Clinical Protocol CS1003-305

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Clinical Protocol

Study CS1003-305

Study Title: A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC)

Document Date: 24-Nov-2022

NCT Number: NCT04194775

Clinical Study Protocol

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Protocol No.:	**CS1003-305**
Current Version Number:	**Version 5.0/ 24-Nov-2022**
Previous Version Number:	**4.0**
EudraCT number:	**2019-003337-41**
Experiment Drug:	**CS1003**
Study Phase:	**III**
Sponsor:	**CStone Pharmaceuticals (Suzhou) Co., Ltd.** E168, 2nd Floor, 218 Xinghu Str., A1 Building, North Block, BioBay, Suzhou Industrial Park, Suzhou, China

Leading principal investigator: PPD

Confidentiality Statement

This confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

Signature Page

Protocol Title:	**A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC)**
Protocol No.:	**CS1003-305**
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This protocol is a confidential document of **CStone Pharmaceuticals (Suzhou) Co., Ltd.** for confidential circulation. I confirm I have read through and understand this protocol and will follow the protocol in the study. Furthermore, I will abide by the ethics principles in Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements during the study. By signing for this document, I agree that I will not make public or disclose any non-public information herein without prior written permission from **CStone Pharmaceuticals (Suzhou) Co., Ltd.**

Note to investigator: Please sign your name and date on this signature page. Fill in printed names of you and your site to conduct this trial. A copy of this signature page will be returned to **CStone Pharmaceuticals (Suzhou) Co., Ltd.**

I have read the full text of the protocol and agree to follow it in the study.

Study Center: _____

Investigator Name: _____

_____ _____

Investigator Signature **Date**

Approval Page

Protocol Title:	**A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC)**
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CStone Pharmaceuticals will carefully fulfill the duties of Sponsors according to current Good Clinical Practice and be responsible for the initiating, submitting, organizing, Sponsoring and monitoring this clinical study. Subjects with serious adverse events during the clinical study will be provided with active intervention and the corresponding treatment expense will be covered by Sponsor according to applicable national regulatory requirements. Adequate financial compensation will be offered to subjects who experience damage confirmed to be consequence of investigational product-induced serious adverse effect.

I have participated in the development of and discussion on this study protocol and agree to its contents. I have fully understood Sponsor's duties related with this trial protocol and agree to conduct clinical study per this protocol and applicable regulatory requirements.

Sponsor: **CStone Pharmaceuticals (Suzhou) Co., Ltd.**

PPD

11-24. 2022

Date

Chief Executive Officer

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

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<tr><td colspan="2">Sponsor: CStone Pharmaceuticals (Suzhou) Co. Ltd.</td></tr>
<tr><td colspan="2">Final Product: N/A</td></tr>
<tr><td colspan="2">Investigational product: CS1003 (or placebo)</td></tr>
<tr><td colspan="2">Active Substance: a humanized, recombinant IgG4 anti-programmed death-1 (anti-PD-1) monoclonal antibody</td></tr>
<tr><td>Title of Study:</td><td>A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC)</td></tr>
<tr><td>Protocol No.:</td><td>CS1003-305</td></tr>
<tr><td>Sites:</td><td>Approximately 74 sites globally</td></tr>
<tr><td>Duration of the Study:</td><td>Screening (up to 28 days), Treatment and Follow-up (including Safety Follow-up, up to 90 days, and Survival Follow-up, every 12 weeks until end of study)</td></tr>
<tr><td>Study Phase:</td><td>III</td></tr>
<tr><td colspan="2">Study Objectives, Estimands and Endpoints:
Primary objective, estimand and primary endpoint:
<table>
<tr><th>Primary Objective:</th><th>Primary Endpoint/Estimand:</th></tr>
<tr><td>• To compare the efficacy of CS1003 in combination with lenvatinib vs. placebo in combination with lenvatinib</td><td>• Primary endpoint: Overall survival (OS)
• Estimand: The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment, withdrawing from or dropping out of the study, and starting of non-protocol anti-cancer treatment. The population-level summary for OS will be estimated by the HR from stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set.</td></tr>
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Secondary objectives and secondary endpoints:
<table>
<tr><th>Secondary Objectives:</th><th>Secondary Endpoints:</th></tr>
<tr><td>• To compare the efficacy of CS1003 in combination with lenvatinib vs. placebo in combination with lenvatinib</td><td>Key secondary endpoints:</td></tr>
</table></td></tr>
</table>

	• Objective response rate (ORR) assessed by Blinded Independent Central Review Committee (BICR) • Estimand: ORR assessed by BICR will be evaluated under the modified while-on-treatment strategy using tumor assessments prior to initiating non-protocol anti-cancer treatment to reflect the effect of the initially assigned randomized study treatment. The population-level summary for ORR evaluated by BICR will be presented by the rate difference between the two groups and the corresponding 95% CI using normal approximation to the binomial distribution, and p-value calculated by Stratified Mantel-Haenszel test for the ITT set. • Progression-free survival (PFS) assessed by BICR based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Estimand: PFS assessed by BICR will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment before BICR assessed disease progression and starting of non-protocol anti-cancer treatment before disease progression. The population-level summary for PFS evaluated by BICR will be estimated by the hazard ratio (HR) from stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set. Other secondary endpoints • PFS evaluated by investigator based on RECIST v1.1 • ORR evaluated by investigators based on RECIST v1.1

	• Duration of response (DoR) and disease control rate (DCR) evaluated by BICR and investigators based on RECIST v1.1
• To compare the safety of CS1003 in combination with lenvatinib vs. placebo in combination with lenvatinib	• Adverse events (AEs), serious adverse events (SAEs), death, vital signs (including blood pressure and pulse, etc.), electrocardiogram (ECG), laboratory tests (including serum chemistry, hematology and urinalysis, etc.) and ECOG performance status, etc.
• To characterize the population pharmacokinetics (PopPK) and immunogenicity of CS1003 when dosed in combination with lenvatinib	• Peak and trough serum concentrations of CS1003 • Number and percentage of subjects who develop anti-CS1003 antibody (ADA)
• To assess the disease/treatment-related patient-reported outcome (PRO), Health related Quality of Life (HRQoL)/Global health status (GHS) and function of subjects treated with CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib	• Time to deterioration (TTD), defined as the time from randomization to the first deterioration of European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30) scale

Exploratory objectives and exploratory endpoints:

Exploratory Objectives:	Exploratory Endpoints:
• To explore the relationship between biomarker and the efficacy of CS1003 in combination with lenvatinib	• Association of baseline PD-L1 expression with the efficacy of CS1003 in combination with lenvatinib
• To evaluate the disease/treatment-related PRO, HRQoL/GHS and function of subjects treated with CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib	• The scores of EORTC QLQ-C30 and EORTC QLQ-HCC18 subscales and the changes from baseline by cycle

• To assess the health status of subjects treated with CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib	• The health utilities index of EQ-5D-5L scale

Study Design:

This study is a multi-center, double-blind, randomized, phase III study to investigate the efficacy and safety of CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib in the treatment of subjects with unresectable advanced HCC, not amenable for locoregional therapy and have no prior systematic treatment for HCC or have progressed after curative treatment and/or locoregional therapy.

Subjects who have completed all eligibility check and fulfilled all the inclusion criteria and none of the exclusion criteria will be randomized in a 2:1 ratio according to stratified block randomization method:

Group A: CS1003, intravenous (i.v.) administration every 21 days (3 weeks) (Q3W);

Lenvatinib 12 mg (if the subject's weight ≥ 60 kg) or 8 mg (if the subject's weight < 60 kg), oral administration, once daily (refer to the prescription information of lenvatinib)

or

Group B: Placebo, i.v. administration every 21 days (3 weeks) (Q3W);

Lenvatinib 12 mg (if the subject's weight ≥ 60 kg) or 8 mg (if the subject's weight < 60 kg), oral administration, once daily (refer to the prescription information of lenvatinib)

Subjects should take lenvatinib with or without food at approximately the same time each day.

See Section 6.6 for instructions on study treatment adjustment during the study.

Randomization will be based on the following stratification factors:

- CCI
- [redacted]
- [redacted]
- [redacted]

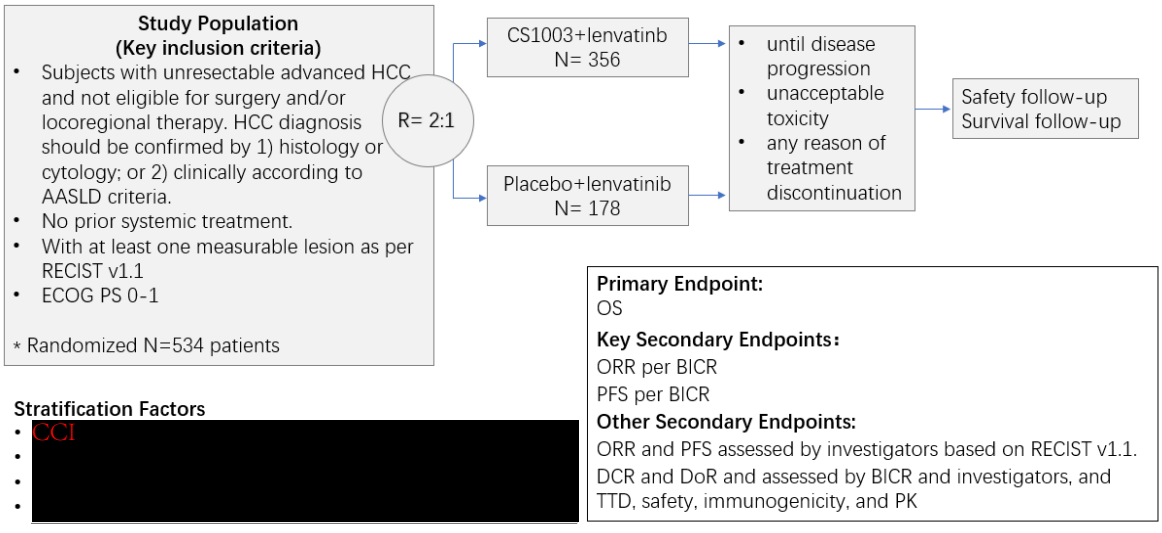
All subjects will be treated until disease progression (PD) or unacceptable toxicity or withdrawal from the study due to other causes, whichever occurs first. If the tumor assessment

has indicated stable disease (SD) or greater benefit, and the study treatment has been tolerable, subjects who are still on treatment at the end of study may continue to receive study treatment with an expansion study or other forms after consultation with Sponsor, and after approval by the health authorities and Ethics Committees.

Anti-cancer response will be evaluated based on RECIST v1.1. Pseudo-progression may occur in subjects who receive treatment with immunotherapies such as CS1003. Therefore, if pseudo-progression is suspected by investigator, study treatment may continue until confirmation of PD with imaging repeated at least 4 weeks later or at the next scheduled imaging assessment, but not to exceed 9 weeks from the initial documentation of PD. Subject must be re-consented and study treatment continuation decision should be notified to the sponsor, and the following criteria must be met in order to continue the study treatment after initial PD.

- Absence of clinical symptoms and signs of disease progression (including worsening of laboratory results);
- The study treatment is tolerable to subject;
- Stable ECOG performance status (PS);
- Absence of rapid progression of disease or tumor at critical anatomical sites (e.g., spinal cord compression) that requires urgent medical intervention.

Study Schema:



Abbreviation:
AASLD: American Association for the Study of Liver Diseases; BICR: Blinded Independent Central Review Committee; PK: Pharmacokinetics; RECIST: Response Evaluation Criteria in Solid Tumors. All efficacy test are based on RECIST v1.1

Planned Number of Randomized Subjects:	A total of approximately 534 subjects (including approximately 356 in CS1003+lenvatinib group and 178 in placebo + lenvatinib group) are planned to be randomized.
Study Population:	**Subjects must meet all of the following inclusion criteria for this study:** **General inclusion criteria** 1. Age ≥18 years on the day of signing informed consent (For Taiwan,

	the lower limit of age is 20 years). 2. Fully informed of the study, with good compliance and willing to provide written informed consent. The informed consent must be signed before performing any protocol-related procedure (that is not a part of subject's routine medical care). **Target Disease-Specific Inclusion Criteria** 3. Subjects with unresectable advanced HCC that is not eligible for surgery and/or locoregional therapy (Stage B or Stage C based on Barcelona Clinic Liver Cancer [BCLC] staging system indicated in Appendix 14.6), and meets either one of the following criteria: 1) histologically or cytologically confirmed diagnosis of HCC, 2) clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria. Patients without cirrhosis require histological confirmation of diagnosis. The curative treatment and/or locoregional therapy must have been completed ≥ 4 weeks prior to the baseline scan for subjects who experienced disease progression. 4. At least one measurable lesion can be assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 14.2) within 14 days prior to randomization. Target lesions in the past radiation fields or that underwent locoregional therapy (e.g., transarterial chemoembolization [TACE] or ablation), if confirmed as radiographic progression, are considered as measurable lesions. 5. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. 6. Life expectancy ≥ 3 months. 7. Child-Pugh ≤ 6 (Child-Pugh A). 8. No prior systemic treatment for advanced HCC, including target therapy, chemotherapy, immunotherapy (immune checkpoint inhibitors, interferons, interleukins), biological therapy (anti-cancer vaccines, cytokines, or growth factors), antibodies/drugs that target at any T cell co-regulatory protein (immune checkpoint), e.g., anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-OX-40, anti-CD137, anti-TIM-3, anti-LAG-3 antibodies, etc. a) Interferon is only allowed for hepatitis treatment with a washout period of no less than 5 half-lives prior to the initiation of study treatment. 9. Subjects with hepatitis B virus (HBV) infection must have HBV DNA

< 2000 IU/mL prior to randomization. Subjects with positive HBsAg and/or detectable HBV DNA must be treated with antiviral therapy for at least 2 weeks prior to the first dose of study treatment and must remain on antiviral therapy during the study.

Subjects with hepatitis C virus (HCV) infection (active or past infection) are allowed to be enrolled and HCV RNA detectable subjects are allowed to receive approved anti-HCV treatment during the study.

10. After the approval from local health authorities is obtained (if applicable), at screening, subjects must agree to provide, if available, tumor tissue for biomarker analysis. When archival tumor tissue is not available, it is optional for the subject to undergo a fresh biopsy to collect tumor tissue if deemed medically safe by the investigator (details are in section 7.5).

Inclusion criteria related to laboratory tests at screening

Adequate organ and marrow function, as defined below.

11. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L
12. Platelet count $\geq 75 \times 10^9$ /L
13. Hemoglobin ≥ 90 g/L
14. Serum albumin ≥ 29 g/L
15. Serum creatinine $\leq$ 1.5 × upper limit of normal range (ULN) or creatinine clearance (CL) ≥ 60 mL/min (according to Cockcroft-Gault equation)

$$\text{For female, CrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 0.85}{72 \times \text{Serum creatinine (mg/dL)}}$$

$$\text{For male, CrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 1.00}{72 \times \text{Serum creatinine (mg/dL)}}$$

16. Serum total bilirubin $\leq 2 \times$ ULN.
17. Aspartate transaminase (AST) and alanine transaminase (ALT):

$$\text{AST} \leq 5 \times \text{ULN}$$
$$\text{ALT} \leq 5 \times \text{ULN}$$

18. Coagulation: International normalized ratio (INR) or prothrombin time (PT) $\leq$ 1.5 × ULN.

Other inclusion criteria

19. Female subjects with childbearing potential must have negative serum pregnancy test result at screening. Female subjects with childbearing potential, and male subjects and their female partners with childbearing potential must agree to use an contraceptive method(s) (detailed contraception guidance is provided in Section 14.7 Appendix 7) from the day of signing informed consent form (ICF), during the study and till at least 6 months after the last dose of study treatment.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

Target disease-specific exclusion criteria

1. Fibrolamellar HCC, sarcomatoid HCC, cholangiocellular carcinoma or mixed cholangiocarcinoma and HCC.
2. History of hepatic encephalopathy.
3. A prior bleeding event due to esophageal or gastric varices within 6 months or other gastrointestinal bleeding events within 28 days prior to screening. Untreated or incompletely treated esophageal or gastric varices that are considered by the investigator to be at high-risk for bleeding (Note: Patients must undergo an esophagogastroduodenoscopy [EGD], and all size of varices [small to large] must be assessed and treated per local standard of care prior to enrollment; patients who have undergone an EGD within 6 months prior to the initiation of study treatment do not need to repeat the procedure). Active gastric or duodenal ulcer.
4. Radiographic evidence of tumor thrombus in the main trunk of portal vein, vena cava or heart involvement on baseline imaging.
5. Malabsorption syndrome or inability to take oral medication due to other causes.
6. HBV and HCV co-infection. (Note: Subject has HCV infection history but HCV RNA is undetectable at screening can be considered as non-HCV infection in this study).
7. Surgery or locoregional therapy for palliative purpose (e.g., to treat bone metastases or metastases causing nerve impingement) within 4 weeks prior to study treatment. Palliative radiotherapy within 2 weeks prior to study treatment. Minor surgery (i.e, simple excision) within 7 days prior to study treatment.
8. Uncontrolled pleural effusion, pericardial effusion that are symptomatic and requiring repeated drainage or oral diuretics at screening.

