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Statistical Analysis Plan
Study CS1001-201
Study Title: A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma
Document Date: 04 Nov 2021
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STATISTICAL ANALYSIS PLAN

TITLE:	**A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma (R/R ENKTL)**
PROTOCOL NUMBER:	**CS1001-201**
STUDY DRUG:	**CS1001**
VERSION NUMBER:	**2.0**
SPONSOR:	**CStone Pharmaceuticals (Suzhou) Co., Ltd.**
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DATE FINAL:	
DATE AMENDED:	

APPROVAL PAGE

A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma (R/R ENKTL)

CS1001-201

Statistical Analysis Plan

Version: 2.0

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[redacted]

_____ Date: _____

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TABLE OF CONTENTS

BACKGROUND

This is a single-arm, multicenter, Phase II clinical trial to evaluate the efficacy and safety of CS1001 in subjects with R/R ENKTL.

STUDY DESIGN

PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint is ORR assessed by IRRC according to Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification. [redacted]

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ANALYSIS TIMING

Statistical analysis is planned to be performed by 24 weeks after the first dose of the last subject.

For US filing purpose, all the analyses will be repeated when all responders have at least 6 months follow-up from the date of first documented response.

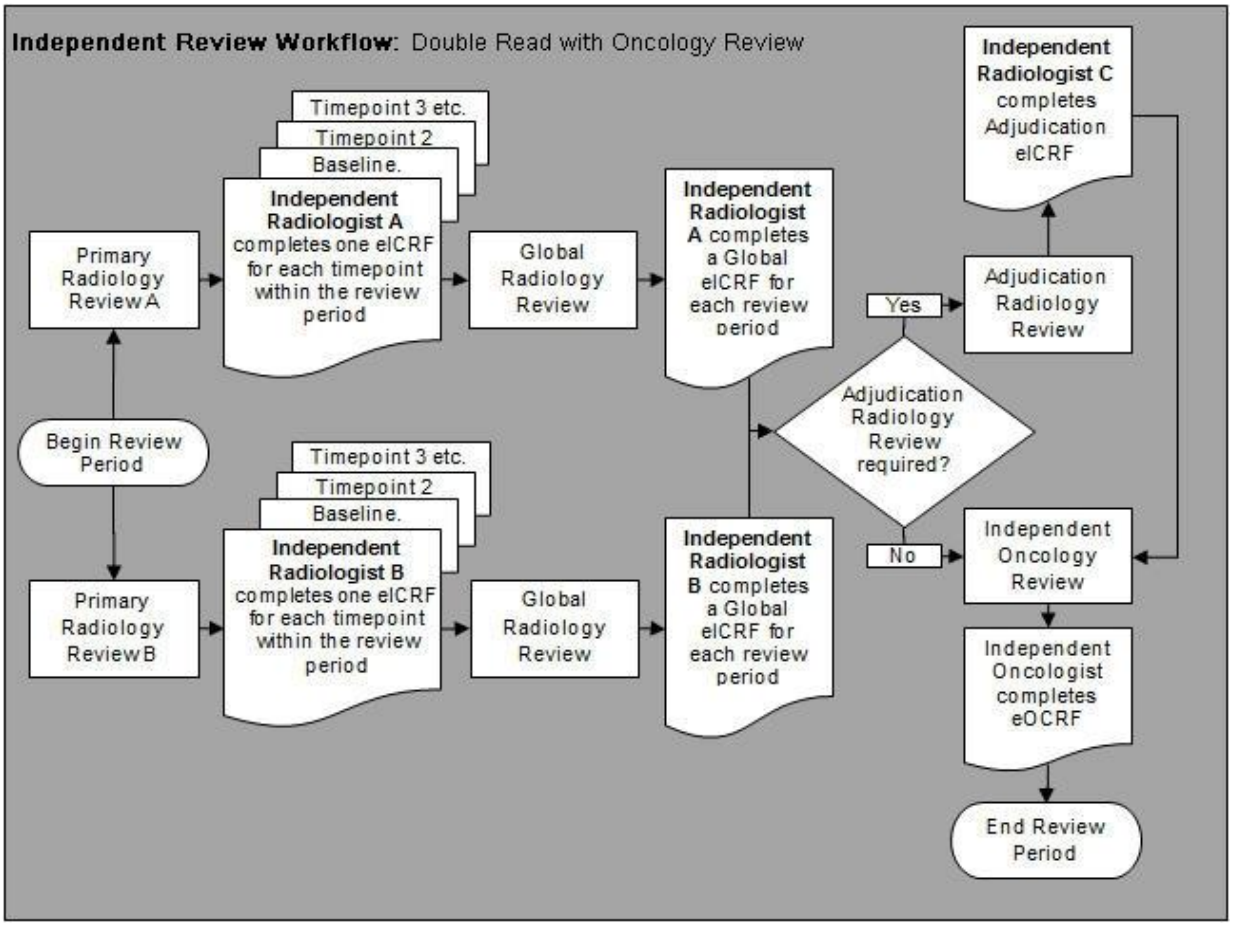
STUDY CONDUCT

INDEPENDENT RADIOLOGICAL REVIEW COMMITTEE

Independent radiological review committee (IRRC) was adopted to provide the independent assessment to tumor response per Lugano 2014 classification. Independent review will be conducted as follows, with further details provided in the IRRC charter:

- **Radiology Review**: A radiology review period consists of the following review steps in the given sequence:
    - **Timepoint by Timepoint Radiology Review:** Each imaging timepoint for a subject will be assessed by two independent reviewers that are board certified with relevant experience in radiology and nuclear medicine (double read), who will assess tumor burden at baseline and determine an overall tumor assessment at each post-baseline timepoint according to the Lugano Classification.
      Both CT/MRI and FDG-PET 5-point scoring assessments will be performed on the same electronic imaging case report form (eICRF). When FDG-PET is available, the Lugano Classification based overall tumor response will be based on CT/MRI and PET 5-point scoring. When FDG-PET is not available, the CT/MRI based assessments will drive the Lugano Classification based overall tumor response.
    - **Global Radiology Review:** Following completion of the timepoint by timepoint radiology review for a review period, the same independent reviewers that are dual board certified in radiology and nuclear medicine or have equivalent experience in both modalities will globally assess the reviewed timepoints and confirm or update their previous overall tumor assessments according to the Lugano Classification.
    - **Radiology Adjudication Review:** Adjudication is required if the independent radiologists' results for a global radiology review are in disagreement as defined in IRRC charter 7.1 Radiology Adjudication Review Paradigm. During radiology adjudication review, an independent radiologist who did not participate in the timepoint by timepoint or global radiology review for the subject will choose the independent radiologist whose global radiology review assessments he/she agrees with most as the final assessment and provide justifying comments.
- **Oncology Review:** Following radiology review and adjudication review (if applicable) for a review period, one independent oncologist (single read) will review radiology review assessments and available clinical data and provide final tumor response assessments per visit, as defined in IRRC charter 8.7 Oncology Review Assessment Criteria.
- **Secondary Radiology Review:** The timepoint by timepoint radiology review and global radiology review for a subset of subjects will be repeated. Secondary radiology review is used for determination of intra-reader and/or inter-reader disagreement or variability for that subset of subjects and will not alter the original read. Further details on the secondary radiology reviews are provided in IRRC charter 12.1 Secondary Review.

This process is outlined in the following independent review workflow diagram:



STATISTICAL METHODS

GENERAL CONSIDERATIONS

All data processing, summarization, and analyses will be performed using Version 9.2 (or later) of the SAS® statistical software package.

In general, categorical data will be summarized using frequencies and percentages in each category, and continuous data will be summarized with descriptive statistics including the number of observations, mean, standard deviation (SD), median, minimum and maximum.

Baseline is defined as the last measurement before the first dose of the study drug.

ANALYSIS SETS

All analysis sets will be identified prior to database lock.

Efficacy Analysis Set (EAS)

Efficacy analysis set (EAS) consists of all subjects who received at least one dose of study drug and had been confirmed as ENKTL by central pathology

Safety Analysis Set (SAS)

Safety analysis set consists of all subjects who received at least one dose of study drug.

Pharmacokinetic Analysis Set (PKAS)

Pharmacokinetic analysis set consists of all subjects who received at least one dose of study drug and have available plasma drug concentration data.

Anti-drug Antibody Analysis Set (ADAAS)

Anti-drug antibody analysis set consists of subjects who received at least one dose of study drug and have available ADA data.

ANALYSIS OF STUDY CONDUCT

Patient Disposition

Subject status and reasons for treatment discontinuation and study discontinuation will be summarized. A listing will be provided for subjects who discontinued from treatment/study as well as the reasons.

The number and percentage of subjects in each analysis set will be summarized and listed.

Protocol Deviation

The major protocol deviations will be summarized and listed.

Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug Dictionary (WHODD) latest version and they will be summarized separately following below definitions for subjects in the safety analysis set:

- Prior medications are defined as medications ended before study drug initiation
- Concomitant medications are defined as medications ongoing or started after study drug initiation.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for subjects in the safety analysis set.

Demographic

The demographic data, including but not limited to age, sex, race, ethnicity, will be summarized for safety analysis set.

Baseline Characteristics

Tumor diagnosis, including but not limited to staging, central pathology results will be summarized and listed for safety analysis set.

Medical history (other than study disease) will be coded with Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for safety analysis set.

Prior Cancer Therapy

Prior systemic cancer therapy will be coded with WHODD and summarized by ATC terms for safety analysis set.

Prior radiotherapy and prior cancer-related surgery/procedure will be summarized for the safety analysis set.

EFFICACY ANALYSES

The analyses of efficacy endpoints are based on the efficacy analysis set.

Primary Efficacy Endpoint

The primary efficacy endpoint is ORR by IRRC based upon Lugano 2014 classification, defined as the proportion of subjects who achieve complete response (CR) or partial response (PR) as the best overall response. Subjects who did not have any post-baseline tumor assessment will be considered as non-responders.

The IRRC-ORR analysis will include subjects with evaluable or measurable lesion at baseline as confirmed by IRRC in EAS.

The 95% CI of ORR will be calculated using the exact binomial (Clopper-Pearson) method to evaluate the precision of the ORR estimate.

Secondary Efficacy Endpoints

The ORR assessed by investigators will be analyzed and provided as described in Section 0. Proportions of subjects who achieve CR, PR, stable disease (SD), and progressive disease (PD) per IRRC evaluation and their 95% CIs will be summarized. This analysis will be performed for subjects with evaluable or measurable lesion at baseline as confirmed by IRRC in EAS. Proportions of subjects with responses per investigator's evaluation and their 95% CIs will also be summarized as for IRRC. This analysis will be performed for subjects with evaluable or measurable lesion at baseline as confirmed by investigators in EAS.

Duration of response (DoR) is defined as the time from the first documented CR or PR (whichever comes first) to the first documented disease progression or death, whichever comes first. DoR will be evaluated in subjects with objective responses per investigator's or IRRC's assessment, respectively. Subjects without event (disease progression or death) as of data cutoff will be censored at the date of the last tumor assessment. If no tumor assessment is performed after the first occurrence of CR or PR, DoR will be censored at the date of first CR or PR. Subjects with subsequent anti-cancer therapy(if any) before event will be cencored at the date of last tumor assessment prior to the initiation of therapy. If an event is observed immediately after two or more consecutive missed tumor assessments, subjects will be censored at the date of last tumor assessment prior to the missing tumor assessments. Kaplan-Meier methodology will be used to analyze DoR and the KM curve will be constructed.

Time to response (TTR) is defined as the time from the first study dose to the first documented CR or PR, whichever comes first. TTR will only be evaluated for subjects

who achieve a response. TTR will be summarized according to the investigator's and IRRC's assessments, respectively.

Progression-free survival (PFS) in months is defined as the time from the date of the first dose to the date of first documented disease progression or death, whichever comes first. The investigators and IRRC will assess the progression of disease based upon the Lugano 2014 classification. Subjects without an event (disease progression or death) will be censored at the date of the last tumor assessment. Subjects without tumor assessment after baseline will be censored at the date of the first dose. 6-month PFS rate refers to the proportion of subjects who are alive without any progression or death at 6 months after the first dose of study drug. 6-month PFS rate will be calculated using the Kaplan-Meier method and the Greenwood formula will be used to derive the variance for the 95% CI calculation.

