techniques.

The overall response rate (ORR) and DOR will be descriptively summarized; exact 95% confidence intervals (CI) will be produced.

1.2 Study Schema



1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

	SCR[a]	Treatment Period (21-day Cycles)[b]								EoT[d]	STFU[e]	LTFU[f]	Notes
		D1	D3	D5	D8	D10	D12	D15[c]	D16-21				
General and Safety Assessments													
Informed consent	X												
Eligibility criteria	X												
Demography	X												
Physical exam	X	X								X			Complete physical exam at screening and EoT. Abbreviated exam D1 of every cycle. See Section 8.4.4 for details.
Height	X												
Weight	X	X	X	X	X	X	X	(X)		X	X		Body weight measured before the start of treatment on C1D1 will be used to calculate the MT-3724 dose in all subsequent cycles. The dose must be re-calculated when the body weight has changed by ≥ 10% from the baseline value; or according to institutional policies should they require adjustment for any change in body weight. (X): Collected only if weekly dosing is implemented.
BMI	X												
Medical history	X												Illnesses that occurred at any time before the start of screening that, in the investigator's opinion, could increase the risk to subject and/or influence the study endpoints should be captured in the medical history as prior illnesses. Illnesses that are active at the time of informed consent should be captured in the medical history as concomitant illnesses.
NHL assessment	X												Initial diagnosis: include the type, histology, staging (Ann Arbor Classification-Cotswold Modification) and grading according to International Prognostic Index (IPI) for NHL At time of relapse: IPI and time to progression after first line of therapy (captured as date of first relapse/progression) Current status: additionally collect the genetic mutational status (eg, MYC, BCL2, and BCL6 rearrangement / overexpression) and molecular subtype (GCB vs ABC) (if available).

Table 1-1. Schedule of Activities

	SCR[a]	Treatment Period (21-day Cycles)[b]								EoT[d]	STFU[e]	LTFU[f]	Notes
		D1	D3	D5	D8	D10	D12	D15[c]	D16-21				
Prior medication	X												Any medication (prescription, OTC, and supplements) used within 4 weeks prior to the start of treatment.
Prior systemic NHL therapy (including SCT and CAR-T)	X												The start and stop date of each individual agent / regimen and outcome should be recorded. The date of the last CD20-based therapy should also be documented in the eCRF.
Prior NHL radiotherapy	X												
NYHA	X	(X)								X			Only applicable to subjects with heart failure. (X): Only collected D1 every 7th cycle
ECOG	X	X								X			
Triplicate 12-lead ECG[g]	X	(X)					(X)			X			Should be obtained as 3 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 at least 5 minutes before the first ECG and during the assessment. (X): Collected: • C1D1: predose, within 10 min before EOI, and 2.0 (± 10 min) after EOI • C1D12: predose and 2.0 h (± 10 min) after EOI
Vital signs (BP, HR, RR, body temperature)[g]	X	X	X	X	X	X	X	(X)		X	X		Should be measured after at least 5 minutes of quiet rest in a sitting or semi-recumbent position. Collect VS at the following times on dosing days (± 10 min): • predose (any time before start of infusion) • 0.5, 1, 2 hours after start of infusion • C1D1: also collect 3 and 4 hours after start of infusion (X): Collected only if weekly dosing is implemented.
LVEF	X												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 since then.
AE review	(X)	X	X	X	X	X	X	X	X	X	X		(X): Events which occur during screening that are related to a protocol screening procedure should be reported as AEs.
Concomitant medication review		X	X	X	X	X	X	X	X	X	X		

Table 1-1. Schedule of Activities

	SCR[a]	Treatment Period (21-day Cycles)[b]								EoT[d]	STFU[e]	LTFU[f]	Notes
		D1	D3	D5	D8	D10	D12	D15[c]	D16-21				
Safety follow-up call								X					Not applicable for weekly dosing
LTFU call												X	
Local Laboratory Assessments													
Albumin		X	X	X	X	X	X						Albumin will be collected within 24 h before infusion and **reviewed prior to each dose in Cycle 1**. Additional assessments of serum albumin should be made in subjects with hypoalbuminemia or other signs and symptoms of CLS as clinically indicated. See Section 6.2 for dose modification guidance for CLS.
CK		X	X	X	X	X	X						CK must be collected within 24 h before infusion in Cycle 1.
Viral serology	X												Serology for HIV, HBV, and HCV is not required if seronegativity is documented in the medical history and there are no clinical signs suggestive of HIV or hepatitis infections, or suspected exposure. Refer to Table 10-1 for specific analytes.
Urinalysis (dipstick)	X	X			X					X	X		Analysis of urine microsediment may be performed at the investigator's discretion by the local lab.
Pregnancy test		(X)								X	X		(X): performed within 72 h before dosing on D1
Central Laboratory Assessments													
Serum rituximab level (if applicable)	X												Only applicable to subjects that have received the last dose of prior RTX (Rituxan® or biosimilar) > 84 days before the start of treatment. See Section 10.2.2.4 for further details.
Hematology	X	X			X					X	X		
Chemistry	X	X			X					X	X		Includes eCrCl (see Section 10.2.2.2).
Coagulation	X	(X)								X			(X): Assessed D1 of every odd cycle.
Thyroid function	X	(X)								X			
HbA1c	X	(X)								X			
PK[g]		X	X				X						Refer to Table 1-2 for detailed time point collection.
Beta-2 microglobulin	X												
MT-3724 ADA/NAb	X	X					(X)			X	X		(X): Day 12 of Cycle 1 only

Table 1-1. Schedule of Activities

	SCR[a]	Treatment Period (21-day Cycles)[b]								EoT[d]	STFU[e]	LTFU[f]	Notes
		D1	D3	D5	D8	D10	D12	D15[c]	D16-21				
B-cells and immunophenotype	X	X					(X)			X	X		(X): Day 12 of Cycle 1 only
Complement	X	X								X			Should be assessed before the start of infusion and 3 hours after the start of infusion (± 10 min), or if a subject experiences a Grade ≥ 2 IRR/CLS/CRS or other hypersensitivity reaction. See Section 10.2.2.3 for details.
Histamine	X	X								X			
Cytokines	X	X								X			
Immunoglobulins	X	X								X			Should be assessed before the start of infusion and 3 hours after the start of infusion (± 10 min).
Optional tumor tissue biopsy										X			Applicable to subjects who had consented for this procedure, exhibit PD, and have accessible peripheral lymph node(s).
Efficacy Assessments													
Radiological assessment	X	Every 6 weeks (± 1 week) starting from C1D1, until disease progression, death, or lost to follow-up AND For subjects without response or SD at EoT: within 7 days of the EoT Visit (only if the previous tumor scan has been performed > 4 weeks before the EoT Visit)											The investigator is encouraged to obtain the screening tumor scan as close as possible to the start of treatment. The original schedule needs to be maintained even if there is a delay is dosing. Subjects who continue to receive treatment beyond progression should also have repeat scans.
EQ-5D	X	(X)								X	X		(X): Collected D1 of every even cycle (C2, C4, C6, etc)
Study Treatment													
Premedication		X	X	X	X	X	X	(X)					Administered within 60 minutes prior to MT-3724 infusion. Refer to Section 6.1.2 for guidance. (X): Only when weekly dosing is implemented.
MT-3724 infusion (TIW)		X	X	X	X	X	X						The first 3 doses of Cycle 1 must be administered at least 2 days (approx. 48 hours) apart. All subsequent doses must be given within ± 1 day of scheduled visit. All 6 doses must be given within the first 16 days, the doses should be at least 20 hours apart, and should not be administered on more than 2 consecutive days.
MT-3724 infusion (weekly schedule)[h]		X			X			X					Starting with Cycle 3, doses will be administered weekly. Doses must be given within ± 2 day of scheduled visit.

ABC = activated B-cell; ADA = anti-drug antibodies; AE = adverse event; BMI = body-mass index; BP = blood pressure; C = cycle; CAR-T = chimeric antigen receptor T-cell therapy; CLS = capillary leak syndrome; CK = creatine phosphokinase; CRS = cytokine release syndrome; CT = computerized tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCrCl = estimated creatinine clearance; eCRF = electronic case report form; EOI = end of infusion; EoT = end of treatment; EQ-5D = EuroQol Group Quality of Life – 5-dimensions; GCB = germinal center B cell; HbA1c = glycated hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency syndrome; LTFU = long-term follow-up; NHL = non-Hodgkin's lymphoma; HR = heart rate; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NAb = neutralizing antibody; NYHA = New York Heart Association; OTC = over-the-counter; PD = progressive disease; PK = pharmacokinetic; RNA = ribonucleic acid; RR = respiratory rate; SCR = screening; SCT = stem cell transplant; SD = stable disease; STFU = short-term follow-up TIW = three times a week.

[a] The screening period is up to 35 days prior to enrollment. All local/central laboratory safety assessments and radiological assessments must be collected within 28 days prior to enrollment.

[b] All assessments are performed any time before dosing unless otherwise indicated. Predose assessments may be performed up to 1 day prior to dosing (except for cytokines/immunoglobulins/complement/histamine which should be collected just prior to dosing).

[c] The Day 15 visit is applicable for subjects receiving the weekly dosing schedule.

[d] Upon discontinuation of treatment, as soon as possible (up to 14 days) after the last dose, and before the start of new therapy.

[e] A STFU visit occurs 30 days (± 3 days) after the last dose. The STFU visit can be done via a clinic visit (recommended) or via a telephone call (if subject cannot attend a clinic visit or has started a new anticancer treatment or a new NHL treatment). If performed via a telephone call, only AEs and concomitant medications will be collected.

[f] LTFU visits should occur every 3 months (± 14 days) after the last dose of MT-3724 for up to 18 months from the last dose. The LTFU Visits will be performed via a telephone call to collect the information about the NHL status (relapsed or not), the start of any new therapy for NHL since the last study visit/phone call or death. Subjects with SD or response should also be followed for radiology assessment until progressive disease, start of new anticancer treatment, or death.

[g] When PK, ECG, and vital signs assessments are scheduled to occur at the same time point, the ECG and vital signs should be done first and in that order, with the timing of assessments based on collecting the PK sample at the protocolled time (eg, if the PK sample is expected 2 hours after EOI, collect the PK sample 2 hour after the infusion, and ECG/VS within 10 minutes before the PK sampling).

[h] The weekly dosing schedule follows procedures on Days 1, 8 and 15.

Table 1-2. Schedule of Pharmacokinetic Samples

	Time Points Relative to Dosing								
	Predose	During Infusion	After EOI						
	Within 4 h Prior SOI	10 m Before EOI	5 m	0.5 h	1 h	2 h	3 h	4 h	
Window			± 1 m	± 5 m	± 5 m	± 5 m	± 10 m	± 10 m	**Notes**
Part 3									If an 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 6 is delayed from D12 to D14, then the PK samples planned for D12 should be drawn on D14. Unscheduled assessments may be performed at any time at the investigator's discretion. Samples for PK must be drawn from a different line than that used for MT-3724 administration.
C1D1	X	X	X	X	X	X	X	X	
C1D3	X	X	X	X	X	X			
C1D12	X	X	X	X	X	X			
CXD1	X	X	X						
Part 4									
C1D1	X	X	X	X	X	X	X		
C1D3	X	X	X			X			
C1D12	X	X	X			X			
CXD1	X	X	X						

C = cycle; D = day; PK = pharmacokinetics, SOI = start of infusion; EOI = end of infusion.

2 INTRODUCTION

2.1 Background

2.1.1 Advanced Stage Cancer Patient Population

Starting with Amendment 9.0 (expansion cohort), Parts 3 and 4 will enroll subjects with relapsed or refractory (r/r) large B-cell lymphoma after 2 or more lines of systemic non-Hodgkin Lymphoma (NHL) therapy and who are not eligible to receive candidates for curative therapy. See Section 5 for all eligibility criteria.

2.1.2 Epidemiology, Classification, and Treatment Standards

Non-Hodgkin's Lymphomas: The 2019 SEER database estimated 74,200 patients in the United States (US) would be diagnosed with NHL, or approximately 26,000 people with diffuse large B-cell lymphoma (DLBCL) or approximately 7.8/100,000 (Howlader, 2019). Amongst B-cell NHL subtypes, DLBCL is the most frequent at approximately 36%, according to the SEER data base. Rates, however, vary by region. In the United Kingdom, the annual incidence of DLBCL is 8.5/100,000 (HMRN, 2020) yet across Europe, the incidence is reported to be approximately 3.8/100,000 (Vitolo, 2016; Møller, 2004) possibly reflecting differences in genetic and environmental risk factors. This latter figure is similar to the incidence of DLBCL in Australia (approximately 2/100,000) (NCCI, 2020). In Taiwan, the incidence of DLBCL is approximately 3/100,000 (Ko, 2018), in South Korea, China and Japan, approximately 3.8/100,000 (Yoo, 2018; Miyoshi, 2018; Sun, 2012).

Lymphoma includes a heterogeneous group of malignancies originating from lymphoid tissues (mainly of lymph nodes) with different biology and prognoses divided into 2 large groups of neoplasms: (1) non-Hodgkin's lymphoma and (2) Hodgkin's disease. Various neoplastic malignant cell lines correspond to each of the cellular components of antigen stimulated lymphoid follicles. Almost 85% of NHLs are of B-cell origin; only 15% are derived from T-cells or Natural Killer cells, and the small remainder arises from macrophages.

Non-Hodgkin Lymphoma represents a progressive clonal expansion of a lymphoid cell line arising from an accumulation of lesions affecting proto-oncogenes or cancer suppressor genes, resulting in cell immortalization. Although a variety of laboratory and imaging studies are used in the evaluation and staging of suspected NHL, a well-processed section of an excised lymph node is the mainstay of pathologic diagnosis. NHL subtypes are characterized by the level of differentiation, the size of the cell of origin, the originating cell's rate of proliferation, and the histologic pattern of growth. Several cytogenetic lesions are associated with specific NHLs, reflecting the presence of specific markers of diagnostic significance in sub-classifying various NHL subtypes.

Non-Hodgkin Lymphoma includes many clinicopathologic subtypes, each with a distinct epidemiology, etiology morphology, immunophenotype, genetic features, clinical characteristics and response to therapy. For many of the B-cell NHL subtypes, the pattern of growth and cell

size may be important determinants of NHL tumor aggressiveness. Non-Hodgkin Lymphoma tumors that grow in a nodular pattern are generally less aggressive than lymphomas that proliferate in a diffuse pattern. Lymphomas of small lymphocytes generally have a more indolent course than those of large lymphocytes, which may have intermediate-grade or high-grade aggressiveness. However, some subtypes of high-grade lymphomas are characterized by small cell morphology.

The treatment of B-cell NHL varies greatly, depending on tumor stage, grade, and type as well as several clinical factors. The 5-year relative survival rate of patients with NHL is approximately 63%. The survival rate has steadily improved over the last 2 decades, due to improvements in medical and nursing care, the advent of monoclonal antibodies (mAbs), including CD20-targeting therapies, validation of biomarkers of response, and the implementation of tailored treatment.

2.1.3 Anti-CD20 mAb Therapy for Non-Hodgkin Lymphoma

Anti-CD20 mAb therapy has become a ubiquitous component of treatment regimens for B-cell malignancies. Clinically active anti-CD20 mAbs used for the treatment of NHL can be separated into 2 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 but have minimal direct antitumor effects. Type II antibodies (tositumomab and obinutuzumab) do not induce redistribution of CD20, have minimal CDC, strong antibody-dependent cell-mediated cytotoxicity 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 appears to be clinically more effective against NHL in direct comparisons, perhaps because of patients' baseline immune status (Maloney, 2012).

A multinational retrospective study (SCHOLAR-1) analyzed overall response rate (ORR) and overall survival (OS) in 636 patients with r/r NHL including DLBCL, follicular lymphoma (FL) and primary mediastinal B-cell lymphoma (PMBCL)based on 2 Phase 3 trials (LYSA/CORAL, CCTG/LY.12) and 2 observational cohorts from MD Anderson and University of Iowa/Mayo Clinic (Crump 2017). For patients with refractory (refractory included patients who relapsed early ie, within 12 months of stem cell therapy) DLBCL, ORR was 26% (CR 7%) to next line therapy, and OS was 6.3 months, with 2-year survival rate of 20%. Overall response rate in patients relapsing after 2nd line therapy was 26% (CR 10%). Response significantly correlated with survival, especially when patients were able to proceed to stem cell therapy thereafter thus emphasizing the importance of novel salvage treatments.

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 (Tedder, 1988). 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 (Beers, 2010). The internalization requires the binding of the fragment crystallizable region (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 (Lim, 2011). CD20 can also be removed from the B-cell surface following the molecular reorganization known as trogocytosis, which occurs during the conjugation between the Fcγ receptor on B-cells and the antigen-presenting immune cells (Beum, 2011). Further, due to their relatively large size, typically, less than 0.01% of the injected dose of an anti-CD20 mAb localizes to NHL tumors in human subjects (Milenic, 1991).

2.2 Molecular Templates Investigational Product Background: MT-3724

MT-3724 is a recombinant homodimeric fusion protein. Each monomer consists of a single chain variable fragment (scFv) with affinity for human CD20 cell surface protein fused to the enzymatically active Shiga-like toxin-I A1 subunit (SLT-I A1). The primary structure of MT-3724 is a single polypeptide chain consisting of 512 amino acids of an approximate molecular weight of 55 kiloDaltons (kDa) (data on file). 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 (Rajagopalan, 2013).

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.

2.2.1 Summary of Clinical Experience

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

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

Across 3 studies (NHL_001, NHL_002 and NHL_003) as of 28 August 2020, capillary leak syndrome (CLS) has been reported in 5 subjects: 2 subjects from NHL_001 dosed at 75 µg/kg/dose, 2 subjects from NHL_002 dosed at 10 µg/kg/dose, and 1 subject from NHL_003 dosed at 25 µg/kg/dose. The maximum severity for all events was Grade 2. After the data cutoff, 1 event of Grade 5 CLS was reported in the NHL_001 study, Part 3 dosed at 50 µg/kg/dose. As a

result, more stringent safety measures are implemented in all MT-3724 trials including this protocol version.

Important identified risks for MT-3724 include infections (including pneumonia and viral infections), CLS, Neutropenia, and Edema and Peripheral Edema. Important potential risks include acute kidney injury, Myalgia/muscle weakness, systemic inflammatory response syndrome (SIRS)/ cytokine release syndrome (CRS), Infusion related reactions, Tumor lysis syndrome, and Reproductive risk.

Adverse events of special interest include Neutropenia, acute kidney injury, CLS, SIRS/CRS.