	9. Clinically meaningful ascites, defined as any ascites is detectable in the physical examination at screening, or is symptomatic, or requires special intervention, e.g., paracentesis or intraperitoneal perfusion (Note: Subjects with limited volume of ascites that is only identifiable by imaging can be enrolled). 10. Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 90 mmHg and cannot be managed by medication. **Medical History and Concomitant Disease-Relevant Exclusion Criteria** 11. History of other malignancy(ies) in the past 5 years, except for malignant disease treated with curative intent and without active disease, e.g., basal cell carcinoma of skin, squamous cell carcinoma of skin, superficial bladder cancer or prostate cancer, breast cancer in situ or cervical cancer in situ. 12. History of or current central nerve system (CNS) metastasis. 13. Active autoimmune disease or history of autoimmune disease that has possibility of relapse or at risk of having these conditions, e.g., history of organ transplantation and requiring immunosuppressants. Subjects with type I diabetes mellitus, hypothyroidism stable on hormone replacement, or dermatological condition that does not require systemic treatment (e.g., leukoderma, psoriasis or alopecia) are allowed to be enrolled. Any uncertainty, consultation with Sponsor's medical monitor is recommended before subjects signing informed consent. 14. Major cardiovascular diseases (e.g., congestive heart failure, unstable angina, atrial fibrillation, severe arrhythmia, etc.); any of acute myocardial infarction, unstable angina, stroke, or transient ischemic attack within 6 months before enrollment; New York Heart Association (NYHA) grade ≥ 2 congestive heart failure (detailed criteria is in appendix 5). 15. Presence of interstitial pneumonitis or non-infectious pneumonitis, which might confound the evaluation or management of pulmonary toxicity associated with study treatment-. 16. Any active infection (except for hepatitis virus infection) requires systemic treatment within 2 weeks prior to the first dose of study treatment. 17. Known history of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS).

	18. Active tuberculosis infection. **Previous Treatment-Relevant Exclusion Criteria:** 19. Any use of traditional Chinese medicine preparation with anti-tumor indication (e.g., Ban Mao capsule, elemene, Kanglaite, Cinobufacini, Xiaoaiping, Huai'er granule, Ganfule tablet, Jinlong capsule and Aidi) within 14 days prior to the first dose of study treatment. 20. Current or prior use of systemic corticosteroid (> 10 mg/day prednisone or equivalent) or other immunosuppressive medication within 14 days before the first dose of study treatment. Note: Inhaled or topical steroid, or adrenal replacement with ≤ 10 mg prednisone or equivalent is permitted if there is no active autoimmune disease. Short-term (≤ 7 days) steroid for prophylactic treatment (e.g., for contrast allergy) or for non-autoimmune conditions (e.g., delayed hypersensitivity caused by contrast allergy) is allowed. Corticosteroid, if required by a subject, should be taken at least two days prior to or after CS1003 or placebo infusion. 21. History of bone marrow transplantation or organ transplantation. **Allergy and adverse reaction** 22. History of anaphylaxis or hypersensitivity to any ingredient of the investigational product. 23. Any contraindication of lenvatinib. **Other exclusion criteria** 24. Known history of drug abuse that would interfere with cooperation with the requirements of the trial. 25. Pregnant or lactating female subjects. 26. History of psychiatric disease that would interfere with cooperation with the requirements of the trial; lack of or with restricted physical capability. 27. QTc interval > 470 msec (as calculated with Fridericia's formula) at screening electrocardiogram (ECG). 28. Any condition that would in the investigator's judgement, prevent the subject from participating in this study. 29. Current participation in another clinical study or use of any investigational drug within 4 weeks prior the first dose of study treatment in this trial.

	30. Major surgery within 4 weeks prior to the first dose of study treatment or planned major surgery during the study (mediastinoscopy, insertion of a central venous access device and insertion of a feeding tube are not considered major surgery). 31. Serious non-healing wound, ulcer, or bone fracture. 32. Urine protein ≥1 g/24 hours (routine urine test, urine protein>1+ will have 24-hour urine collected to assess proteinuria).
Planned Study Duration:	CCI [redacted]
End of Study:	CCI [redacted].
Dosage and Administration of Study Treatment:	**Investigational product:** CS1003 (or placebo), 100 mg/4 mL/vial **Basic Treatment:** Lenvatinib, 4 mg/capsule **Dosage and administration:** Group A: CS1003 is administered at 200 mg by i.v. infusion Q3W. Lenvatinib is orally administered at 12 mg or 8 mg, with or without food, once daily, at approximately the same time every day (refer to the prescription information of lenvatinib). or Group B: Placebo is administered by i.v. infusion Q3W. Lenvatinib is orally administered at 12 mg or 8 mg, with or without food, once daily, at approximately the same time every day (refer to the prescription information of lenvatinib). When lenvatinib and CS1003/placebo are administrated on the same day, lenvatinib is to be taken first, and the i.v. infusion of CS1003 or placebo will be initiated within 30 minutes after lenvatinib administration. Refer to Section 6.6 for instructions on study treatment-related dose adjustment during the study.
Statistical Methods:	The primary endpoint is OS, defined as the time from randomization to the date of death of any cause. The key secondary efficacy endpoints include ORR and PFS assessed by BICR based on RECIST v1.1.

The other secondary efficacy endpoints include:

- PFS assessed by investigators based on RECIST v1.1
- ORR assessed by investigators based on RECIST v1.1
- DCR assessed by BICR and investigators based on RECIST v1.1
- DoR assessed by BICR and investigators based on RECIST v1.1
- TTD in EORTC QLQ-C30

Primary and secondary analyses (OS, PFS, ORR and DCR) are performed in all randomized subjects (intention-to-treat set). DoR analysis is performed in subjects with an objective response. TTD analysis is performed in all subjects with baseline PRO and at least once post-baseline PRO assessment. For efficacy analyses, subjects will be grouped according to treatment allocation at randomization.

Safety analysis set is defined as all randomized subjects who received any study treatment. Randomized subjects who haven't received any dose of study treatment are not included in the safety analysis set. For safety analysis, subjects will be grouped by the actual received treatment group (patients who receive any dose of CS1003 incorrectly will be counted in the CS1003-treated group).

Sample size determination:

The primary endpoint of this study is OS.

Number of events and sample size are estimated based on the following hypotheses:

- Randomization ratio is 2:1.
- Type I error is controlled for two-sided test at 0.05.
- OS will be tested with log-rank test.
- CCI [redacted]
- One interim analysis of OS will be conducted. Type I error will be controlled using Lan-DeMets approximation to the O'Brien-Fleming boundary.
- Survival times are exponentially distributed
- CCI [redacted]

Based on the above hypotheses, CCI [redacted]

Interim analyses

CCI [redacted]

Log-rank test will be used for OS hypothesis, with its analysis boundaries shown in the table below:

CCI [redacted]

IDMC

An independent data monitoring committee (IDMC) is established to monitor safety data regularly and make recommendations to the Sponsor. The IDMC will also monitor the data for OS interim analysis and make recommendations to the Sponsor according to the pre-defined boundaries. Membership, roles and responsibilities, and implementation details of the IDMC will be described in the IDMC charter.

1.2 SCHEDULE OF ACTIVITIES

Table 1.2-1 Study Assessments and Procedures Schedule

Study cycle	**Screening**	**Randomization**	**Treatment (1 cycle = 21 days)**								**Follow-up**			
			1	**2**	**3**	**4**	**5**	**6**	**Cn**	[x] **End of Treatment (EOT) visit**	**Safety follow-up visit 1 (FU1)**	**Safety follow-up visit 2 (FU2)**	**Safety follow-up visit 3 (FU3)**	[y] **Survival follow-up**
Date of visit (Day)	**-28 to -1**	**-3 to 1**	**1**	**22 (±3)**	**43 (±3)**	**64 (±3)**	**85 (±3)**	**106 (±3)**	**C(n-1)D1+21 (±3)**	**0-7 days after investigator's decision of EOT**	**30±7 (days) after the last dose**	**60±7 (days) after the last dose**	**90±7 (days) after the last dose**	**Every 12 weeks ±14 days**
[a] Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics	X													
Medical History	X													
Diagnosis and Confirmation of cancer	X													
Prior Anti-Cancer Treatment	X													
[b] Tumor Tissue	X													
Height	X													
Weight	X		X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X		X	X	X	X	X	X	X	X	X			
[c] HBV, HCV and HIV tests	X						X		HBV-DNA or HCV-RNA is re-tested every 4 cycles for subjects with positive HBsAg/ HBcAb or positive HCV antibody	X	X			

[d] Physical Examination	X		X	X	X	X	X	X	X	X	(X)			
[e] Vital signs	X		X	X	X	X	X	X	X	X	X			
[f] 12-Lead Electrocardiogram (ECG)	X		X		X		X		Every 2 cycles	X	X			
[g] Echocardiogram	X		As clinically indicated											
[h] EGD	X													
[i] Laboratory Tests	X		X	X	X	X	X	X	X	X	X			
[j] AFP	X						X		Every 4 cycles	X	X			
[k] Coagulation Parameters	X		X	X	X	X	X	X	X	X	X			
[l] Thyroid Function	X		X		X		X		Every 2 cycles	X	X			
[m] Pregnancy Test	X		Every 2 cycles (every cycle in monthly intervals in EU countries)							X	X	X^{m}	X^{m}	
[n] Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
[o] Subsequent Anti-Cancer Treatment										X	X	X	X	X
[p] Tumor Imaging	X		**In the first 48 weeks:** every 6 weeks ± 7 days **After the first 48 weeks**: every 12 weeks ± 7 days; additional imaging is allowed as clinically indicated											
[q] PK Blood Sampling			X	X	X	X			(X)	X				
[r] ADA Sampling			X	X	X	X			(X)	X			X	
[s] Patient-Reported Outcome (PRO)	X		X	X	X	X	X	X	Every 2 cycles	X	X			X
[t] Randomization		X												
[u] CS1003 or Placebo Administration			X	X	X	X	X	X	X					
[v] Lenvatinib Administration			X	X	X	X	X	X	X					
[w] Review Treatment Compliance				X	X	X	X	X	X	X				
Survival status														X

Abbreviations: C, cycle; D, day; ADA, anti-drug antibody; ECOG, Eastern Cooperative Oncology Group Electrocardiogram; ECG, electrocardiogram; EGD, esophagogastroduodenscopy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PK, pharmacokinetics; PRO, patient-reported outcomes using EORTC QLQ-C30, EORTC QLQ-HCC18 and EQ-5D-5L scales; SAE, serious adverse event.

a. Subjects must provide written informed consent. Subjects must be assessed based on all the inclusion/exclusion criteria and eligibility is confirmed prior to randomization. Re-screening under limited conditions should be allowed only once after consultation with the Sponsor. Subject must undergo another informed consent process for re-screening and be allocated a new subject number. Assessments which are part of the patient's clinical standard of care may be performed before obtaining the written informed consent, if within the acceptable screening window.

b. During screening, subjects without cirrhosis require histological confirmation for HCC diagnosis (refer to Inclusion Criterion 3 for full details on HCC diagnosis). Under regulatory approval (if applicable), tumor tissue samples for exploratory biomarker assessment need to be collected. Tumor tissue samples can be archival formalin-fixed paraffin-embedded (FFPE) tissue block collected previously within 5 years before randomization (preferably within 12 months), or 3-5 freshly sectioned unstained slides (freshly sectioned within 6 months). When archival tissue is not available, it is optional for the subjects to have a fresh biopsy to collect tumor tissue collection if deemed medicinally safe by the investigator. Refer to section 7.5 and Lab Manual for detailed requirements for tumor sample collection.

c. All subjects must receive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and hepatitis C virus (HCV) antibody tests. Those with positive HBsAg or positive HBcAb must have hepatitis B virus (HBV) DNA titer test. Subjects with positive HCV antibody must have HCV RNA test. Thereafter, HBV-DNA and/or HCV-RNA tests are repeated every 4 cycles started from Cycle 5 Day 1 (C5D1) for subjects with positive HBsAg or HBcAb or positive HCV antibody during study treatment phase (i.e. on C5D1, C9D1, C13D1 and so on), at the end-of-treatment (EOT) visit and safety follow-up visit 1 (no need to repeat the tests if there are available results obtained within 7 days prior to the EOT visit or safety follow-up visit 1).

d. A complete physical examination will be performed at screening and at every treatment cycle before administration of study treatment. Refer to Appendix 14.1 for detailed physical examination items. Physical examination will be performed at safety follow-up 1 when indicated by symptoms. All abnormal findings and any newly developed or worsened physical examination abnormality or related symptoms will be recorded.

e. Vital signs including temperature, pulse, respiratory rate and blood pressure must be taken at screening and at every treatment cycle before administration of drugs. If vital signs at screening are taken within 3 days prior to the first dose of study treatment, the measurements don't need to be repeated before the first dose. Tympanic approaches (if applicable) can be used for temperature monitoring. All abnormal findings and any newly developed or worsened vital sign abnormality or related symptoms will be recorded.

f. ECG should be performed before any planned vital sign measurement or blood sampling, if possible. The evaluations are performed at the following time points: at screening and every 2 cycles starting from Cycle 1 Day 1 during treatment, at the end-of-treatment visit and safety follow-up visit 1. Additional ECGs will be performed as clinically indicated. If ECG at screening is taken within 7 days prior to the first dose of study treatment, the measurements do not need to be repeated before the first dose. For ECG performed within 7 days prior to the end of treatment visit or safety follow-up visit 1, it is not necessary to repeat the measurements in these two visits. The ECG at each study treatment administration visit must be performed within 3 days prior to the administration of study treatment.

g. Echocardiogram evaluation is required at screening and will be performed as clinically indicated throughout treatment period.

h. EGD: All patients must undergo an EGD and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. The patients who have undergone an EGD within 6 months prior to the initiation of study treatment do not need to repeat the procedure.

i. Routine laboratory tests include hematology, serum chemistry and urinalysis are performed at screening, before administration of study treatment at each cycle, end-of-treatment visit and safety follow-up visit 1. If laboratory test at screening is performed within 7 days prior to the first dose of study treatment, the laboratory test of the first cycle before the first dose will not be required. When laboratory test and administration of CS1003 or lenvatinib are to be on the same day (e.g., the first day [D1] of each treatment cycle), the test result must be available before starting the study treatment. The laboratory tests at each study treatment administration visit must be performed within 3 days prior to the administration of study treatment. For laboratory tests with available results performed within 7 days prior to the end of treatment visit or safety follow-up visit 1, it's not necessary to repeat the tests in these two visits. Hematology test includes complete blood count and hemoglobin. Serum chemistry tests include blood urea or urea nitrogen (BUN), creatinine, sodium, potassium, magnesium, chloride, calcium, phosphate, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), total cholesterol, total protein and albumin. Urinalysis includes specific gravity, pH, urine glucose, protein, 24-hour urine protein (as clinical indicated), urine casts, ketones, occult blood and white blood cells. Refer to Appendix 14.1 for detailed test items.

j. AFP test is performed at screening and once every 4 cycles started from Cycle 5 Day 1 during treatment period until safety follow-up 1 (inclusive). For AFP test with available result performed within 7 days prior to the end of treatment visit or safety follow-up visit 1, it is not necessary to repeat the test in these two visits.

k. The coagulation tests are performed at screening, before administration of study treatment at each cycle, end-of-treatment visit and safety follow-up visit 1. If the test at screening is performed within 7 days prior to the first dose of study treatment, the laboratory test of the first cycle before the first dose will not be required. When laboratory test and administration of CS1003 or lenvatinib are to be on the same day (e.g., the first day [D1] of each cycle), test result must be available before starting the study treatment. Laboratory tests performed within 7 days prior to the end of treatment visit or safety follow-up visit 1 are not required to be repeated at these two visits. Refer to Appendix 14.1 for detailed test items.