Overall survival (OS) is defined as the time from the date of the first dose to the date of death from any cause. Subjects without death will be censored at the date of the last date known to be alive. Subjects without any data after baseline will be censored at the date of the first dose. The detailed analysis methodology described for PFS will also be used for the analysis of OS.

Sensitivity Analyses

The IRRC-ORR analysis will be repeated for subjects in the safety analysis set.

Subgroup Analyses

Subjects will be grouped based upon their demographics (for example age, sex) and baseline characteristics (for example ECOG PS, prior treatment lines) to evaluate the consistency among all subgroups

Exploratory Analyses

Exploratory analysis will be performed to identify the relationship between biomarkers and the efficacy of the study drug. The consistency of ORR (yes or no) between IRRC evaluation and investigator's evaluation will also be assessed.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Pharmacokinetic Analyses

Descriptive analysis will be performed for serum concentration of CS1001 in samples taken at planned sampling time points. The data in this study will be pooled with that from other CS1001 trials to develop a population PK model. This model will be used to evaluate internal and external covariates and their influence on the PK of CS1001. Furthermore, the exposure-response analysis will be performed on specific efficacy and safety endpoints. Separate analysis plans will be developed for the population PK analysis and exposure response analysis. Results of the above group PK and exposure-response analyses will be recorded in separate reports.

Immunogenicity Analyses

Immunogenicity evaluation results will be reported for the following parameters. Number and percentage of subjects who have positive anti-drug antibody (ADA) at baseline; number and percentage of subjects with at least one positive ADA test result in any time point following the first dose of study drug; number and percentage of subjects who develop treatment-induced ADA any time after the first dose of study drug; number and percentage of subjects with treatment-enhanced ADA any time after the first dose of study drug.

Treatment-induced ADA positive is defined as: Patients who had a baseline-negative ADA result and at least one positive ADA result at any time after first study drug administration.

Treatment-enhanced ADA positive is defined as: Patients who had a baseline-positive ADA result and at least one enhanced (greater than baseline fourfold) result at any time after first study drug administration.

Treatment unaffected ADA is defined as: Patient with positive ADA results at baseline and all post-baseline titer result are not greater than fourfold the baseline titer result or

Patient with positive ADA results at baseline and all post-baseline results are negative or missing.

For subjects who are confirmed positive ADA, further testing will be performed for ADA neutralizing antibody (NAb). The following additional summaries will be provided:

- Number and percentage of subjects who have positive ADA neutralizing antibody (NAb) test result at baseline.
- Number and percentage of subjects who have at least one positive NAb test result at any time point following the first dose of investigational product.

SAFETY ANALYSES

The safety analyses will be based on the safety analysis set.

Exposure of Study Medication

Descriptive statistics will be performed to summarize the exposure to study drug, including duration of treatment exposure in months, number of cycles, cumulative actual dose. etc.

Adverse Events

All AEs will be coded using the MedDRA dictionary. The severity will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

The number of subjects experiencing treatment-emergent adverse events (TEAEs) will be summarized. TEAE was defined as:

- AE occurred on or after study treatment initiation or
- AE occurred before study treatment initiation but worsened on or after study treatment initiation

In addition, serious TEAEs, severe TEAEs (Grade ≥ 3), treatment-related TEAEs, immune-related TEAEs (assessed by the investigator), infusion-related reactions, and TEAEs leading to study drug discontinuation or interruption will also be summarized.

A subject experiencing multiple AEs under the same PT or SOC will be counted only once for that PT or SOC by maximum severity.

Adverse events of special interest (AESIs) will be assessed by the sponsor. The following summaries will be provided:

- For each AESI category, the number and percentage of subjects who experienced at least one of the following events will be summarized by treatment group: AESI, serious AESI, AESI with NCI-CTCAE grades 3-5, immune-related adverse events evaluated by investigator, AESIs resulting in CS1001/placebo discontinuation, AESIs resulting in CS1001/placebo interruption (including AESIs resulting in delayed treatment cycle of CS1001/placebo), AESIs resulting in death, AESIs requiring systemic corticosteroid, and AESIs requiring high-dose systemic corticosteroid.
- AESIs by the most serious NCI-CTCAE grade, PT and treatment group will be summarized.
- AESIs by PT, outcome of adverse events and treatment group will be summarized.
- Time to onset and duration of each AESI will be summarized using Kaplan-Meier method.
- The number and percentage of subjects who experienced thyroid or diabetes mellitus related AESI at least once and used corresponding concomitant medications will be summarized.

All AEs will be listed by subject.

Death

Death reasons will be summarized. All deaths will be listed by subject.

Laboratory Data

The laboratory data will be converted to Standard International (SI) units. The absolute value and change from baseline of each lab parameters will be summarized by scheduled visit.

Grading of laboratory data

Laboratory data will be derived programmatically according to the NCI CTCAE version 4.03. The calculation of CTC grades will be based on the observed laboratory values only, clinical assessments will not be considered. A shift table will be produced to reflect the grade change at the worst post-baseline assessment from the baseline visit.

Liver function parameters

The number and percentage of subjects with Liver Function Laboratory Findings will be summarized based on the event criteria as below:

Parameter	Criteria
ALT	>3xULN; >=5xULN; >=10xULN; >=20xULN
AST	>3xULN; >=5xULN; >=10xULN; >=20xULN
ALT or AST	>3xULN; >=5xULN; >=10xULN; >=20xULN
Total bilirubin (TBIL)	>=1.5xULN; >=2xULN
ALP	>=1.5xULN
ALT and/or AST & TBIL	ALT and/or AST>3xULN & TBIL >=1.5xULN ALT and/or AST>3xULN & TBIL >=2xULN
ALT and/or AST & TBIL & ALP	ALT and/or AST>3xULN & TBIL >=2xULN & ALP <2xULN

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g., a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5xULN.

12-Lead Electrocardiogram (ECG)

The analyses of 12-lead ECG data are based on the safety analysis set.