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

2.2.2 Guidance to the Investigator for Capillary Leak Syndrome

Capillary leak syndrome typically occurs during earlier cycles of treatment. Capillary leak syndrome is suspected if the subject experiences at least 2 of the following signs and/or symptoms within the same cycle (unless unequivocally related to underlying condition):

- Hypoalbuminemia
- Hypotension
- Edema (peripheral or central, all types) and/or weight gain

Subjects should be closely monitored for signs and symptoms of CLS. This includes monitoring of vital signs (temperature, heart rate, blood pressure [BP], respiration rate), body weight and edema of any type including both peripheral edema and central edema (such as pleural effusion or signs of dyspnea), and monitoring of laboratory parameters including hemoconcentration (eg, hematocrit, Hb), and especially albumin and creatine phosphokinase (CK) in case of clinical symptoms indicative of CLS.

Refer to the MT-3724 CLS management guide.

Refer to Section 6.2 for dose modification guidelines.

3 OBJECTIVES AND ENDPOINTS

3.1 Part 3 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the safety of MT-3724 as monotherapy in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	• adverse events (AE) • laboratory abnormalities • vital signs
Secondary	
• To evaluate the efficacy of MT-3724 as monotherapy in subjects with relapsed or	• Overall response rate is defined as the proportion of subjects with either a complete response (CR)

OBJECTIVES	ENDPOINTS
refractory DLBCL based on the overall response rate (ORR) by the Lugano Classification for Lymphoma (Cheson, 2014)	or a partial response (PR) as determined by independent, blinded central review
• To evaluate additional measures of efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Overall response rate, defined as the proportion of subjects with either a CR or a PR as determined by investigator assessment • duration of tumor response (DOR), defined as time from initial documentation of tumor response (CR or PR) to disease progression • disease control rate (DCR), defined as proportion of subjects who have achieved CR, PR and stable disease (SD; defined as SD for 6 months or longer)
• To evaluate the pharmacokinetics (PK) of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Pharmacokinetics parameters, where calculable, include: maximum observed plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration time curve from 0 to 4 hours (AUC_{0-4}), AUC from 0 to infinity (AUC_{0-inf}), AUC from dosing to last measurable concentration (AUC_{last}), half-life ($t_{1/2}$), volume of distribution (V_z), and clearance (CL)
• To evaluate the pharmacodynamics of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• B-cell count • Immunophenotyping • Circulating immunoglobulins (IgA, IgG, IgM)
• To evaluate the immunogenicity of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• incidence of anti-drug antibodies (ADA)
Exploratory	
[redacted]	

3.2 Part 4 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• To determine the efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL based on the ORR by the Lugano Classification for Lymphoma (Cheson, 2014)	• overall response rate is defined as the proportion of subjects with either a CR or a PR as determined by independent, blinded central review
Key Secondary	
• To determine additional measures of efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Duration of tumor response, defined as time from initial documentation of tumor response (complete response [CR] or partial response [PR]) to disease progression
Secondary	
• To determine the safety of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• adverse events • laboratory abnormalities • vital signs
• To evaluate the effect of MT-3724 on the QT/QTc interval in subjects with relapsed or refractory DLBCL	• electrocardiograms (ECGs) • adverse events suggestive of cardiotoxicity
• To determine additional measures of efficacy of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• overall response rate, defined as the proportion of subjects with either a CR or a PR as determined by investigator assessment • disease control rate (DCR), defined as proportion of subjects who have achieved CR, PR and SD (defined as SD for 6 months or longer) • progression-free survival (PFS), defined as the time from study enrollment to the earliest date of disease progression or death from any cause • overall survival (OS), defined as the time from study enrollment to death from any cause
• To determine the pharmacokinetics (PK) of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• Pharmacokinetics parameters, where calculable, include: C_{max}, t_{max}, AUC_{0-4}, AUC_{0-inf}, AUC_{last}, $t_{1/2}$, V_z and CL
• To determine the pharmacodynamics of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• B-cell count • Immunophenotyping • Circulating immunoglobulins (IgA, IgG, IgM)
• To determine the immunogenicity of MT-3724 as monotherapy in subjects with relapsed or refractory DLBCL	• incidence of ADA
Exploratory	
[redacted]	

OBJECTIVES	ENDPOINTS
[redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 1-2, multiple ascending dose study: Part 1, enrolled subjects with progressive B cell NHL with measurable disease (lesion ≥ 1.5 cm or absolute peripheral blood monoclonal CD20-positive/CD5-positive B-lymphocyte count ≥ 5000 cells/µL) who had received standard treatment with at least 1 anti-CD20 antibody containing front-line regimen that resulted in initial response, followed by relapse/recurrence and who were not eligible for any further approved biologic therapy, chemotherapy and/or autologous stem transplantation and/or refused alternative approved therapies and/or were unlikely to achieve clinical benefit from any therapy of higher priority by investigator assessment.

The Part 2 maximum tolerated dose (MTD) expansion cohort was a multi-center, multinational, Phase 2 open-label, single-arm evaluation of MT-3724 given as monotherapy in repeat doses in subjects with relapsed or refractory DLBCL who had received 2 or more prior lines of systemic NHL therapy. Only subjects with relapsed/refractory DLBCL were to be enrolled in Part 2. Preliminary data indicated this DLBCL sub-population had a positive response to treatment given at doses up to and including the MTD.

Parts 3 and 4 will be a multi-center, multinational, open-label, single-arm evaluation of MT-3724 given as monotherapy in repeat doses in subjects with relapsed or refractory DLBCL who have received 2 or more lines of prior therapy.

Eligible subjects will be identified and treated through competitive enrollment across multiple global sites.

4.1.1 Part 3

In Part 2 of the study, the MTD of MT-3724 was determined to be 50 µg/kg/dose administered on Days 1, 3, 5, 8, 10, and 12 of each 21-day cycle. The dose and schedule is now adjusted due to observations of CLS in subjects treated in the Part 3 of the study.

Part 3 will be a continuation of the expansion of the MTD cohort with the intention to verify the safety, dose and dosing schedule in approximately 25 subjects (see Section 6.1).

Part 3 will include 2 new cohorts of subjects, which will be enrolled sequentially with step-up dosing. At least 6 subjects must be enrolled on a cohort with no more than 1 dose-limiting

toxicity (DLT) for that dose and treatment schedule to be declared the MTD. The MTD will be used to establish the recommended phase 2 dose (RP2D).

The DLT assessment period is 21 days. DLTs will be assessed during Cycle 1 of each enrolled dose cohort.

Starting with enrollment into Cohort 1, a minimum of 6 eligible subjects will be enrolled into 1 of 2 predefined sequential dose cohorts, unless precluded by DLTs. Each dose cohort is deemed intolerable if 2 or more DLTs occur at any time in Cycle 1.

If permitted by the safety results, the MT-3724 dose escalation is planned to proceed in sequential dose cohorts. Before each dose escalation decision, the sponsor, investigators and independent pharmacovigilance physician will review all available data in the current dose cohort. The safety management team 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.

4.1.1.1 Subject Evaluable for Dose Decisions

Subjects in Part 3 will be evaluable for dose decisions if they satisfy one of the following criteria:

- Have had a DLT after at least one dose of MT-3724 in Cycle 1; or
- In the absence of toxicities that have delayed or caused omission of doses, subjects have received at least 4 of 6 (67%) doses of MT-3724 within 21 days

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

4.1.2 Part 4

The goal of Part 4 is to provide sufficient evidence to test the null hypothesis that the true response rate with MT-3724 $\leq$ 17% vs the alternative hypothesis that the true response rate with MT-3724 $\geq$ 32% at the 1-sided alpha level of 0.025 with high statistical power. At least 88 evaluable subjects will be required to test the null hypothesis vs the alternative hypothesis in Part 4. If at least 23 of 88 subjects respond at the end of Part 4, then the null hypothesis is rejected in favor of the alternative hypothesis and the effectiveness of MT-3724 as monotherapy will have been proven. Under the stated null and alternative hypotheses, Part 4 carries 90.4% power at the 1-sided alpha level of $<$ 0.025.

4.1.3 Parts 3 and 4

All study procedures will be the same for Parts 3 and 4. After eligibility is assessed in the screening period (up to 35 days), subjects enter the treatment period. Each treatment cycle will be 21 days in length. Treatment will continue until death, disease progression, unacceptable toxicity, withdrawal of consent, or another reason for withdrawal, or until study discontinuation. Refer to Section 6.1.1.4 for details regarding treatment beyond progression.

End of Treatment: After discontinuation from treatment, all subjects should undergo the End of Treatment (EoT) Visit as soon as possible (up to 14 days) after the last dose of MT-3724 and before start of new therapy.

Short-term Safety Follow-up: The Short-term Follow-up (STFU) Visit for safety assessment should occur 30 days (± 3 days) after the last dose of MT-3724, except for subjects who withdrew consent and objected to further data collection, started new therapy for DLBCL or started another investigational drug.

Long-Term Follow-up: Long-term Follow-up (LTFU) Visits should occur every 3 months (± 14 days) after the last dose of MT-3724 for up to 18 months from the last dose. Subjects who discontinue the study for disease progression will be followed only for OS. Subjects with CR, PR, or SD should also be followed for radiology assessment until progressive disease (PD), death, or start of new anticancer treatment.

4.2 End of Study

4.2.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s) for the purposes of conducting the primary analysis. This date is defined as when the last subject has completed all planned assessments for clinical outcomes.

End of Study (End of trial): The end of the study is defined as the date of the last visit of the last subject in the study or last scheduled procedure shown in the Schedule of Activities for the last subject in the trial globally.

5 STUDY POPULATION

NOTE: The investigator or sub-investigator must judge all pre-admission vital signs, physical examination (PE), laboratory or any safety variables to be within normal limits or clinically insignificant. If local standard of care (SoC) procedures or tests were performed prior to signing of the informed consent form (ICF) but are still within 35 days (or 28 days for laboratory safety and radiographic assessments) of the planned dose Day 1, then those results/data can be used for the intended protocol screening procedure. If various parameters within a given procedure are missing from the SoC procedures, then only those missing parameters need to be collected. The medical monitor will also review all screening data to confirm each subject's eligibility prior to dosing initiation. Any laboratory results that exclude study participation may be repeated to confirm accurate exclusion from the study. A subject who is no longer excluded upon retest will be reviewed again by the medical monitor prior to dosing initiation.

In addition, prior to first dose of MT-3724 on Cycle 1 Day 1 (C1D1), the investigator must confirm there have been no changes in the subject's health that would render them medically inappropriate to begin protocol therapy.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 10.1.4). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects meeting ALL of the following inclusion criteria will be eligible for participation of the study:

1. Subjects must be informed about the study and fully consent to participation as demonstrated by signing the written ICF before any screening procedure.
2. Male and female subjects ≥ 18 years of age at the time of informed consent
3. Subjects must have relapsed or refractory DLBCL according to the Revised European American Lymphoma/World Health Organization classification (Swerdlow, 2016). Subjects must have proof of CD20+ DLBCL, based on either:
   a. historical biopsies (obtained with diagnosis of relapsed or refractory disease), or
   b. fresh biopsies
   c. bone marrow biopsy, excisional lymph node biopsy, and core biopsy of any involved organ are all acceptable methods; Fine Needle Aspirate is not acceptable.

   NOTE: Composite lymphoma (DLBCL and indolent histology in the same specimen) is also acceptable.
4. Subjects must have received at least 2 SoC regimens (including anti-CD20 antibody therapy) appropriate for DLBCL treatment.
   a. Subjects whose prior therapy includes CAR-T-cell therapy are eligible
   b. Subjects who underwent stem cell transplant (SCT) > 100 days for autologous SCT or > 180 days for allogeneic SCT before study drug administration.
   c. Subjects who have been ineligible for SoC DLBCL treatment(s) may be eligible at the investigator's discretion, upon sponsor approval.
5. Subjects must have at least 1 bi-dimensional tumor lesion at screening that is measurable by CT and/or magnetic resonance imaging (MRI) according to the Lugano criteria (Cheson, 2014). Bi-dimensionally measurable tumor lesion by CT and/or MRI is defined as longest diameter of > 1.5 cm for lymph nodes and > 1.0 cm for extranodal disease.
6. Subjects must have life expectancy of > 3 months from the start of treatment.
7. Subjects must have ECOG performance status of 0-2.
8. Subjects must have met ALL the following laboratory criteria:
   a. absolute neutrophil count (ANC) ≥ 1.0×10^9/L with no myeloid growth factors (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor preparations) administered within 2 weeks of C1D1
   b. platelet count ≥ 50×10^9/L with no Thrombopoietin-receptor agonists agents or platelet transfusions given within 2 weeks of C1D1

c. hemoglobin ≥ 8.0 g/dL with no erythropoietin stimulating agents or peripheral red blood cell (PRBC) transfusions within 2 weeks of C1D1
d. creatinine clearance (CLcr) to be ≥ 50 ml/min either measured or estimated using the Cockcroft-Gault formula (Section 10.2.2.2).
e. total bilirubin (or direct bilirubin for patients with Gilbert's disease) < 1.5 × upper limit of normal (ULN)
f. alanine transaminase (ALT) ≤ 3.0 × ULN (or ≤ 5.0 x ULN if liver involvement).
g. aspartate aminotransferase (AST) ≤ 3.0 × ULN (or ≤ 5.0 x ULN if liver involvement).
h. international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN (unless on therapeutic anticoagulants)
i. Activated partial thromboplastin time ≤ 1.5 x ULN (unless on therapeutic anticoagulants)

9. Have adequate serum albumin, as determined by:
   a. albumin ≥ 3.0 g/dL
10. QT interval correction for heart rate using Fridericia's formula (QTcF) ≤ 480 ms determined as the average of 3 QTcF values from the triplicate ECG obtained at screening.
11. Women of reproductive potential must have a negative highly sensitive pregnancy test within 72 hours before the start of treatment. Women who are postmenopausal or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) may be considered as not of reproductive potential.
12. Subjects of reproductive potential must agree either to abstain continuously from heterosexual intercourse or to use a highly effective birth control method from signing the informed consent until the STFU visit for females and until 90 days after the last dose of MT-3724 for males. Refer to Section 10.4 for guidance on contraception.
13. Subject must be able to comply with all study-related procedures and medication use.

5.2 Exclusion Criteria

Subjects who meet ANY of the following criteria must be excluded:

Prior or Current Therapies

1. Received any amount of anti-CD20 mAbs within the following periods before the start of treatment:
   a. Rituximab (Rituxan®/MabThera® or rituximab biosimilar): within 84 days (12 weeks); if a subject has received rituximab within 37 weeks before the start of treatment, then serum rituximab level must be negative (< 500 ng/mL) at screening.
   b. Obinutuzumab (Gazyva®/Gazyvaro®): 184 days
   c. Ofatumumab (Arzerra®): 88 days
   d. Any other anti-CD20 agents (eg, investigational agents), the washout period is 5 half-lives. The investigator must contact the medical monitor to discuss the most

appropriate washout for non-approved CD20-targeting agents, where the half-life ($t_{1/2}$) is not known.

2. Received approved or investigational treatment for DLBCL (except anti-CD20 agents where exclusion criterion 1 applies and radioimmunoconjugates) within 4 weeks before the start of treatment. For small molecules (MW < 0.9 kDa), the washout is 5 half-lives or at least 2 weeks. Radioimmunoconjugates are excluded within 12 weeks before the start of treatment.
3. Received radiation therapy to tumor lesions that would serve as target lesions (measurable disease) within 4 weeks before the start of treatment, unless the lesion exhibited objective progression between radiation therapy and screening according to the Lugano Classification (Cheson, 2014).
   a. Palliative radiation therapy to non-target lesions may be permitted at the investigator's discretion after consultation with the medical monitor and sponsor. See Section 6.5 for more information on permissible use of palliative radiotherapy.
4. Require the use of systemic immune modulators during study treatment:
   a. Systemic immune modulators include, but are not limited to, systemic corticosteroids at doses > 20 mg/day of prednisone equivalent, cyclosporine and tacrolimus. Please see Section 6.1.3 for more details and exceptions.
   b. The use of non-steroidal anti-inflammatory drugs (NSAIDS) is permitted.
5. Received any live vaccines within 4 weeks before the start of treatment.
6. Prior treatment with MT-3724.

Medical History

7. Current evidence of Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1 toxicity (due to prior anticancer therapy) before the start of treatment, except for hair loss and those Grade 2 toxicities listed as permitted in other eligibility criteria.
8. Current evidence of significant (CTCAE Grade ≥ 2) infection or wound within 4 weeks before the start of treatment.
   a. Subjects with Grade 2 infection that has stabilized or improved with oral anti-infectives before the start of treatment may be eligible at the sponsor's discretion.
9. Known or suspected hypersensitivity to the study drug or excipients contained in the study drug formulation.
10. Current evidence of hypersensitivity or other underlying illness requiring systemic corticosteroids at doses > 20 mg/day prednisone equivalent
11. Current evidence of uncontrolled human immunodeficiency syndrome (HIV), HBV or HCV at screening. Serology testing is not required if seronegativity is documented in the medical history, and if there are no clinical signs suggestive of HIV or hepatitis infections, or suspected exposure. The following exceptions apply for subjects with positive viral serology:
    a. Subjects with HIV and an undetectable viral load and CD4+ T-cell (CD4+) counts ≥ 350 cells/mL may be enrolled, but must be taking appropriate opportunistic infection prophylaxis, if clinically relevant.

b. Subjects with positive HBV serology are eligible if they have an undetectable viral load and the subject will receive antiviral prophylaxis for potential HBV reactivation per institutional guidelines.
c. Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is below the lower limit of detection. Concurrent antiviral HCV treatment per institutional guidelines is allowed.

12. Current evidence of incomplete recovery from surgery or radiotherapy before start of treatment, or planned surgery or radiotherapy from the start of treatment until the EoT visit, except minor elective surgery deemed acceptable by the investigator or palliative radiation therapy to non-target lesions, as described in Section 6.5.
13. History of cardiovascular, renal, hepatic or any other disease within 3 months before the start of treatment that in the investigator's opinion, 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.
14. History or current evidence of neoplastic disease that is histologically distinct from NHL, except cervical carcinoma in situ, superficial noninvasive bladder tumors, curatively treated Stage I-II non-melanoma skin cancer. Subjects with prior, curatively treated cancer > 2 years ago before the start of treatment can be enrolled.
15. Current evidence of new or growing brain or spinal metastases during screening. Subjects with known brain or spinal metastases may be eligible if they:
    a. Had radiotherapy or another appropriate therapy for the brain or spinal metastases; concurrent prophylactic treatment is allowed
    b. Neurologic symptoms must be stable and no worse than Grade 2
    c. Have evidence of stable brain or spinal disease on CT or MRI scan obtained within 4 weeks before signing the informed consent and compared with prior imaging results
    d. Do not require steroid therapy (or, if applicable, have been stable on dose of no more than prednisone 20 mg/day or equivalent by C1D1)
16. Women who are pregnant or breastfeeding.
17. History of non-adherence to the schedule of procedures or medication use.
18. Current evidence of Graft vs Host Disease
19. 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 (New York Heart Association [NYHA] Class III or IV) at screening or left ventricular ejection fraction (LVEF) ≤ 45%, assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 1 month before starting study treatment (inclusion of subjects with LVEF between 40% to 45% should be discussed with the medical monitor and approved by the sponsor). (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 since then).