l. Thyroid function tests are performed at screening, before first dose of study treatment and every two treatment cycles thereafter, at the end-of-treatment visit and safety follow-up visit 1. If the test at screening is performed within 7 days prior to the first dose of study treatment, the laboratory test of the first cycle before the first dose will not be required. For laboratory tests with available results performed within 7 days prior to the end of treatment visit or safety follow-up visit 1, they are not required to be repeated at these two visits. Refer to Appendix 14.1 for detailed test items. When the investigator encounters the difficulty in having all thyroid-function test results ready before the Day 1 dosing in certain cycle, a subject may continue with the dosing at the investigator's discretion only if the subject is not showing any symptom suspected of abnormal thyroid function. The investigator should continue to monitor the subject's condition and take immediate actions if necessary.

m. Female subjects of childbearing potential (except those with record of sterilization operation or after menopause) must receive serum pregnancy test at screening and have available results prior to the first study treatment. If the pregnancy test at screening is performed within 7 days prior to the first dose of study treatment, the test of the first cycle before the first dose will not be required. Urinary or serum pregnancy test will be performed every 2 cycles throughout treatment period, at the end of treatment visit, and at safety follow-up visit 1. If a subject has had pregnancy test done within 7 days prior to the end of treatment visit or safety follow-up visit 1, the tests at these two visits will not necessarily be repeated. Subjects with positive urine pregnancy test must receive serum pregnancy test for confirmation, and negative result must be obtained before any administration of study treatment at each treatment cycle. For EU countries, the pregnancy test should be done at every cycle in monthly intervals and in safety follow-up visit 2 and 3. Additional pregnancy tests may also be undertaken if requested by Institutional Review Board/Ethics Committees (IRB/ECs) or local regulations.

n. Adverse events (AEs): All AEs and serious adverse events (SAEs) will be recorded during the reporting period from subject signing the informed consent, throughout the treatment period and safety follow-up, till 90 days after the last dose of the study treatment, or the subject starts a new anti-cancer treatment, whichever occurs earlier, after which time, only related SAEs need to be recorded and reported. AEs that occur after safety follow-up visit 1 can be collected at safety follow-up visit 2 and 3 by phone calls.

o. Subsequent anti-cancer treatment: information of subsequent anti-cancer treatment (after the end of study treatment) will be collected at each subsequent scheduled visit starting from the end-of treatment visit, including generic drug names of the treatment, starting date and ending date of treatment.

p. Tumor imaging evaluation: Tumor response assessment will be performed based upon Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Refer to Appendix 14.2 for details. Tumor imaging will be conducted using CT or MRI according to the investigator's decision. MRI is preferred for brain imaging, or CT is also permitted if a subject has any contraindication against MRI. For each subject, the same imaging method, equipment and technical parameters should be used throughout the study. The same investigator or radiologist should perform the imaging evaluation throughout the study, if possible. Contrast agent should be used if not contraindicated. Tumor assessment performed within 14 days prior to the randomization can be used as the baseline tumor evaluation if accepted by investigators. Baseline tumor evaluation should include brain, chest, abdomen, pelvis and any other site with suspected lesion. The tumor imaging will be performed every 6 weeks (±7 days) after the randomization in the first 48 weeks, and every 12 weeks (± 7 days) thereafter, until PD confirmed by radiological examination, withdrawal of informed consent, lost to follow-up, death, or end of study, whichever occurs first. Subjects who discontinue study treatment due to causes other than PD will continue to receive radiological assessments at pre-determined time points until PD, subject withdraws informed consent, lost to follow-up, end of study, or death, whichever occurs first. Subjects that are without brain metastasis as confirmed by brain imaging at screening are not required to receive regular brain imaging in the following visits. Additional brain imaging can be arranged by the investigator as clinically indicated. Other additional imaging is also allowed as clinically indicated. For any investigator-suspected pseudo-progression, prior to discontinuation of study treatment, a re-imaging will be performed at least 4 weeks later or at the next regularly scheduled imaging time point to confirm disease progression. (Note that the repeated radiologic examination must be performed no later than 9 weeks after the first recorded disease progression). For tumor radiologic evaluation performed within 28 days prior to the end of treatment visit or safety follow-up visit 1, they are not required to be repeated at these two visits.

All the images will be transferred to central radiology laboratory for blinded independent central review (BICR, refer to BICR Guidance for details) till the number of PFS events for PFS analysis has been reached.

q. Refer to Table 1.2-2.

r. Refer to Table 1.2-2.

s. Patient-reported outcomes (PRO) are collected through EORTC QLQ-C30, EORTC QLQ-HCC18 and EQ-5D-5L questionnaires completed by subjects on paper before any other evaluation at each visit. Before subject leaves the site, the investigator should review completeness of all questionnaires. These PROs should be assessed prior to any examinations scheduled on Day 1 of the first 6 treatment cycles, and then every 2 cycles from treatment Cycle 8 Day 1 on until the end-of-treatment visit (i.e. treatment C8D1, C10D1, C12D1, C14D1, and EOT), and safety follow-up visit 1. If PROs are assessed within 7 days prior to the end-of-treatment visit or safety follow-up visit, they are not required to be repeated in these two visits. During survival follow-up, an assessment is performed every 12 weeks unless the subject withdraws the ICF or the Sponsor ends this study. During survival follow-up, PRO could be collected at the site when subject comes for a visit or by phone calls. PRO assessment has a time window of -7 days (±7 days for EOT visit and visits thereafter), except the one on C1D1 which must be conducted on the same day and prior to any examinations scheduled on that day.

t. A subject can be randomized when eligibility is confirmed by the investigators. The first dose of study treatment should be administered within 3 days of randomization.

u. Subjects will receive CS1003 or placebo every 21 days (3 weeks), ± 3 days if necessary (but the interval between two doses must be ≥ 18 days) until end of treatment visit, disease progression, unaccepted toxicity, withdrawal of ICF, lost to follow-up, death or end of study, whichever occurs first.

v. Lenvatinib is administered once daily. When lenvatinib is given on the same day as CS1003 or placebo, please refer to Section 6.6.2 for details on administration and dose modification.

w. Treatment compliance will be monitored using drug dispense and return log, subject's medical record and electronic case report form (eCRF). Subjects should record the dose and time of lenvatinib administration every day and submit the record to the study coordinator at the next visit. At the end of treatment, subjects should return all used and unused drug containers for compliance evaluation.

x. End-of-treatment visit: Subjects who discontinue study treatment due to any reason should receive end of treatment visit within 7 days after the investigator determines discontinuation of treatment. If end of treatment visit is within the time window of safety follow-up visit 1, it will be done according to the safety follow-up requirements, and same test items will not be repeated.

y. Subjects should be contacted by telephone follow-up or site visit every 12 weeks (± 14 days) (or more frequently as needed) from the last dose of study treatment until lost to follow-up, death or end of study. Data on subject's survival, the subsequent anti-cancer therapy, PRO, and drug-related SAE will be collected in these telephone visits/site visits.

Table 1.2-2 Time Points of Blood Sampling for CS1003 PK and ADA

Study Day		Time	Time window[a]	PK Blood Sampling[b]	ADA Blood Sampling[b]
Cycle 1	D1	0 (before administration)	Within 60 minutes before administration	X	X
		EOI[c]	+ 30 minutes	X	
Cycle 2	D1	0 (before administration)	Within 60 minutes before administration	X	X
Cycle 3	D1	0 (before administration)	Within 60 minutes before administration	X	X
Cycle 4	D1	0 (before administration)	Within 60 minutes before administration	X	X
		EOI[c]	+ 30 minutes	X	
Cycle 8, and every 4 cycles thereafter	D1	0 (before administration)	Within 60 minutes before administration	X	X
End-of-treatment (EOT) visit	—	—	—	X	X
Safety follow-up visit 3	—	—	—		X

Abbreviations: EOI, end of infusion; ADA, anti-drug antibody; PK, pharmacokinetics; D1, day 1.

[a] PK and ADA sampling time window is calculated based on the administration of CS1003

[b] ADA and PK sample of 3.5 mL whole blood each.

[c] PK and ADA blood sampling follows the "rule of distal end" after the end of infusion; blood samples are taken from veins on the opposite limb of the infusion limb or on the limb without infusion site.

2 INTRODUCTION

2.1 GENERAL INTRODUCTION OF THE INVESTIGATIONAL PRODUCT

CS1003 (previously known as WBP3052B and WBP 3052) is a humanized, recombinant IgG4 anti-PD-1 monoclonal antibody for injection. CS1003 is supplied as 100 mg/4.0 mL/vial. The manufacturing process demonstrates good stability and feasibility in pharmic research.

2.2 MECHANISM OF ACTION AND BACKGROUND

PD-1 is an immune checkpoint protein that plays a critical role in modulating the stimulatory and inhibitory signals of the immune system.[1] The two known ligands of PD-1, PD-L1 and PD-L2, are both cellular surface proteins that belong to B7 family. Tumor cells and tumor infiltrating immune cells express PD-L1 and inhibit T cell proliferation in the tumor microenvironment. The anti-PD-1 antibody binds to PD-1 to inhibit PD-1/PD-L1 interaction, thereby enhancing T cell activation as well as the T cell-mediated immune response against tumor cells.

Recent clinical trials have shown that inhibition of PD-1/PD-L1 signaling with PD-1 or PD-L1-specific antibodies is effective for several malignancies and can produce a long-lasting response in a subset of patients. [2] PD-1 blocking antibodies have shown clinical efficacy in patients with advanced melanoma, lung cancer and kidney cancer. [2-4] In addition, combination therapy with anti-PD-1 antibody and anti-CTLA-4 antibody has been approved for BRAF-mutant advanced melanoma and is being tested in other cancer types. Many other combination therapies based on anti-PD-L1/PD-1 antibodies have also entered the clinical development phase. [3,5] In the past 5 years, the anti-PD-1 monoclonal antibodies approved by the United States (US) Food and Drug Administration (FDA) include pembrolizumab (Keytruda®, MSD, US), nivolumab (Opdivo®, BMS, US) and cemiplimab (Libtayo®, Sanofi/Regeneron). Anti-PD-L1 monoclonal antibodies approved by FDA include atezolizumab (Tencentriq®, Genentech, US), Avelumab (Bavencio®, Pfizer, US) and durvalumab (Imfinzi®, AstraZeneca, UK). The approved indications cover a wide span of human malignancies, including melanoma (2014), non-small cell lung cancer (2015), renal cell carcinoma (2015), Hodgkin's lymphoma (2016), head and neck cancer (2016), urothelial carcinoma (2016), gastric cancer (2017) , hepatocellular carcinoma (2017), solid tumors with high microsatellite instability (MSI-H) or mismatch repair defects (dMMR) and metastatic cutaneous squamous cell carcinoma (2018), proving the survival benefit and controllable toxicity of the drugs. [3, 6-9] In the past two years, three anti-PD-1 antibodies have also been approved in China, which are toripalimab (Tuoyi®, TopAlliance Biosciences), sintilimab (Tyvyt®, Innovent) and karelizumab (Ailituo®, Hengrui Medicine) with approved indications of melanoma, relapsed / refractory Hodgkin's lymphoma and relapsed / refractory Hodgkin's lymphoma, respectively. In addition, many more indications are undergoing pivotal registration trials or submission for approval. The approval of these drugs demonstrates the key role of PD-1/PD-L1 immune checkpoint inhibitors in immune-oncology therapy.

Among them, nivolumab (Opdivo®) and pembrolizumab (Keytruda®) have been approved by US FDA as second-line treatment for advanced hepatocellular carcinoma (HCC), marking a milestone in the use of anti-PD-1/PD-L1 antibodies to treat HCC. [10, 11]

In 2018 European Society of Medical Oncology (ESMO) Congress, the latest data of an early clinical study on immune checkpoint inhibitor in combination with vascular endothelial growth factor inhibitor (VEGFi) in patients with advanced HCC was reported. The objective response rate (ORR) of patients with advanced HCC treated by first-line atezolizumab and bevacizumab combination therapy was up to 32%, and the 6-month progression-free survival (PFS) rate was 65%. The safety profile reflected the additive toxicity of individual drugs. Grade 3/4 treatment-related adverse events (AEs) occurred in 27% of patients. No new toxicity was found, nor any death due to treatment was reported.[12] A clinical study of pembrolizumab combined with lenvatinib for first-line treatment of advanced HCC was reported at the 2019 American Association of Cancer Research (AACR) Congress with an ORR of 36.7% and a median PFS (mPFS) of 9.7 months [6]. Besides, the LEAP-002 study was reported in the 2022 European Society of Medical Oncology (ESMO) Congress. The median OS was 21.2 months with pembrolizumab plus lenvatinib and 19 months with placebo plus lenvatinib (HR=0.840; 95% CI: 0.708, 0.997; P=0.0227; HBV subgroup: HR=0.75; 95% CI: 0.58, 0.97). The mPFS was 8.2 months with pembrolizumab plus lenvatinib and 8.1 months with placebo plus lenvatinib (HR=0.834; 95% CI: 0.712, 0.978). [13] In addition, compared to sorafenib, camrelizumab combined with rivoceranib improved median OS (22.1 months vs. 15.2 months, HR=0.62; 95% CI: 0.49, 0.80; P < 0.0001) and median PFS (5.6 months vs. 3.7 months, HR=0.52; 95% CI: 0.41, 0.65; P < 0.0001). [14]

These clinical data suggested potential clinical benefit and controllable safety of drugs targeting at PD-1/PD-L1 signaling pathway in combination with VEGFi as first-line treatment in patients with advanced HCC that is unresectable and not eligible for local treatment.

2.3 PRECLINICAL STUDIES OF CS1003

2.3.1 PHARMACOLOGY

For the first time, CS1003 was characterized in a series of non-clinical in vivo studies of binding, inhibition and functional cell assays as well as in mice and monkeys. Surface plasma resonance (SPR), Enzyme-Linked Immunosorbent Assay (ELISA) and flow cytometry analysis showed that CS1003 can bind to PD-1 in humans, mice and monkeys with high affinity and specificity and can effectively inhibit PD-L1/PD-1 interaction. Therefore, downstream signaling can be suppressed. In cell-based assays, CS1003 not only enhances the activity of T cells in allogeneic mixed lymphocyte reactions, but also enhances the memory response towards the re-stimulation of CMV pp65 peptide in autologous mixed lymphocyte reactions. Thus, CS1003 blocks the inhibitory signals to T cells and promotes initial or memory T cell activation. Cytokine release studies were performed in human Peripheral Blood Mononuclear Cell (PBMC), and showed that soluble CS1003 does not stimulate the release of cytokines by the original human PBMC without the involvement of T cell receptors. To evaluate the in vivo antitumor activity of CS1003 monotherapy, a Cloudman S91 mouse melanoma model and PD-1 humanized mouse model (host mice that express humanized PD-1) transplanted with MC38-hPD-L1 mouse colon cancer cells (tumor

cells that express human PD-L1) were used. CS1003 was able to inhibit tumor growth in both models.

CS1003 plus lenvatinib showed good anti-tumor activity which was superior to that of each monotherapy in PD-1 humanized mice (host mice that express humanized PD-1) transplanted with MC38-hPD-L1 mouse colon cancer cells (tumor cells that express human PD-L1). The tumor inhibition rates of CS1003 1 mg/kg monotherapy group, lenvatinib 1 mg/kg monotherapy group and CS1003 1 mg/kg + lenvatinib 1 mg/kg group were 56.4%, 68.2% and 86.9%, respectively. The combination of CS1003 1 mg/kg and lenvatinib 1 mg/kg significantly enhanced the antitumor activity of each single drug ($p < 0.05$).

2.3.2 PHARMACOKINETICS

The pharmacokinetics (PK) of CS1003 was characterized in the non-GLP single dose and multiple dose studies in mice and cynomolgus monkeys. In a study, a single intravenous (i.v.) infusion of CS1003 3, 10, and 30 mg/kg and multiple-dose infusions of 10 mg/kg were administered. Serum concentration of CS1003 and anti-drug antibody (ADA) were determined using a validated ELISA method. When the dose increased from 3 to 30 mg/kg, the systemic exposure of CS1003 in mice increased proportionally with dose, with no significant differences between genders. In the 10 mg/kg multiple dose group, no systemic exposure of CS1003 was detected in any of the mice after 3rd dosing due to ADA formation.

PK studies using single i.v. infusion of CS1003 2, 6 and 18 mg/kg and multiple i.v. injections of 6 mg/kg were performed in study-naive cynomolgus monkeys. When the dose increased from 2 to 18 mg/kg, the systemic exposure of CS1003 in cynomolgus monkeys increased proportionally with dose, with no significant difference between genders. In the 6 mg/kg multiple dose group, systemic exposure of CS1003 after 4th dosing decreased in some of the monkeys due to ADA formation.

