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

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STATISTICAL ANALYSIS PLAN

Version 1.0

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1. INTRODUCTION

This statistical analysis plan (SAP) is based on Molecular Templates' Protocol # MT-3724_NHL_003, titled "A Phase 2a Open-label Study to Investigate Safety and Tolerability (including the MTD), Efficacy, Pharmacokinetics, Pharmacodynamics and Immunogenicity of MT-3724 in Combination with Lenalidomide in Subjects with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma". See the study Protocol for details on study rationale, conduct and endpoints.

The purpose of this SAP is to provide details of the statistical analyses specified in the study protocol. The SAP summarizes key aspects of the study to provide context for statistical methods and presents details of the planned statistical methods following the completion of the trial.

This study will be conducted in compliance with the study protocol and ICH guideline E9

(Statistical Principles for Clinical Trials 1998).

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to determine the safety and tolerability (including the MTD) of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-Cell NHL

2.1.2 Secondary Objectives

The secondary objectives of the study are to:

- Characterize the PK of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-cell NHL
- Assess the PD of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-cell NHL
- Assess the immunogenicity of MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-cell NHL
- Assess the tumor response to MT-3724 in combination with lenalidomide in subjects with relapsed or refractory B-cell NHL

3. INVESTIGATIONAL PLAN

3.1 Study Design

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

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

Part 1 will include MT-3724 dose escalation according to the modified 3+3 design to identify the MTD of MT-3724 in combination with fixed standard doses of LEN. If permitted by the safety results, the MT-3724 dose escalation is planned to proceed in three sequential dose cohorts (Cohorts 1-3).

The purpose of Part 2 is to confirm the safety and tolerability of the MTD of MT-3724 from Part 1 in the MTD Expansion Cohort, where MT-3724 will be given at the MTD in combination with LEN. In addition, the PK, PD, immunogenicity and tumor response at the MTD of MT-3724 in combination with LEN will be more thoroughly evaluated in Part 2.

See the study protocol for full study design details.

3.2 Treatment

MT-3724 will be administered as intravenous (IV) infusion over 1 hour.

In Part 1 (MT-3724 dose escalation), the starting MT-3724 doses in each of the planned cohorts will be:

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

Additional interim dose cohorts may be evaluated only if warranted by the safety results in the previous planned cohorts. The maximum dose of MT-3724 that will be given in this study is 50 ug/kg/dose.

In Part 2 (Expansion Cohort), the starting MT-3724 dose will be the MTD of MT-3724 from Part 1.

The administered dose of MT-3724 for subjects will be capped at 6000 µg per infusion. Intra-subject escalation of MT-3724 dose is not permitted in this study. The guidance for treatment modification (dose interruption / delay, dose reduction or treatment discontinuation) is outlined in the study protocol.

3.2.1 Dosing Schedule

MT-3724 Dosing Schedule

Cycles 1-2

In Cycle 1 and Cycle 2, MT-3724 should be administered as 1-hour IV infusion on Day 1, 3, 5, 8, 10 and 12 of each 28-day cycle.

Any of the scheduled MT-3724 doses may be administered on different dosing days at investigator's discretion up to D21. However, no more than two MT-3724 doses can be administered on consecutive days.

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

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

MT-3724 may be continued in C3-C4 (with or without LEN) if supported by the investigator's assessment of the benefit-risk ratio.

Cycles 3-4 (if applicable or beyond)

If treatment is continued, then dosing in C3-C4, MT-3724 should be administered as 1-hour IV infusion weekly (Day 1, 8, 15 and 22 of each 28-day cycle). Any of the scheduled weekly MT-3724 doses may be administered within ±2 days at investigator's discretion. MT-3724 should not be administered between D24-D28 in C3-C4.

Lenalidomide Dosing Schedule

In both parts of the current study, subjects will self-administer LEN qd PO with or without food, around the same time each day, on the first 21 consecutive days (Day 1-Day 21) of each 28-day cycle. LEN cannot be administered between D22-D28 in any cycle.