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

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) deemed related to a protocol screening procedure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Informed consent is required before subjects can be rescreened if outside the original 35-day screening window. See Section 10.1.4 for Informed Consent Process details.

6 STUDY TREATMENT

6.1 Study Treatment(s) Administered

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

6.1.1 Investigational Product: MT-3724

MT-3724 is the only investigational medicinal product in this study.

MT-3724 will be supplied as a sterile aqueous solution (pH [redacted]) in a 2 ml vial containing 2.0 mL of MT-3724 (0.5 mg/ml) in a formulation buffer comprised of sorbitol [redacted] mM), sodium citrate [redacted] mM) and polysorbate-20 [redacted]%). Vials are shipped frozen. Each vial will be labeled with the

drug name, lot number, storage conditions, and US Food and Drug Administration (FDA)-required Investigational Product statement.

MT-3724 vials must be stored in a secure facility at [redacted] 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 [redacted] dextrose in water or normal saline for intravenous (IV) administration. All doses should be administered over 1 hour (54 – 75 minutes) through an IV line. See Pharmacy Manual for detailed instructions and worksheets regarding study drug preparation and administration.

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

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

6.1.1.1 Dose Rationale

Administration of fixed doses of MT-3724 generated early signs and symptoms of an acute innate immune response, limiting a tolerable dose to 50 µg/kg/dose in a monotherapy setting. However, given the short $t_{1/2}$ of MT-3724 and its mechanism of action, it is expected that the C_{max} is critical for cytotoxicity. Furthermore, rapid-onset AEs can be reduced in frequency and severity with other antibody therapies by incrementally increasing dose over time, as described below.

To mitigate safety risks, the proposed step-up dose regimen for MT-3724 will not exceed the MTD of 50 µg/kg/dose identified in Parts 1 and 2 of the study. In addition, the maximum dose will be 1200 µg at the 10 µg/kg dose level, 3000 µg at the 25 µg/kg dose level and 6000 µg at the 50 µg/kg dose level.

6.1.1.2 Dose Selection

Part 3:

Two dosing cohorts are planned to complete Part 3 of the protocol to confirm the tolerable dose and schedule. A minimum of 6 subjects will be enrolled in each cohort. Following the completion of the Part 3, Part 4 of the protocol will be initiated using the regimen identified as tolerable in Part 3. Dose-limiting toxicity will be assessed during Cycle 1 of Cohorts 1 and 2. The dose and schedule are described in Table 6-1.

Cohort 1:

The starting MT-3724 dose for each subject will be 10 µg/kg for the first 2 doses (D1, D3) and then increased to 25 µg/kg for the remaining doses (D5, D8, D10, D12) of the first 21-day cycle and all doses of Cycle 2 (D1, D3, D5, D8, D10, D12). Dosing will then continue at 25 µg/kg weekly (D1, D8, D15), beginning with Cycle 3 (Table 6-1).

If fewer than 2/6 subjects have a DLT in Cohort 1, then the study will proceed to Cohort 2. If 2 or more subjects have a DLT in Cohort 1, the study will be stopped.

Cohort 2:

The starting MT-3724 dose in each subject will be 10 µg/kg for the first 2 doses (D1, D3). The dose will then be increased to 25 µg/kg for 2 doses (D5, D8) and then the dose will be increased to 50 µg/kg for the remaining doses (D10, D12) of the first 21-day cycle and all doses of Cycle 2. Dosing will then continue at 50 µg/kg weekly (D1, D8, D15) beginning with Cycle 3 (Table 6-1).

If fewer than 2/6 subjects have a DLT in Cohort 2, then the study will continue to Part 4 using the Cohort 2 dose and schedule. If 2 / 6 subjects experience a DLT in Cohort 2, the study will continue to Part 4 using the Cohort 1 dose and schedule.

Table 6-1. Step-up Dosing Schedule for Cohorts 1 and 2

Day	MT-3724 Dose (µg/kg)[a,b]	
	Cohort 1 (n = 6)	Cohort 2 (n = 6)
Cycle 1 D1, D3	10	10
Cycle 1 D5, D8	25	25
Cycle 1 D10, D12	25	50
Cycle 2 D1, D3, D5, D8, D10, D12	25	50
Cycle 3+ D1, 8, 15 (weekly dosing)	25	50

[a] The total administered dose of MT-3724 must not exceed 1200 µg per infusion for the 10 µg/kg dose; 3000 µg per infusion for the 25 µg/kg dose and 6000 µg per infusion for the 50 µg/kg dose in all treatment cycles.

[b] Each dose of MT-3724 must be preceded by premedication administered within 60 minutes before the start of each infusion (see Section 6.1.2).

Part 4:

The study will continue to Part 4 using the tolerable dose and schedule determined in Part 3.

Parts 3 and 4:

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

The total administered dose of MT-3724 must not exceed 1200 µg per infusion for the 10 µg/kg dose; 3000 µg per infusion for the 25 µg/kg dose and 6000 µg per infusion for the 50 µg/kg dose.

The guidance for treatment modification (dose interruption / delay, dose reduction or treatment discontinuation) is presented in Section 6.2.

6.1.1.3 Dose Schedule

All doses of MT-3724 will be administered as IV infusion over 1 hour (window = 54 to 75 minutes) in a 21-day cycle according to the schedule specified in each cohort (Table 6-1).

NOTE: Each dose of MT-3724 must be preceded by premedication administered within 60 minutes before the start of each infusion (see Section 6.1.2)

All doses should be administered within the first 16 days of the 21-day cycle. For Cycle 1 and 2 doses are preferably administered on Days 1, 3, 5, 8, 10, and 12 (± 1 d). For Cycle 3 and later doses are preferably administered on Days 1, 8, and 15. All cycles should use the following guidelines:

- The first 3 doses of Cycle 1 must be administered at least 2 days (approximately 48 hours) apart.
- All subsequent doses must be at least 20 hours apart (more than 5 half-lives of MT-3724 in serum), and must not be administered on more than 2 consecutive days.

The first dose of the first cycle will require approximately 5 hours in the clinic which include approximately 4 hours of post-dose safety assessments. Subsequent doses will require approximately 3 hours in the clinic which include approximately 2 hours of safety assessments post-dose (see also Section 1.3, Schedule of Activities (SoA)).

No more than 14 days should elapse between cycles. If more than 14 days elapse, the investigator must consult with the medical monitor before initiating the next cycle of treatment. Refer to Section 6.2 for dose modification guidelines and management of toxicities.

Treatment will continue until death, disease progression, unacceptable toxicity, withdrawal of consent, or another reason for withdrawal, or until study discontinuation.

6.1.1.4 Treatment Beyond Progression

For subjects who have radiological, but not clinical, evidence of disease progression within 3 months of C1D1, in lieu of discontinuation, the investigator may continue treatment at the dose they are given at the time progression is identified if s/he believes the benefit outweighs the risk and provided the conditions identified below are met.

Conditions for continued treatment:

- absence of symptoms and signs, including worsening of laboratory values, indicating unequivocal PD,
- no decline in Eastern Cooperative Oncology Group performance status (ECOG PS) due to PD,
- absence of tumor progression at critical anatomical sites (eg, leptomeningeal disease),
- subject's written consent to defer any standard treatment options that may exist in favor of continuing MT-3724 treatment at the time of initial progression.

Radiological assessments should be repeated in 4 to 6 weeks from the time of initial progression.

6.1.2 Other Protocol-required Intervention

Premedication Before MT-3724 Infusion

Premedication as described in Table 6-2 must be given within 60 minutes before the start of each MT-3724 infusion. The specific drugs in each of the 3 classes listed below can be selected at the investigator's discretion or according to the institutional guideline. Cases where a subject has a contraindicating medical condition that precludes pre-treatment with any of the categories below must be discussed with the Medical Monitor.

Table 6-2. Premedication

Premedication Class	Cycle 1	Cycle 2	Cycle 3+
Oral anti-pyretic agent	325-1000 mg acetaminophen (or equivalent)	325-1000 mg acetaminophen (or equivalent)	325-1000 mg acetaminophen (or equivalent)[1]
Intravenous H1 histamine receptor antagonist	50-100 mg diphenhydramine (or equivalent)	50-100 mg diphenhydramine (or equivalent)	50-100 mg diphenhydramine (or equivalent)[1]
Intravenous corticosteroid agent with a short biological half-life	250-1000 mg methylprednisolone (or equivalent)	250-1000 mg methylprednisolone (or equivalent)[1]	250-1000 mg methylprednisolone (or equivalent)[1]

[1] Dose adjustment permitted following MM approval.

6.1.3 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments are prohibited during the study:

- All systemic treatment for lymphoma
- Radiation therapy to tumor lesions that would serve as target lesions (measurable disease). Palliative radiation therapy to non-target lesions may be permitted (see Section 6.5).
- Systemic immune modulators, unless used for a treatment-emergent adverse event (TEAE) or as a premedication for MT-3724.
  - The immune modulators include, but are not limited to, systemic corticosteroids at doses > 20 mg/day or prednisone equivalent for more than 1 week, cyclosporin and tacrolimus.
- Any live vaccines from 4 weeks before the start of treatment, during the treatment and after the last dose of MT-3724 while peripheral B cells are depleted.

6.2 Dose Modification

The investigator may modify the MT-3724 treatment in an individual subject by:

- Dose interruption defined as changes made during the current dose (eg, temporary or permanent stop the IV infusion).
- Dose delay will be used for changes to dose schedule (eg, postpone the date of the next dose). A maximal dose delay of 14 days is allowed, a delay exceeding 14 days should be discussed with the medical monitor.
- Dose reduction (according to Table 6-3)
  - Medical monitor must be notified when dose is reduced.
- Permanent discontinuation.

Refer to Table 6-4 for guidance on dose modification of MT-3724 treatment (dose interruption, dose delay, dose reduction or permanent discontinuation) if deemed at least possibly related to MT-3724 by the investigator. Except where expressly prohibited (see Section 6.1.3), the use of concomitant medications is allowed at the investigator's discretion for management of toxicities.

6.2.1 Dose Modification for Treatment-emergent Adverse Experiences

The following actions are recommended after any of the TEAEs listed in Table 6-4 occur.

- The investigator should notify the medical monitor acting on behalf of the sponsor about the TEAE within 24 hours of the awareness.
- The investigator should monitor the subject and if necessary, perform unscheduled diagnostic procedures and therapeutic interventions, including those not specified in the study protocol.
- If a subject experienced Grade ≥ 2 IRR, or another Grade ≥ 2 hypersensitivity event, Grade ≥ 2 CRS or Grade ≥ 2 CLS, then 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 at the investigator's discretion. See Table 6-3 for recommended dose reduction steps. The number of MT-3724 dose reductions per subject is not limited, except that the reduced dose cannot be < 5 µg/kg/dose (this is 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 may be **restarted** if the TEAE that previously led to treatment modification has resolved to Grade ≤1 or the subject's baseline within the time frame deemed appropriate at the investigator's discretion.
    - After the resolution of the TEAE, the MT-3724 dose for continued treatment may be the same or reduced, as determined according to the stopping rules (if applicable) or at the investigator's discretion

MT-3724 treatment must be **permanently discontinued** if a TEAE that previously led to treatment modification did not resolve to Grade ≤1 or baseline within 14 days.

Table 6-3. Dose Reduction Steps

Dose Reduction[a]	**Dose µg/kg/dose**		
Full Dose	**10**	**25**	**50**
First Reduction (~ 25%)	8	19	38
Second Reduction (~ 50%)	5	13	25

[a] Other reductions require consultation and agreement of the medical monitor.

Table 6-4. MT-3724 Dose Modification Guidance and Specific Management of Toxicities

		Specific Management	MT-3724 Dose Modification[a]
Neutropenia or Thrombocytopenia			
ANC AND Platelet	> 500/µl or < 500/µl for < 5 days ≥ 25,000/µl		No change
ANC AND / OR Platelet	< 500/µl for ≥ 5 days, OR febrile neutropenia [c] < 25,000 for ≥ 7 days with or without active bleeding, OR < 50,000/µl for ≥ 7 days with clinically significant bleeding [b]		Decrease by 1 dose level
Infusion-related Reaction or Other Hypersensitivity Event			
IRR OR Hypersensitivity reaction	Grade ≥ 2	Infusion must be interrupted.	Treatment may be restarted or permanently discontinued at the investigator's discretion. If the MT-3724 re-treatment after Grade 2 IRR is allowed, then it must occur: • Only after the appropriate delay (ie, resolution of symptoms). • At the reduced dose and/or reduced infusion rate, where both will be chosen at the investigator's discretion. • After the appropriate anti-allergic prophylaxis according to the premedication guidance in this protocol (see Section 6.1.2) or the institutional guideline.
	Grade ≥3		MT-3724 treatment must be permanently discontinued

Table 6-4. MT-3724 Dose Modification Guidance and Specific Management of Toxicities

	Specific Management	MT-3724 Dose Modification[a]
Nonhematological TEAEs		
Grade ≥ 2 CRS	Subjects should be closely monitored for signs of CRS. This includes: • Monitoring of vital signs (temperature, heart rate, BP, respiration rate), body weight and clinical symptoms including headache, myalgia, muscle weakness, edema, neurological and gastro-intestinal symptoms, abdominal pain, and fatigue • Monitoring of laboratory parameters of hematology, albumin, kidney and liver function and cytokines in case of clinical symptoms indicative of CRS Investigators should consider supportive measures while on trial regardless of dosing or timing of dosing.	May trigger a modification of MT-3724 treatment (dose interruption, dose delay, dose reduction or permanent discontinuation) if deemed at least possibly related to MT-3724 by the investigator.

Table 6-4. MT-3724 Dose Modification Guidance and Specific Management of Toxicities

	Specific Management	MT-3724 Dose Modification[a]
Grade ≥ 2 CLS: As defined in CTCAE v5.0, or if at least 2 of the following within the same cycle (unless unequivocally related to underlying condition) reaches the level of Grade 2: • Hypoalbuminemia • Hypotension • Edema (peripheral or central, all types) and/or weight gain	Subjects should be closely monitored for signs of CLS. This includes: • Monitoring of vital signs (temperature, heart rate, BP, respiration rate), body weight, edema of any type including both peripheral edema and central edema (such as pleural effusion or signs of dyspnea). • Monitoring of laboratory parameters including hemoconcentration (eg, hematocrit, Hb), and especially albumin and CK in case of clinical symptoms indicative of CLS. Investigators should consider supportive measures while on trial regardless of dosing or timing of dosing. If a subject experiences Grade 2 hypotension, orthostasis, edema, or hypoalbuminemia, normal saline and/or an albumin infusion may be given, as needed.	Treatment modification due to CLS: • For Grade ≥ 3 CLS, the MT-3724 treatment must be permanently discontinued. • For Grade 2 CLS, the MT-3724 treatment must be held, and may only be restarted after: ○ a minimum of 7 days has elapsed after onset of CLS, and ○ all signs and symptoms of CLS have resolved to at least grade 1, and ○ albumin has remained ≥ 3.0 g/dL for at least 5 days post last albumin infusion (if required) without additional albumin substitution Subsequent doses of MT-3724 must be: • reduced by at least 25%, and • administered once weekly or subject may be permanently discontinued at the investigator's discretion.

Table 6-4. MT-3724 Dose Modification Guidance and Specific Management of Toxicities

		Specific Management	MT-3724 Dose Modification[a]
SCr increase ≥ 1.5-3.0 times above baseline or 1.5-3.0 x ULN in the absence of dehydration or bleeding			May trigger a modification of MT-3724 treatment (dose interruption, dose delay, dose reduction or permanent discontinuation) if deemed at least possibly related to MT-3724 by the investigator
Any Grade ≥ 3 electrolyte abnormality that does not resolve, with or without intervention, to Grade < 2 within 72 hours			
Any other Grade ≥3 nonhematological toxicity excluding the following: • Nausea, vomiting, or diarrhea, if manageable with antiemetic or antidiarrheal agents within 7 days of onset • Fatigue lasting ≤72 hours • Grade 3 laboratory abnormalities, if asymptomatic and without a clear clinical correlate			
Hepatotoxicity			
AST and / or ALT OR Bilirubin	≤ 5.0 x ULN (isolated) ≤ 1.5 x ULN (isolated)		• No change in treatment • Monitor subject
AST and / or ALT OR Bilirubin	> 5 x ULN – 8.0 x ULN (for subjects enrolled with AST/ALT < 3 x ULN) > 1.5 x ULN – 5.0 x ULN		• Temporarily or permanently (see next row) discontinue treatment • Monitor subject • Continue at dose reduced by 1 dose level after abnormal values resolve to Grade ≤ 1 or baseline values
AST or ALT	> 8.0 x ULN for any period of time (for any subject)		• Permanently discontinue treatment

Table 6-4. MT-3724 Dose Modification Guidance and Specific Management of Toxicities

		Specific Management	MT-3724 Dose Modification[a]
	> 5 x ULN for more than 2 weeks (for subjects enrolled with AST/ALT 3-5 x ULN)		
AST and / or ALT AND Bilirubin	> 3.0 x ULN (without findings of cholestasis defined as serum ALP < 2 × ULN) > 2.0 x ULN or INR > 1.5		• Permanently discontinue treatment
AST and / or ALT OR Bilirubin	> 3.0 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) > 5.0 x ULN		• Permanently discontinue treatment

NOTE: These are recommendations in situations where a possible relatedness to study drug is assumed. These recommendations cannot consider all clinical circumstances; therefore, the investigator is encouraged to contact the sponsor and/or medical monitors to discuss alternative courses of action.

The number of MT-3724 dose reductions per subject is not limited, except reductions beyond what is outlined in Table 6-3 require consultation with the medical monitor.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BP = blood pressure; CLS = capillary leak syndrome; CRS = cytokine release syndrome; INR = international normalized ratio; IRR = infusion-related reaction; ULN = upper limit of normal; TEAE = treatment-emergent adverse event.

[a] MT-3724 dose reduction by 1 dose level translates to an approximate reduction by 25% to 33%, see Table 6-3. The actual amounts for either agent will be determined by the investigator after consultation with sponsor and medical monitor.

[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 1 hour).

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study will be conducted as a single-arm, open-label, non-randomized study, where all eligible subjects will be assigned to MT-3724 treatment.

Assignment of the screening slots and treatment slots will be done on the basis of competitive enrollment across multiple sites.