Overall interpretation of 12-lead ECG results will be summarized by visit.

Patient listing of clinically significant abnormal 12-lead ECG results will be provided.

ECOG Performance Status

The analyses of ECOG performance status are based on the safety analysis set.

Shift table will be produced for ECOG performance status at highest post-baseline visits and baseline.

Vital Signs

The analyses of vital signs are based on the safety analysis set.

Each vital sign parameter at each visit will be summarized, along with the absolute change from baseline.

MISSING DATA

The imputation for missing results will not be performed. The censoring rules for efficacy endpoints can be found in section 4.5.

Missing/Incomplete dates will be imputed according to Appendix 3. The output of listings will display the dates before imputation.

INTERIM ANALYSES

No formal efficacy interim analyses are planned.

LIST OF ABBREVIATION

Abbreviation	Full Name of Abbreviation
ADA	Anti-drug Antibody
ADAAS	Anti-drug Antibody Analysis Set
CI	Confidence Interval
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DoR	Duration of Response
EAS	Efficacy Analysis Set
ECOG	Eastern Cooperative Oncology Group
eICRF	Electronic Imaging Case Report Form
eOCRF	Electronic Oncology Case Report Form
FDG	Fluorodeoxyglucose
IRRC	Independent Radiological Review Committee
MRI	Magnetic Resonance Imaging
NAb	Neutralizing antibody
NCI	National Cancer Institute
OS	Overall Survival
PD	Progression
PD-1	Programmed Death-1
PD-L1	Programmed Death Ligand 1

Abbreviation	Full Name of Abbreviation
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
PR	Partial response
PT	Preferred Term
R/R ENKTL	Relapse Or Refractory Extranodal Natural Killer / T cell lymphoma
SAS	Safety Analysis Set
SD	Stable Disease
SOC	System Organ Class
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TTR	Time To Response
ULN	Upper limited normal
UNK	Unknown
WHODD	WHO Drug Dictionary

APPENDIX 1 PROTOCOL SYNOPSIS

Version 3.0Date: 25 Feburary 2021	**Protocol No.:** CS1001-201
Experimental Drug: CS1001	
Title of Study: A Single-Arm, Multicenter, Phase II Clinical Trial of CS1001 in Subjects with Relapsed or Refractory Extranodal Natural Killer/ T Cell Lymphoma (R/R ENKTL)	
Number of Sites: Multiple sites	
Study Phase: Phase II	

Objectives and Endpoints:

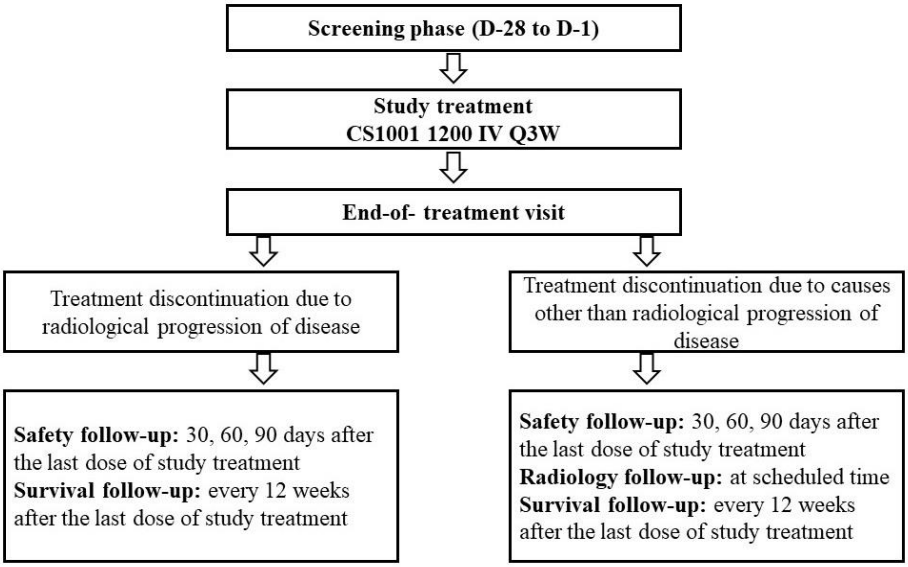
Objectives	Endpoints
Primary objectives	**Primary endpoints**
To evaluate the efficacy of CS1001 in subjects with R/R ENKTL	Objective response rate (ORR) assessed by the independent radiological review committee (IRRC) according to *Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification*
Secondary objectives	**Secondary endpoints**
To evaluate the efficacy of CS1001 in subjects with R/R ENKTL	ORR assessed by investigators; Complete response rate (CRR), partial response rate (PRR), time to response (TTR), duration of response (DoR) assessed by IRRC and investigators
To evaluate the safety of CS1001 in subjects with R/R ENKTL	Frequency and severity of adverse events (AEs) and frequency of serious adverse events (SAEs)
To characterize the pharmacokinetics (PK) of CS1001	To determine the peak and trough serum concentration of CS1001
To evaluate the immunogenicity of CS1001	Number and percentage of subjects with anti-drug antibody (ADA)
Exploratory objectives	**Exploratory endpoints**
To evaluate the progression-free survival (PFS) and overall survival (OS) of R/R ENKTL subjects	6-months PFS rate, 6-month OS rate

To evaluate genetic aberrations in R/R ENKTL by whole-exome sequencing test of tumor tissues	The association between genetic aberrations and efficacy

Study design and methods:

This is a multicenter, single-arm phase II study to evaluate the efficacy and safety of CS1001 monotherapy in R/R ENKTL.

Eighty eligible patients with R/R ENKTL who failed prior asparaginase-based treatment regimen(s) are assigned to receive CS1001 1200 mg intravenous (IV) infusion every three weeks (Q3W) until disease progression, intolerable to study treatment, consent withdrawal, death, or other causes specified in the protocol. The duration of treatment will be up to 24 months.