4. CHANGES TO PLANNED ANALYSIS

The statistical methods described in this SAP take precedence over the protocol. Additional exploratory efficacy endpoints have been added.

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- [redacted]

5. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

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

Analyses will be performed using SAS for Windows statistical software, version 9.2 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services (Cincinnati, OH) will perform all efficacy and safety statistical analyses.

Subject data will be listed, sorted by cohort and subject number. Dose escalation cohorts and MTD expansion cohort will be reported separately and combined at the recommended phase 2 dose.

5.1 Data Quality Assurance

Molecular Templates, or its designated representative, will conduct a pre-study visit for each study site to verify the qualifications of the investigator, inspect study site facilities, become familiarized with site staff assigned to the study, and inform the investigator of responsibilities and procedures for ensuring correct study documentation.

A study coordinator at the investigative site will enter subject data into a remote data capture

database (RDC) by completing electronic case report forms (eCRFs). All information recorded in the eCRFs for this study must be consistent with the investigator's source documentation for the study participants. The investigative site will make available source documents to CTI personnel monitoring the study. The study monitor will verify consent of all subjects to participate in the study and will perform 100% source document verification of the eCRF data.

A CTI Clinical Data Associate (CDA) will review the data for discrepancies via programmed electronic consistency checks, data listings, or manually. Any discrepancies discovered via the data review process will be issued as queries in the RDC system to the investigative site for resolution. Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for analysis.

Data may be pulled by CTI Biostatistics for interim analysis at a time when source verification and query resolution is ongoing. No interim statistical analysis is planned during either part of this study. An interim statistical analysis may be performed only pursuant to a health authority request.

All SAS programs used to create analysis datasets and output will be validated by ensuring that the ".log" files are void of all errors, warnings and notes indicative of problems. Additionally, each program will be checked to ensure that it performs according to the program specification. All programs are developed and validated by separate members of the CTI Biostatistics Department.

At the time of analysis, a quality control (QC) review of database values listed in SAS output will be compared to the database. The sample size of fields to undergo QC review will be determined by utilizing American National Standards Institute (ANSI) sampling procedures[1]. Sampling procedures are conducted using "normal" inspection criteria (Inspection Level II, Single, and Normal) and an Acceptable Quality Level (AQL) of 0.010%. The following shows the sampling criteria:

Single Normal sampling procedure for Acceptable Quality Level (AQL) 0.010%

Number of Fields	Sample Size	Accept/Reject Criteria
2-8	2	0/1
9-15	3	0/1
16-25	5	0/1
26-50	8	0/1
51-90	13	0/1
91-150	20	0/1
151-280	32	0/1
281-500	50	0/1
501-1,200	80	0/1
1,201-3,200	125	0/1
3,201-10,000	200	0/1
10,001-35,000	315	0/1
35,001-150,000	500	0/1
150,001-500,000	800	0/1

Number of Fields	Sample Size	Accept/Reject Criteria
500,001-up	1,250	0/1

5.2 Analysis Sets

The following analysis populations are defined for this study:

Safety Population

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

Efficacy Evaluable Population

The efficacy evaluable population will include patients who have at least one post-baseline radiographic evaluation or those that were discontinued for clinical progression.

PK Population

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

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

Immunogenicity Population

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

PD Population

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

5.3 Assessment Windows

Data will be summarized based on the CRF (Study Visit) in which it was collected even if the assessment is outside of the specified visit window. In data listings, the relative day of all dates will be presented. Such days will be measured relative to Day 1, the day in which the first dose of study drug is received.

The last post-baseline visit where data were collected will be flagged for each subject. These visits will be combined for analysis of laboratory and vital sign results.

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

will serve as the baseline. Screening procedures should be performed up to 28 days before Day 1 C1D1.

If a repeat laboratory sample was drawn for a visit, the values from the repeat sample will be used for summary and analysis purposes. In this case, only the repeat sample values will be listed.