6.3.2 Blinding

Not applicable; this is an open-label study.

6.4 Study Treatment Compliance

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

6.5 Concomitant Therapy

New medication (either prescription or OTC) or concomitant medication reported by the subject or subject's medical records between the screening medical history and the start of treatment should be reported as concomitant medication. During the treatment and until the STFU visit, concomitant medications will be reported by verbal probes at every visit to the clinic or at every phone contact; in addition, subject's spontaneous reports will be captured.

Except where expressly prohibited (see Section 6.1.3), the use of concomitant medications is permitted at the investigator's discretion for management of toxicities.

Concomitant use of platelet transfusion for thrombocytopenia, packed red blood cells (RBC) or blood transfusion for anemia or G-CSF for leukopenia are permitted for supportive care at the investigator's discretion, but only after the investigator has properly assessed if the MT-3724 treatment should be modified due to drug-related cytopenia.

Palliative therapy, such as radiotherapy, which spares at least 50% of bone marrow producing regions, to non-target lesions or intrathecal chemotherapy, is allowed at the investigator's discretion after consultation with the medical monitor and sponsor.

While the use of certain immunomodulators is prohibited as described in Section 6.1.3, the use of NSAIDS is permitted.

Reasons for Caution

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

Subjects treated with B-cell depleting mAb, similar to MT-3724, have been shown to have impaired humoral and/or cellular immune responses to neo-antigens for variable periods of time during or after the treatment. Therefore, investigators should use caution about the potential for immune suppression when prescribing concomitant medications or vaccines.

6.6 Treatment After the End of the Study

The sponsor may decide to initiate an open-label rollover study after the study ends. If the sponsor decides to initiate an open-label rollover study and that study is approved under applicable regulatory requirements and a local ethics committee, or if providing the study drug for continued treatment of study subjects is required by the local country's regulatory mechanism, then study subjects may be eligible for continued treatment of MT-3724. However, the sponsor reserves the unilateral right, at its sole discretion, to determine whether to supply MT-3724 and by what mechanism, after the study and before the product(s) is/are available commercially.

7 SUBJECT WITHDRAWAL, REPLACEMENT AND STUDY DISCONTINUATION

7.1 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 from signing the consent until the EoT Visit.

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

All subjects who permanently discontinue study treatment for any reason should have an EoT Visit performed as described in the Schedule of Activities (Section 1.3).

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

7.2 Subject Replacement

Subjects that have signed the informed consent but never received at least 1 dose of study drug may be replaced. Subjects who are not evaluable for dose decisions during the DLT assessment period will be replaced.

7.3 Study Discontinuation

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

7.4 Lost to Follow-up

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

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

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

For subjects who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 General Study Periods

Each subject's participation will comprise of 4 sequential periods: screening, treatment, STFU for safety, and LTFU for efficacy.

8.1.1 Screening and Enrollment

A signed written ICF will be obtained before any screening procedure may begin.

Screening procedures will be performed within 35 days before the start of treatment on C1D1, except for central and local laboratory safety assessments and radiographic assessments (must be collected within 28 days of start of treatment) and the determination of LVEF (see Section 8.4.7 for the permitted windows for this assessment).

After the investigator determines that all eligibility criteria have been fulfilled (see Section 5), the medical monitor should review the screening results and acknowledge the investigator's decision that the subject may start treatment.

8.1.2 Treatment Period

Treatment begins on Day 1 of Cycle 1 when the first dose of investigational product is administered to a subject. During clinic visit days all protocol-required predose assessments have to be performed prior to administration of MT-3724.

Treatment will continue until death, disease progression, unacceptable toxicity, withdrawal of consent, or another reason for withdrawal, or until study discontinuation. Refer to Section 6.1.1.4 for details regarding treatment beyond progression.

8.1.3 End of Treatment Visit

The EoT Visit will occur upon discontinuation of treatment, as soon as possible (up to 14 days) after the last dose, and before the start of new therapy, except for subjects who withdrew consent and objected to further data collection, or were lost to follow-up.

End of Treatment visit should be performed in-clinic; however the EoT visit may be performed by telephone call, but only if a subject cannot attend a clinic visit or has started a new anticancer treatment. In such instances, missed assessments (eg, laboratory assessments, PE), are not considered deviations.

8.1.4 Short-term Follow-up Visit

The STFU Visit for safety assessment should occur 30 days (± 3 days) after the last dose of MT-3724, except for subjects who withdrew consent and objected to further data collection, started new therapy for DLBCL or started another investigational drug.

The STFU Visit can be done via a clinic visit (recommended) or via a telephone call (if subject cannot attend a clinic visit or has started a new anticancer treatment or a new DLBCL treatment). In such instances, missed assessments (eg, laboratory assessments, PE), are not considered deviations.

8.1.5 Long-term Follow-up

The LTFU Visits should occur every 3 months (± 14 days) after the last dose of MT-3724 for up to 18 months from the last dose. The LTFU Visits will be performed via a telephone call to collect the information about death (if any), the DLBCL status (relapsed or not) and the start of

any new therapy for DLBCL or any other investigational drug since the last study visit/phone call. Subjects with CR, PR, or SD should also be followed for radiology assessment until PD, death, or new anticancer treatment. Radiology data can be obtained from existing medical records if assessments were performed as SoC between LTFU visits.

8.2 General Assessments

8.2.1 Demographics

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

8.2.2 Non-Hodgkin Lymphoma Assessment

The NHL assessment will be performed at screening by documenting the tissue sampling method used to confirm the CD20+ DLBCL histology at relapse, and the disease status at the initial diagnosis and at screening.

The following information about NHL will be documented:

- Status at initial diagnosis:
  - Non-Hodgkin Lymphoma type histology
  - Staging (Ann Arbor Classification-Cotswold Modification) (Lister, 1989)
  - Grading (International Prognostic Index [IPI]) for NHL
- Status at time of relapse:
  - International Prognostic Index
  - Time to progression after first line therapy (captured as date of first relapse/progression)
- Status at screening:
  - Histology showing DLBCL and CD20+ status confirmation by historical or fresh biopsy (bone marrow, lymph node, organ) in relapse or refractory setting
  - Date of most recent relapse
  - Staging (Ann Arbor Classification-Cotswold Modification) (Lister, 1989)
  - Grading (IPI)
  - Genetic mutational status (eg, MYC, BCL2 and BCL6 rearrangement / overexpression)
  - Molecular subtype (germinal center B cell [GCB] vs activated B cell [ABC])

The prognostic assessment instruments (Ann Arbor Classification with Cotswold Modification [Lister, 1989] and IPI [NHL Project, 1993]) are described in Section 10.5.

8.2.3 Prior Systemic Therapy

Prior systemic therapy for NHL (including SCT and CAR-T) administered at any time before the start of treatment will be assessed.

Each regimen (line of treatment) should be documented in sequential order of past use with the outcome of therapy. The start and stop dates of each individual agent / regimen (ie, line of treatment) should be recorded. The date of the last CD20-based therapy should also be documented in the eCRF.

8.2.4 Prior Radiotherapy

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

8.3 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.3.1 Radiological Assessment of Tumor Response

At baseline, both a positron emission tomography-computed tomography (PET-CT) and a computed tomography of diagnostic quality (CT-dq; or MRI) should be collected. Note, if the CT-portion of the PET-CT is of diagnostic quality, a separate CT-dq scan need not be obtained. For follow-up scans, while the same methodology (eg, PET-CT, CT-dq) should be used throughout the study (both PET-CT/CT-dq whenever possible), PET-CT should be used in subjects with fluorodeoxyglucose (FDG)-avid tumor histology while CT-dq and/or MRI should be used in subjects with tumor histology of low or variable FDG avidity. Irrespectively, CT-dq and/or MRI should be used at baseline and in subsequent follow-up scans in lieu of PET-CT if the latter cannot be used at the frequency prescribed per protocol because of access limitations. Methodology may vary per imaging availability, upon consultation with the sponsor. The same technique (eg, slice thickness, field of view) should be used for all scans during the study treatment period.

The radiological tumor response assessment should be performed as indicated in the SoA (Section 1.3). The original schedule needs to be maintained even if there is a delay is dosing.

Unscheduled tumor response assessment by fluorodeoxyglucose-positron emission tomography-CT (or CT-dq and/or MRI) may be obtained at the investigator's discretion. Complete remission and PR should be confirmed by repeated radiologic evaluation between 4 weeks to 8 weeks after the initial response assessment. For subjects treated beyond progression, radiological evaluation must be repeated in 4 to 6 weeks from initial scan showing progression.

The investigators at each investigational site will determine the preliminary tumor response based on the radiologist's measurement of all anatomic regions involved with the measurable disease according to Lugano Classification for Lymphoma ([Cheson, 2014], Section 10.6).

Preferably, all scans from 1 subject should be interpreted by the same investigator and the same radiologist at each investigational site.

8.3.2 Independent Centralized Review of Efficacy Results

Digital images from all tumor response assessments must be available to be sent to the independent central review (ICR) service at any time during the study. All images sent to the ICR service must be anonymized by the investigational sites and provided digitally as Digital Imaging and Communications in Medicine (DICOM) format. The investigator must assure that the images are of acceptable diagnostic quality and fulfill the requirements outlined in the Imaging Manual. Additional specific information on the handling (ie, collection, shipment, tracking) of the images sent to the ICR will be provided in the Imaging Manual.

The definitive treatment response assessment will be determined by the ICR service at the central imaging laboratory using the Lugano Classification (Cheson, 2014).

The reviewers at the central imaging laboratory will be board-certified radiologists, experienced and independent radiologists with strong expertise in clinical radiology as well as the use of Lugano Classification in clinical trials with novel hematology-oncology agents. The central reviewers must not be otherwise involved in this study, ie, listed or identified as investigator or sub-investigator who is directly involved in the treatment or evaluation of study subjects. Central reviewers will be isolated from knowledge of investigator PD assessments through read lock procedures and communication controls. Except for the baseline visit, the ICR will be blinded to the subject's identity and all other data (eg, demography, MT-3724 dose modification, TEAEs, disease characteristics).

8.3.3 Quality of Life

The standardized EuroQol Group Quality of Life (QoL) – 5-dimensions (EQ-5D) questionnaire with 5 questions will be used for the QoL assessment.

8.4 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Subjects will be monitored for signs of CLS and CRS during and after their infusions. Vital signs will be monitored up to 4 hours after the start of infusion on C1D1, and up to 2 hours after the start of infusion for each subsequent infusion. In addition, subjects will remain in-clinic for PK sampling for 5 hours from the start of infusion on C1D1 and for 3 hours from the start of infusion on C1D3 and C1D12, where they will be observed for signs of CLS and CRS.

8.4.1 Medical History

Relevant medical history will be recorded at screening. This will include prior surgery, prior and concomitant illnesses and allergy history. The prior systemic anticancer therapy, radiotherapy and tumor related biopsies or surgery will be collected and documented on separate eCRF forms.

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

8.4.2 Prior and Concomitant Medications

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

Medications taken within 4 weeks before the start of treatment on C1D1 will be regarded as prior medications (prior NHL therapy will be captured separately). The medications taken after the start of treatment on C1D1 will be regarded as concomitant medications.

8.4.3 Physical Measurements

Height (in meters [m]) and weight (in kilograms [kg]) will be measured; body-mass index (BMI) will be then be calculated.

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

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

8.4.4 Physical Examinations

Physical examination (PE) will be performed by a physician or a qualified delegate at the investigating site.

A complete PE including neurological examination and ECOG assessment will be performed at the following time points:

- At screening
- At the EoT Visit

An abbreviated PE including ECOG will be performed at the following time points:

- Before MT-3724 dose on D1 of each cycle

The investigator or delegate at the site will perform the PE and evaluate the results. The overall PE result will be categorized as 'normal', 'abnormal, not clinically significant (abnormal NCS)',

or 'abnormal, clinically significant (abnormal CS)'. All abnormal CS results of the PE should be reported as AE(s) in the eCRF and followed up at the investigator's discretion. Comments about abnormal NCS results, either overall or for individual aspects or body parts, will not be collected in the eCRF.

The performance status will be assessed by the Eastern Cooperative Oncology Group (ECOG) scale (see Section 10.7) at the same time points as complete and abbreviated PEs.

8.4.4.1 Complete Physical Examination

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

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

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

8.4.4.2 Abbreviated Physical Examination

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

- General appearance

- Skin (paleness, jaundice, redness/rash, acneiform changes)
- Ears, eyes (jaundice, inflammation) nose, throat (presence of petechial bleedings, gingival bleeding)
- Lungs
- Heart
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)
- Lymph nodes
- Extremities (petechial bleedings, ulcers, signs of thrombosis), hands and feet (signs of hand-foot syndrome/palmar-plantar erythrodysesthesia)
- Abbreviated neurological examination to include the following assessments:
  - Oculomotor testing, pupil accommodation, double images
  - Motor system: muscle strength of arms
  - Sensory system: pain and touch sensation of thighs
  - Mental Status (awareness of self and environment)
  - Posture
  - Coordination: finger-to-nose and heel-to-shin test

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

8.4.5 New York Heart Association

The classification of cardiac function will be performed for subjects with heart failure according to the NYHA (Section 10.8).

8.4.6 Vital Signs

Vital sign assessments (BP; systolic and diastolic, respiratory rate [RR], heart rate [HR] and body temperature) will be assessed at time points indicated in the SoA (Section 1.3).

Body temperature will be measured in Fahrenheit (°F) or Celsius (°C). BP, RR, and HR will be measured using an automated digital (preferred) or manual assessment.

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

For BP and HR assessments, the subject must rest quietly in a sitting or semi-recumbent position for at least 5 minutes before and during the assessments. When the PK, ECG and vital signs assessments are scheduled to occur at the same time point, refer to the SoA for timing of collection.

Any clinically-significant abnormality of vital signs should be followed up by repeat assessment(s), where number and timing will be determined at the investigator's discretion. If

confirmed on repeat assessment(s), the abnormal CS results should be reported as AE(s) in the eCRF and followed up at the investigator's discretion. Comments about abnormal NCS result will not be collected in the eCRF.

8.4.7 Left Ventricular Ejection Fraction

The LVEF assessment will be performed at screening. A pre-study LVEF assessment is acceptable if obtained within 6 months before screening and at least 28 days after the last cancer therapy provided the subject has not received any potentially cardiotoxic agents since then.

Left ventricular ejection fraction should be assessed by ECHO. If ECHO is not available or appropriate according to the institutional standard, then MUGA scan is permitted. The same modality should be used throughout the study.

8.4.8 Electrocardiograms

All ECG recordings will be obtained using standardized equipment supplied for this study by the sponsor or contract research organization (CRO). The investigator or delegate at the site will assess the ECG results for the bedside safety assessment. All recordings will be transferred to a central review facility. The sponsor may initiate to have the ECG recordings analyzed by an ICR service at the central facility.

Standard resting 12-lead ECG assessments will be performed after the subject has rested quietly for at least 5 minutes in supine or semi-recumbent position.

All ECG recordings will be obtained in triplicate (3 standard ECGs obtained in close succession, and no more than 2 minutes apart).

When the PK, ECG and vital signs assessments are scheduled to occur at the same time point, refer to the SoA (Section 1.3) for timing of collection.

If any of the ECG printouts in a triplicate is of poor quality, additional ECG(s) may be obtained as soon as possible at the same time point until 3 ECGs of adequate quality are obtained. Such additional ECG(s) do not have to be reported as unscheduled assessments.

The investigator or delegate at the site will assess the ECG results for the bedside safety assessment. The QT interval corrected according to the Fridericia's formula (QTcF) will be used for safety assessment. The 3 QTcF values from a triplicate ECG should be averaged to yield the mean QTcF value. If not available on the ECG printout, the QTcF value will be calculated using an online calculator.

The overall ECG assessment will be categorized as 'normal', 'abnormal, not clinically significant (abnormal NCS)', or 'abnormal, clinically significant (abnormal 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 of ECGs should be followed up by repeat assessment(s), where number and timing will be determined at the investigator's discretion. If confirmed on repeat assessment(s), the abnormal CS results should be reported as AE(s) in the eCRF and followed up at the investigator's discretion. Comments about abnormal NCS result will not be collected in the eCRF.

NOTE: If a subject reports an AE post-dose while in the clinic, a 12-lead ECG should be obtained and reviewed as part of the AE evaluation if clinically indicated. This AE will be reported in the eCRF, and the ECG analyzed and reported according to site specific procedures.

8.4.9 Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

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

Laboratory test results will be graded according to the CTCAE v. 5.0 criteria. Out of range results considered to be CS 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 a CS AE and needs to be reported as such in the eCRF, unless associated with disease progression. Confirmed Grade 2 abnormal laboratory results will be assessed on a case by case basis for clinical significance based upon the subject's baseline value, 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.

8.4.10 Safety Follow-up Phone Calls

A safety follow-up phone call should be performed to evaluate ongoing AEs, occurrence of new AEs and use of concomitant medication the third week of each cycle, unless the subject is receiving weekly dosing.

8.5 Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Section 10.3. For AEs of CLS, CRS/ SIRS, and IRRs, individual symptoms and grade should be reported on the appropriate eCRF.

8.5.1 Time Period and Frequency for Collecting Adverse Event Information

The AE reporting period will begin on the day of the first dose of study drug unless deemed related to a protocol screening procedure after signing informed consent until the STFU visit or phone call, or until the start of new cancer therapy (unless the investigator believes the AE is related to MT-3724), whichever occurs first.

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

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

All AEs that occur in enrolled subjects during the AE reporting period specified in the protocol must be recorded, regardless of the relationship of the AE to MT-3724. 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.

8.5.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.5.3 Regulatory Reporting Requirements for Serious Adverse Events

If an SAE occurs at any time from the time of start of treatment until the STFU Visit, it must be reported to the CRO responsible for clinical safety management and the medical monitor acting on behalf of the sponsor (see list of contacts). The investigator must report any SAE due to any cause, whether or not related to the study drug(s), within 24 hours of the time when s/he became aware of the event. The investigator must send a preliminary report of any such SAE to the study safety monitor via the electronic data capture (EDC) system within 24 hours or if this is not possible, via email or fax using an SAE Report Form, or at a minimum by telephone.

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

Appropriate remedial measures should be taken to treat the SAE, and the response to treatment should be recorded. Subjects must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the investigator. Clinical, laboratory, and diagnostic measures should be employed as needed 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 study manual.

8.5.3.1 SUSAR

An unexpected SAE that is at least possibly related to the study drug will be considered a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The sponsor will determine if a reported SAE meets the criteria for SUSAR and confirm the decision with the medical monitor and the CRO responsible for clinical safety management. The sponsor has a legal responsibility to notify regulatory authorities, investigators, and in some locations Ethics Committees (ECs)/Institutional Review Boards (IRBs) regarding potentially serious risks from clinical trials. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ ECs, and investigators.