2.3.3 TOXICOLOGY

The toxicology studies of CS1003 were carried out in cynomolgus monkeys. The safety of CS1003 was assessed by single- and multiple-dose toxicity tests through i.v. infusion, hemolysis and allergy tests, and tissue cross-reaction tests. The results showed that CS1003 was negative for hemolysis *in vitro*, positive for allergic reactions, and cross-reactive with cynomolgus monkey and human tissues. The maximum tolerated dose (MTD) of the single-dose toxicity test for cynomolgus monkeys was 1000 mg/kg. In the 29-day multiple-dose GLP study in cynomolgus monkeys, the drug was well tolerated in animals (with a maximum ADA positive rate of 70%), and the main histopathological finding was mononuclear infiltration in multiple organs (related to the pharmacological effect of CS1003); the highest non-severely toxic dose (HNSTD) was 100 mg/kg, and CS1003 exposure covered the range of clinically expected exposures.

2.4 CLINICAL STUDIES

CS1003 is in the clinical development phase, and its safety, tolerability, PK and preliminary anti-tumor activity data in humans have been accumulating. Two phase I studies of CS1003, CS1003-101 has been completed and CS1003-102 is ongoing. For more information, please refer to the latest CS1003 Investigator's Brochure (IB).

2.4.1 CS1003-101: THE FIRST IN HUMAN (FIH) STUDY OF CS1003

CS1003-101 phase I study (NCT03475251) is the first-in-human (FIH) study on CS1003 which was initiated in Australia in May 2018. This is a multicenter, open-label, multiple-dose, dose-escalation and expansion phase Ia / Ib study to evaluate the clinical safety, tolerability, PK, and preliminary efficacy of CS1003. The study is composed of two stages: Phase Ia as dose escalation and Phase Ib as indication expansion. A modified 3+3 dose-escalation scheme was applied in Phase Ia. Four dose levels were planned to be explored: 1, 3, 10 mg/kg, Q3W (once every three weeks) and 200 mg fixed dose, Q3W. Subjects with the selected tumor types will be enrolled and treated at the RP2D dose level in Phase Ib.

Phase 1a:

As of 31 May 2021, a total of 21 subjects were treated with CS1003 across 4 cohorts (1 mg/kg, N = 3; 3 mg/kg, N = 5; 200 mg fixed dose, N = 8; 10 mg/kg, N = 5). In general, the treatment appeared safe and tolerable. The median duration of treatment was 15.0 (range: 3.0 to 126.3) weeks. One subject in the 3 mg/kg group switched to the extension phase and no patients remained on treatment.

DLT evaluation was completed among all of the 21 subjects and no DLTs were observed. All of the 4 dose levels were assessed as safe and tolerable by the Safety Monitoring Committee (SMC). MTD was not reached and the Maximum Administered Dose (MAD) is 10 mg/kg Q3W. Of all 21 treated subjects, 18 (85.7%) experienced at least one treatment-emergent adverse event (TEAE), and 15 (71.4%) had at least one treatment-related AE (TRAE). The most frequent TRAEs were fatigue (n=6, 28.6%), rash (n=5, 23.8%), and pruritus (n=4, 19.0%). Three subjects (14.3%) experienced at least one Grade 3-5 TRAE, with 1 subject having Grade 3 psoriasis and Grade 4 lipase increased, 1 patient having Grade 3 colitis and 1 patient having Grade 3 autoimmune hepatitis. Three subjects reported treatment-related SAE of colitis (G3), pyrexia (G1) and autoimmune hepatitis (G3).

During the study, 9 subjects (42.9%) experienced at least one immune-related adverse events (irAE). The most frequently reported irAEs included rash (n=3, 14.3%), pruritus (n=2, 9.5%) and diarrhoea (n=2, 9.5%).

No dose reductions due to TEAE were reported. Five (23.8%) patients experienced TEAEs leading to permanent discontinuation of CS1003. Two (9.5%) patients reported TEAEs (one Grade 5 pulmonary embolism and one Grade 5 multiple organ dysfunction syndrome) leading to death in this study, but neither of them was considered related to CS1003.

PK analysis using samples from 21 subjects indicated that the systemic exposure of CS1003 was proportional to dose ranging from 1 to 10 mg/kg, with similar exposure at 3 mg/kg and 200 mg fixed dose. The terminal elimination half-life ($t_{½}$) of CS1003 ranged from 291 to 335 h .

As of 31 May 2021, 21 patients were included in EAS. One (1) patient had confirmed complete response (CR) and 2 patients had confirmed partial response (PR). Seven (7) patients achieved stable disease (SD) and 8 patients had progressive disease (PD). Three patients were classified as not applicable (NA) as no post-baseline response assessments were available.

CS1003 appears well tolerated up to 10 mg/kg with an expected PK profile. The preliminary safety profile and anti-tumor activity observed support continued investigation of CS1003. 200 mg fixed-dose Q3W is selected as the preliminary RP2D based on the non-clinical data, preliminary safety, anti-tumor activity and PK data collected during dose escalation in Phase Ia, and the recommended dosages of other approved anti-PD-1 monoclonal antibodies (mAbs). A phase Ib study is ongoing to further evaluate the safety and efficacy of CS1003 at 200 mg Q3W in selected tumor types.

Phase 1b:

Arm information can be found in the list below:

Arm	Dose regimen	Tumor types
1	200 mg Q3W	Soft Tissue Sarcoma
2	200 mg Q3W	Malignant Pleural Mesothelioma
3	200 mg Q3W	Bladder cancer, Merkel-cell carcinoma, gastric cancer, esophageal carcinoma, small-cell lung cancer (SCLC), large-cell lung cancer (LCLC), head and neck squamous cell carcinoma (HNSCC) or cutaneous squamous cell carcinoma (cuSCC). Any solid tumors with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR). Or other tumor types after discussion with the medical monitor and in consultation with the Sponsor.
4	400 mg Q6W	Bladder cancer, Merkel-cell carcinoma, gastric cancer, esophageal carcinoma, small-cell lung cancer (SCLC), large-cell lung cancer (LCLC), head and neck squamous cell carcinoma (HNSCC) or cutaneous squamous cell carcinoma (cuSCC). Any solid tumors with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR). Or other tumor types after discussion with the medical monitor and in consultation with the Sponsor.

As of 31 May 2021, 56 subjects treated with CS1003 at 200 mg Q3W (Arm 1, 2, 3) and 31 subjects treated at 400 mg Q6W (Arm 4) were included in the safety analysis. A total of 85 (97.7%) subjects experienced at least one TEAE and 49 (56.3%) subjects reported TRAEs. A total of 37 (42.5%) patients reported SAEs. The most common SAEs (>1 patient) by preferred term overall were pneumonia (n=3, 3.4%) and urinary tract infection, colitis, small intestinal obstruction, Type 1 diabetes mellitus, and anaemia (n=2, 2.3% each). A total of 41 (47.1%) patients reported irAEs in Part 1 Phase Ib. The most common irAEs (≥5% patients)

by preferred term overall were pruritus (n=13, 14.9%), hypothyroidism (n=8, 9.2%), arthralgia (n=7, 8.0%), and rash, hyperthyroidism and fatigue (n=6, 6.9% each).

One (1) patient in Arm 3 (200 mg Q3W group) experienced TEAEs (one Grade 3 cancer pain which was considered unrelated to CS1003; one Grade 1 alanine aminotransferase increased and one Grade 2 aspartate aminotransferase increased which were considered related to CS1003) leading to permanent discontinuation of CS1003. Two (6.5%) patients in Arm 4 (400 mg Q6W group) experienced a TEAE (one Grade 3 hepatitis which was considered related to CS1003; one Grade 5 cardiac failure which was considered unrelated to CS1003) leading to permanent discontinuation of CS1003 and 1 patient experienced a TEAE (cardiac failure) leading to death, which was considered unrelated to CS1003.

ORR: Overall, the ORR was 25.3% (95% CI: 16.6%, 35.7%). Three (10.3%) patients in Arm 3 and 1 (3.2%) patient in Arm 4 achieved a confirmed CR. Four (20.0%) patients in Arm 1, 1 (14.3%) patient in Arm 2, 4 (13.8%) patients in Arm 3, and 9 (29.0%) patients in Arm 4 achieved a confirmed PR. A total of 27 (31.0%) patients achieved the best overall response of SD. A total of 27 (31.0%) patients had PD as the best overall response. Eleven (11) patients were classified as not applicable (NA) as no post-baseline response assessments were available.

DCR: The overall DCR was 56.3% (95% CI: 45.3%, 66.9%).

DOR: There was a total of 22 responders in Part 1 Phase Ib. The overall median DOR in Part 1 Phase Ib was not reached.

PFS: A total of 61 (70.1%) patients had PFS events (13 deaths and 48 PDs). The overall median PFS in Part 1 Phase Ib was 4.1 months (95% CI: 2.3, 8.1). Patients in Arms 2 and 4 had longer median PFS (7.8 and 8.2 months, respectively) than patients in Arms 1 and 3 (4.1 and 2.2 months, respectively).

2.4.2 CS1003-102: A BRIDGING CLINICAL STUDY IN CHINA

CS1003-102 phase I study (NCT03809767) is a bridging study on CS1003 which was initiated in China based on the preliminary data from the FIH study in Australia. This is a multicenter, open-label, dose-escalation and expansion phase Ia / Ib study to evaluate and confirm the clinical safety, tolerability, PK, and preliminary efficacy of CS1003 in subjects with advanced solid tumors or lymphoma at 200 mg Q3W, the RP2D determined in Phase Ia of the FIH study. CS1003-102 study is composed of two stages: Phase Ia as dose escalation and Phase Ib as indication expansion. A modified 3+3 dose-escalation scheme was applied in Phase Ia. Two dose levels were planned to be investigated: fixed doses 60 mg and 200 mg, Q3W. Subjects with the selected tumor types will be enrolled and treated at the RP2D dose level in Phase Ib.

Phase 1a:

As of 13 August 2021, 19 patients were assigned to study treatment, receiving CS1003 60 mg fixed dose (n=7) and CS1003 200 mg fixed dose (n=12). The median duration of study treatment was 9.1 weeks, with a range of 3.0 to 77.0 weeks. As of the data cut-off date, 19

patients discontinued from study treatment permanently and no patients remained on study for treatment of CS1003. In general, the treatment appeared safe and tolerable.

As of 13 August 2021, The SMC of the trial has cleared both 2 dose levels evaluated. No DLT was observed, and MTD was not reached.

The most frequent TRAEs were asthenia (n=6, 31.6%), blood bilirubin increased (n=6, 31.6%) and bilirubin conjugated increased (n=4, 21.1%). Three (15.8%) subjects experienced at least one Grade ≥3 TRAE.

Six (31.6%) patients had at least one SAE during the study, including diarrhoea, small intestinal obstruction, death, pneumonia, white blood cell count increased, interstitial lung disease, and peripheral embolism. Interstitial lung disease (Grade 3) and white blood cell count increased (Grade 4) (each reported by 1 patient) were considered as treatment-related by the investigators. Ten (52.6%) subjects experienced irAEs. The most frequent irAEs were asthenia (n=4, 21.1%), rash (n=3, 15.8%) and hypothyroidism (n=3, 15.8%).

PK data were available in 19 patients , the exposure of CS1003 increased proportionally with dose in the range of 1mg/kg to 10mg/kg including 200 mg fixed dose, and the concentration-time profiles exhibit general PK properties of an IgG4 mAb. PK exposure at 200 mg Q3W is similar to that observed in the FIH study conducted in Australia.

As of 13 August 2021, among the 18 evaluable subjects, 3 subjects achieved confirmed partial response.

CS1003 appears well tolerated in Chinese subjects with a PK profile comparable to that observed in the FIH study conducted in Australia. The preliminary safety and efficacy data supports continued investigation of CS1003. A phase Ib study is ongoing to further evaluate the safety and efficacy of CS1003 at 200 mg Q3W in selected tumor types in Chinese subjects.

Phase 1b:

As of 13 August 2021, 20 patients treated with CS1003 + targeted drug therapy were included in the safety analysis. The median treatment durations of CS1003 and the targeted drug were 46.6 (range: 9.9-100.3) and 45.0 (range: 9.1-100.3) weeks, respectively.

A total of 20 (100%) patients experienced at least one TEAE, and all of them experienced at least one CS1003-related TRAE. The most frequent CS1003-related TRAEs were aspartate aminotransferase increased, blood bilirubin increased, blood thyroid stimulating hormone increased and hypothyroidism (n=7, 35.0% each). Bilirubin conjugated increased, gamma-glutamyltransferase increased, and hyponatraemia were the Grade 3 AEs related to CS1003, which were also related to lenvatinib.

Six (30.0%) patients reported 8 SAEs, including gastric ulcer, pneumonia, aspartate aminotransferase increased, blood bilirubin increased, diabetes mellitus, hypertonic bladder, benign prostatic hyperplasia and haemoptysis (each reported by 1 patient). Two (10.0%) patients experienced CS1003-related SAEs: 1 patient experienced increased aspartate aminotransferase and increased blood bilirubin, and the other patient experienced diabetes mellitus. During the study, 18 (90.0%) patients experienced at least one irAE. The most frequent irAEs were blood thyroid stimulating hormone increased (n=7, 35.0%) and

hypothyroidism (n=7, 35.0%). Five (25.0%) patients experienced at least one Grade ≥ 3 irAE: gamma-glutamyltransferase increased (Grade 3, 2 patients), diabetes mellitus, hyperglycaemia and hyponatraemia (all Grade 3, 1 patient each).

In general, the CS1003 + lenvatinib combination therapy shows a manageable safety profile in Chinese pts with uHCC as first line treatment.

For most updated data regarding CS1003 monotherapy or in combination with other agents including lenvatinib, please refer to the latest version of CS1003 Investigator's Brochure.

2.5 OVERALL BENEFIT/RISK ASSESSMENT

There are huge unmet needs in the first-line treatment for advanced HCC (Refer to Section 4.2.1 for details). The number of new cases of HCC in the world is about 841,000 every year, and the new cases in China accounts for about 50% of them. [17, 18] Majority of patients with HCC are at intermediate stage or advanced stage at their first diagnosis and have lost the opportunity of getting radical treatment. [19] Advanced HCC that is unresectable or unsuitable for locoregional treatment is a serious life-threatening disease. Most of Chinese patients with HCC have concomitant liver diseases (e.g., chronic hepatitis B, chronic hepatitis C, liver cirrhosis, etc.), which makes the treatment more challenging. [20] The available treatment options are very limited and usually of poor effect, leaving the clinical needs unmet. Therefore, there's urgent need for novel first-line therapies to improve the survival and response rate.

Immunotherapy including anti-PD-1 and anti-PD-L1 monoclonal antibodies with PD-1 and PD-L1 as the target has made great progress in the treatment of various advanced malignancies. Among them, Opdivo® (nivolumab) and Keytruda® (pembrolizumab) have been approved by US FDA as second-line treatment for advanced HCC, marking a milestone in the use of anti-PD-1/PD-L1 antibodies to treat HCC.[3,4] The recently reported results of KEYNOTE-524 study showed encouraging efficacy and acceptable safety of pembrolizumab in combination with lenvatinib in patients with advanced HCC [6].

In this study, lenvatinib is selected as a basic component of the combination therapy. The expected adverse events of lenvatinib include diarrhea, hypertension, decreased appetite and fatigue, etc.

According to CS1003's mechanism of action and the clinical safety information of products with the same mechanism of action, expected possible adverse events in this trial are all kinds of inflammation caused by immune system activation, such as pneumonitis, colitis, hepatitis, nephritis and endocrine inflammation, etc. According to available clinical data of anti-PD-L1 and anti-PD-1 antibodies, although incidence of adverse effects is high, the drugs are well tolerated with only a small number of subjects discontinuing study due to adverse effects, and majority of the adverse effects can well resolve after treatment. Early symptoms of immune-related adverse effects are quite heterogeneous. Therefore, investigators should pay special attention to early symptoms and signs of immune-related reactions so as to make accurate and timely judgment with respect to dose modification and adequate intervention in a timely manner.

According to the clinical safety and efficacy analysis results, CS1003 could be well tolerated by subjects and demonstrated preliminary anti-tumor activity.

To ensure a favorable risk/benefit evaluation is continuously carried out in subjects, the Independent Data Monitoring Committee (IDMC) will monitor the safety and clinical activity of the investigational treatment throughout the study.