5.4 Handling of Dropouts or Missing Data

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

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

- Have had a DLT irrespective of the number of MT-3724, lenalidomide doses received in C1; or
- In the absence of DLT, have received at least 4 of 6 (83%) doses of MT-3724 and both doses of lenalidomide in C1

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

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

5.5 Multiple Comparisons

There are no multiple comparisons.

5.6 Data Derivations and Transformations

Not applicable.

6. STUDY PATIENTS

6.1 Disposition of Subjects

A table of counts of all safety subjects will be provided. Reasons for not completing study medication as planned and reasons for premature withdrawal will be tabulated by dose level.

6.2 Protocol Deviations

Distribution for the types of protocol deviations and the number of subjects that deviate from the protocol will be tabulated for the dose levels.

6.3 Demographic Characteristics

Descriptive statistics will be used to summarize the demographic characteristics (age, gender, race, ethnicity, weight, and height) for the safety analysis set.

6.4 Baseline Characteristics

Subject baseline characteristics; including demographics, medical history, physical examination, ECG, and vital signs will be summarized descriptively.

6.5 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be categorized into either non-cancer related or cancer related. Summaries and listings of each category will be presented separately.

6.6 Prior and Concomitant Medications

Prior medications within 30 days of consent and inter-current concomitant medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of safety subjects using concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class and by preferred name.

All prior and concomitant medication data will be listed, sorted by dose level, investigative site and subject number, start and stop date. Information listed will include medication, indication, dose, and route of administration.

7. EFFICACY ANALYSIS

7.1 Primary Efficacy Endpoint and Analysis

The primary endpoints of this study are safety related and therefore there are no primary efficacy endpoints.

7.2 Secondary Analysis

A secondary analysis of efficacy to evaluate response to MT-3724 in combination with lenalidomide will be performed in this trial. The efficacy parameters of interest are objective response rate (ORR), best objective response rate (BORR), and duration of response (DOR). All efficacy summaries will be based on the safety population.

6.1.1 Objective Response Rate

The ORR measures the proportion of subjects with a reduction in tumor size (Partial Response or Complete Response) using the five-point scale (5PS) per the Lugano Classification for Lymphoma (2) adjusted according to LYRIC (lymphoma response to immunomodulatory therapy criteria) (3). An overview of LYRIC is presented in the protocol. The proportion of subjects with a Partial Response or Complete Response will be summarized and presented at each scheduled visit. The ORR representing clinically significant clinical benefit in this study will comprise the Lugano Score 1, 2 or 3, or the CR, CRu or PR. The number and percentage of subjects with clinically significant results will be presented.

6.1.2 Best Objective Response Rate

The best ORR (BORR) at all time points will be reported. Subjects who experience disease progression before undergoing the first tumor assessment will be added to the disease progression stratum. The BORR will be descriptively summarized by the treatment group / cohort; the exact 95% confidence intervals will also be produced.

6.1.3 Duration of Response

All subjects achieving clinically significant clinical benefit according to the response criteria (CR, CRu, PR, or stable disease for at least 3 months) will be included in the analysis of the duration of tumor response (DOR).

DoR is defined as the time interval (days) from date of the first objective response (CR, CRu, or PR; achieved after the date of exposure to MT-3724) to the date of disease progression.

Duration of Response (days) =

$$\textit{Date of Progression after } 1^{st} \textit{ Objective Response} - \textit{Date of } 1^{st} \textit{ Objective Response} + 1$$

- If the subject does not have a response of CR, CRu, or PR the Duration of Response will be set to missing.
- Subjects not meeting the criteria for progression or death by the analysis cutoff date will be censored at their last evaluable disease assessment date and their first response will be noted as ongoing.
- For death or PD after more than 1 missed evaluation, the duration will be censored at the last visit.

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

6.1.4 Progression-free Survival

Progression-free survival (PFS) is the time from study drug administration until disease progression or death. The disease assessment by the RECIST V1.1 criteria occurs at Screening, months 1, 3, 6, 9, 12, 18 and 24.