8.5.3.2 Pregnancy Reporting Instructions

Pregnancy should be avoided from 4 weeks before the start of treatment, until the STFU Visit. Acceptable contraception is specified in the inclusion criteria, see Section 5.1 and Section 10.4.

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

If pregnancy occurs during treatment in a subject the investigator must immediately discontinue MT-3724 and report the pregnancy to the CRO responsible for clinical safety management and the medical monitor acting on behalf of the sponsor, along the same timelines as a SAE (see Section 8.5.3).The subject must be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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

8.6 Pharmacokinetics

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 (refer to Table 1-2 for specific time points). 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. Please note, samples for PK must be drawn from a different line than that used for MT-3724 administration.

In addition, for subjects who will have cerebrospinal fluid (CSF) collected at any time point in the study as part of their SoC, a portion of the sample collected will be used by the sponsor to evaluate for the presence of MT-3724 in CSF.

8.7 Pharmacodynamics

8.7.1 Peripheral Blood

Pharmacodynamic markers will be the B-cell count and the immunophenotype in peripheral blood, as determined by flow cytometry, and circulating immunoglobulins (IgA, IgG, IgM).

Serial blood samples for pharmacodynamic assessment will be collected as indicated in the SoA (Section 1.3). Unscheduled assessments may be performed at any time at the investigator's discretion.

8.7.2 Optional Tumor Tissue Biopsy

Optional biopsy of the tumor tissue may be performed at the EoT Visit in those subjects who had been discontinued due to PD, had consented for this procedure and have accessible peripheral lymph node(s).

The purpose of the biopsy is to assess if the disease progression is associated with the loss of CD20 positivity of tumor cells.

Subjects may also have a biopsy to confirm CR, in the absence of PET/CT scans.

8.8 Immunogenicity Assessments

Antibodies to MT-3724 will be evaluated in blood samples collected from all subjects according to the SoA (Section 1.3). Additionally, blood samples should also be collected at the final visit from subjects who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Blood samples will be screened for anti-drug antibodies (ADA) that bind MT-3724. All ADA positive samples will have the titer reported and screened for neutralizing antibodies (NAb), reported as positive or negative. Other analyses may be performed such as verifying the stability of antibodies to MT-3724.

The detection and characterization of antibodies to MT-3724 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to MT-3724 will also be evaluated for MT-3724 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s). Refer to the appropriate informed consent for the maximum duration of storage. Samples will be stored at a facility selected by the sponsor to enable further analysis of immune responses to MT-3724.

9 STATISTICAL CONSIDERATIONS

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

Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum); categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier plots, medians and range. Where confidence limits are appropriate, the confidence level will be 95% (2-sided), unless otherwise stated. There are no inferential statistical methods for this study design.

Individual data (including relevant derived variables) will be presented by variable in by-subject listings. Results of statistical analyses, descriptive summary statistics and supportive listings will also be presented.

Detailed methodology for summary and statistical analyses of the data collected in Parts 3 and 4 of this study will be documented in a statistical analysis plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment and documented in the clinical study report.

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA).

9.1 Statistical Hypothesis and Sample Size Determination

In Part 3, approximately 25 subjects will be enrolled as a continuation of the expansion of the MTD cohort with the intention to verify the safety, dose and dosing schedule (completion of the Phase 1b).

In Part 4, approximately 88 evaluable subjects will be enrolled. If at least 23 of 88 evaluable subjects respond at the end of Part 4, then the null hypothesis is rejected in favor of the alternative hypothesis and the effectiveness of MT-3724 as monotherapy will have been proven. Under the stated null and alternative hypotheses, Part 4 carries 90.4% power at the 1-sided alpha level of < 0.025.

9.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full analysis set (FAS) population	All subjects who received at least 1 dose of MT-3724 monotherapy treatment. This will be the primary population for the assessment of efficacy endpoints.
Modified full analysis set (mFAS) population	All subjects who have at least 1 post-baseline efficacy assessment; subjects without a post-baseline efficacy assessment will not be considered evaluable for the primary efficacy analysis. Subjects who discontinue due to disease progression or die, prior to disease assessment will be included.
PK analysis population	All subjects who received any amount of MT-3724 and for whom the on-treatment PK data are considered to be sufficient and interpretable.
Immunogenicity analysis population	All subjects who have received any amount of MT-3724 and have valid post-baseline immunogenicity assessment will be included in the analysis set for the immunogenicity analysis.
Pharmacodynamic analysis population	All subjects who have received any amount of MT-3724 and have at least 1 valid post-baseline pharmacodynamic assessment.
Safety analysis population	All subjects who received at least 1 dose of MT-3724 monotherapy treatment. For this study, this is equivalent to the FAS population.

9.3 Statistical Analyses

9.3.1 General Considerations

Starting with Amendment 9 of the study protocol MT-3724_NHL_001, the study will be a multi-center, single-agent, open-label study consisting of 2 parts: Part 3 will complete the Phase 1b portion of this to verify the safety, dose and dosing schedule. Part 4 is a Phase 2 design and will provide independent confirmation of the efficacy of MT-3724.

Each of the 2 parts (Parts 3 and 4) will include LTFU after the last dose of MT-3724 for up to 18 months from the last dose. Subjects who discontinue the study for disease progression will be followed only for OS. Subjects who discontinue the study for reasons other than disease progression will be followed for PFS, as reported by investigators and OS.

9.3.1.1 Baseline Definition

The assessment obtained (and entered into EDC) at the most recent time before the start of MT-3724 treatment will be the baseline for all post-baseline assessments.

For all efficacy endpoints, the tumor scan obtained before MT-3724 Dose 1 during the screening (if available) will serve as the baseline; Pre-study tumor scan should be collected as close as possible to the start of treatment and evaluable for the ICR (ie, performed according to the Imaging Acquisition Guidance provided in the Imaging Manual).

9.3.1.2 Subject Disposition

A detailed description of subject disposition will be provided. It will include:

- The number of subjects who were included in the FAS, safety and efficacy evaluable analysis sets
- A summary of subjects who complete the protocol
- A summary of reasons for subject discontinuation
- A summary of reasons for subjects with treatment failure
- An account of all identified protocol violations

All subjects enrolled in the study will be accounted for in the summation.

9.3.1.3 Demographic and Baseline Characteristics

Demographic characteristics including age, gender, race, and ethnicity will be presented in the form of tabular summary statistics for all FAS subjects. Other subject baseline characteristics including weight, height, BMI, initial stage of disease, and performance status will be presented similarly.

9.3.2 Efficacy Analysis

The primary efficacy variable (Part 4) is the overall tumor response rate (ORR).

The secondary efficacy variables in Part 3 are overall response rate, DCR, DOR; and in Part 4 the secondary efficacy variables are the DCR, DOR, PFS, and OS.

The definitive treatment response assessment (ie, the tumor response used to derive the primary and secondary efficacy endpoints) will be determined by response assessment using the Lugano Classification (Cheson, 2014). The sponsor will have the definitive treatment response assessment determined by the blinded, ICR service at the central imaging laboratory using the Lugano Classification.

9.3.2.1 Primary Efficacy Variable (for Part 4)

The primary efficacy variable is the ORR. The ORR is defined as the percent of subjects with CR or PR determined by the blinded, ICR according to the Lugano Classification for Lymphoma (Cheson, 2014), relative to the FAS population.

Overall response rate will be summarized by number and percentage of subjects meeting the definition of ORR along with the corresponding 2-sided 95% binomial exact confidence intervals (CI), separately for Parts 3 and 4.

In Part 4, with n = 88 subjects, if ≥ 23 ORRs are seen, the null hypothesis is rejected in favor of the alternative hypothesis and the effectiveness of MT-3724 as monotherapy will have been proven.

Subjects with missing disease assessments such that objective response cannot be determined will be assumed to be non-responders in the analysis.

9.3.2.2 Secondary Efficacy Variables

The secondary efficacy variables will be PFS, DCR, DOR and OS. All secondary efficacy variables will be determined from the radiological tumor scans according to the Lugano Classification for Lymphoma (Cheson, 2014) relative to the FAS population.

Secondary efficacy variables will be evaluated separately for Parts 3 and 4.

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

For subjects who continue to receive treatment after radiographic PD, and have confirmed PD at next assessment, the time of PD will be that of the first detection.

The DOR will be defined as the time from the first documented objective response (CR or PR) to the date of PD or death from any cause. Subjects who have not progressed at the time of data base lock will be censored at the date of their last tumor assessment.

The PFS will be defined as the time from the start of treatment with MT-3724 on C1D1 to the date of PD or death from any cause. Subjects who have not progressed at the time of data base lock will be censored at the date of their last tumor assessment.

For both DOR and PFS, those subjects who have no data on progression (eg, subjects who discontinued the study due to other reasons than progression and who were not followed up until progression) and/or have no data on tumor assessment after baseline and are still alive will be censored at the subject's date of first dose.

The OS will be defined as the time from the start of treatment with MT-3724 until death from any cause.

The DOR, PFS and OS will be summarized descriptively using the Kaplan-Meier methods (K-M median and corresponding 95% CI, quartiles, number of events, number censored, Kaplan-Meier figure). Since these methods assume missing data are missing at random, supportive analyses will be conducted assuming data are missing not at random.

As a secondary sensitivity analysis for efficacy (eg, study drug exposure, lines of prior therapy, DOR to prior therapy, subject subsets), the mFAS population will be utilized. The same statistical techniques will be applied on each efficacy endpoint on the mFAS population.

Data listings will be created to support each analysis and to present all efficacy data.

The value for the percent change from baseline in the sum of product of perpendicular diameters (SPD) as the measurement of tumor lesion size in each individual subject will be listed by time points. The values for the percent change from baseline in SPD values at each time point will be plotted for individual subjects ("spider plot"). The largest value for the percent change from baseline in SPD will be plotted on a histogram ('waterfall' plot).

9.3.2.3 Quality of Life

Quality of life is assessed via the EQ-5D. The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale. The EQ-5D descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The response for each of the dimensions is ordered categorical: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems and 5 = unable to/extreme problems. The EQ-5D domains will be summarized descriptively in terms of the percent of subjects falling into each ordered category at any given timepoint; the data will also be explored by cumulative and adjacent logit analyses.

The EQ visual analogue scale records the respondent's self-rated health on a vertical, visual analogue scale where the extremes are '100 = Best imaginable health state' and '0 = Worst imaginable health state'. The change in visual analog scale score from baseline to any given time point will be summarized descriptively.

9.3.3 Safety Analysis

All subjects who receive any dose (any amount) of MT-3724 monotherapy treatment will be included in the summaries and listings of safety data. Overall safety profile will be characterized by type, frequency, severity, timing, duration, AEs' relationship to study drug, laboratory abnormalities, and vital signs. All analyses will be descriptive. All AE data will be summarized separately for Parts 3 and 4 and also combined (Parts 3 and 4).

Baseline values are defined as the last valid value prior to study drug administration. Baseline safety data will be presented along with subsequent safety values assessed during or after drug administration.

9.3.3.1 Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system and the severity of the toxicities will be graded according to the NCI CTCAE v 5.0. Adverse event data will be summarized separately for Parts 3 and 4 and also combined (Parts 3 and 4).

In all summaries, emphasis will be placed on TEAEs, namely, those with initial onset or those that worsen in severity after the first dose of MT-3724. Adverse events will be summarized by the frequency of subjects experiencing TEAEs corresponding to MedDRA System organ class and preferred term and by worst NCI CTCAE grade. Summaries will also be provided of treatment related TEAEs, namely, those judged by the investigator to be related or likely related to MT-3724.

Adverse events resulting in discontinuation of MT-3724 treatment or withdrawal from the study, Grade 3 or higher, SAEs, and deaths on-study will be tabulated.

9.3.3.2 Laboratory Tests

Laboratory data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes from baseline using descriptive statistics.

For those analytes with CTCAE version 5.0 severity criteria specified, abnormal laboratory values will be summarized by shift tables displaying numerical values and percentages classified by baseline grade and maximum grade on treatment.

All laboratory data will be presented in data listings.

9.3.3.3 Vital Signs and Physical Examination Findings

Vital signs data will be summarized by the observed valued at each scheduled assessment, together with the corresponding changes from baseline using descriptive statistics.

Physical examination findings will be presented in data listings.

9.3.4 Other Analyses

9.3.4.1 Pharmacokinetic Analysis

Pharmacokinetics data will be summarized separately for Part 3 and Part 4. The PK parameters will be estimated using standard noncompartmental methods as data permit. Pharmacokinetics parameters, where calculable, include: C_{max}, t_{max}, AUC_{0-4}, AUC_{0-inf}, AUC_{last}, $t_{1/2}$, V_z, and CL. Actual sample collection times will be used rather than scheduled collection times. Serum concentrations below the limit of quantification will be treated as 0. Embedded missing serum concentrations (ie, missing values between 2 observed values) will be estimated using linear extrapolation. This is consistent with using the trapezoidal rule to calculate AUC. Other missing serum concentrations will be excluded from calculations to estimate PK parameters.

[redacted]

9.3.4.2 Pharmacodynamic Analysis

B-cell count and immunophenotyping results obtained by flow cytometry will be presented as absolute values and percentage change from pre- to post-dose time points. The absolute values and changes from baseline by time point during the treatment will be tabulated and plotted for the pharmacodynamic analysis set.

Details of the descriptive statistical analyses of pharmacodynamic data will be provided in a separate statistical analysis plan. Pharmacodynamic data will be summarized separately for Part 3 and Part 4.

[redacted] The details of the exposure-response modeling analysis will be described in a separate Modelling and Simulation (M&S) Analysis Plan and the results will be presented in a separate M&S report.

9.3.4.3 Immunogenicity Analysis

Data for the ADA against MT-3724 will be obtained. The ADA titer will be determined for ADA samples confirmed as a positive result. The data for the NAb against MT-3724 will be reported as positive or negative. These data will be summarized separately for Part 3 and Part 4.

The number and percent of subjects with a detectable ADA titer, and separately with a positive NAb result, will be summarized by time point for each treatment group/cohort. The individual subject's ADA and NAb results will be listed by time point during the treatment; the listings will be presented for the pharmacodynamic analysis set. The individual subject's ADA titer will be plotted by time point during the treatment.

Details of the descriptive statistical analyses of immunogenicity data will be provided in a separate statistical analysis plan.

9.4 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established to monitor and evaluate the safety of subjects on an ongoing basis and to maintain oversight of the study data and monitoring process. The committee will consist of at least 1 independent experienced oncologist, statistician, and pharmacovigilance physician, the sponsor and its representatives and any other person the study team considers necessary to assist with study decisions. The committee will meet prior to starting Part 4, and according to the DSMB Charter established at the beginning of the trial. The DSMB will meet periodically during the expansion cohort. The DSMB will meet to discuss the overall incidence of serious related AEs (SAEs and AEs with CTCAE Grade 3 or 4) and Adverse Events of Special Interest to ensure that subject safety is addressed appropriately. The sponsor has the discretion to suspend enrollment for safety or efficacy reasons at any time pending DSMB review. The DSMB will also meet at unscheduled times according to clinical necessity. All SAEs and suspected Adverse Events of Special Interests will be reported to the DSMB by the

sponsor in accordance with regulatory timelines. Refer to the DSMB Charter for additional details.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Investigators and Study Administrative Structure

Physician Responsible for Study and Data Monitoring Committee Contact:

[redacted], M.D., MBA
Chief Medical Officer, Molecular Templates, Inc.
Harborside Plaza 5, Suite 1510
185 Hudson Street
Jersey City, NJ 07311
Tel: [redacted]

Contract Research Organization: A Contract Research Organization (CRO) will be managing all or part of this clinical trial on behalf of Molecular Templates. All contact information including each site's assigned clinical research associate and medical monitor will be provided in the Site Reference Manual provided at the site initiation visit.

Safety Laboratory Tests: All standard safety laboratory tests (see Section 10.2) will be performed by a central laboratory. Unscheduled safety labs for critical AE management may be performed by the site's local laboratory. Results from these laboratories will be entered into the study's data base by electronic transfer for central lab results or manually for local lab results.

Central Laboratory Tests: Flow cytometry, serum cytokines, PK (serum and CSF), serum Rituximab, anti-drug antibodies (ADA)/Immunogenicity, and the optional biopsy analyses will be performed by a central laboratory. All contact information will be provided in the Laboratory Manual provided at the site initiation visit.

Central Review Services: Electrocardiogram recordings will be obtained using standardized equipment supplied for this study by the sponsor or CRO. The investigator or delegate at the site will assess the electrocardiograms (ECG) results for the bedside safety assessment. All recordings will be transferred to a central review facility. The sponsor may initiate to have the ECG recordings analyzed by an independent central review (ICR) service at the central facility.

All radiology data collected for this study will be transferred to a central imaging laboratory. The sponsor will have the definitive treatment response assessment determined by the ICR service at the central imaging laboratory.

Clinical Trial Supply: MT-3724 will be shipped frozen to sites by a central vendor. Specific instructions for ordering study drug and contact information for each site will be provided in the Study and Pharmacy Manuals provided at the site initiation visit.

10.1.2 Regulatory and Ethical Considerations

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor, its authorized representative and investigators abide by Good Clinical Practice (GCP) as described in International Conference on Harmonisation (ICH) guideline E6 (ICH, 2016), and in 21 Code of Federal Regulations (CFR) Parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the most recent revision of the Declaration of Helsinki (WMA, 2013) that is recognized by the US Food and Drug Administration (US FDA) and the European Medicines Agency.

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom significant trial-related duties have been delegated.

Prior to initiation, the principal investigator will submit the study protocol, Investigator's brochure, sample ICF, and any other documents that pertain to subject information, recruitment methods and advertisements, to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The principal investigator must also submit any other information that may be requested to the IRB/IEC for review and approval. Each investigator's IRB/IEC will review these materials in accordance with GCP guidelines. The investigator will request that the IRB/IEC provide written approval and will keep on file records of initial study approval.

After approval by the committee, the following documentation will be sent to the study manager before the study commences:

- Confirmation of IRB/IEC approval of the protocol.
- Confirmation of IRB/IEC approval of the ICF and applicable addenda.
- A list of IRB/IEC members, their representative capacity, and their affiliation (a current Health and Human Services General Assurance number will suffice).

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF provided by Molecular Templates or its agents. The investigator may not make changes to this protocol without Molecular Templates agreement.

The investigator must conduct the study according to the most recent, approved protocol version. For deviations, the investigator or designee must document and explain any deviation from the protocol. The investigator should also notify the IRB/IEC of deviations from the protocol or SAE occurring at the site as per the IRB/IEC standard operating procedure, as well as other AE reports received from Molecular Templates or its representative and provided to the investigator, in accordance with local procedures.