An outbreak of respiratory disease (COVID-19) is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect participants, site staff and society as a whole.

Both European Medicine Agency (EMA) [15] and FDA [16] as well as national health authorities in other countries/regions have issued guidelines that aim to provide recommendations for actions on conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect subjects participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the regulatory agencyguidelines, where applicable.

The IMP, CS1003, is an anti-PD-1 antibody and an immunomodulator. However, the risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (e.g., commute to the site) and have additional human contact (e.g., with site staff and other participants of the clinical study). However, the risk of being infected with SARS-CoV-2 and developing symptoms of COVID-19 is lesser for the subjects if they are coming to the site than if they themselves leave home for any other reasons.

To ensure a favourable risk/benefit evaluation is continuously carried out in subjects, the Independent Data Monitoring Committee (IDMC) will monitor the safety and clinical activity of the investigational treatment throughout the study. The decision to adjust the clinical trial conduct should be based on risk assessment of each individual subject and measures implemented should prioritize subjects' safety (top priority) followed by data validity within acceptable local regulation. This should be documented on an ongoing basis.

Mitigation Plan

In order to safeguard the subjects' and study team's safety while ensuring procedures are done within local restrictions due to virus curbing efforts by government, a study specific COVID-19 Risk and Benefit Assessment and Mitigation Plan with various mitigation measures have been put in place but dependent on the local regulations and site's requirement and approval. This COVID-19 Risk and Benefit Assessment and Mitigation Plan includes measures such as the Independent Data Monitoring Committee (IDMC) will monitor the safety and clinical activity of the investigational treatment throughout the study. The decision to adjust the clinical trial conduct should be based on risk assessment of subject and measures implemented should prioritize subjects' safety (top priority) followed by data validity within acceptable local regulation. This COVID-19 Risk and Benefit Assessment

and Mitigation Plan will be updated based on the COVID-19 situation. The contract research organization should inform the sponsor before the implement of mitigation plan.

3 OBJECTIVES, ESTIMANDS AND ENDPOINTS

3.1 PRIMARY OBJECTIVE, ESTIMAND AND ENDPOINT

Primary Objective:	Primary Endpoint/Estimand:
• To compare the efficacy of CS1003 in combination with lenvatinib vs. placebo in combination with lenvatinib	• Primary endpoint: Overall survival (OS) • Estimand: The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment, withdrawing from or dropping out of the study, and starting non-protocol anti-cancer treatment. The population-level summary for OS will be estimated by the HR from the stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set.

3.2 SECONDARY OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Secondary Objectives:	Secondary endpoints:
• To compare the efficacy of CS1003 in combination with lenvatinib vs. placebo in combination with lenvatinib	Key secondary endpoints: • Objective response rate (ORR) evaluated by Blinded Independent Central Review Committee (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Estimand: ORR assessed by BICR will be evaluated under the modified while-on-treatment strategy using tumor assessments prior to initiating non-protocol anti-cancer treatment to reflect the effect of the initially assigned randomized study treatment. The population-level summary for ORR evaluated by BICR will be presented by the rate difference between the two groups and the corresponding 95% CI using normal approximation to the binomial distribution, and p-value calculated by Stratified Mantel-Haenszel test for the ITT set.

	• Progression-free survival (PFS) assessed by BICR based on RECIST v1.1 • Estimand: PFS assessed by BICR will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment before BICR assessed disease progression and starting of non-protocol anti-cancer treatment before disease progression. The population-level summary for PFS evaluated by BICR will be estimated by the hazard ratio (HR) from stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set. Other secondary endpoints: • PFS assessed by investigators based on RECIST v1.1 • ORR evaluated by investigators based on RECIST v1.1 • Disease control rate (DCR) and duration of response (DoR) evaluated by BICR and investigators based on RECIST v1.1
• To compare the safety of CS1003 in combination with lenvatinib vs. placebo in combination with lenvatinib	• Adverse events (AEs), serious adverse events (SAEs), death, vital signs including blood pressure and pulse, etc., electrocardiogram (ECG), laboratory tests (including serum chemistry, hematology and urinalysis, etc.) and ECOG performance status, etc.
• To characterize the population pharmacokinetics (PopPK) and immunogenicity of CS1003 when dosed in combination with lenvatinib	• Peak and trough serum concentrations of CS1003

	• Number and percentage of subjects who develop anti-CS1003 antibody (ADA)
• To evaluate the disease/treatment-related patient reported (PRO), Health related Quality of Life (HRQoL)/Global health status (GHS) and function of subjects treated with CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib	• Time to deterioration (TTD), defined as the time from randomization to the first deterioration of EORTC QLQ-C30 scale

3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory objectives:	Exploratory endpoints:
• To explore the relationship between biomarker and the efficacy of CS1003 in combination with lenvatinib	• Association of baseline PD-L1 expression with the efficacy of CS1003 in combination with lenvatinib
• To evaluate the disease/treatment-related PRO, HRQoL/GHS and function of subjects treated with CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib	• The scores of EORTC QLQ-C30 and EORTC QLQ-HCC18 subscales scores and the changes from baseline by cycle
• To evaluate the health status of subjects treated with CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib	• The health utilities index of EQ-5D-5L scale

4 STUDY DESIGN

4.1 OVERALL DESIGN

4.1.1 STUDY DESCRIPTION

This study is a multi-center, double-blind, randomized, phase III study to investigate the efficacy and safety of CS1003 in combination with lenvatinib compared to placebo in combination with lenvatinib in the treatment for subjects with advanced HCC, who has no prior systematic treatment for HCC and is not amenable for surgery or locoregional therapy or have progressed after surgery or locoregional therapy.

Approximately 534 subjects are planned to be enrolled in this study. Eligible subjects will be randomized in a 2:1 ratio into the following two groups according to stratified block randomization method by Interactive Voice Response System (IVRS) and/or Interactive Web Response System (IWRS):

Group A: CS1003 in combination with lenvatinib

Or

Group B: Placebo in combination with lenvatinib

Randomization will be based on the following stratification factors:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]

Subjects randomized to group A/B will receive CS1003 or placebo in combination with lenvatinib:

- CS1003 (200 mg) or placebo is administered by i.v. infusion, Q3W.
- Lenvatinib is orally administered at 12 mg or 8 mg, with or without food, once daily, at approximately the same time every day (refer to the prescription information of lenvatinib).

All subjects will be treated until PD or unacceptable toxicity or the withdrawal from the study due to other causes, whichever occurs first (refer to Section 5.7.1).

Tumor assessments will be performed at 6 weeks (±7 days) after the randomization every 6 weeks (±7 days) for the first 48 weeks from the date of randomization, and then every 12 weeks (±7 days) thereafter, regardless of treatment schedule, until PD confirmed by radiological examination per RECISIT v1.1, subject withdraws informed consent, lost to

follow-up, end of study, or death, whichever occurs first. Subjects who discontinue study treatment due to causes other than PD will continue to receive radiological assessments at pre-determined time points until PD, subject withdraws informed consent, lost to follow-up, end of study, or death, whichever occurs first.

Dosing delay for CS1003/placebo and dosing adjustment for lenvatinib will only occur under the circumstance that investigator make a causality assessment between study treatments (CS1003/placebo or lenvatinib) and AE/SAE (refer to Sections 6.6.1 and 6.6.2).

4.1.2 SCHEMA OF STUDY DESIGN

This study will be conducted in three stages: screening, treatment and follow-up. Refer to the Study Schema in synopsis (Section 1.1).

4.1.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The Independent Data Monitoring Committee (IDMC) will be established for the purpose of monitoring the safety of investigational treatment and OS interim analysis. IDMC consisting of independent experts (including at least one oncologist and one statistician) who are not involved in the study, will carry out evaluation based on acceptable benefit/risk ratio and make recommendations to the Sponsor on issues such as whether the study should continue, whether the protocol needs to be revised, or whether the study should be discontinued. The final decision will be made by the Sponsor.

All data provided to IDMC for official safety and/or efficacy analyses will be kept blinded to the Sponsor. Refer to the IDMC charter for the constitution, roles and responsibilities and execution of IDMC.

4.1.4 SCREENING

Written informed consents must be obtained from subjects before carrying out any protocol-specified screening test or assessment. Subjects are evaluated for eligibility according to the inclusion criteria (Section 5.2) and exclusion criteria (Section 5.3). All eligibility screening must be completed within 28 days prior to the first dose of study treatment.

4.1.5 TREATMENT

After screening, eligible subjects will be randomized at 2:1 by stratified block randomization method (Section 5.5.2) to receive CS1003 + lenvatinib or placebo + lenvatinib.

The study treatment will begin within 3 days after the randomization. All subjects will receive assigned treatment until progression of disease, unacceptable toxicity, subject withdraws informed consent, death, other causes specified in the protocol or the end of study, whichever occurs first (refer to Section 5.7.1).

CS1003 (200 mg) or placebo is administered by i.v. infusion Q3W. Lenvatinib is orally administered at 12 mg (if the subject's weight ≥ 60 kg) or 8 mg (if the subject's weight < 60 kg), with or without food, once daily, at approximately the same time every day (refer to the prescription information of lenvatinib). When lenvatinib and CS1003/placebo are administrated on the same day, lenvatinib is to be taken first, and the i.v. infusion of CS1003 or placebo will be initiated within 30 minutes after lenvatinib administration.

If in the investigator's opinion, the subject may still benefit clinically from treatment in the case of pseudo-progression and can tolerate the treatment, the subject is permitted to continue CS1003 + lenvatinib treatment or placebo + lenvatinib (refer to Section 6.6.3).

4.1.6 FOLLOW-UP

Follow-up visit includes safety follow-up and survival follow-up.

- Safety follow-up:
  - The safety follow-up visit continues until 90 days after the last dose of study treatment, or the subject starts a new anti-cancer treatment, whichever occurs earlier. Three safety follow-up visits will be conducted at 30, 60 and 90 days after the last dose of study treatment. Subjects will receive the safety follow-up at 30 and 90 days at the site, and telephone or on-site safety follow-up at 60 days. The follow-up visit at 90 days could be arranged together with the first survival follow-up visit.
- Survival follow-up: Subjects will receive a follow-up visit every 12 weeks during survival follow-up. Telephone follow-up is acceptable.

AEs that occur during follow-up period will be reported as stated in Section 8.

4.2 STUDY RATIONALE

4.2.1 RATIONALE FOR SELECTING FIRST-LINE TREATMENT AND PATIENT POPULATION FOR ADVANCED CARCINOMA CANCER

The number of new cases of HCC in the world is about 841,000 every year, and the new cases in China accounts for about 50% of them [15, 16]. Majority of patients with HCC are at intermediate stage or advanced stage at their first diagnosis and have lost the opportunity of getting radical treatment [17]. Advanced HCC that is unresectable or unsuitable for locoregional treatment is a serious life-threatening disease. Most of Chinese patients with HCC have concomitant liver diseases (e.g., chronic hepatitis B, chronic hepatitis C, liver cirrhosis, etc.), which makes the treatment more challenging [18]. The available treatment options are very limited and usually of poor effect, leaving the clinical needs unmet.

In a pivotal phase III trial (REFLECT), lenvatinib exhibited clinical benefit. The median OS was 13.6 months in the experimental group (n=478) and 12.3 months in the control group treated with sorafenib (n=476) (HR 0.92, 95% CI 0.79 to 1.06). The median PFS was 7.4 months and 3.7 months respectively (HR 0.66, 95% CI 0.57 to 0.77). ORR was 24.1% and 9.2%, respectively (OR 3.13, 95% CI 2.15 to 4.56) [21]. In August 2018 and September 2018, US FDA and China National Medical Product Administration (NMPA) issued approval to lenvatinib as first-line therapy for unresectable HCC.

Table 4.2.1-1 First-Line Therapies Approved to Treat Advanced HCC

Clinical Study	Experimental group vs. control group	Number of subjects	mOS (months)	mTTP (months)	mPFS (months)	DCR (%)
SHARP[22]	Sorafenib vs. placebo	602	10.7 vs 7.9	5.5 vs 2.8	--	43 vs 32
ORIENTAL[23]	Sorafenib vs. placebo	226	6.5 vs 4.2	2.8 vs 1.4	--	35.3 vs 15.8
REFLECT[21]	Lenvatinib vs. sorafenib	954	13.6 vs 12.3	8.9 vs 3.7	7.4 vs 3.7	73.8 vs 58.4

Some other phase III studies in HCC didn't show survival benefit of sunitinib, brivanib, sorafenib in combination with erlotinib compared to sorafenib [24-26].

In summary, it has been indicated that there's an urgent need for new first-line therapies to improve the survival and response of patients with unresectable advanced HCC not suitable for local therapy.

4.2.2 RATIONALE FOR CS1003 AND LENVATINIB COMBINATION THERAPY

In recent years, immunotherapy including anti-PD-1 and anti-PD-L1 monoclonal antibodies with PD-1 and PD-L1 as the target has made great progress in the treatment of various advanced malignancies. Among them, nivolumab (Opdivo®) and pembrolizumab (Keytruda®) have been approved by US FDA as second-line treatment for advanced HCC, marking a milestone in the use of anti-PD-1/PD-L1 antibodies to treat HCC [3,4].

Mechanism studies showed that targeted therapy could improve the potency of immune checkpoint inhibitor by modifying the immune microenvironment of HCC [26, 27]. Combination of these drugs has synergistic effect on tumor regression and facilitates to increase or prolong anti-cancer response of immune system. This provides a rationale for conducting a clinical study of anti-PD-1/PD-L1 antibodies in combination with targeted therapy.

In 2019 ESMO Asia Congress, data of phase III study of atezolizumab in combination with bevacizumab as first-line therapy of advanced HCC was reported that the OS hazard ratio (HR) is 0.58 (95% CI: 0.42, 0.79; P = 0.0006) and BICR assessed PFS HR is 0.59 (95% CI: 0.47, 0.76; P < 0.0001). The safety profile reflected the additive toxicity of individual drugs and underlying disease [12]. In the 2019 AACR Congress, the latest data of an early clinical study on immune checkpoint inhibitor in combination with VEGFi in patients with advanced HCC was reported. In a clinical study of pembrolizumab + lenvatinib as first-line therapy in patients with advanced HCC (n = 30), the ORR was 36.7%, mPFS was 9.7 months [6]. In 2022 ESMO Congress, data of phase III study of lenvatinib plus pembrolizumab vs lenvatinib as first-line (1L) therapy for advanced HCC showed that OS HR was 0.84 (95% CI: 0.70, 0.99, P=0.0227, HBV subgroup: 0.75 (95% CI: 0.58, 0.97)), median OS were 21.2 months and 19.0 months, respectively[13]. Also in 2022 ESMO Congress, data of phase III study of camrelizumab (SHR-1210) plus rivoceranib vs sorafenib as first-line therapy of advanced HCC was reported that the OS hazard ratio (HR) was 0.62 (95% CI: 0.49, 0.80; P < 0.0001) and median OS were 22.1 months and 15.2 months, respectively [14].

These clinical data suggested potential clinical benefit and controllable safety of drugs targeting at PD-1/PD-L1 signaling pathway in combination with VEGFi as first-line treatment in patients with advanced HCC that is unresectable and not eligible for local treatment.

CS1003 plus lenvatinib showed good anti-tumor activity which was superior to that of each monotherapy in PD-1 humanized mice (host mice that express humanized PD-1) transplanted with MC38-hPD-L1 mouse colon cancer cells (tumor cells that express human PD-L1). The tumor inhibition rates of CS1003 1 mg/kg monotherapy group, lenvatinib 1 mg/kg monotherapy group and CS1003 1 mg/kg + lenvatinib 1 mg/kg group were 56.4%, 68.2% and 86.9%, respectively. The combination of CS1003 1 mg/kg and lenvatinib 1 mg/kg significantly enhanced the antitumor activity of each single drug ($p < 0.05$).

In summary, it appears rational to conduct a study investigating CS1003 + lenvatinib in patients with unresectable advanced HCC not suitable for local therapy.

4.2.3 RATIONALE FOR LENVATINIB AS BASIC TREATMENT AND SELECTION OF CONTROL MEDICATION

According to NCCN Guideline for HCC and Guideline for Primary HCC Diagnosis and Treatment (2018) developed by Chinese Society of Clinical Oncology, the recommended first-line systemic treatment for patients with unresectable advanced HCC with extrahepatic metastasis or vascular invasion is lenvatinib (Class IA) [30, 31].