PFS is defined as the interval between the date of first infusion of and the date of PD or death, whichever is first reported.

PFS (days) =

$$\textit{Date of Progression} - \textit{Date of } 1^{st} \textit{ Infusion} + 1$$

The following Kaplan-Meier (KM) estimates will be provided:

- 25th, 50th (i.e., median) and 75th KM percentiles with 95% CIs
- Number and percent of subjects censored/not censored

KM estimates of the proportion of subjects event-free at: 3, 6, 12, 18, and 24 months (note: not all estimates may be provided for interim analyses)

7.3 Pharmacokinetic and Pharmacodynamic Analyses

MT-3724 serum concentration/time data from all eligible subjects will be subjected to noncompartmental analysis (NCA) using the software package Phoenix WinNonlin (Certera, Princeton NJ). PK parameters will be stratified by MT-3724 dose group and summary statistics will be generated. Exploratory analyses between PK and PD results as well as clinical responders will be conducted, as appropriate. Details will be provided in a separate analysis plan for this study objective.

7.4 Immunogenicity Analyses

Data for the ADA against MT-3724 will be obtained as titer, if the screening and confirmation assays are positive, while the data for the neutralizing antibodies (NA) against MT-3724 will be obtained as either positive or negative. The number and percent of subjects with a detectable ADA titer, and separately with a positive NA result, will be summarized by time point for each treatment group/cohort. The individual subject's immunogenicity results will be listed by time point for each subject by treatment group/cohort. Details of the immunogenicity analyses will be provided in a separate analysis plan for this study objective.

8. SAFETY ANALYSIS

All safety summaries will be conducted using the safety analysis set. No formal hypothesis testing will be performed to compare differences between dose levels.

8.1 Extent of Exposure

The total number of doses received, the expected total dose, the actual dose administered, and outcome of infusion will be summarized and presented. Information in the listing will include total dose of MT-3724 administered, start and stop times, outcome of infusion, and duration of interruption (if applicable).

8.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject who is administered study drug, whether or not the event is considered related to the investigational product. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study drug. Examples of AEs include but are not limited to:

- Abnormal test findings
- Clinically significant symptoms and signs
- Changes in PE
- Hypersensitivity
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication

Any AE or SAE occurring after the subject provides informed consent and prior to receiving investigational product that is considered by the Investigator to be related to study procedures, will be reported.

8.2.1 Pre-treatment-emergent Adverse Events

Pre-treatment AEs include those aspects of the patient's medical history that were ongoing at consent, as well as the new or worsening AEs reported between the screening medical history and the start of treatment. These AEs will be assessed by verbal probes and from medical history. The pre-treatment AEs will be listed by subject but not summarized.

8.2.2 Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to exposure of study drug or an event already present that worsens in either severity or frequency following exposure.

8.2.3 Adverse Event Severity

The CTCAE v.5.0 will be used for grading the severity of AEs. Every effort should be made to find the appropriate AE term and definition of severity in the CTCAE v.5.0. If the AE term chosen by the investigator is not listed in the CTCAE v.5.0, then the highest severity level on the scale in the following table will be assigned to the investigator's AE term.

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

Grade	Description
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.

8.2.4 Adverse Event Relationship to Study Medication

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

The following should be considered when assessing causality:

- Temporal associations between the agent and the event
- Effect of de-challenge and/or re-challenge
- Pre-existing risk factors
- A plausible mechanism
- Concurrent illnesses.

The investigator and separately, the Medical Monitor on behalf of the sponsor, will determine the causal relationship / relatedness to the study drug(s) according to the classification in the following table:

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

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

For all purposes of subject management, DLT assignment and treatment modification, the causality assessment of "at least probably", "possibly" or "definitely" will be treated as "related", while the causality assessment of "unlikely" and not related" will be treated as "unrelated".