For immune therapies such as CS1001, **pseudo-progression** may occur due to immune cell infiltration and other mechanisms as manifested by an apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, for progressive disease (PD) suspected by the investigator as pseudo-progression, treatment may continue until confirmation of PD with repeated imaging at least 4 weeks later (or preferred at the next scheduled regular imaging time point). All of the following criteria must be met to continue the treatment:

Absence of clinically significant symptoms and signs of PD (including worsening laboratory values)
Stable Eastern Cooperative Oncology Group Performance Status (ECOG PS)
Absence of rapid progression of disease or PD at critical anatomical sites that necessitates urgent medical intervention

The primary endpoint of this trial is ORR, defined as the percentage of subjects whose best overall response (BOR) is either CR or PR, as assessed by IRRC based on Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification (hereinafter referred to as 'Lugano 2014 classification'). The final efficacy analysis of the primary endpoint will be performed when the last subject completes the efficacy assessment of up to 24 weeks.

Safety follow-up visits should be conducted 30, 60, 90 days after the last dose of study treatment. Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier. Survival follow-up should be conducted every 12 weeks

after the last dose of study treatment. Apart from subjects who discontinue treatment due to disease progression assessed by tumor imaging, radiological assessment should be performed at scheduled time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.

Key Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Subjects who are willing to participate in this trial; fully understand and are fully informed of this trial, and are able to provide written informed consent form (ICF); are willing and able to follow all study procedures.
2. Subjects are ≥ 18 years and ≤ 75 years of age on the day of signing informed consent.
3. Subjects must have a histologically confirmed ENKTL at the study site. Both nasal and non-nasal ENKTL are allowed.
4. Subjects must have relapsed or refractory ENKTL failing asparaginase-based chemotherapy or chemoradiotherapy. (Relapse: disease progression after response to the last treatment; refractory: no response to the last treatment.)
5. ECOG PS of 0 or 1.
6. Life expectancy ≥ 12 weeks.
7. Subjects must have at least one evaluable or measurable lesion per Lugano 2014 classification [An evaluable lesion is a lymph node or extranodal lesion with radioactive uptake higher than liver on ^{18}F-Fluorodeoxyglucose/ Positron Emission Tomography (^{18}FDG/PET) and with typical lymphoma characteristics on PET and (or) computed tomography (CT); Measurable lesion: the longest diameter (LDi) is of > 15 mm for nodal lesion or >10 mm for extranodal lesion (if the only measurable lesion has received prior radiotherapy, the subject must have evidence of radiological progression after radiotherapy), and concurrent elevated uptake of ^{18}FDG]. Absence of measurable lesion with diffuse ^{18}FDG uptake increase in the liver should be ruled out first.
8. Subjects must provide stained tumor tissue sections and corresponding pathological reports or unstained tumor tissue sections (or tissue block) for central pathology review. Investigators may enroll subjects before the result of central pathology review.
9. Subjects must have adequate organ function and bone marrow function without severe hematopoietic disorder, or heart, lung, liver or kidney dysfunction or immune deficiency (no blood transfusion, granulocyte colony-stimulating factor or other relevant medical supporting care within 14 days before the first dose of study treatment):
    a) Absolute neutrophil count ≥ 1.0×10^9 /L;
    b) Platelets ≥ 50×10^9 /L;
    c) Hemoglobin ≥ 8 g/dL;
    d) Creatinine clearance ≥ 40 mL/min (according to Cockcroft-Gault equation);
    e) Serum total bilirubin ≤ 1.5 × ULN, unless considered to be due to Gilbert's disease, where it must be ≤3 × ULN
    f) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤ 2.5 × ULN;
    g) Coagulation: International normalized ratio (INR) ≤ 1.5 × ULN; prothrombin time (PT) and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN (unless the subject is on anti-

coagulant therapy and PT and APTT at screening are within the expected range for patients on anti-coagulant).

10. Subjects with prior anti-cancer treatment can only be enrolled when the toxicity of prior anti-cancer treatment has recovered to baseline or ≤ Grade 1 according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03. For patients with irreversible Grade 2 toxicities (e.g. thrombocytopenia, anemia, neurotoxicity, alopecia, and hearing impairment) that is anticipated to be unlikely to worsen during study treatment, the subject can be enrolled after approval by the medical monitor of the sponsor.
11. Women of childbearing potential (WOCBP, as defined in Section 4.1.4) must have a negative serum pregnancy test ≤7 days before the first dose of investigational product. WOCBP or fertile men and their WOCBP partners must agree to use an effective contraceptive method from providing signed ICF through 6 months after the last dose of the investigational product. (Refer to Section 4.1.5 for details.)

Exclusion Criteria:

1. Aggressive natural killer-cell leukemia or ENKTL patients who have any degree of leukemic involvement will be excluded.
2. Concomitant with hemophagocytic lymphohistiocytosis.
3. Current or historical primary central nervous system lymphoma (PCNSL) or secondary CNS involvement.
4. Prior allogeneic organ transplantation.
5. Allogenic hematopoietic stem cell transplantation (HSCT) ≤ 5 years before the first dose of investigational product. (Patients are permitted to enroll if they received allogenic HSCT more than 5 years before the first dose of investigational product and without any current graft-versus-host reaction.)
6. Current participation in another clinical study or use of any investigational drug within 4 weeks before the first dose of investigational product in this trial.
7. Autologous HSCT within 90 days before the first dose of investigational product.
8. Subjects with an active autoimmune disease that requires systemic treatment in the past two years. (Hormone replacement therapy is not considered as systemic therapy such as the patient has type I diabetes mellitus, hypothyroidism that can be managed with thyroid hormone replacement only, or adrenal insufficiency or pituitary insufficiency that requires a physiological dose of corticosteroid replacement). Subjects are permitted to enroll if they have an autoimmune disease that didn't require any systemic treatment in the past two years.
9. Subjects received systemic corticosteroid or any other immunosuppressive therapy within 14 days before the first dose of the investigational product; subjects are permitted to use topical, ocular, intra-articular, intranasal and inhaled corticosteroids (with minimal systemic absorption); a short course (≤ 7 days) of corticosteroids for prophylaxis (e.g., hypersensitivity to contrast media) or for treatment of non-autoimmune conditions (e.g., delayed hypersensitivity caused by contacting allergens).]
10. A known additional malignancy within 5 years piror to the first dose of investigational product. Subjects with locally curable malignancies (including basal cell carcinoma of skin, squamous cell carcinoma of skin, breast cancer in situ or cervical cancer in situ, etc.) that have undergone curative therapy are permitted to enroll.
11. Subjects who have had prior chemotherapy, immunotherapy, biological therapy (including cancer vaccine, cytokine therapy or growth factors to treat cancer) used as a systemic treatment for cancer, within 28 days before the first dose of investigational product.