In the lenvatinib group (n=476) of REFLECT study, the incidence rate was 94% for treatment-related adverse events and 57% for grade ≥3 adverse events. The common adverse events included hypertension (42%), diarrhea (39%) and decreased appetite (34%) [19].

A clinical study on pembrolizumab + lenvatinib as first-line therapy in subjects with advanced HCC (n=30) was reported in the 2019 AACR Congress. The incidence rate was 73% for grade ≥3 treatment-related adverse events. The common adverse events included hypertension (23.3%), AST elevation (16.7%) and diarrhea (10%) [6]. The safety and adverse event profile of pembrolizumab + lenvatinib was comparable to that of lenvatinib. No unexpected adverse event was reported. Based on current data, the safety of lenvatinib + immunotherapy is controllable. Therefore, in this study, lenvatinib is selected as the basic treatment of control group.

4.2.4 RATIONALE OF BIOMARKER ANALYSIS

In HCC, the correlation of the PD-L1 expression level and the efficacy of immune checkpoint inhibitor in combination with medications targeting at the anti-angiogenesis factors or their receptors hasn't been well established yet. In the recent phase I/II studies including KEYNOTE-224 and CheckMate-040, there was no clear correlation of PD-L1 level in tumor cells and the efficacy of nivolumab monotherapy, but it's still worthy to investigate the correlation of PD-L1 expression level in tumor cells and tumor-infiltrating immune cells and the efficacy of immune checkpoint inhibitors in a larger clinical study [27, 32]. The data reported in the 2018 ASCO Congress showed that, in the clinical tissue sample

analysis of 180 Chinese subjects with HCC, the percentage of patients with positive PD-L1 expression (≥1%) in tumor cells (36%) was higher than the reported percentage in KEYNOTE-224 (13%) and CheckMate-040 (20%), further indicating the necessity of exploring PD-L1 expression status in Chinese patients with HCC [33].

In summary, we would like to explore the biomarkers prudently in this trial by running tumor sample testing, in order to provide more evidence and guidance in the future clinical use of CS1003.

4.2.5 RATIONALE OF DOSE SELECTION

CS1003 will be dosed at 200 mg i.v. ,Q3W in the study. The rationales of the dose selection of CS1003 are based on the results from the pre-clinical studies and 2 clinical studies (CS1003-101 , CS1003-102) .

(1) Evaluation of the clinical results from the dose escalation studies of CS1003 (CS1003-101 and CS1003-102) across different tumor types.

- CS1003-101 is a first-in-human, multicenter, open-label, dose-escalation and expansion phase 1a/b study to evaluate the clinical safety, tolerability, PK, and preliminary efficacy of CS1003 in Australian patients with advanced solid tumors. As of March 21, 2019， in the completed dose escalation part, four dose levels of CS1003 administrated at Q3W have been explored (1 mg/kg, N = 3; 3 mg/kg, N = 5; 200 mg fixed dose, N = 8; 10 mg/kg, N = 5), and no DLT was observed. Systemic exposure of CS1003 exhibited a proportional increase with dose, ranging from 1 to 10 mg/kg. And in the ongoing dose expansion part, 2 dosing schedules (200 mg Q3W in Arms 1-3 and 400 mg Q6W in Arm 4) of CS1003 in subjects with selected tumor. CS1003 shows similar exposure at 3 mg/kg and at the fixed dose of 200 mg. After a single intravenous (i.v.) infusion of CS1003 200 mg fixed dose, the rang of mean C_{max} and $AUC_{0\text{-}21d}$ were 44.4-59.2 μg/mL and 386-524 day*μg/mL, respectively. The mean C_{min} at steady state ranged from 16.6 to 24.4 μg/mL. After a single intravenous (i.v.) infusion of CS1003 3 mg/kg dose, the mean C_{max} and $AUC_{0\text{-}21d}$ were 58.4 μg/mL and 500 day*μg/mL, respectively. The mean C_{min} at steady state was 27.0 μg/mL. The TEAE and TRAE profiles suggest no clear dose-dependent increase in toxicity across the 4 different doses levels and preliminary anti-tumor activity was observed at dose of 3 mg/kg and above, including 200mg Q3W fixed dose. The post dose incidence of anti-drug antibodies (ADA) appears to be low (11.7%, 7/60) in CS1003-treated subjects based on the preliminary ADA data.

- CS1003-102 is a multicenter, open-label, dose-escalation and expansion phase 1a/b bridging study to further evaluate the clinical safety, tolerability, PK, and preliminary efficacy of CS1003 in Chinese patients with advanced solid tumors or lymphomas based on the preliminary data from CS1003-101. In the completed dose escalation part, two dose levels of CS1003 administrated at Q3W have been explored (60 mg, N = 7; 200 mg, N = 12), no DLT was observed. And in the ongoing dose expansion part, The PK data of CS1003 from 5 Chinese patients with advanced solid tumors or lymphoma in the ongoing CS1003-102 study showed that after a single intravenous infusion of 200 mg fixed dose of CS1003,

the C_{max} and $AUC_{0\text{-}21d}$ of CS1003 were 59.8 μg/mL and 410 day*μg/mL, respectively, and the mean C_{min} at steady state was 17.4 μg/mL, similar to what was observed at the same dose in Study CS1003-101. Therefore, PK of CS1003 was comparable between the Australian patients enrolled in CS1003-101 and the Chinese patients enrolled in CS1003-102. Preliminary anti-tumor activity was observed at both dose levels in total of 16 evaluable patients. Two patients in 60 mg group achieved confirmed PR, and one patient in 200 mg group achieved PR which had not yet been confirmed at the data cut-off date. Pseudo-progression was also observed in another patient in 200 mg group, who was evaluated as progressive disease (PD) at the first post-baseline tumor assessment and continuously received CS1003 beyond progression, and then tumor regression in target lesions compared to baseline was observed at the following tumor assessment. The post-dose incidence of ADAs in CS1003-treated Chinese subjects in the CS1003-102 study appears to be low based on the limited ADA data， ie less than 7% (6/86) of drug induced and enhanced ADA positive.

- The preliminary popPK analysis of CS1003 using the dataset (total 33 subjects) from CS1003-101 and CS1003-102 studies demonstrates that the simulated magnitude of the effect of body weight on CS1003 exposure is minor, which also supports the flat dosing of CS1003.

(2) *in vitro* receptor binding study and preclinical animal studies.

- The binding affinity of CS1003 to cynomolgus monkey PD-1 (K_D=8.74E-09) and human PD-1 (K_D=6.13E-09) is comparable.

- Receptor occupancy study revealed that a mean concentration of CS1003 ≥7.39 μg/mL in blood could saturate receptor occupancy in cynomolgus monkey, and most likely also in human. In both clinical studies CS1003-101 and CS1003-102, after multiple intravenous infusion of CS1003, the mean C_{min} at steady state were higher than 7.39 μg/mL at dose levels of 3 mg/kg or 200 mg fixed dose. Therefore, it is believed that doses of 3 mg/kg Q3W or 200 mg fixed dose could completely occupy PD-1 receptors in peripheral blood mononuclear cells (PBMCs) throughout the dose interval.

(3) comparable *in vitro* activity and clinical PK characteristics between CS1003 and other marketed anti-PD-1 monoclonal antibodies.

- With the wide therapeutic index and flat exposure-response relationships for safety and efficacy, also considering the convenience of dosing, the anti-PD-1 mAbs (monoclonal antibodies) are ideal agents for flat dosing. The recommended dosage in approved labeling for marketed anti-PD-1 mAbs in most cases are fixed flat doses. For example, nivolumab is 240 mg, Q2W (once every 2 weeks) or 480 mg Q4W (once every 4 weeks); pembrolizumab is 200 mg, Q3W and cemiplimab is 350 mg Q3W.

- A comparison of CS1003 to marketed anti-PD-1 mAbs suggests similar PK properties of CS1003 to that of nivolumab, pembrolizumab and cemiplimab. Furthermore, CS1003 also demonstrates the comparable in vitro binding affinity to human PD-1 among these marketed anti-PD-1 mAbs. In addition, CS1003

demonstrates similar exposure at 3 mg/kg and at the fixed dose of 200 mg, and the corresponding mean Cmin of CS1003 at steady state . Therefore, the fully occupied PD-1 receptor could be achieved at either 3 mg/kg or 200 mg, while 200 mg fixed-dose offers better dosing convenience and reduced dosing errors.

In conclusion, based on the pre-clinical data, PK, safety, and preliminary anti-tumor data collected from the ongoing CS1003-101 and CS1003-102 studies, together with recommended dosage for other approved anti-PD-1 mAbs, 200 mg Q3W is selected as the dose regimen to be used as the recommended dose regimen for the Phase 3 study of CS1003, including its combination with lenvatinib. No dosage adjustment is needed for different geographic regions since the PK profiles are similar between Chinese patients and Caucasian patients and there is not known ethnic difference of sensitivity for CS1003 as well as other approved anti-PD-1 mAbs.

4.3 END OF STUDY

The entire study will end when the number of events reaches the target for final OS analysis (CCI [redacted]), or when Sponsor terminates this study, whichever occurs first.

4.4 TREATMENT AFTER END OF STUDY

Subjects potentially benefiting from the study treatment may continue to receive study treatment after treatment period is completed until progression of disease, unacceptable toxicity, initiation of other anti-cancer treatment, lost to follow-up, death or end of the study, whichever occurs first.

Subject still on treatment at the end of the study may continue treatment in another expansion study after approval from the health authorities and Ethics Committees, or in other forms in consultation with Sponsor, if they have achieved stable disease or response and can tolerate the adverse effect.

The Sponsor reserves the right to stop providing investigational product in any of the following situations:

a) The marketing application is rejected by the health regulatory authority.

b) The study is discontinued due to safety issues。

c) Subjects are able to obtain medication from government or private individual-initiated healthcare program.

d) There are alternative treatments available in the local market.

5 STUDY POPULATION

5.1 GENERAL CONSIDERATIONS

The study population are subjects with unresectable advanced HCC and unsuitable for locoregional treatment. Subjects who may benefit from treatment in the protocol will be enrolled in this trial according to the following criteria. All relevant medical and non-medical conditions must be considered when assessing the eligibility for individual patient.

The investigators or designated personnel must ensure enrolled subjects meet all the inclusion criteria and none of the exclusion criteria.

5.2 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria for this study:

General inclusion criteria

1. Age ≥18 years on the day of signing informed consent (For Taiwan, the lower limit of age is 20 years).
2. Fully informed of the study, with good compliance and willing to provide written informed consent. The informed consent must be signed before performing any protocol-related procedure (that is not a part of subject's routine medical care).

Target Disease-Specific Inclusion Criteria

3. Subjects with unresectable advanced HCC that is not eligible for surgery and/or locoregional therapy (Stage B or Stage C based on Barcelona Clinic Liver Cancer [BCLC] staging system indicated in Appendix 14.6), and meets either one of the following criteria: 1) histologically or cytologically confirmed diagnosis of HCC, 2) clinically confirmed diagnosis of HCC according to American Association for the study of Liver Diseases (AASLD) criteria. Patients without cirrhosis require histological confirmation of diagnosis. The curative treatment and/or locoregional therapy must have been completed ≥ 4 weeks prior to the baseline scan for subjects who experienced disease progression.
4. At least one measurable lesion can be assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 14.2) within 14 days prior to randomization. Target lesions in the past radiation fields or that underwent locoregional therapy (e.g., TACE or ablation), if confirmed as radiographic progression, are considered as measurable lesions.
5. Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
6. Life expectancy ≥ 3 months.
7. Child-Pugh ≤ 6 (Child-Pugh A).
8. No prior systemic treatment for advanced HCC, including target therapy, chemotherapy, immunotherapy (immune checkpoint inhibitors, interferons, interleukins), biological

therapy (anti-cancer vaccines, cytokines, or growth factors), antibodies/drugs that target at any T cell co-regulatory protein (immune checkpoint), e.g., anti-PD-1, anti-PD-L1, anti-CTLA-4, anti-OX-40, anti-CD137, anti-TIM-3, anti-LAG-3 antibodies, etc.

a) Interferon is only allowed for hepatitis treatment with a washout period of no less than 5 half-lives prior to the initiation of study treatment.

9. Subjects with hepatitis B virus (HBV) infection must have HBV DNA < 2000 IU/mL prior to randomization. Subjects with positive HBsAg and/or detectable HBV DNA must be treated with antiviral therapy for at least 2 weeks prior to the first dose of study treatment and must remain on antiviral therapy during the study.

   Subjects with hepatitis C virus (HCV) infection (active or past infection) are allowed to be enrolled and HCV RNA detectable subjects are allowed to receive approved anti-HCV treatment during the study.

10. After the approval from local health authorities is obtained (if applicable), at screening, subjects must agree to provide, if available, tumor tissue for biomarker analysis. When archival tumor tissue is not available, it is optional for the subject to undergo a fresh biopsy to collect tumor tissue if deemed medically safe by the investigator (details are in section 7.5).

Inclusion criteria related to laboratory tests at screening

Adequate organ and marrow function, as defined below.

11. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L

12. Platelet count $\geq 75 \times 10^9$ /L

13. Hemoglobin ≥ 90 g/L

14. Serum albumin ≥ 29 g/L

15. Serum creatinine $\leq 1.5 \times$ upper limit of normal range (ULN) or creatinine clearance (CL) ≥ 60 mL/min (according to Cockcroft-Gault equation)

$$\text{For female, CrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 0.85}{72 \times \text{Serum creatinine (mg/dL)}}$$

$$\text{For male, CrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 1.00}{72 \times \text{Serum creatinine (mg/dL)}}$$

16. Serum total bilirubin $\leq 2 \times$ ULN.

17. Aspartate transaminase (AST) and alanine transaminase (ALT):

    AST $\leq 5 \times$ ULN

    ALT $\leq 5 \times$ ULN

18. Coagulation: International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN.

Other inclusion criteria

19. Female subjects with childbearing potential must have negative serum pregnancy test result at screening. Female subjects with childbearing potential, and male subjects and their female partners with childbearing potential must agree to use an contraceptive method(s) (detailed contraception guidance is provided in Section 14.7 Appendix 7) from the day of signing informed consent form (ICF), during the study and till at least 6 months after the last dose of study treatment.

5.3 EXCLUSION CRITERIA

Subjects who meet any of the following criteria will be excluded from the study:

Target disease-specific exclusion criteria

1. Fibrolamellar HCC, sarcomatoid HCC, cholangiocellular carcinoma or mixed cholangiocarcinoma and HCC.
2. History of hepatic encephalopathy.
3. A prior bleeding event due to esophageal or gastric varices within 6 months or other gastrointestinal bleeding events within 28 days prior to screening. Untreated or incompletely treated esophageal or gastric varices that are considered by the investigator to be at high-risk for bleeding (Note: Patients must undergo an esophagogastroduodenoscopy [EGD], and all size of varices [small to large] must be assessed and treated per local standard of care prior to enrollment; patients who have undergone an EGD within 6 months prior to the initiation of study treatment do not need to repeat the procedure). Active gastric or duodenal ulcer.
4. Radiographic evidence of tumor thrombus in the main trunk of portal vein, vena cava or heart involvement on baseline imaging.
5. Malabsorption syndrome or inability to take oral medication due to other causes.
6. HBV and HCV co-infection. (Note: Subject has HCV infection history but HCV RNA is undetectable at screening can be considered as non-HCV infection in this study).
7. Surgery or locoregional therapy for palliative purpose (e.g., to treat bone metastases or metastases causing nerve impingement) within 4 weeks prior to study treatment. Palliative radiotherapy within 2 weeks prior to study treatment. Minor surgery (i.e, simple excision) within 7 days prior to study treatment.
8. Uncontrolled pleural effusion, pericardial effusion that are symptomatic and requiring

repeated drainage or oral diuretics at screening.

9. Clinically meaningful ascites, defined as any ascites is detectable in the physical examination at screening, or is symptomatic, or requires special intervention, e.g., paracentesis or intraperitoneal perfusion. (Note: Subjects with limited volume of ascites that is only identifiable by imaging can be enrolled.)

10. Uncontrolled hypertension defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 90 mmHg and cannot be managed by medication.

Medical History and Concomitant Disease-Relevant Exclusion Criteria

11. History of other malignancy(ies) in the past 5 years, except for malignant disease treated with curative intent and without active disease, e.g., basal cell carcinoma of skin, squamous cell carcinoma of skin, superficial bladder cancer or prostate cancer, breast cancer in situ or cervical cancer in situ.