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

10.1.3 Financial Disclosure

All described guidelines and procedures apply equally to investigators and sites enrolling in Parts 1, 2, 3 and 4 of this study. In accordance with the FDA regulation (21 CFR Part 54) on Financial Disclosure by Clinical Investigators, Molecular Templates is required to include in marketing applications to the FDA either:

- Certification of the absence of certain financial interests or arrangements of clinical investigators,
  OR
- Disclosure of certain financial interests or arrangements of clinical investigators.

Molecular Templates will request a statement attesting to any such financial arrangements. Disclosure is required for those financial interests other than the Clinical Study Agreement for this study. A statement will be required 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.

10.1.4 Informed Consent Process

- The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained. If local SoC procedures or tests were performed prior to signing of the ICF but are still within 35 days of initiation of dosing, unless otherwise specified (eg, LVEF), then those results/data can be used for the intended protocol screening procedure. If various parameters within a given procedure are missing from the SoC procedures, then only those missing parameters need to be collected.
- The investigator's IRB/IEC will review and approve the study protocol and subject ICF and any other materials the investigator prepares for recruitment of subjects (eg, advertisements, study information brochures). All investigator generated subject information and recruitment materials must also be provided to Molecular Templates and its agents for review and approval. The ICF will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations.
- Before being enrolled, the principal investigator or one of his/her sub-investigators must explain orally and in writing the nature, duration, purpose of the study, and the action of the study drug in such a manner that the subject or legally authorized representative is aware of possible risks, inconveniences, or adverse effects that may occur. The ICF must be in a language that is understandable to the subject or legally authorized representative. The subject or legally authorized representative will have sufficient time to read the document

prior to being asked if there are any questions about the study procedures. A qualified and trained member of the study team must respond to these questions (eg, a study staff member who has been specifically trained on the protocol). Where required by local law, the person who informs the subject must be the investigator or another physician designated by the investigator. The subject should be informed that they may withdraw from the study at any time. The subject will receive all information that is required by the local 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 (eg, 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.

10.1.5 Data Protection

- Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the electronic case report form (eCRF), and if the subject name or any other personal identifier appears on any other document (eg, pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor.
- Study findings stored on a computer will be stored in accordance with local data protection laws.
- The subjects will be told that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.1.6 Study Monitoring

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

10.1.7 Source Documents

10.1.7.1 Case Report Forms and Study Records

It is a regulatory obligation of the investigator to maintain adequate and accurate case histories (source documentation) designed to record all observations and data pertinent to the investigation for each subject. Source Documents are the documents where information regarding a subject is

first recorded. Investigator subject files or hospital records are generally the basis of source document information. All source documentation must be available during site visits for the assigned Monitor to review and compare with the completed eCRFs. The investigator must maintain source documents.

If the site is required to use a subject's medical / hospital record to submit to sponsor/CRO, all subject identifiers must be made invisible to maintain subject's anonymity and confidentiality.

For this trial Monitors will perform source document verification as per the monitoring plan. It is critical that all information contained in the eCRF can be corroborated by the Source Documents that are used. Source documents may include but are not limited to all original documents, data, and records (eg, 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, 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 as required by local authorities), subject study identification (eg, 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 eCRFs, with the exception of central laboratory data, which will be provided to the investigator on a laboratory report and submitted to the clinical database via electronic transfer from the testing laboratory. Local laboratory data will be entered into the case report form (CRFs) by trained and qualified study staff.

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

All potentially eligible and appropriately consented study candidates will be entered into the study's electronic data base with the initiation of screening. This information will be retained for all dosed subjects as well as subjects who fail 1 or more screen procedures or withdraw consent following screening and never progress to receive study drug.

For all enrolled subjects, eCRF pages will be completed for all study activities (eg, MT-3724 administration/dosing, safety assessments, procedures) These entries will be completed from the baseline visit forward until the end of the study (early termination or study completion) and combined with the screen entries be included in each subject's complete study documentation package.

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 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 eCRFs. The investigator will retain a copy of all eCRF pages completed at their site.

10.1.7.2 Access to Source Documentation

Domestic and foreign regulatory authorities, the IRB/IEC, and an auditor authorized by the sponsor may request access to all source documents, eCRF, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. 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 audit, the sponsor must be notified within 24 hours of the investigator's notification by the inspecting authority.

10.1.7.3 Retention of Data

Study documents for all parts of this study must be retained until at least 5 years after the last marketing approval in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product (eg, via notification of the FDA or local regulatory authority). The investigator/institution may not destroy records without written authorization from the sponsor. If an investigator leaves the institution at which the study was conducted, arrangements must be made to ensure another responsible party is designated to maintain the records.

Unless otherwise noted, all described guidelines and procedures apply equally to subjects enrolled in all parts of this study. The following records must be retained by the investigator/institution for a minimum of 2 years after the sponsor has notified the FDA that investigations have been discontinued or after the FDA has approved the new drug application:

- Signed ICFs for all subjects
- Subject identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the investigator and the IRB
- Composition of the IRB or other applicable statement
- Record of all communications between the investigator and Molecular Templates and/or CRO

- List of sub-Investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all subjects
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements must be documented in writing to the sponsor.

10.1.8 Data Quality Assurance

- Data will be recorded in an FDA CFR Part 11-compliant eCRF, also known as the electronic data capture (EDC) system.
- Data reported on the eCRF must accurately reflect the corresponding source documents, or the discrepancies must be explained. No data are to be recorded directly on the eCRFs (ie, the eCRF 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.
- 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.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. All clinical parameters should be entered into the eCRF /EDC as soon as possible after each study visit, preferably within 5 business days of the visit.

10.1.9 Publication and Disclosure Policy

All described guidelines and requirements apply equally to investigators and sites enrolling in all parts of this study. The information developed in the clinical study will be used by Molecular Templates in connection with the development of the investigational product. As such, the information may be disclosed to other investigators or regulatory authorities to obtain marketing approval. In order for Molecular Templates to use the clinical research information, the investigator is obligated to provide all of the information they obtain regarding the investigational product.

Both Molecular Templates and the investigator are free to present or publish the results of the study. Any party proposing a publication will provide the other with a copy of the proposed publication for review and comment prior to the submission for publication. Manuscripts must be submitted 30 days in advance of submission and abstracts within 10 days. The sponsor must be acknowledged in all publications.

10.2 Appendix 2: Clinical Laboratory Tests

10.2.1 General Guidance

- The tests detailed in Table 10-1 will be performed by the central laboratory or local laboratory as indicated. All screening laboratory tests must be collected within 28 days of start of treatment.
- The same laboratory should analyze all scheduled laboratory tests throughout the study.
- Local laboratory for chemistry and hematology should be collected to assess subject status / safety if results from central laboratory will not be available predose, whenever central laboratory assessments are scheduled. These results need only be entered in the electronic data capture (EDC) if there is a clinically significant (CS) finding, related to an AE except albumin and creatine phosphokinase (CK) collected during Cycle 1 which are collected locally and should be entered in the case report form (CRF) irrespective of clinical significance.
- For serial blood samples (PK analyses), an in-dwelling catheter ("hep lock") placed in an extremity other than that used for MT-3724 infusion can be used to obtain the multiple blood samples stipulated in the protocol on dosing days.
- A standalone Laboratory Manual will provide complete instructions regarding how these samples should be collected, stored, and shipped.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1. Protocol-Required Laboratory Assessments

<table>
<tr><th colspan="3">Central Laboratory</th><th colspan="2">Local Laboratory</th></tr>
<tr><td>Hematology</td><td colspan="2">Chemistry</td><td colspan="2">Local Chemistry</td></tr>
<tr><td rowspan="2">hematocrit
hemoglobin
platelet count
RBC[b]
WBC[c]</td><td rowspan="8">Albumin
ALP
ALT (SGPT)
amylase
AST (SGOT)
β-HCG[a]
β-2 microglobulin
bicarbonate
bilirubin (total and direct)
BUN
calcium
chloride
CK[e]
creatinine</td><td rowspan="8">eCrCl[a]
GGT
glucose (fasting, plasma)
HbA1c
LDH
lipase
magnesium
phosphorous
potassium
protein (total)
sodium
uric acid</td><td>Albumin</td><td>CK[e]</td></tr>
<tr><td colspan="2">Urinalysis macroscopic[a]</td></tr>
<tr><td>Coagulation</td><td>glucose
ketones
leukocytes
nitrites</td><td>occult blood
pH
protein
specific gravity</td></tr>
<tr><td>aPTT
INR or PT</td><td colspan="2">Urinalysis microscopic (optional)[a]</td></tr>
<tr><td>Thyroid function</td><td>bacteria
casts
crystals
epithelial cells</td><td>mucous threads
RBC
WBC</td></tr>
<tr><td>free T4
TSH</td><td colspan="2">Viral Serology (if applicable[d])</td></tr>
<tr><td colspan="2">Other Central Laboratory Analytes</td><td>anti-HIV-1 antibody
anti-HIV-2 antibody
HBsAg
anti-HBsAg antibody</td><td>anti-HBcAg antibody
HCV- RNA quantitation
anti-HCV antibody</td></tr>
<tr><td colspan="3">anti-drug antibodies (ADA and NAb titer)</td><td colspan="2">Virology (if applicable)
HIV viral load</td></tr>
</table>

Table 10-1. Protocol-Required Laboratory Assessments

B-cell count and immunophenotype (flow cytometry) complement[a] cytokines (serum)[a] histamine[a] immunoglobulins (IgA, IgG, IgM) serum MT-3724 concentration (PK) CSF MT-3724 concentration (PK) serum rituximab concentration (if applicable) [a]	HBV viral load HCV viral load
	Other local laboratory tests
	CD4+ T-cell counts (if applicable) Pregnancy test (if applicable)
NOTES:	

ADA = anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-HCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CK = creatinine phosphokinase; CSF = cerebrospinal fluid; eCrCl = estimated creatinine clearance; freeT4 = free thyroxin; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HbA1c = glycated hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NAb = neutralizing antibodies; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WBC = white blood cell.

[a] See Section 10.2.2 for analyte-specific guidance.

[b] RBC indices (mean cell volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration) and distribution widths (red cell and platelet).

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

[d] The serology for individual virus(es) may be omitted at the investigator's discretion if seronegativity is documented in the medical history and there are no clinical signs of HIV or hepatitis infections, or suspected exposure.

[e] If CK is elevated > ULN, CK isoenzymes must be analyzed.

10.2.2 Analyte-specific Guidance

10.2.2.1 Pregnancy Test

Only applicable for women of childbearing potential. Women who are postmenopausal (> 1 year since last menstrual cycle) or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) may be considered as not of reproductive potential.

Treatment with MT-3724 may proceed only if the pregnancy test is documented as negative at the most recent assessment. See Section 8.5.3.2 for the guidance about reporting the onset of pregnancy during the study.

10.2.2.2 Creatinine Clearance

The creatinine clearance (CLcr) will be derived from the serum creatinine (SCr) values obtained from the blood chemistry assessment. The CLcr will be calculated using the Cockcroft-Gault formula:

$$CLcr = \{((140–age) \times weight) / (72 \times SCr)\} \times 0.85 \text{ (if female)}$$

Where CLcr = mL/minute; SCr = serum creatinine (mg/dL); age = years; and weight = kg.

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

10.2.2.3 Complement, Histamine, and Cytokines

If a subject experienced a Grade ≥ 2 infusion-related reaction (IRR), or another Grade ≥ 2 hypersensitivity event, Grade ≥ 2 cytokine release syndrome (CRS) or Grade ≥ 2 CLS, the investigator should obtain serum samples for complement, and histamine, and cytokines as soon as possible after the treatment-emergent adverse event (TEAE) onset. These samples should be marked "STAT" and shipped immediately to the central laboratory.

10.2.2.4 Rituximab Concentration

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

The serology for RTX concentration should not be assessed in subjects who have received RTX within 84 days before the start of treatment (automatically ineligible based on this criterion). When 37 weeks have elapsed since the last treatment with RTX, [redacted] The serology for RTX concentration should not be assessed for subjects who never received RTX.

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

10.2.2.5 Urinalysis

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

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Event

The term adverse event (AE) 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 eCRF page. Clinically significant (CS) 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 electrocardiogram (ECG) abnormalities should also be recorded as AEs when considered CS 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 (eg, leading to hospitalization).

Adverse events will be assessed by verbal probes and subject's spontaneous reports from the start of treatment until the STFU Visit or until the start of new anticancer therapy (unless the investigator believes the AE is related to MT-3724), whichever occurs first. Any AEs that occur during screening which are due to study-mandated procedures should also be reported. 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 or qualified delegate for completeness, relatedness and accuracy of severity grading to ensure appropriate reporting practice. Medical Monitor acting on behalf of the sponsor will review cumulative AE data at appropriate intervals, as well as the serious AEs as they are reported.

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

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

10.3.2 Definition of Serious Adverse Event

An SAE is defined as any AE that meets 1 or more of the following criteria:

- The event is fatal or life-threatening.
- The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns).
- The event results in unplanned in-patient hospitalization or prolongation of an existing hospitalization.
- Is or results in a congenital abnormality or birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent 1 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. 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 AE 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.

10.3.3 Adverse Event Terminology

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

10.3.4 Severity

Severity will be classified according to the criteria provided by the Common Toxicity Criteria guidelines from the National Cancer Institute (CTCAE) v5.0. Accessible at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

If the AE is not listed in the CTCAE v5.0, then the highest severity level reached according to the scale in Table 10-2 will be assigned. Every effort should be made to find the appropriate AE term and definitions of severity in the modified CTCAE v. 5.0.

Table 10-2. Classification of Adverse Events by Severity

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

10.3.5 Causality / Relatedness

Causality should be assessed for the study drug (MT-3724) as detailed in the eCRF. Causal relationship to protocol-required procedure(s) should also be considered and reported accordingly in the eCRF.

The following should be considered when assessing causality:

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

The investigator will determine the causal relationship / relatedness to the study drug according to the classification in Table 10-3.

Table 10-3. Classification of Adverse Events by Causality / Relationship to the Study Drug

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

For all purposes of subject management, dose-limiting toxicity (DLT) assignment and treatment modification, the causality assessment of:

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

10.3.6 Expected and Unexpected Adverse Events and SUSARs

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

An unexpected AE is an AE that is not identified by type, severity grade, or frequency in the Reference Safety Information (RSI) section of the Investigator's Brochure for MT-3724 (IB, 2020) or in the MT-3724 safety reports to the health authorities (eg, DSUR).

The Safety Department of the CRO responsible for clinical safety management 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.

10.3.7 Action Taken with Study Treatment

Any action with the study treatment during the AE management and follow-up should be documented in the eCRF using the categories listed below.

- Drug withdrawn
- Dose interrupted
  - Infusion interrupted and resumed

    - Infusion stopped
    - Dose delayed
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

The action “dose increased” is not available in this study.

10.3.8 Outcome

The outcome of the AE should be documented as follows:

- Recovered / resolved
- Recovered / resolved with sequelae
- Not recovered / not resolved
- Fatal
- Unknown

10.3.9 Dose Limiting Toxicity (DLT) 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 Cycle 1
   a. If a TEAE that fulfills a DLT criterion is observed in cycle ≥ 2 of Part 3, then the sponsor may declare this event a DLT after consultation with the investigator(s).
2. The TEAE is at least possibly related to MT-3724, as determined by the sponsor after consultation with the investigator(s).

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

POTENTIALLY QUALIFYING TREATMENT-EMERGENT ADVERSE EVENTS: Any TEAE listed below may represent a DLT for MT-3724 in this study.

Hematological Treatment-Emergent Adverse Events

- Grade ≥ 3 febrile neutropenia (absolute neutrophil count [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 granulocyte colony-stimulating factor (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 CS bleeding (ie, bleeding requiring platelet transfusion)
- Grade 4 thrombocytopenia (< 25,000/µl) with or without bleeding
- Grade 4 anemia

Nonhematological Treatment-Emergent Adverse Events

- Grade ≥ 2 Cytokine Release Syndrome (CRS)
- Grade ≥ 2 Capillary Leak Syndrome (CLS), (change in albumin must be a decrease by at least 0.5 g/dL compared to C1D1)
- Grade ≥ 3 Acute kidney injury
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) increase ≥ 5.0 times upper limit of normal (ULN) (> 8.0 times for those with liver involvement)
- Aspartate aminotransferase and/or ALT increase ≥ 3.0 times ULN with concomitant increase in total bilirubin ≥ 2.5 times ULN

- Total bilirubin ≥ 4.0 times ULN

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

- Grade ≥ 3 infusion-related reaction or other Grade ≥ 3 hypersensitivity reaction
- Any Grade ≥ 3 electrolyte abnormality that does not resolve, with or without intervention, to Grade < 2 within 72 hours.
- Any other Grade ≥ 3 nonhematological toxicity **excluding** the following:
  - Nausea, vomiting, or diarrhea, if manageable with antiemetic or antidiarrheal agents within 7 days of onset
  - Fatigue lasting ≥ 72 hours
- Grade 3 laboratory abnormalities, if asymptomatic and without a clear clinical correlate, as determined by the sponsor after consultation with investigator(s).

Any other toxicity at least possibly related to MT-3724, irrespective of the type or severity, that would qualify as DLT, as determined by the sponsor after consultation with investigator, considering the severity, duration, poor response to remedial therapy and/or inadequate resolution. This may be Grade 1 or Grade 2 toxicity that notably limits the activities of daily life to the extent that makes dose reduction necessary to ensure subject's compliance (eg, long-lasting fatigue or anorexia).

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female subjects of reproductive potential must agree either to abstain continuously from heterosexual intercourse or to use a highly effective birth control method from signing the ICF

until the STFU. Male subjects of reproductive potential must agree to abstain continuously from heterosexual intercourse, have had a vasectomy, or use a condom with or without spermicidal agent from time of signing the ICF until 90 days after the last treatment with study drug.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive MT-3724.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.5.3 and Section 8.5.3.1. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Staging of NHL

Ann Arbor Staging System With Cotswold Modification (Lister, 1989)

Ann Arbor stage is determined as outlined in Table 10-4, for calculation of the 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 10-4. Ann Arbor Staging System With Cotswold Modification

Ann Arbor Staging System Features		
Stage[a]	I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
	II	Involvement of 2 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 extranodal site(s) beyond that designated E
Cotswold Modifications		
For All Stages		
A		No symptoms
B		Fever (> 38ºC), drenching sweats, weight loss (10% body weight over 6 months)
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.
For Stages I to III		
E		Involvement of a single, extranodal site contiguous or proximal to known nodal site

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

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

The International Prognostic Index (IPI) for Aggressive non-Hodgkin Lymphoma (NHL) is used to assess the prognostic score of subjects at diagnosis with aggressive NHL.