12. Subjects who underwent a major surgical procedure within 28 days before the first dose of investigational product or radiotherapy within 90 days before the first dose of investigational product.
13. Any use of traditional Chinese medicines or herbal preparations with anti-tumor indications within 7 days before the first dose of investigational product.
14. Has received a live vaccine within 28 days before the first dose of investigational product. (Attenuated influenza vaccine is allowed).
15. Known history of human immunodeficiency virus (HIV) infection and/or acquired immune deficiency syndrome (AIDS).
16. Subjects at the active phase of chronic hepatitis B or with active hepatitis C. Subjects who are hepatitis B surface antigen (HBsAg) positive or hepatitis C virus (HCV) antibody-positive at screening must not be enrolled until further definitive testing with hepatitis B virus (HBV) DNA titers (≤ 2500 copies/mL or 500 IU/mL) and HCV RNA tests (≤ the lower limit of detection) can conclusively rule out the presence of active hepatitis B or C that requires treatment, respectively. Subjects that carry the hepatitis B virus, with stable hepatitis B (HBV DNA titer ≤ 2500 copies/mL or 500 IU/mL) after medical treatment or with cured hepatitis C are permitted to enroll.
17. History of interstitial lung disease (except for those induced by radiation therapies and are asymptomatic).
18. Active tuberculosis infection.
19. Any active infection requiring systemic anti-infection therapy within 14 days before the first dose of investigational product.
20. Subjects who have received prior therapy with an anti-programmed cell death protein-1 monoclonal antibody (anti-PD-1 monoclonal antibody), anti-programmed cell death-ligand 1 monoclonal antibody (anti PD-L1 monoclonal antibody) or anti cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody (anti-CTLA-4 monoclonal antibody).
21. Subjects with a known severe allergy to monoclonal antibodies (≥ Grade 3 per CTCAE v 4.03) or uncontrolled allergic asthma.
22. Women in pregnancy or lactation.
23. Subjects with active alcohol or drug dependence.
24. Subjects with uncontrollable concomitant diseases including but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina, active gastrointestinal ulcer or hemorrhagic disorders.
25. Subjects with a history of psychiatric disease; or subjects with incapacity or limited capacity.
26. Underlying condition that in the investigator's opinion would increase the risk of investigational product administration or confound the assessment for its toxicity.
27. Subjects in the investigator’s opinion are not suitable for participating in this trial.

Number of Subjects:

Approximately 80 subjects with R/R ENKTL will be enrolled

Study Treatment:

CS1001 1200 mg, intravenous infusion for no less than 60 minutes, every 3 weeks (Q3W; 21 days).

Duration of Study:

This trial will be divided into three periods: screening period (28 days before the first dose of investigational product), treatment period (up to 2 years), and the follow-up period.

Study Evaluation:

Safety:

Safety assessments will include vital signs, physical examinations, electrocardiograms (ECG), ECOG PS, radiology, and incidence and severity of adverse events (AEs) and serious adverse events (SAEs).

AEs will be coded using the preferred term (PT) and system organ class (SOC) in Medical Dictionary for Regulatory Activities (MedDRA), International Conference for Harmonization (ICH).

The safety of the investigational product will be assessed according to CTCAE v4.03.

Efficacy:

Efficacy evaluation will be performed by investigators and IRRC based on Lugano 2014 classification. Contrast-enhanced CT will be performed at screening and every 12 weeks after the first dose of investigational product. Examined sites include head and neck region (that must include nasal cavity, palatum durum, anterior cranial fossa, and nasopharynx), chest, abdomen, and pelvis. For patients allergic to CT contrast media, enhanced magnetic resonance imaging (MRI) will be used as an alternative. Positron emission tomography / computed tomography (PET/CT) will be performed at screening, Week 12, and Week 24. Only enhanced CT will be used for follow-up tumor imaging after first radiological CR or Week 24, whichever comes first. For patients without any measurable lesion, follow-up with PET/CT will be performed until radiological confirmation of CR or progression if the patient hasn't reached CR in the first 24 weeks. Additional PET/CT will be performed if follow-up enhanced CT reveals residual lesion or suspected progression.

If contrast media for CT can be injected when PET/CT is performed and meet requirements on PET/CT and contrasted CT, additional enhanced CT can be skipped. View *Central Radiology Manual* for details.

Apart from subjects who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.

Pharmacokinetics and Immunogenicity:

Samples will be analyzed for serum CS1001 concentrations and anti-drug antibody (ADA) using a validated immunoassay. The neutralizing antibody of CS1001 will be tested as needed if the neutralizing antibody assay method is established.

Statistical Methods:

Population:

Efficacy analysis set (EAS) consists of all subjects who receive any dose of CS1001 and have the disease under study confirmed by central pathology.

Safety analysis set (SAS) consists of all subjects who receive any dose of CS1001.

Primary efficacy analyses:

The primary efficacy endpoint is ORR assessed by IRRC, defined as the proportion of subjects who achieve CR or PR as the best overall response in all subjects with evaluable or measurable lesions in EAS.

The 95% confidence interval (CI) of ORR will be calculated using the exact binomial (Clopper-Pearson) method to evaluate the precision of the ORR estimate.

The statistical analysis will be performed by 24 weeks after the first dose of last subject.

Secondary efficacy analyses:

Proportions of subjects who achieve CR, PR, SD, and PD per IRRC evaluation and their 95% CIs will be summarized. This analysis will be performed in EAS subjects with evaluable or measurable lesion at baseline judged by IRRC. Proportions of subjects with responses per investigator's evaluation and their 95% CIs will be summarized. This analysis will be performed in EAS subjects with evaluable or measurable lesion at baseline judged by investigators.

Duration of response (DoR) is defined as the time from the date of the first documented CR or PR (whichever comes first) to the date of the first documented disease progression or death, whichever comes first. DoR will be evaluated in subjects with objective responses per investigator's or IRRC's assessment, respectively.