12. History of or current central nerve system (CNS) metastasis.

13. Active autoimmune disease or history of autoimmune disease that has possibility of relapse or at risk of having these conditions, e.g., history of organ transplantation and requiring immunosuppressants. Subjects with type I diabetes mellitus, hypothyroidism stable on hormone replacement, or dermatological condition that does not require systemic treatment (e.g., leukoderma, psoriasis or alopecia) are allowed to be enrolled. Any uncertainty, consultation with Sponsor's medical monitor is recommended before subjects signing informed consent.

14. Major cardiovascular diseases (e.g., congestive heart failure, unstable angina, atrial fibrillation, severe arrhythmia, etc.); any of acute myocardial infarction, unstable angina, stroke, or transient ischemic attack within 6 months before enrollment; New York Heart Association (NYHA) grade ≥ 2 congestive heart failure (detailed criteria is in appendix 5).

15. Presence of interstitial pneumonitis or non-infectious pneumonitis, which might confound the evaluation or management of pulmonary toxicity associated with study treatment.

16. Any active infection (except for hepatitis virus infection) requires systemic treatment within 2 weeks prior to the first dose of study treatment.

17. Known history of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS).

18. Active tuberculosis infection.

Previous Treatment-Relevant Exclusion Criteria:

19. Any use of traditional Chinese medicine preparation with anti-tumor indication (e.g.,

Ban Mao capsule, elemene, Kanglaite, Cinobufacini, Xiaoaiping, Huai'er granule, Ganfule tablet, Jinlong capsule and Aidi) within 14 days prior to the first dose of study treatment.

20. Current or prior use of systemic corticosteroid (> 10 mg/day prednisone or equivalent) or other immunosuppressive medication within 14 days before the first dose of study treatment. Note: Inhaled or topical steroid, or adrenal replacement with ≤ 10 mg prednisone or equivalent is permitted if there is no active autoimmune disease. Short-term (≤ 7 days) steroid for prophylactic purpose (e.g., for contrast allergy) or for non-autoimmune conditions (e.g., delayed hypersensitivity caused by contrast allergy) is allowed. Corticosteroid, if required by a subject, should be taken at least two days prior to or after CS1003 or placebo infusion.

21. History of bone marrow transplantation or organ transplantation.

Allergy and adverse reaction

22. History of anaphylaxis or hypersensitivity to any ingredient of the investigational product.

23. Any contraindication of lenvatinib.

Other exclusion criteria

24. Known history of drug abuse that would interfere with cooperation with the requirements of the trial.

25. Pregnant or lactating female subjects.

26. History of psychiatric disease that would interfere with cooperation with the requirements of the trial; lack of or with restricted physical capability.

27. QTc interval > 470 msec (as calculated with Fridericia's formula) at screening electrocardiogram (ECG).

28. Any condition that would in the investigator's judgement, prevent the subject from participating in this study.

29. Current participation in another clinical study or use of any investigational drug within 4 weeks prior the first dose of study treatment in this trial.

30. Major surgery within 4 weeks prior to the first dose of study treatment or planned major surgery during the study (mediastinoscopy, insertion of a central venous access device and insertion of a feeding tube are not considered major surgery).

31. Serious non-healing wound, ulcer, or bone fracture.

32. Urine protein ≥1 g/24 hours (routine urine test, urine protein>1+ will have 24-hour urine

collected to assess proteinuria).

5.4 OTHER ELIGIBILITY CRITERIA CONSIDERATIONS

To assess any potential impact on subject eligibility with regards to safety, the investigator must refer to the Investigator Brochure (IB) of CS1003 or the label of lenvatinib for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study treatment being used in this study.

5.5 SCREENING AND RANDOMIZATION

5.5.1 SCREENING

Investigators must take record of all subjects entering into screening visit. In the screening visit (from Day -28 to Day -1), the principal investigator or trained personnel will:

1. Obtain written ICF from the subject before performing any study-related procedure.
2. Determine if the subject meets the inclusion (Section 5.2) and exclusion criteria (Section 5.3). The detailed procedure is described in Section 7.6.1.
3. Re-screening under limited conditions should be allowed after consultation with the sponsor. Rescreening is allowed only once for each subject. If a subject discontinues participation, the screening number of this subject will not be used for others.
4. To ensure only those who are qualified for the clinical trial to be enrolled in the study, CStone (or contracted CRO) will implement the eligibility review process for all subjects to be enrolled. Study sites will complete the study specific eligibility review form and send this form along with other redacted supporting documents deemed as necessary to CStone (or contracted CRO) for review and approval before randomization, if the process does not contradict with local regulations. A detailed guideline will be developed to ensure compliance with relevant data protection, privacy legislation and local regulations.

5.5.2 RANDOMIZATION

Eligible subjects will be randomized (at 2:1) using the IVRS/IWRS into one of the two treatment groups.

Randomization will be conducted based on the following stratification factors:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]

Each subject will be allocated a screening number using IVRS/IWRS and according to the chronological order of enrollment. Once a screening number has been assigned to a subject, the same screening number will not be assigned to other subjects. Subjects are advised to receive the first treatment dose on the day of randomization and no later than 3 days after randomization.

Detailed randomization procedures are described in the IVRS/IWRS Manual.

5.5.3 SUBJECT REPLACEMENT

In this study, any randomized subject will not be replaced.

5.6 PROCESS OF HANDLING INADEQUATE ENROLLMENT

Subjects who fail to meet the eligibility criteria must not, under any circumstances, be enrolled or receive study treatment. There can be no exceptions to this rule.

Where a subject does not meet all the eligibility criteria but is incorrectly started on treatment, the investigator should inform the sponsor immediately, and a discussion should occur between the sponsor and the investigator regarding whether to continue or discontinue the subject from study treatment. The sponsor must ensure all decisions are appropriately documented.

5.7 TREATMENT DISCONTINUATION AND STUDY WITHDRAWAL

5.7.1 CRITERIA FOR STUDY TREATMENT DISCONTINUATION

Subjects must discontinue study treatment if any of the following criteria is met:

1. Any clinical adverse event (AE) or concurrent disease, in the investigator's judgment, that suggests continuing to participate in the study is not of the greatest interest to the subject.
2. Occurrence of toxicity specified in Section 6.6.
3. Progression of disease.
4. Subject who receives any prohibited treatment during the trial that compromises the assessment of safety and efficacy may be determined to discontinue study treatment by the investigator in consultation with the Sponsor’s medical monitor.
5. Any intercurrent condition that compromises subject's ability to continue study treatment.
6. Pregnancy of female subject.
7. Subject or the legal guardian’s decision to discontinue study treatment. According to Deceleration of Helsinki and other applicable regulatory requirements, all subjects have the right to discontinue participation at any time and for any reason. The investigator or the site must not hold bias in their future treatment.

8. Subject with poor compliance who doesn't receive treatment of the right dose at the right time despite investigator's effort in communication and coordination, which may lead to significant uncorrectable bias in the study results, may be determined to discontinue study treatment by the investigator in consultation with the Sponsor's medical monitor.

9. Other conditions that make study treatment inappropriate judged by the investigator (e.g., worsening in clinical symptoms or signs, no clinical benefit from continuing treatment per investigator's judgment).

In any case, the primary reason for study treatment discontinuation will be recorded in the original medical record. If the subject discontinues the study treatment for any reason, the investigator should make every effort to persuade the subject to attend end-of-treatment visit and safety follow-up (within at least 90 days after the last dose of study treatment) for those who have received at least one dose of study treatment.

If a subject develops fever or symptoms suspected of being a result of COVID-19 infection during the study they will be instructed to follow-up with their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority. Withdrawal of a subject under such conditions is at the discretion of the Investigator, following discussion with Sponsor to protect the safety of the subject, other study participants or study site staff.

5.7.2 FOLLOW-UP OF SUBJECTS WHO DISCONTINUE STUDY TREATMENT

Subjects who discontinue study treatment must be followed up. Safety and/or survival follow-up data will be collected as per required till the subject dies or end of this study. Apart from subjects who discontinue study treatment due to disease progression, radiological assessment should be performed at pre-determined time points until disease progression, subject withdraws informed consent, lost to follow-up, death or the end of this study whichever occurs first.

Lost-to-follow up is defined as being unable to contact the subject or having insufficient data to determine subject's status after specified contact attempts by site. In this study, at least three attempts at each scheduled visit till scheduled survival follow up visit 3 should be made before determining it as a lost-to-follow up. A subject that refuses to receive survival follow-up is not lost-to-follow up.

Study sites will contact subject who is not reachable, if possible, to determine the reason and try best to rearrange follow-up visit. The process, date and means of contacting the subject will be recorded in the source documents.

5.7.3 STUDY WITHDRAWAL

The reason why subject withdraws from the study will be recorded in the source medical record and eCRF. Possible reasons may include:

- Subject withdraws informed consent (to study treatment and assessment);

- Lost to follow-up;
- Death.

A subject who withdraws the informed consent of study treatment, assessment and information disclosure will not receive study treatment or receive any follow-up assessment or have any follow-up survival data collected. The Sponsor will keep the data and information obtained before the informed consent withdrawal. If a subject only withdraws the informed consent of study treatment and assessment but not the information disclosure, the survival-related data of the subject will still be collected till the end of the study, if possible.

6 STUDY TREATMENTS

6.1 INVESTIGATIONAL PRODUCTS (IPs)

In this study, CS1003 (or placebo) and lenvatinib are both considered as the study treatment while CS1003 (or placebo) is the investigational product and lenvatinib is selected as the basic treatment for HCC. Eligible subjects are randomized to one of the 2 groups:

- Experimental group: CS1003 in combination with lenvatinib
- Control group: placebo in combination with lenvatinib

CS1003 is a monoclonal antibody drug which is liquid for single use and diluted with normal saline (0.9% sodium chloride injection) or 5% dextrose prior to i.v. administration.

6.1.1 DOSAGE FORM AND STRENGTH OF INVESTIGATIONAL PRODUCTS

The dosage forms and strengths of investigational products are listed in Table 6.1.1.1-1.

Table 6.1.1.1-1 Dosage Form and Strengths of Investigational Products

• CS1003	Dosage: injection Strengths: 100 mg/4 mL/vial CS1003 is prepared at 25 mg/mL in 20 mM histidine/histidine hydrochloride, 200 mM sucrose, and 0.02% Polysorbate 80; pH 5.5 Shelf life: 36 months, tentatively Storage: Stored in refrigerator at 2℃ to 8℃. Do not freeze the medication and keep away from light. Any occurrence of temperature excursion must be immediately reported to the Sponsor. The study centers are responsible for the storage of investigational products in a secure area and in accordance with regulatory requirements.
• Placebo	Placebo that matches CS1003

6.1.2 PACKAGE AND LABEL OF INVESTIGATIONAL PRODUCTS

CS1003 and placebo will be supplied as injection formulation in 100 mg/4 mL/vial. All investigational products will be labeled in compliance with International Conference on

Harmonization (ICH) Good Clinical Practice (GCP) requirements. The label content will be designed according to Sponsor's process. All drugs will be dispatched as the trial-specific main materials.

A uniform format will be applied to the drug labels. The labeling contains the following information: protocol number, name of investigational product (and "For clinical trial use only"), strength, storage, batch number, kit number, shelf life and Sponsor, etc.

All the records of kit number and expiry dates as well as labels for all investigational products will be kept in the Sponsor's study file.

6.2 BASIC TREATMENT

In this study, lenvatinib is selected as the basic treatment for HCC and not considered as IP.

Lenvatinib will be supplied as capsules of 4 mg/capsule, with a shelf life to 48 months.

The study centers are to store lenvatinib under the temperature as required by the drug label and to maintain proper storage temperature logs. Any occurrence of temperature excursion must be immediately reported to the Sponsor. Refer to Section 6.6.2 for instructions on dose adjustment of lenvatinib during the study.

6.3 MANAGEMENT OF STUDY TREATMENT

The study treatment handling liability will be executed as per requirements in Appendix 14.8.

The responsible person at sites must properly document, including but not limited to, the quantity and date of the receipt, dispensing and return of the IPs (CS1003 and placebo) and basic treatment (lenvatinib). Subject's compliance and drug accountability will be evaluated by maintaining appropriate documentations of medication receipt, dispensing, and return.

Information contained in the records include but are not limited to:

- Record of the drugs delivered by the Sponsor (date and quantity received)
- Disposal of unused and non-dispensed IPs and lenvatinib
- Subject identification information for IP and lenvatinib dispensing
- Dosage and date of all IPs and lenvatinib dispensed to the subjects
- Quantity and date of lenvatinib returned by subject

At the end of treatment, subjects should return all used and unused drug containers for compliance evaluation.

6.3.1 DISPENSE AND STORAGE OF STUDY TREATMENT

The IPs and lenvatinib will both be provided to sites by Sponsor at scheduled dates. A designated person (investigator or authorized person) of each site is responsible for the receipt, management and dispensing of study treatments, and ensures that the study

treatments are kept in safe area with limited access, and under defined environmental conditions.

The responsible person at the study site will confirm the receipt of IPs and lenvatinib in writing and use the study treatment within the framework specified in the protocol. An accurate record of the shipment, dispensing and return of IPs and lenvatinib will be maintained. The study treatment will be dispensed by a member of the study team. This person should ensure and record the dispensing of study treatment as planned; the quantity of dispensed and returned IPs and lenvatinib and corresponding dates will be recorded in the source document.

Each site must maintain the storage temperature log and store it in adequate file. If there is a problem with the quality or appearance of IPs or lenvatinib, the study treatment should not be dispensed to any subject and Sponsor should be contacted immediately.

6.3.2 STUDY TREATMENT ASSIGNMENT

The screening number will be assigned to each subject provides informed consent. For subjects eligible for enrollment, the investigator enters information on the relevant stratification factors of each subject into the IVRS/IWRS, and submits application. Then the investigator will receive a study treatment-kit number. More details are provided in the IVRS/IWRS Manual.

Subjects will be randomized to treatment group A or B at a 2:1 ratio according to a central randomization method:

Group A: CS1003 + lenvatinib

or

Group B: Placebo + lenvatinib

6.3.3 PREPARATION AND ADMINISTRATION OF INVESTIGATIONAL PRODUCT

CS1003, placebo and lenvatinib will be provided to sites by Sponsor before the initiation of this study.

For administration of CS1003 or placebo in each cycle of a specific subject, the investigator or designated personnel will get kit numbers of drugs for preparation through IVRS/IWRS. CS1003 or placebo is to be administered as an i.v. infusion whose process complies with local clinical guidelines. (Infusion using a volumetric pump through a 0.2 micrometer in-line filter is recommended.) The first infusion must be administered no less than 90 minutes. In the absence of infusion-related toxicity, the second infusion must be administered no less than 60 minutes. And in the absence of infusion-related toxicity during second infusion, the subsequent infusions must be administered no less than 30 minutes. The infusions should be completed with sufficient volume of diluent flush at the end; the end of flushing represents

the end of the entire infusion process. CS1003 or placebo should be used under the supervision of a physician with experience in the use of intravenous infusions.

The below instructions are recommended guidance for preparing CS1003 or placebo. See the Pharmacy Manual for additional information on preparation and other special requirements.

1. Ensure that the original CS1003 or placebo is clear, colorless and free of any particulate matter on visual inspection before the preparation. To avoid issues such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, and so on, it is important to use a separate sterile syringe and needle for each vial. Multiple attempts of drawing the solution from the same vial are prohibited. Any vial that has remaining solution should be discarded as specified and should not be used again.

2. Remove proper volume of the diluent from a 100 ml infusion bag and inject the CS1003 or placebo original solution to maintain the final concentration of 1 mg/mL - 10 mg/mL. Refer to the following example for drug formulation:

   CS1003 at 200 mg & target final concentration at 2 mg/mL:

   Volume of CS1003 or placebo original solution needed for preparation: 8 mL

   Volume of the final mixture: 100 mL

   Volume of diluent removed from infusion bag: 100 mL – 100 mL + 8 mL = 8 mL

3. Mix by gently inverting several times. Do not shake.

4. Visually inspect the final solution. If the solution is not clear or the contents appear to contain precipitate, the solution should be discarded and recorded in the drug management log.

5. Record time and dose (in mg) of IP preparation in the preparation sheet.

The CS1003 drug solution or placebo contains no preservatives. The diluted CS1003 solution or placebo solution cannot be frozen and must be stored as follows:

- From dilution to end of infusion, at room temperature for no more than 4 hours, including the storage time of the drug solution vial at room temperature, the time of the infusion solution stored in the infusion bag at room temperature, and the entire infusion process.
- From dilution to end of infusion, in the refrigerator (2°C to 8°C) for no more than 24 hours. If the prepared CS1003 or placebo infusion solution is stored in the refrigerator, the infusion solution should recover to room temperature prior to administration.