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

1. age > 60 years
2. Ann Arbor Stage III or IV disease
3. serum lactic dehydrogenase (LDH) ≥ 450 IU/L
4. ECOG performance status of 2, 3, or 4
5. extranodal sites ≥ 2

Subjects will be documented to be in 1 of 4 risk groups:

Low risk	0-1 risk factors
Low-intermediate risk (2 points)	2 risk factors
High-intermediate risk (3 points)	3 risk factors
High risk (4-5 points)	4-5 risk factors

10.6 Appendix 6: Lugano Classification for Response Assessment in Lymphoma (Including the 5PS)

Tumor response will be evaluated according to the Lugano Classification for Lymphoma (Cheson, 2014) (Table 10-5).

Table 10-5. Lugano Classification of Response Assessment in Lymphoma

Response and Site	PET-CT-Based Response	CT and/or MRI-Based Response
Complete	**Complete metabolic response (CMR)**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	5PS score of 1, 2, or 3[a] with or without residual mass (see Table 10-6) It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesion(s)	None	None
Bone Marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5 on the 5PS (see Table 10-6) with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease. At end of treatment (EoT), these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value; when no longer visible, 0 x 0 mm. For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation.
Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal.
New lesion(s)	None	None

Table 10-5. Lugano Classification of Response Assessment in Lymphoma

Response and Site	PET-CT-Based Response	CT and/or MRI-Based Response
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 EoT	< 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 2: 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesion(s)	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma

Table 10-5. Lugano Classification of Response Assessment in Lymphoma

Response and Site	PET-CT-Based Response	CT and/or MRI-Based Response
Bone Marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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.

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in 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 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] See original paper Cheson, 2014 for more detailed information on immune related response.

Lugano 5PS Range (Cheson, 2014)

The 5PS ranges from a score of 1 (where no uptake is discernible in the lesion) to a score of 5 (where the uptake in the lesion is markedly increased compared to the uptake in the liver parenchyma). A single 5PS score, which represents the most FDG-avid (ie, metabolically intense) area of disease (across all index and non-index lesions), is assigned for each PET/CT scan in the study, see Table 10-6.

Table 10-6. 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

10.7 Appendix 7: ECOG Performance Status

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

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death

10.8 Appendix 8: New York Heart Association Functional Classification

The stages of heart failure will be assessed according to the New York Heart Association (NHYA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

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

10.9 Appendix 9: Abbreviations

Abbreviation	Definition
ABC	activated B cell
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
AUC_{0-4}	area under the plasma concentration time curve from 0 to 4 hours
AUC_{0-inf}	area under the plasma concentration time curve from 0 to infinity
AUC_{last}	area under the plasma concentration time curve from dosing to last measurable concentration
BP	blood pressure
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CAR-T	chimeric antigen receptor T-cell
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine phosphokinase
CL	clearance
CLcr	creatinine clearance
CLS	capillary leak syndrome
cm	centimeter
C_{max}	maximum observed plasma concentration
CR	complete remission; complete response
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CS	clinically significant
CSF	cerebrospinal fluid
CT	computerized tomography
CT-dq	computed tomography of diagnostic quality
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma

Abbreviation	Definition
DLT	dose-limiting toxicity
DOR	duration of tumor response
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EoT	end of treatment
EQ-5D	EuroQol Group Quality of Life – 5-dimensions
FAS	Full analysis set
Fc	fragment crystallizable region
FDA	Food and Drug Administration
GCB	germinal center B cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma glutamyl transferase
HBsAg	hepatitis B surface antigen
[redacted]	[redacted]
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICR	independent central review
IEC	Independent Ethics Committee
Ig	immunoglobulin
IND	investigational new drug
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRR	infusion-related reactions
IV	intravenous
kDa	kiloDaltons
Kg	kilogram
L	liter
LDH	lactic dehydrogenase
LTFU	long-term follow-up

Abbreviation	Definition
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
mg	milligram
ml	milliliter
mM	millimolar
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquistion
NAb	neutralizing antibody
NCI	National Cancer Institute
NCS	not clinically significant
NHL	non-Hodgkin Lymphoma
NSAIDS	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	objective response or overall response rate
OS	overall survival
PD	progressive disease
PE	physical examination
PET	positron emission tomography
PFS	Progression-free survival
PK	pharmacokinetics
PR	partial response
PRBC	peripheral red blood cell
PT	prothrombin time
QTcF	QT interval correction for heart rate using Fridericia's formula
RBC	red blood cell (count)
RP2D	recommended phase 2 dose
RR	respiratory rate
SAE	serious adverse event
scFv	single chain variable fragment
SCr	serum creatinine
SCT	stem cell transplant
SD	stable disease
SGOT (AST)	serum glutamic-oxaloacetic transaminase

Abbreviation	Definition
SGPT (ALT)	serum glutamic-pyruvic transaminase
SIRS	systemic inflammatory response syndrome
SLT-I A1	Shiga-like toxin-I A1 subunit
SoC	standard of care
SPD	sum of product of perpendicular diameters
STAT	urgent, rush
STFU	short-term follow-up
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TIW	three times a week
t_{max}	time to achieve C_{max}
ULN	upper limit of normal
US	United States
V_z	volume of distribution
WBC	white blood cell (count)

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12 SUMMARY OF CHANGES

12.1 Version 11

Version 11.0 (12 February 2021) replaces versions 10.0 (14 August 2020), 9.0 (14 April 2019) and 9.1 (29 June 2020)

Rationale for changes:

Considering a recent Grade 5 CLS event, MTEM has completed the CLS safety assessment and has proposed CLS mitigation strategies and safety monitoring plans for all protocols evaluating MT-3724. This includes the addition of 2 dose-escalation cohorts to evaluate step-up dosing, modified dose caps, CLS-management, including increased monitoring of albumin and CK, and DLT-assessment. These changes, as well as administrative changes, and other necessary changes to account for these additions, are described below.

Editorial changes that do not impact meaning were made and are not listed below.

Summary of changes made:

Change	Rationale	Affected protocol sections
Increased number of subjects from 20 to 25 in Part 3, thereby increasing the total number of subjects from 108 to 113.	To account for evaluation of 2 additional cohorts	Synopsis Overall Design 4.1.1 Part 3 (overall study design) 9.1 Statistical Hypothesis and sample size determination
Added description of 2 dose escalation cohorts with step-up dosing. Subjects will start at 10 µg/kg and increase in dose will be based on cohort. After the first 2 cycles, subjects will be dosed weekly.	An analysis of available data showed that dose and dose-associated PK parameters were associated with an increased risk for CLS. This, in conjunction with the observation that all CLS events occurred within a few days post initial dosing (or re-dosing after an initial CLS), suggests that lower doses at start of treatment may reduce the risk of CLS events.	1. Synopsis Study treatment 1.2 Study schema 1.3 Schedule of activities 4.1.1 Part 3 (overall study design) 4.1.1.1 Subject evaluable for dose decisions (new section added in this amendment) 6.1.1.1 Dose Rationale 6.1.1.2 Dose Section 6.3.1 Randomization
Removed reference to switching to weekly dosing in cases of clinical benefit	All subjects will be switched to weekly dosing staring with Cycle 3 with this amendment, therefore this no longer applies	Synopsis Study treatment Treatment beyond progression 1.3 Schedule of activities 6.1.1.3 Dose Schedule 6.1.1.4 Treatment beyond progression
Added DLT criteria	Added criteria since dose escalation was reintroduced to this protocol	10.3.9 Dose Limiting Toxicity (DLT) Criteria

Change	Rationale	Affected protocol sections
Updated dose cap so that it is based on max of 120 kg body weight rather than absolute total dose of 6000 µg per infusion	An analysis of available data showed an association with total dose administered and CLS, therefore dose caps have been updated to potentially reduce the risk of CLS events.	6.1.1.1 Dose Rationale 6.1.1.2 Dose Selection
Modified dose reduction steps	To account for different doses introduced with step-up dosing	6.2.1 Dose Modification for Treatment Emergent Adverse Experiences
Added guidance to the investigator for CLS, including dose modification	Provide additional information on signs and/or symptoms of CLS, and management of CLS	2.2.2 Guidance to the Investigator for Capillary Leak Syndrome 6.2.1 Dose Modification for Treatment Emergent Adverse Experiences – Table 6-4. MT-3724 Dose Modification Guidance and Specific Management of Toxicities.
Added requirement for collection of albumin and CK (local lab) prior to each dose in Cycle 1, and require albumin to be reviewed prior to dosing	Added collection and review of albumin prior to each dose of Cycle 1 to mitigate CLS. Added collection of CK prior to each dose of Cycle 1 to evaluate if this is a potential biomarker of CLS.	1.3 Schedule of activities 10.2.1 General Guidance (Appendix 2: Clinical Laboratory Tests) Table 10-1
Updated premedication requirements, including requirement to premedicate prior to each dose	Added more clarification on premedication	1.3 Schedule of activities 6.1.2 Other Protocol-required Intervention
Updated requirement for first 3 doses of Cycle 1 to be at least 2 days (approx. 48 hours) apart rather than at least 48 hours apart	To allow for flexibility with respect to dosing while maintaining window	Synopsis Study treatment 1.3 Schedule of activities 6.1.1.3 Dose Schedule
Removed reference to reverting to TIW dosing in case of progression and clarified that subjects will remain on dose received at time of progression	All subjects will be on weekly dosing schedule starting Cycle 3 with this amendment, therefore this no longer applies; and clarified dose administration at time of progression since dose escalation has been re-introduced to this protocol	Synopsis Overall design, treatment beyond progression 6.1.1.4 Treatment beyond progression
Added clarification under dose modification that MT-3724 treatment may be restarted if the TEAE that led to modification resolved to Grade ≤ 1 (new text: "or the subject's baseline")	To allow for treatment to be restarted if subject's baseline condition that led to modification was more severe than grade 1	6.2.1 Dose Modification for Treatment Emergent Adverse Experiences
Added updated clinical experience to reflect IB update (vs 6)	Provided update of clinical experience based on IB version 6, given grade 5 CLS event	2.2.1 Summary of Clinical Experience
Added clarification regarding subject replacement	To account for replacement of subjects ineligible for DLT assessment	7.2 Subject replacement

Change	Rationale	Affected protocol sections
Added requirement for DSMB assembly prior to starting Part 4, and other administrative changes	To ensure sufficient oversight prior to initiating Part 4, Administrative changes made to reflect DSMB charter and best practices	9.4 Data Safety Monitoring Board
Updated action taken with study treatment for AE management	Administrative change to correspond with CDISC	10.3.7 Action Taken with Study Treatment (Adverse Events)

12.2 Version 10

Version 10.0 (14 August 2020) replaces versions 9.0 (14 April 2019) and 9.1 (29 June 2020)

Rationale for changes:

1. Updated schedule of activities (Tables 1-1 and 1-2) to correct errors that were inadvertently made when version 8 was updated to version 9.
2. Language permitting the administration of live vaccines during treatment has been removed, as use of live vaccines with anti-CD20 products and subsequent B-cell depletion is not recommended.
3. Updated the inclusion criterion #4 to specify that the required prior 2 lines of treatment should be appropriate for DLBCL and not any NHL.
4. Updated requirement to change dose if body weight changes from > 10% to ≥ 10%.
5. Updated entry criterion on LVEF to be at least 45% rather than greater than 45%.
6. Clarification has been added on the duration of the in-clinic visit during which subjects will be monitored for signs of CLS and CRS.
7. Additional changes to the summary of changes for amendment 9.0 were added as they were erroneously left out. Those items are in bolded text.
8. Other editorial changes that do not impact meaning were made and are not listed below.

List of changes made:

Section	Revision Made
Schedule of activities: Table 1-1	• Added ECG at EoT • Added Chemistry and removed coagulation at STFU • Added samples missing from screening: complement, histamine, immunoglobulins, cytokines, B-cells and immunophenotype, and MT-3724 ADA/NAb and removed concomitant medication review during screening • Provided clarification on how prior systemic therapy should be recorded • Provided clarification that the safety calls are not required for subjects dosed on weekly schedule • Provided clarification regarding radiological exams for subjects who continue to receive MT-3724 beyond progression and that they are every 6 weeks starting from C1D1 • Reworked note for triplicate ECGs for clarification

Section	Revision Made
	• Changed that subject has to have rested quietly from 5 to 10 minutes to at least 5 minutes. • Updated footnotes to match protocol text and provide clarification on Day 15 visit • Updated requirement to change dose if body weight changes from > 10% to ≥ 10% • Pregnancy test moved from central lab to local lab to allow for real-time assessment
Schedule of activities Table 1-2	• Removed PK samples from C1D3 and C1D12 at both the 0.5 h- and 1 h-after end of infusion timepoints for subjects in Part 4 • Added "within" to "4 hr prior to SOI" to clarify that the PK samples can be drawn within 4 hours prior to SOI and not at 4 hr prior to SOI
Synopsis, Number of subjects	• Removed "who have received at least 2 standard of care systemic NHL treatment regimens (including anti-CD20 antibody therapy) will be enrolled" to avoid redundancy
Synopsis, Sections 3.1, 3.2 and 8.7.1	• Provided clarification that immunoglobulins are collected as pharmacodynamic endpoints
Synopsis; Section 4.1.3	• Removed "Safety" from Long Term Safety follow-up since LTFU visits are not done for safety; and also removed "Visits may occur by telephone contact when radiology data can be obtained from medical records" as it was less clear than what is stated in the section on LTFU (Section 8.1.5)
Synopsis, Section 5.1	• Updated inclusion criterion #4 to specify that the prior treatments need to be appropriate for DLBCL (changed from "Subjects must have received at least 2 standard of care regimens (including anti-CD20 antibody therapy) for NHL treatment" to "Subjects must have received at least 2 standard of care regimens (including anti-CD20 antibody therapy) for appropriate for DLBCL treatment." • Updated inclusion criterion 4b to remove reference to hematologic recovery (deleted: "and exhibited a full hematological recovery (consistent with the existing inclusion criteria requirements and without peripheral red blood cell [PRBC] or platelet transfusions within 2 weeks of C1D1) prior to relapse are eligible." • Updated inclusion criteria #8 to include guidance on use of treatments affecting bone marrow function • Updated inclusion criteria numbering as #11 was skipped in version 9. • Updated inclusion criterion #11 to require pregnancy test within 72 hours of C1D1 rather than 7 days of C1D1, for consistency. • Updated inclusion criterion #12 to clarify contraception requirements after treatment, in alignment with Appendix 4.
Synopsis; Section 5.2	• Exclusion criterion #1 – added sub-bullet D to provide more guidance for investigational CD20 agents. • Exclusion criterion #2 – added clarification on CD20 agents "except anti-CD20 agents where exclusion criterion 1 applies" • Exclusion criterion #5 - removed "unless the investigator believes the benefits outweigh risks, after consultation with the medical monitor and with sponsor approval." • Exclusion criterion #12 – added "or palliative radiation therapy to non-target lesions, as described in Section 6.5" as it was erroneously removed with amendment 9 • Exclusion criterion #19e – corrected LVEF requirement from < 45% to ≤ 45%
Synopsis; Section 6.1.1.2	• Changed requirement for all doses to be administered within 14 days to within 16 days to allow for more flexibility while maintaining roughly 2-week dosing window. • Added clarification on the duration of the clinic visit post-dose.

Section	Revision Made
	• Rearranged paragraph on weekly dosing for clarity. • Updated requirement to change dose if body weight changes from > 10% to ≥ 10%.
Synopsis; Section 6.1.1.3	Added language to clarify that subjects for who have disease progression within 3 months of switching to weekly dosing, the investigatory may revert to the original dosing schedule, if conditions already outlined in that section are met.
Section 6.1.3	Removed: "unless the investigator believes the benefits outweigh risks, after consultation with the medical monitor and with sponsor approval" and added further prohibition on use of live vaccinations: "during the treatment and after the last dose of MT-3724 while peripheral B cells are depleted."
Section 6.4	Changed "subject notes" to "clinic notes" to clarify that compliance is not based on subject diary as treatment is given in-clinic.
Section 8.2.2	Status at screening – clarified that histology at screening is specifically for DLBCL rather than NHL
Section 8.2.3	Provided clarification on how prior systemic therapy should be recorded (to allow for flexibility based on EDC capabilities)
Section 8.4	Added: "Subjects will be monitored for signs of CLS and CRS during and after their infusions. Vital signs will be monitored up to 4 hours after the start of infusion C1D1, and up to 2 hours after the start of infusion for each subsequent infusion. In addition, subjects will remain in-clinic for PK sampling for 5 hours from the start of infusion on C1D1 and for 3 hours from the start of infusion on C1D3 and C1D12, where they may also be observed for signs of CLS and CRS."
Section 8.4.2	Added clarification that medications taken within 4 weeks before the start of treatment on C1D1 will be regarded as prior medications
Section 8.4.3	Updated requirement to change dose if body weight changes from > 10% to ≥ 10%.
Section 8.4.6	Changed that subject has to have rested quietly from 5 to 10 minutes to at least 5 minutes.
Section 8.4.8	Changed "Any clinically significant abnormality of vital signs should be followed…" to "Any clinically significant abnormality of ECGs should be followed…" Reworked note for triplicate ECGs for clarification (removed "ie, the maximum 4 minutes total for 3 ECGs."
Section 8.4.9	Removed "immediately" from "In the event of an unexplained clinically-significant abnormal laboratory test value, the test should be repeated immediately and followed up…"
Section 8.4.10	Added clarification that the safety follow-up call is not applicable for subjects dosed on the weekly schedule since subjects are seen in-clinic on weekly basis
Section 10.1	Updated that MT-3724 will be shipped frozen instead of "on dry ice"
Section 10.1.2	Changed requirement for investigator to obtain written approval of all study-related documents to only obtaining written documentation for initial study approval. Changed "The investigator must conduct the study according to the signed, written protocol" to "The investigator must conduct the study according to the most recent, approved protocol version". These changes were made to better accurately reflect what is done in practice.
Section 10.1.4	Informed consent process updated to more accurately reflect what is done in practice in this global clinical trial.
Section 10.1.5	Removed that "subject initials" will be collected in the eCRF and added that any personal identifiers should be obliterated.
Section 10.1.7.1	Removed mention of site reference manual as it not needed to be stated, and also removed examples of source documentation.