Time to response (TTR) is defined as the time from the date of the first study dose to the date of the first documented CR or PR, whichever comes first. TTR will only be evaluated for subjects who achieve ORR. TTR will be summarized according to the investigator's and IRRC's assessment, respectively.

Kaplan-Meier method will be used to analyze DoR; KM plots will be provided. DoR analysis will only be performed in subjects with objective responses.

Exploratory efficacy analyses:

Progression-free survival (PFS) is defined as the time from the date of the first study dose to the date of first documented disease progression or death, whichever comes first.

Overall survival (OS) is defined as the time from the date of the first study dose to the date of death irrespective of its cause.

Kaplan-Meier method will be used to analyze PFS and OS.

Sample size:

The primary efficacy endpoint is ORR assessed by IRRC according to Criteria for Response Assessment of Lymphoma: Lugano 2014 Classification.

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Pharmacokinetic analysis:

Descriptive statistics will be summarized for the serum concentration of CS1001 for blood samples taken at pre-specified time points.

Safety analysis:

All adverse events will be described according to MedDRA and graded according to the NCI CTCAE v4.03. All adverse events that occurred during or after investigational product administration will be summarized by NCI CTCAE grade. Besides, SAEs, severe AEs (Grade 3, 4, or 5 events), drug-related AEs, and AEs causing discontinuation of or changes in investigational product administration will each be summarized. Multiple occurrences of the same event will only be counted once for the most severe event. The proportion of subjects with at least one AE will be reported.

All deaths that occur during the study or within the follow-up period after the last dose/discontinuation of investigational product will be reported.

Specific laboratory tests, vital signs, physical examinations, and 12-lead ECGs and their changes from baseline will be summarized. The values at baseline and each time point following baseline will be presented by crosstabs, when appropriate.

Immunogenicity:

Immunogenicity evaluation results will be reported for the following parameters. Number and percentage of subjects who have positive ADA at baseline; number and percentage of subjects with at least one positive ADA test result in any time point following the first dose of the investigational product; number and percentage of subjects who develop treatment-induced ADA any time after the first dose of the investigational product; number and percentage of subjects with treatment-enhanced ADA any time after the first dose of investigational product.

Biomarkers:

Biomarker measurements will be presented for available data. Graphical and/or tabular forms will be used to describe genetic aberrations and their relationship with the efficacy of anti-cancer treatment.

The statistical method will be described in detail in the statistical analysis plan.

APPENDIX 2 SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Activities

Trial Period	Screening	Treatment	Follow-up

Treatment cycles or visits	Screening	1	2	3	4	N	End-of-treatment Visit[1]	Safety follow-up[2]	Radiology follow-up[3]	Survival follow-up[4]
Time of visit and time window	Day -28 to Day -1	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+7 days	After the last dose 30, 60, 90 days ± 3 days		After the last dose Every 12 weeks (± 7 days)
Study Procedures										
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics and medical history	X									
Prior medications and concomitant medications[5]	X	X	X	X	X	X	X	X		
Clinical procedures/assessments										
Adverse events[6]	X	X	X	X	X	X	X	X		
12-Lead ECG[7]	X						X	X		
Height, weight, and vital signs[8]	X	X	X	X	X	X	X	X		
Physical examination and ECOG	X	X	X	X	X	X	X	X		

performance status[9]										
Subsequent anti-cancer treatment									X	X
Survival status										X
Study treatment										
CS1001[10]		X	X	X	X	X				
Laboratory procedures/assessments (at study sites)										
Pregnancy test[11]	X						X	X		
Hematology, serum chemistry, urinalysis[12]	X		X	X	X	X	X	X		
Coagulation functions[13]	X									
Virology[14]	X									
Thyroid functions[15]	X			X		X	X	X		
EBV DNA[16]	X		X	X	X	X				
Laboratory procedures/assessments (performed by central laboratory)										
Central pathology[17]	X									
PK[18]		X	X	X	X	X	X	X		
ADA[19]		X	X	X	X	X	X	X		
Efficacy evaluation										
Radiology examinations[20]	X					X			X	
Bone marrow aspiration and biopsy[21]	X									

Sample collection for biomarkers										
Blood sample collection[22]	X									
Tumor tissue[23]	X									

1. End-of-treatment (EOT) follow-up: EOT date will be the decision-making date for discontinuing the study treatment by investigators. EOT visit should occur 0-7 days after the EOT date.
2. Safety follow-up: Safety follow-up visit should be conducted at 30, 60, 90 days (± 3 days) after the last dose of investigational product. If the EOT visit occurs in the time window of the first safety follow-up visit (30± 3 days), the same tests and examinations don't need to be repeated. It is recommended to complete all protocol required follow-up evaluations for the safety follow-up at 60 ± 3days and 90± 3 days after the last dose, or AEs and concomitant medications can be collected through phone call. Safety follow-up period refers to the 90 days after the last dose of the investigational treatment or the start of new anti-cancer treatment, whichever occurs earlier.
3. Radiology follow-up: Apart from subjects who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.
4. Survival follow-up: Survival status will be assessed every 12 weeks by telephone after the last dose of investigational product.
5. Concomitant medications: All concomitant medications received from 30 days before the screening will be recorded until 90 days after the last dose of study treatment or the start of new anti-cancer treatment, whichever occurs first.
6. Adverse events (AEs): All AEs will be recorded from signing informed consent to 90 days after the last dose of investigational product or starting new anti-cancer therapy, whichever comes first. Thereafter only study treatment-related SAEs need to be recorded. AEs that occur after the safety follow-up visit can be recorded by telephone follow-up 60 days and 90 days after the last dose.
7. Electrocardiogram (ECG): ECG will be performed at screening, EOT visit, and safety follow-up visit. The frequency of ECGs may be increased if clinically indicated.
8. Height, weight, and vital signs: Height will only be measured at screening, weight at screening, EOT visit, and safety follow-up visit. Vital signs include temperature, pulse, respiratory rate, and blood pressure.
9. Physical examination and ECOG performance status: Overall physical examination will be performed at screening, EOT visit, and safety follow-up visit. The lymphoma-specific physical examination will be performed during the treatment period.
10. Study treatment: The study treatment is CS1001 1200 mg, IV, Q3W, administered on the first day of each cycle after completing all the clinical and laboratory procedures/assessments.
11. Pregnancy test: Blood human chorionic gonadotrophin test is performed as a pregnancy test only in women of childbearing potential at screening (within 7 days before the first dose), EOT visit, and safety follow-up visit. An additional urine pregnancy test may be performed if clinically indicated. A serum pregnancy test is needed if the urine test reveals a positive result.
12. Hematology, serum chemistry, and urinalysis: Hematology includes complete blood count with differentials and hemoglobin. Serum chemistry tests include blood urea/urea nitrogen, creatinine,