8.2.5 Serious Adverse Events

A serious adverse event (SAE) is any AE that meets one or more of the following criteria:

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

emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

8.2.6 Adverse Event Summaries

All AEs (serious and non serious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

For treatment-emergent AEs (TEAEs), the following will be summarized and presented for the safety analysis set:

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of subjects experiencing a TEAE
   b. the number and percentage of subjects experiencing a TEAE by relationship to study medication (for each study medication)
   c. the number and percentage of subjects experiencing a TEAE by greatest grade
   d. the number and percentage of subjects experiencing a TEAE leading to study dose interruption
   e. the number and percentage of subjects experiencing a TEAE leading to dose delay
   f. the number and percentage of subjects experiencing a TEAE leading to dose reduction
   g. the number and percentage of subjects experiencing a TEAE leading to study withdrawal
   h. the number and percentage of subjects experiencing a TEAE of special interest (IRR, CRS, and CLS)
   i. the number and percentage of subjects experiencing a treatment emergent SAE (TESAE)

ii. the number and percentage of subjects experiencing a TEAE by SOC, PT

iii. the number and percentage of subjects experiencing a TEAE by SOC, PT and relationship to study medication (for each study medication)

iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and greatest grade

v. the number and percentage of subjects experiencing a TEAE leading to dose interruption by SOC and PT

vi. the number and percentage of subjects experiencing a TEAE leading to dose delay by SOC and PT

vii. the number and percentage of subjects experiencing a TEAE leading to dose reduction by SOC and PT

viii. the number and percentage of subjects experiencing a TEAE leading to study withdrawal by SOC and PT

ix. the number and percentage of subjects experiencing a TEAE of special interest by SOC and PT

x. the number and percentage of subjects experiencing a TESAE leading to dose interruption by SOC and PT

xi. the number and percentage of subjects experiencing a TESAE leading to dose delay by SOC and PT

xii. the number and percentage of subjects experiencing a TESAE leading to dose reduction by SOC and PT

xiii. the number and percentage of subjects experiencing a TESAE leading to study withdrawal by SOC and PT

xiv. the number and percentage of subjects experiencing a TESAE of special interest by SOC and PT

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the safety analysis set. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the SOC could appear larger than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs.

All occurrences of all AEs will be listed for each subject, grouped by cohort. The listing will contain the following information: treatment group, verbatim term, SOC, PT, severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal and whether it is a TEAE. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the

onset date is missing a month or a day, then these events will be presented before any complete dates.

8.2.7 Dose Limiting Toxicity (DLT)

The number and percentage of subjects experiencing a DLT will be summarized and presented by dose level. A listing of DLTs will also be presented.

8.3 Clinical Laboratory Assessments

Laboratory assessments will be summarized by presenting descriptive statistics of raw data and change from baseline. Listings will include flags for values outside of the reference ranges, and clinical significance if a laboratory result is deemed abnormal.

The following tests will be performed by the central laboratory:

- Hematology
- Chemistry (with eGFR)
- HbA1c
- Coagulation (aPTT and either INR or PT)
- Thyroid function (TSH and FT4)
- Serum cytokines
- Histamine
- Complement
- Immunoglobulins
- B-cell count and immunophenotype (flow cytometry)

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

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

A shift table displaying baseline CTCAE grade to maximum post-baseline CTCAE grade will be presented for hematology and chemistry lab values.

8.4 Physical Examination

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

8.5 Vital Signs

Vital sign data including weight, systolic blood pressure, diastolic blood pressure, heart rate, and temperature, will be summarized by presenting descriptive statistics of raw data and change from baseline values at each visit.

A shift table displaying baseline to maximum post-baseline values and last post-baseline value will be presented.

8.6 ECG Results

The following ECG results will be summarized.

- Heart rate
- PR interval
- QRS duration
- RR interval
- QT interval
- QT interval corrected according to Fridericia's formula (QTcF)

The results of the overall ECG review by the investigator or delegate will also be summarized. Comments for abnormal CS results of the ECG will be listed.