Section	Revision Made
	Clarified that subject identifiers should be made invisible without prescribing method of making it so (changed "lined through with black marker" to "made invisible") Deleted "/Medical records" from "Source Documents/Medical records" since medical records are source documents. Deleted "microfiches" as they are not likely to be used as source documents. Added clarification that ICF for amendments are to be saved as source documents per local authorities.
Section 10.2	Removed histamine from under chemistry; added pregnancy test to local laboratory
Section 10.2.1	Deleted "If possible, the blood for chemistry assessments should be drawn after a subject has fasted for at least 2 hours, to facilitate a more reliable interpretation of the plasma glucose result. The compliance with this recommendation (Yes / No) will be entered in the eCRF for every chemistry assessment." since this is not required to assess MT-3724 safety.
Administrative Global Changes	Changed abbreviation for standard of care from SOC to SoC to avoid confusion with System Organ Class and spelled out System organ class as it only appeared once. Spelled out abbreviation for NHL upon first appearance. Changed CT/MRI to CT and/or MRI for more clarity. Updated CRF to eCRF. Updated name of European Agency for the Evaluation of Medicinal Products to European Medicines Agency Updated Appendix 9, Abbreviations, to include the new terms introduced in this amendment Updated NHL to DLBCL where appropriate Editorial updates for inclusion/exclusion criteria in synopsis to match that in body of protocol

12.3 Version 9

Version 9.0 (14 April 2020) replaces version 8.0 (15 February 2019)

Amendment 9.0 is applicable to all investigators participating in this protocol. For practical reasons, this amendment only specifies the study conduct of Part 3 and Part 4 of the protocol.

Rationale for changes:

1. The statistical aspect of the study design that had been a Simon 2-stage in 100 subjects (termed "Part 3") has been changed. Instead, the statistical aspect of the study includes a continuation of an expansion cohort at the Recommended Phase 2 Dose (RP2D) (now termed "Part 3") in approximately 20 subjects and a new Phase 2 portion (termed "Part 4") that will evaluate approximately 88 subjects. The total sample size has increased from 100 to approximately 108. Importantly, the primary endpoints were adjusted to safety for Part 3 and efficacy for Part 4.
    - The first 20 subjects enrolled will contribute to the completion of the MTD expansion cohort (Part 3). This is considered to be important because the existing sample size of subjects evaluated at the RP2D included only 6 subjects, and only 3 were treated for more than one cycle. Thus, these additional subjects will better inform the safety and

tolerability of monotherapy at the RP2D before starting the Phase 2 portion of the trial (Part 4).

2. The goal of Part 4 is to provide sufficient evidence to test the null hypothesis that the true response rate with MT 3724 ≤ 17% versus the alternative hypothesis that the true response rate with MT 3724 ≥ 32% at the 1-sided alpha level of 0.025 with high statistical power. Under the stated null and alternative hypotheses, Part 4 carries 90.4% power at the 1-sided alpha level of < 0.025. Since this is an open-label trial, formal futility analysis has been removed from the protocol, as this will occur on an ongoing basis with input from a Data Safety Monitoring Board.
3. Subjects are now required to have histologically confirmed CD20+ DLBCL obtained at the time of relapse to be eligible for this study. This is to confirm the study enrolls the appropriate patient population whose disease has the potential to respond to this therapy based upon based upon the mechanism of action of MT-3724.
4. Other changes to inclusion/exclusion criteria have been made to ensure consistency across the MT-3724 program of studies and to modify criteria which were unnecessarily stringent. These latter changes include allowing subjects with seropositive human immunodeficiency virus (HIV)/hepatitis B virus (HBV)/hepatitis C virus (HCV) the option to enroll in this study provided they have non-detectable viral loads (HIV/HBV/HCV), a minimum number of CD4+ cells (for subjects with HIV) and receive appropriate prophylactic treatments; also, a reduced washout period (consistent with the relevant half-life for subjects whose last treatment included small molecules [as opposed to monoclonal antibodies]). The current safety data do not indicate a heightened risk for study subjects to have new or reactivated viral infectious diseases.
5. Predose medication requirements have been updated to clarify that subjects must receive predose medications with all doses in Cycle 1, rather than allowing predose medications at the investigator's discretion, which may reduce incidence and/or severity of innate immune responses typically observed early in Cycle 1.
6. The protocol was modified to allow subjects continued treatment with MT-3724, rather than the prior limitation of therapy to a maximum of 12 cycles, contingent upon demonstration of continued clinical benefit and tolerability of study treatment. Given the current safety profile which includes subjects' exposure for up to 9 cycles, it is reasonable to allow subjects continued treatment with MT-3724 provided there is a favorable benefit-risk ratio, in the opinion of the treating investigator.
7. The clinical assessment tool termed LYRIC has been removed and replaced with Lugano (Cheson, 2014) since LYRIC was designed primarily for use with checkpoint inhibitors. Instead, the protocol now allows for treatment beyond progression if the investigator believes the benefits outweigh the risks, while requiring certain standard criteria to be met (ie, ensuring the subject is not exhibiting clinical deterioration, has no impending organ impairment, and agrees to sign an ICF again, acknowledging the potential risks of continuing investigational therapy and foregoing other treatment options).
8. The screening period has been increased from 28 days to 35 days to allow for central laboratory processing of screening samples.

9. The safety event collection period starting point has been updated from "signing of the informed consent" to "Cycle 1 Day 1". This was implemented to avoid collecting unrelated pre-treatment AEs; and to avoid confounding understanding of MT-3724 safety profile with toxicities from other cancer therapies. An AE/SAE during the screening period will only be collected if it is deemed related to a protocol screening procedure.
10. Respiratory rate and temperature assessments have been added to vital signs and quality of life analysis language has been added as these were inadvertently omitted from previous versions of the protocol.
11. Please note, the protocol has been transferred into a new TransCelerate-based protocol template for improved organization, readability, and reduction in redundancy of information. Some sections are new to the protocol (eg, Sections 5.3, 6.6, 7.4, 8.8, and 10.4) and utilized template language to offer additional guidance to investigators, sites, IRB/IECs, and health authorities. In line with the template transfer, the background material formerly provided in Section 2 has been drastically reduced to provide a concise summary on disease and investigational product (MT-3724) background. Appropriate references to the Investigator's Brochure have been included which contains detailed information.
12. Vast majority of changes made were to provide clarifications to existing language.

<u>High-level summary of changes made</u>:

Section	Revision Made
Global	Administrative and editorial changes were made throughout the protocol (including updates to protocol version, approval date, and study contact information; and correction of typographical, grammatical, and formatting errors).
Global	Objective response will be based on the Lugano Classification for Lymphoma; the "adjustment according to LYRIC" has been removed (and its associated reference).
Global	Screening window increased from 28 days to 35 days.
Global	Long-term follow-up visit frequency has increased to every 3 months (instead of every 6 months). Long-term follow-up now ends up to 18 months after the last dose (instead of "until death or loss to follow-up").
Schedule of Activities	Added predose ECG collections Other changes made are covered in text relevant protocol sections
Synopsis; Sections 3.1 and 3.2	• Add Part 3 and Part 4 study objectives and endpoints • Part 4 revisions: ○ Move duration of tumor response to key secondary endpoint ○ Additional exploratory objectives and endpoints were added ○ [redacted]
Synopsis; Section 4.1	Updated to indicate Parts 1 and 2 are closed and add design language for Parts 3 and 4.
Synopsis; Sections 4.1, 6.1.1.2	Removed limitation of 6 cycles of treatment, subjects will now be treated until death, disease progression, unacceptable toxicity, withdrawal of consent, or another reason for withdrawal, or until study discontinuation
Synopsis; Section 6.1.1.3	Added option to treat subjects beyond progression if certain criteria are met.
Synopsis; Sections 4.1, 8.1.5	Frequency of long-term follow-up visits have been increased from every 6 months to every 3 months (for up to 18 months from the last dose of MT-3724).

Section	Revision Made
Synopsis; Sections 1.3, 6.1.1.2	Cycle 1 dose schedule was clarified to indicate that the first 3 doses of Cycle 1 must be administered at least 48 hours apart.
Synopsis	Number of subjects has been updated to reflect expected number of subjects that are to be enrolled in Parts 3 and 4 of this study.
Synopsis; Section 9.1	Number of subjects has been updated to reflect expected number of subjects that are to be enrolled in Parts 3 and 4 of this study.
Section 5	**Modified text to remove information that is already described in the inclusion/exclusion criterion to avoid redundancy**
Synopsis; Section 5.1	Inclusion criteria have been updated to include patients with proof of CD20+ DLBCL based on historical biopsies; fresh biopsies; bone marrow biopsy; excisional lymph node biopsy, or core biopsy of any involved organ
Synopsis; Section 5.1	Inclusion criteria have been updated as follows: to include anti-CD20 antibody therapy for NHL treatment; the amount of time before study drug administration for autologous SCT or allogenic SCT have been clarified to be ≥ 100 and ≥ 180 days, respectively; hematological recovery has been clarified to be consistent with the existing inclusion criteria requirements and without PRBC or platelet transfusions within 2 weeks of C1D1
Synopsis; Section 5.1	Inclusion criteria have been updated to clarify tumor lesion at screening must be bi-dimensional and that only CT or MRI methods according to the Lugano criteria are acceptable
Synopsis; Section 5.1	Peripheral blood total lymphocyte count has been removed as an inclusion criteria
Synopsis; Section 5.1	Total bilirubin has been updated to be < 1.5 only, as an inclusion criteria
Synopsis; Section 5.1	LVEF criteria have been removed as inclusion criteria (combined with exclusion criterion on cardiovascular disease)
Synopsis; Section 5.1	ALT and AST criteria have been updated to ≤ 3.0 x ULN (or ≤ 5.0 x ULN if liver involvement) from ≤ 2.5 (or ≤ 5.0 x ULN if liver involvement)
Synopsis; Section 5.1	Inclusion criteria have been updated to change reliable birth control methods to highly effective birth control methods; specific methods have been replaced with a reference to Section 10.4 for guidance
Synopsis; Section 5.2	Exclusion criteria have been updated to provide washout periods for small molecules
Synopsis; Section 5.2	Exclusion criteria regarding palliative radiation therapy within 4 weeks before the start of treatment has been removed and is now permitted at investigators discretion with consultation with the medical monitor and sponsor.
Synopsis; Section 5.2	Exclusion criteria has been updated to require the use of systemic immune modulators during study treatment and permit the use of NSAIDS
Synopsis; Section 5.2	Exclude potential subjects if they received any live vaccines except injectable flu (inactivated or recombinant) vaccine within 4 weeks before the start of treatment, unless the investigator believes the benefits outweigh risks, after consultation with the medical monitor and with sponsor approval.
Synopsis; Section 5.2	Removed exclusion criteria "received allogeneic stem cell transplant" **and added exclusion criteria of "Current evidence of Graft vs Host Disease"**.
Synopsis; Section 5.2	Exclude prior treatment with MT-3724
Synopsis; Section 5.2	Remove exclusion criteria: subjects with grade 2 neuropathy may be eligible at investigator's discretion

Section	Revision Made
Synopsis; Section 5.2	Updated language regarding HIV, HBV, and HCV exclusion; added that subjects with HIV and an undetectable viral load and CD4+ T-cell (CD4+) counts ≥ 350 cells/mL may be enrolled, but must be taking appropriate opportunistic infection prophylaxis, if clinically relevant.
Synopsis; Section 5.2	Subjects with positive HBV serology are eligible if they have an undetectable viral load and will receive antiviral prophylaxis for potential HBV reactivation per institutional guidelines.
Synopsis; Section 5.2	Subjects with positive HCV serology are eligible if quantitative PCR for plasma HCV RNA is below the lower limit of detection. Concurrent antiviral HCV treatment per institutional guidelines is allowed.
Synopsis; Section 5.2	Serology testing is not required if seronegativity is documented in the medical history and there are no clinical signs suggestive of HIV or hepatitis infections, or suspected exposure.
Synopsis; Section 5.2	Current evidence of incomplete recovery from surgery or radiotherapy must be before start of treatment, not at screening. **Also changed that planned surgeries/radiotherapy restriction is only up until EOT and not STFU**.
Synopsis; Section 5.2	History of another primary malignancy within the past 3 years (except for ductal breast cancer in situ, non-melanoma skin cancer, prostate cancer not requiring treatment, and cervical carcinoma in situ) that required systemic drug therapy or radiotherapy. Has been revised to: 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 previous cancer curatively treated > 2 years before the start of treatment
Synopsis; Section 5.2	Subjects with radiotherapy or other appropriate therapy for known brain or spinal metastases may be eligible and concurrent prophylactic treatment is allowed. Neurologic symptoms must be stable and no worse than grade 2. They may be eligible if they have evidence of stable brain or spinal disease on CT or MRI scan obtained within 4 weeks before signing informed consent and compared with prior imaging results. They must not require steroid therapy or if applicable, have been on dose of no more than 20 mg a day of prednisone or equivalent by C1D1.
Synopsis; Section 5.2	Exclusion criteria have been updated to include history or current evidence of significant cardiovascular disease
Section 5.3	Screen failures procedures have been defined and a minimal set of screen failure information has been listed
Section 6.1.1	Dose administration timing has been added: all doses should be administered over 1 hour (54 – 75 minutes).
Section 6.1.1.1	Removed language referring to Part 2 and the measuring of weight before the first dose of MT-3724 in subsequent cycles. The re-calculation of dosage based on bodyweight change is no longer at investigator's discretion but according to institutional policies.
Section 6.1.1.2	The dosage administration window has been updated to 54 to 75 minutes rather than the previously used +15 minutes.
Section 6.1.1.2	Clarified that each dose of MT-3724 should be preceded by premedication administered within 60 minutes before the start of infusion in Cycle 1.
Section 6.1.1.2	Removed: The choice of premedication agents and their doses for MT-3724 doses after C1D1 may be determined at the investigator's discretion or according to the institutional guideline.
Section 6.1.1.2	Added: The first 3 doses of Cycle 1 must be administered at least 48 hours apart while all other doses remain at least 20 hours apart.
Section 6.1.1.2	Updated information regarding treatment dose schedule and discontinuation criteria.

Section	Revision Made
Synopsis; Section 6.1.1.3	Added option to treat subjects beyond progression if certain criteria are met.
Section 6.1.2	Provided acceptable dosage ranges for 3 classes of premedications before MT-3724 infusion and updated adjustment language.
Section 6.1.3	Updated excluded treatments, medical devices, and/or procedures during study period to all systemic treatment for lymphoma, radiation therapy to target tumor lesions, systemic immune modulators and any live vaccines.
Section 6.2	Restructured entire section, all former subsections and lists of hematological and nonhematological TEAEs have been converted into Table 6-2 “MT-3724 Dose Modification Guidance and Specific Management of Toxicities” to provide clear guidance in a more organized manner.
Section 6.2	Removed immunoglobulins from list of serum samples for the investigator to obtain if the subject experienced grade 2 or greater adverse events
Section 6.2	Replaced the time frame determined at investigators discretion with baseline to within 14 days for discontinuation of MT-3724 in the case of TEAE
Section 6.2	Updated language and footnotes regarding infusion-related reaction or other hypersensitivity events in Table 6-2
Section 6.5	Removed language permitting inactivated or recombinant flu vaccines (these are permitted; only live vaccines are excluded though with exceptions). Updated to include palliative therapy, such as radiotherapy, which spares at least 50% of bone marrow producing regions, to non-target lesions or intrathecal chemotherapy, is allowed at the investigator’s discretion after consultation with the medical monitor and sponsor. While the use of certain immunomodulators is prohibited as described in Section 6.1.3, the use of NSAIDS is permitted.
Section 6.6	Added language allowing for possible initiation of an open-label rollover study.
Section 7.1	Removed language regarding premature withdrawal from study and early termination.
Section 7.3	Removed language regarding continuation of treatment.
Section 7.4	Added section to define lost to follow-up and give guidance to sites on how to handle subjects that may be lost to follow-up.
Section 8.2.2	Screening NHL assessment revised to clarify what information is to be collected from various time points in disease history.
Section 8.2.3	Clarifications made regarding what type of information is to be collected for prior systemic therapies.
Section 8.3.1	Clarifications made regarding what types of scans should be used and when for radiological assessments of tumor response. Also added clarification that the original schedule needs to be maintained even if there is a delay is dosing.
Section 8.3.2	**Removed “(ie, the tumor response used to derive the primary efficacy endpoint)” since it is not applicable to Part 3 and is extraneous.**
Section 8.4.1	Clarifications made regarding new illnesses and/or worsening of concomitant illnesses detected during the screening period (medical history vs AE).
Section 8.4.2	Clarified definition of concomitant medication.
Section 8.4.3	Clarified language regarding changes of > 10% in body weight resulting in dose adjustments.
Section 8.4.4	Added subsections to clarify what constitute complete and abbreviated physical examinations **and removed window of 72 hours**.

Section	Revision Made
Section 8.4.6	Added respiratory rate as a vital sign measurement and that temperature should be assessed at same time as BP, HR, and RR. Also clarified language regarding timing of PK, ECG, and vital signs measurements.
Section 8.4.7	Updated when a pre-study LVEF assessment would be acceptable for screening purposes (protocol now allows up to 6 months before screening and at least 28 days after last cancer therapy); **also updated that ECHO is preferred over MUGA**.
Section 8.4.8	Clarified language regarding timing of PK, ECG, and vital signs measurements.
Section 8.4.9	Clarified language regarding Grade 3 or Grade 4 abnormal laboratory tests; should be reported as a clinically significant AE unless associated with disease progression.
Section 8.5	Added statement "For AEs of CLS, CRS/SIRS, and IRRs, individual symptoms and grade should be reported on the appropriate CRF."
Section 8.5.1; Section 8.5.3	AE/SAE reporting period redefined to start at first dose of study drug. AEs/SAEs will be reported during the screening period only if they are deemed related to a protocol screening procedure.
Section 8.5.2.3	**Removed mention that MT-3724 needs to be discontinued if partner of male subject becomes pregnant**
Section 8.5.6	Clarified that PK samples should not be drawn from the same line as that used for study drug administration. Also added language that if CSF is collected at any time as part of standard of care, a portion of the sample collected will be used to evaluate for presence of study drug.
Section 8.7.2	Added language that biopsies may be used to confirm CR, in absence of PET/CT scans.
Section 8.8	Added details regarding collection and analysis of immunogenicity samples.
Section 9	The entire statistical considerations sections has been updated to provide appropriate information addressing the new parts of the study (Parts 3 and 4), the associated sample size, objectives/endpoints, etc.
Section 9.3.2.3	Quality of life analysis was added as a new section in this amendment.
Section 10.1.6	Language has been altered to allow remote online monitoring of sites in light of recent guidance released on global pandemic.
Section 10.1.7	Text regarding examples of source documentation has been deleted as it was inaccurate. **Text describing screen procedures CRF has been removed as it was also inaccurate.**
Section 10.3	Updated classification of adverse events for clarification **and removed "For example, an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious" since it was inaccurate.**
Section 10.5	**For Cotswold modifications, X, moved this to be applicable for all stages and not just Stages I to III. In addition, removed reference to different tumor types since Parts 3 and 4 are specific to DLBCL and 5-year survival rates based on risk since it's extraneous information.**