sodium, potassium, magnesium, chloride, calcium, phosphate, fasting blood glucose, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total cholesterol, total protein, and albumin. Urinalysis includes specific gravity, pH, urine glucose, urine protein, urine casts, ketones, and blood cells. These tests will be performed at screening (within 7 days before the first dose of investigational product), 3 days before each dosing starting from Cycle 2, EOT visit, and safety follow-up visit.

13. Coagulation function: Coagulation function tests including PT, APTT, and INR will be performed at screening.

14. Virology: Tests for HBsAg, HCV antibody, and HIV antibody will be performed at screening. Subjects who are HBsAg positive must receive further HBV DNA test. Subjects who are HCV antibody positive must receive further HCV RNA test.

15. Thyroid function: Thyroid function test including free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) tests will be performed at screening (within 7 days before the first dose of investigational product), thereafter 3 days before investigational product administration every other cycle (Cycle 3, 5, 7 and so on), EOT visit and safety follow-up visit.

16. EBV DNA: EBV DNA test will be performed at screening and 3 days before each dosing starting from Cycle 2. For subjects who achieve radiological CR, the EBV DNA test will be performed every other cycle thereafter.

17. Central pathology: Stained tumor tissue sections and corresponding pathological report or unstained tumor tissue sections (or tissue block) must be collected at screening for central pathology review. Both fresh and archival biopsies are accepted and can be used by central pathology. Investigators may enroll subjects before obtaining the result of the central pathology review. For subjects whose diagnosis is not ENKTL per central pathology laboratory's evaluation, investigators in consultation with sponsor medical monitors will determine whether to continue or discontinue the subject from treatment. View *Central Pathology Manual* for detailed instructions.

18. Pharmacokinetics (PK): Blood samples will be collected within 60 minutes before infusion as pre-treatment samples at Cycle 1, 2, 3, 4, and 8, and within 30 minutes after infusion at Cycle 1 and 4 in the treatment period. Blood samples for PK testing will be collected at the EOT visit and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment. View *Central Laboratory Manual* for detailed instructions.

19. Immunogenicity: Pre-treatment blood samples are collected (within 60 minutes before dosing) at Cycle 1, 2, 3, 4, and every 4 cycles thereafter (e.g., Cycle 8, 12, 16, and so on). Blood samples for ADA testing will be collected at the EOT visit and safety follow-up visit at 30 days, and 90 days after the last dose of study treatment. View *Central Laboratory Manual* for detailed instructions.

20. Radiology assessment: Efficacy evaluations will be performed by investigators and IRRC based on Lugano 2014 classification. Contrast-enhanced CT will be performed at screening and every 12 weeks after the first dose of investigational product. Examined sites include head and neck region (that must include nasal cavity, palatum durum, anterior cranial fossa, and nasopharynx), chest, abdomen, and pelvis. For subjects allergic to CT contrast media, enhanced MRI will be used as an alternative. Systemic PET/CT examination will be performed at screening, Week 12, and Week 24. Only enhanced CT will be used for follow-up after first radiological CR or Week 24, whichever comes first. For subjects without any measurable lesion, follow-up with PET/CT will be performed until radiological confirmation of CR or progression if the subject hasn't reached CR in the first 24 weeks. Additional PET/CT will be performed if follow-up enhanced CT reveals residual lesion or suspected progression. If contrast media for CT can be injected when PET/CT is performed and meet requirements on PET/CT and contrasted CT, additional enhanced CT can be skipped. View *Central Radiology Manual* for details. Apart from subjects

who discontinue treatment due to radiological disease progression, tumor assessment should be performed at pre-specified regular time points until radiological disease progression, the start of new anti-cancer treatment, death, or the end of this trial, whichever occurs first.

21. Bone marrow aspiration and biopsy: Bone marrow aspiration and biopsy should be performed at screening for all subjects. Subjects with positive bone marrow aspiration/biopsy result or indeterminate overall bone marrow assessment at screening will undergo bone marrow aspiration and biopsy when achieving CR/CMR based upon radiology for confirmation. Immunohistochemistry (IHC) analyses should be performed under a microscope no matter bone marrow involves or not（Suggest detecting CD56、TIA-1、CD3、GrB、perforin, and EBER hybridization in situ, etc.).
22. Blood sample for biomarker testing: A whole blood sample of 2 mL will be taken as genetic control in whole-exome sequencing for tumor tissue. View *Central Laboratory Manual* for details.
23. Tumor tissue for biomarker testing: Seven (7) unstained tumor tissue sections are collected at screening for whole-exome sequencing of tumor tissue. View *Central Laboratory Manual* for details.

APPENDIX 3 HANDLING OF MISSING DTAES

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APPENDIX 4 SUMMARY OF CHANGES

The substantive changes included in current version relative to Version 1 (dated 09July2020) are itemd as follows:

- [redacted]
- Section 2.3: clarify another round analysis will be performed for US filing when all responders have at least 6 months follow-up from the date of first documented response to address one of FDA's comments on protocol 3.0
- Section 4.2: remove biomarker analysis set given the ammount of subjects with biomaker sample is pretty low
- Section 4.5.2: add two more censoring rules for DoR per FDA's comments on protocol 3.0
- Section 4.6.2: remove not applicable ADA anslysis and add NAb analysis
- Section 4.7.2: add analysis regarding AESI as assessed by sponsor
- Appendix 1 and Appendix 2: protocol ammendent from 2.0 to 3.0