QTcF values will also be categorized according to their values as defined in ICH E14:

- $\leq$ 450 ms
- > 450 ms to $\leq$ 480 ms
- > 480 ms to $\leq$ 500 ms
- > 500 ms

and categorized according to their change from baseline into the categories

- $\leq$ 30 ms
- > 30 ms to $\leq$ 60 ms
- > 60 ms

The categories described above will be summarized in frequency tables using number of patients (n) and percentages for each dose cohort.

9. INTERIM ANALYSIS

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

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

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

10. SAMPLE SIZE AND POWER CALCULATIONS

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

This is an exploratory Phase 2a study, so the formal power calculation is not deemed necessary to justify the sample size. The proposed sample size is deemed sufficient for the adequate characterization of the study objectives and would be typical of the sample sizes of exploratory Phase 1b / 2a studies with novel anti-cancer agents

11. REFERENCES

1. American National Standards Institute. Sampling Procedures and Tables for Inspection by Attributes, ANSI/ASQC Z1.4-1993

12. APPENDICES

12.1 Appendix A: Schedule of Assessments

Insert schedule of assessments from protocol.

12.2 Appendix B: Example HLA Mismatch Calculations

HLA: Mismatched Antigens

DONOR	RECIPIENT					
	A01	A02	B07	B08	DR13	DR15
A01						
A02						
B07						
B08						
DR13						
DR15						

0 Antigen Mismatch

DONOR	RECIPIENT					
	A01	A02	B07	B08	DR13	DR15
A01						
A03						
B07						
B08						
DR13						
DR15						

1 Antigen Mismatch

DONOR	RECIPIENT					
	A01	A02	B07	B08	DR13	DR09
A01						
A02						
B44						
B08						
DR13						
DR15						

2 Antigen Mismatch

DONOR	RECIPIENT					
	A01	A11	B07	B22	DR08	DR15
A01						
A02						
B07						
B08						
DR13						
DR15						

3 Antigen Mismatch

DONOR	RECIPIENT					
	A01	A02	B07	B08	DR13	DR15
A03						
A02						
B60						
B51						
DR13						
DR14						

4 Antigen Mismatch

DONOR	RECIPIENT					
	A01	A02	B27	B08	DR11	DR15
A24						
A33						
B07						
B08						
DR13						
DR17						

5 Antigen Mismatch

DONOR	RECIPIENT					
	A01	A02	B07	B08	DR13	DR15
A24						
A33						
B27						
B56						
DR17						
DR18						

6 Antigen Mismatch

MATCH MISMATCH

Homozygosity: Instances in which antigens are not defined are typically a result of homozygosity. Homozygosity is defined as the condition of having identical genes at one or more loci (A, B, DR). As HLA genes are inherited from the mother and the father, if the mother and father share an antigen or multiple antigens, it is possible for a child to inherit the same A and/or B and/or DR antigen from both parents. When this occurs, antigens suspected to be duplicated are termed "blank", and the results will appear as shown below.

		RECIPIENT					
		A01		B03		DR13	
DONOR	A01						
	B03						
	DR13						

Example 1
0 Antigen Mismatch
("blanks" on donor and recipient)
No antigens differ between the recipient and donor. This combination would qualify as a 0 antigen mismatch.

		RECIPIENT					
		A01	A02	B03	B44	DR13	DR17
DONOR	A01						
	B03						
	DR13						

Example 2
0 Antigen Mismatch
("blanks" on donor only)
Because the donor does not express any antigens the recipient does not express, this combination would also qualify as a 0 antigen mismatch.

		RECIPIENT					
		A01		B03		DR13	
DONOR	A01						
	A02						
	B03						
	B44						
	DR13						
	DR17						

Example 3
3 Antigen Mismatch
("blanks" on recipient only)
If Example 2 is reversed and the donor expresses antigens that the recipient does not, these will qualify as mismatched antigens. The recipient immune system *may now recognize the A02, B44, and DR 17 from the donor* as foreign and mount an immune response.

MATCH **MISMATCH** **SUSPECTED MATCH**