Lenvatinib is orally administered at 12 mg (if the subject's weight ≥ 60 kg) or 8 mg (if the

subject's weight < 60 kg), with or without food, once daily, at approximately the same time every day (refer to the prescription information of lenvatinib). When lenvatinib and CS1003/placebo are administrated on the same day, lenvatinib is to be taken first, and the i.v. infusion of CS1003 or placebo will be initiated within 30 minutes after lenvatinib administration.

Lenvatinib should be swallowed as a whole or can be mixed (not opened or crushed) with a tablespoon of water or apple juice in a glass cup to form a suspension. The capsule must be left in the liquid for at least 10 minutes and stirred for at least 3 minutes to dissolve the capsule shell, and subject should swallow the suspension. After the suspension is taken, the same amount of water or apple juice (one tablespoon) must be added to the glass cup, stirred several times, and then all the liquid in the glass cup is completely taken by the subject.

If a subject misses a dose and cannot take it within 12 hours, there's no need to take this dose anymore. The next dose should be taken at the regular medication time. Adverse effects such as nausea, vomiting and diarrhea should be actively treated prior to any dose adjustment (interruption, dose reduction) of this product; gastrointestinal toxicity should be actively treated to reduce the risk of renal insufficiency or renal failure.

6.3.4 RETURN AND DESTRUCTION OF STUDY TREATMENT

The study treatment will be returned in the study. The original records of receipt, dispensing, use, return, and return records for all IPs and lenvatinib (unused, partially used, or empty package) are provided to the study monitor for reconciliation.

All unused IPs and lenvatinib must be accounted at site and return to depot, a third party delegated by Sponsor will account for the destruction activity. Used IPs and lenvatinib can be destroyed at site or by a third party delegated by Sponsor. Study personnel should ensure, develop and record adequate process of study treatment handling in compliance with applicable regulations, guidelines and policies.

The study treatment will be destroyed per Sponsor's approval.

6.4 BLINDING AND UNBLINDING

Only in a few situations, individual subjects can be unblinded before the unblinding for the interim analysis or final analysis:

1. Unblinding for expedited safety report to regulatory authorities;
2. Under medical emergencies, the investigator believes it is necessary to know the subject's treatment allocation information to guide the emergency medical measures;
3. Unblinding for other reasons, for example, to assess potential important safety issues, or at the request of the regulatory authorities.

6.4.1 UNBLINDING FOR EXPEDITED REPORTING TO REGULATORY AUTHORITIES

Unless approved for unblinding exemption, the sponsor will unblind all suspected unexpected serious adverse reaction (SUSAR) for the expedited reporting to regulatory authorities. The personnel authorizing the unblinding process will be from the sponsor's pharmacovigilance team.

Blindness is still maintained for, for example, research delivery team members and biostatisticians who perform analysis and interpretation of the study results at the end of this study.

6.4.2 UNBLINDING UNDER MEDICAL EMERGENCY SITUATIONS

The investigator can only break the blindness of the subject's treatment allocation during the clinical study when it makes a difference to the safety of the subject, that is, when the study treatment allocation affects the subject's treatment. Where possible, discuss with the sponsor’s medical monitor before making an unblinding decision. If unblinding occurs, the cause of the unblinding must be recorded in the original document.

6.4.3 UNBLINDING FOR OTHER REASONS

In special situations, it may be necessary to break the blindness of treatment in one or more subjects, for example, to facilitate further assessment of potentially important safety issues, or to the requests of the regulatory authorities. The unblinding decision, as well as all unblinding procedures will be recorded in the meeting minutes or in the notes to the documents.

Cases requiring unblinding for assessment of potential safety issues are usually blinded in the drug safety database. Cases unblinded per requested by the regulatory authorities are documented as unblinded in the drug safety database.

In addition, bioassay laboratories will be unmasked to avoid unnecessary tests of blood samples from the control group.

All other cases that are not unblinded during the study period for the aforementioned reasons should remain blind until the end of the study.

6.5 COMPLIANCE TO STUDY TREATMENT

Administration of study treatment must be recorded. The dosing of IP and lenvatinib will be monitored by the principal investigator or his/her assistant for ensuring treatment compliance. The exact time of dosing (starting and ending of infusion) and dose administered should be recorded. For infusion interruption, the cause of interruption should be recorded.

Subjects on lenvatinib treatment should maintain a written documentation of the dose of lenvatinib and time of administration every day and submit the written record to study coordinator at each visit.

Overdose is defined as the subject has taken (accidentally or intentionally) a dose exceeding the protocol defined dose in the protocol. Subjects with a suspected overdose should be

managed with appropriate supportive therapy as determined by the investigator in consultation with the medical monitor. See section 8.6 overdose for more information.

6.6 STUDY TREATMENT ADJUSTMENT

6.6.1 CS1003 OR PLACEBO DOSE ADJUSTMENT

Dose reduction is not allowed for CS1003 or placebo in this study. If infusion is not possible at the scheduled visit time, it should be administered as soon as possible. If a dosing delay occurs, the next scheduled dosing time will be adjusted accordingly, and each treatment cycle should be 21 days (± 3 days). Any subject whose next dose will be >12 weeks from the last dose should discontinue treatment and enter the follow-up phase, unless the dosing delay is related to a preventive vaccination, or the investigator and sponsor's medical monitor agree on the benefit/risk assessment after discussion and conclude that the subject should continue to receive study treatment (e.g., subjects with clinical benefit who need to extend corticosteroid tapering down duration for irAE). In the event of CS1003- or placebo-relevant adverse event, CS1003 or placebo dosing may be interrupted or discontinued according to the following guidance. The withholding of CS1003 or placebo should last not more than 12 weeks.

Administration of study treatment may be adjusted (including delay, interruption, and discontinuation) at the Investigator's discretion after discussion with the sponsor for subjects with confirmed active COVID-19 infection, subjects suspected of having a COVID-19 infection, and subjects who have been exposed to someone infected by COVID-19. Confirmatory test to resume study treatment may be done as per local guidance/practice after consultation with the sponsor.

6.6.1.1 CRITERIA OF CS1003 OR PLACEBO DOSING WITHHOLDING

- Any grade 2 drug-related adverse event (non-dermal event) other than:
  - Grade 2 drug-related fatigue or abnormal laboratory test result that doesn't require postponing study treatment
  - Grade 2 drug-related hypothyroidism or hyperthyroidism
- Any grade 3 drug-related dermal adverse event
- Any grade 3 drug-related abnormal laboratory test result except for the following situations:
  - For grade 3 lymphocytopenia, there's no need to delay study treatment.
  - Study treatment will be delayed when grade ≥ 2 drug-related toxicity occurs in a subject whose baseline AST, ALT and total bilirubin level are within normal range.
  - Study treatment will be delayed when AST, ALT ≥ 5 × baseline level AND ≤ 10 × ULN, or bilirubin ≥ 3 × baseline level AND ≤ 5 × ULN, if the subject's baseline AST, ALT or total bilirubin levels are out of the normal range.
- Any adverse event, abnormal laboratory test result or intercurrent condition that in the

investigator's opinion requires postponing study treatment.

6.6.1.2 CRITERIA FOR RESUMING CS1003 OR PLACEBO TREATMENT

When a drug-related AE is estimated to resolve to grade ≤ 1 or baseline level within 12 weeks after the last dosing, study medication (CS1003 or placebo) dosing may be resumed except for the following situations:

- A subject may resume treatment if there's grade 2 fatigue.
- A subject without any grade 3 drug-related dermal AE may resume treatment although grade 2 dermal toxicity remains.
- A subject may resume treatment despite grade 2 AST/ALT or total bilirubin abnormality, if subject's baseline data reveals grade 1 AST/ALT or total bilirubin abnormality. (But if the treatment withholding is due to other causes, the treatment resuming in a subject with grade 2 AST/ALT or total bilirubin elevation will be reevaluated.)
- Subjects with AST/ALT and total bilirubin abnormality that meets the criteria of permanent discontinuation (refer to Section 6.6.1.3) should discontinue study treatment permanently.
- Study treatment should not be resumed if drug-related diarrhea or colitis hasn't fully recovered to baseline level.
- Criteria for Resuming Treatment after Treatment-Related Pulmonary Toxicity
  - In the event of grade 1 progressive pneumonitis where the treatment needs to be interrupted, the immunotherapy can resume if radiological evidence shows improvement.
  - Immunotherapy can resume when a grade 2 pneumonitis improves to grade ≤ 1.
- For drug-related endocrinological disease that can be well controlled only by physiologic hormone replacement therapy, the investigator may resume the subject's treatment after consultation with and approval from the Sponsor's medical monitor.

The investigational product administration can be delayed three times due to toxicity. However, if the treatment needs to be delayed the fourth time due to toxicity, the subject will permanently discontinue study treatment after the investigator consults the sponsor. Please refer to Section 6.6.1.3 for details.

6.6.1.3 CRITERIA FOR PERMANENT DISCONTINUATION OF CS1003 OR PLACEBO

Investigational product will be **permanently discontinued** if any of the following drug-related adverse events occurs.

- Grade 2 drug-related uveitis, ophthalmodynia or blurred vision which requires systemic treatment, or drug-related uveitis, ophthalmodynia or blurred vision that cannot recover to grade 1 within the recovery time window despite with any topical treatment.

- Grade ≥ 3 infusion reaction during or after CS1003 or placebo infusion.
- In the event of severe (grade 3-4) pneumonitis, immunotherapy should be discontinued permanently.
- Any grade 3 non-dermal drug-related adverse event that lasts for > 7 days, except for the following situations.
  - A subject who develops grade 3 drug-related uveitis, non-infectious pneumonitis, bronchospasm, and hypersensitivity or infusion reaction must discontinue treatment permanently regardless the duration of adverse event.
  - A subject with grade 3 drug-related endocrinological disease that can be well controlled by physiologic hormone replacement therapy only doesn't need to permanently discontinue study treatment.
  - Usually a subject with grade 3 drug-related abnormal laboratory test result doesn't need to discontinue treatment except for the following situations:
    - A subject with grade 3 drug-related thrombocytopenia that lasts for > 7 days or has severe, uncontrollable bleeding event should discontinue study treatment permanently.
    - A subject with any of the following abnormal liver function test (LFT) should discontinue study treatment permanently:
      - AST or ALT > 5-10 × ULN for > 2 weeks
      - AST or ALT > 10 × ULN
      - Total bilirubin > 5 × ULN
      - AST or ALT > 3 × ULN and concurrent total bilirubin > 2 × ULN
- Discontinue study treatment permanently for any grade 4 drug-related adverse event or abnormal laboratory test result except for the following situations:
  - Grade 4 neutropenia lasting for ≤ 7 days
  - Grade 4 lymphocytopenia or leukopenia
  - Solitary grade 4 electrolyte disorder/imbalance that can be corrected by electrolyte supplementation/adequate treatment in 72 hours without any clinical consequence.
  - Grade 4 drug-related endocrinological adverse events that can be resolved or well controlled by physiologic hormone (e.g., glucocorticoid, thyroid hormone) replacement treatment, e.g., adrenal insufficiency, ACTH deficiency, hyperthyroidism or hypothyroidism or decreased sugar tolerance, don't trigger treatment discontinuation. But the investigator should communicate and get approval from Sponsor's medical monitor first.
- Any event that causes the next dosing to delay > 12 weeks from the last dose requires permanent study drug discontinuation, except for any of the following situations:

– Dosing is delayed for longer time for corticosteroid tapering and handling drug-related adverse event; subject is allowed to continue treatment when Sponsor's medical monitor approves it. If the next dosing will be at > 12 weeks from the last dosing, the investigator must restart the subject treatment after consultation with Sponsor's medical monitor. Tumor assessment will be performed per protocol despite delayed dosing. Follow-up visits will still be carried out for safety evaluation; a visit will be added during treatment withholding as clinically indicated.

– If the next dosing has to be at > 12 weeks from the last dose due to non-drug related reasons, the investigator may restart the subject treatment after consultation with the Sponsor's medical monitor. Tumor assessment will be performed per protocol despite delayed dosing. Follow-up visits will still be carried out for safety evaluation; a visit will be added during treatment withholding if clinically indicated.

Continuation of lenvatinib treatment is allowed if the subject permanent discontinued with CS1003 or placebo.

6.6.2 LENVATINIB

6.6.2.1 LENVATINIB DOSE ADJUSTMENT

In this study, dose adjustment is permitted for lenvatinib. The dosing of lenvatinib may need to be interrupted or adjusted to manage the toxicity according to the prescription information of lenvatinib. In the event of dose reduction, the dose of lenvatinib may be reduced to 8 mg or 4 mg once daily. If further reduction is needed, the dose of lenvatinib may be reduced to 4 mg every other day. Once reduced, the following doses will keep the current reduced dose, or be reduced further if needed. If the subject has been on a stable lower dose for 3 weeks or longer and there's no other toxicity that requires dose adjustment, in the judgment of the investigator, the dose of lenvatinib may be upregulated.

Refer to the prescription information of lenvatinib and Table 6.6.2.1-1 for detailed lenvatinib monitoring, dose modification and discontinuation instructions.

Table 6.6.2.1-1 Instructions of Monitoring, Dose Modification and Discontinuation for Lenvatinib

Starting dose		**Body weight ≥ 60 kg** **12 mg (4 mg/capsule x 3 capsules, oral administration, once daily)**	**Body weight < 60 kg** **8 mg (4 mg/capsule x 2 capsules, oral administration, once daily)**
Continuous and unacceptable grade 2 or 3 adverse event [a]			
Adverse event	Dose modification	Modified dose [b] (Body weight ≥ 60 kg)	Modified dose [b] (Body weight < 60 kg)
At first occurrence [c]	Withhold treatment till the event resolves to grade 0-1 or baseline [d]	8 mg (4 mg/capsule x 2 capsules) Oral administration, once daily	4 mg (4 mg/capsule x 1 capsule) Oral administration, once daily

At second occurrence (The same event or new different event)	Withhold treatment till the event resolves to grade 0-1 or baseline [d]	4 mg (4 mg/capsule x 1 capsule) Oral administration, once daily	4 mg (4 mg/capsule x 1 capsule) Oral administration, every other day
At third occurrence (The same event or new different event)	Withhold treatment till the event resolves to grade 0-1 or baseline [d]	4 mg (4 mg/capsule x 1 capsule) Oral administration, every other day	Discontinue
Life-threatening adverse event (grade 4): Discontinue treatment [e]			

a Adverse events including nausea, vomiting and diarrhea, etc. should be well managed before withholding or reducing the dose of lenvatinib.

b Based on the previous dose level, the dose is gradually tapered down following 12 mg, 8 mg or 4 mg once daily or 4 mg every other day.

c At first occurrence of hematological adverse reaction or proteinuria - no need for dose modification.

d Treatment can be resumed when hematological adverse reaction resolves to grade 2 or proteinuria resolves to < 2 g/24 hours.

e Adverse reactions of grade 4 laboratory abnormality, if judged as not life-threatening, can be managed as grade 3 adverse reactions.

6.6.2.2 LENVATINIB WITHHOLDING AND PERMANENT DISCONTINUATION

The lenvatinib treatment can be withheld for 30 days at maximum due to toxicity/adverse event. After 30 days, the treatment will be permanently discontinued. In a subject with treatment response, if the treatment has been withheld for more than 30 consecutive days, the further treatment should be decided in consultation with the Sponsor's medical monitor.

Refer to Table 6.6.2.2-1 for instructions on lenvatinib dose modification for adverse reactions, adapted from the prescription information of lenvatinib.

Continuation with CS1003 or placebo is allowed if the subject permanent discontinued with lenvatinib.

Table 6.6.2.2-1 Lenvatinib Dose Modification for Adverse Reactions

Adverse Reaction	**Severity**	**Intervention**	**Dose reduction and restoration of lenvatinib mesylate**
Hypertension	Grade 3 (Despite the optimal blood pressure control treatment)	Withhold	Resolve to grade ≤ 2. Refer to Table 6.6.2.2-2 Recommendations for

Adverse Reaction	Severity	Intervention	Dose reduction and restoration of lenvatinib mesylate
			Hypertension Management
	Grade 4	Discontinue	Treatment resumption is not allowed
Proteinuria[a]	≥ 2 g/24 hours	Withhold	Resolve to < 2 g/24 hours
Nephrotic Syndrome	-	Discontinue	Treatment resumption is not allowed
Renal dysfunction or failure	Grade 3	Withhold	Resolve to grade 0-1 or baseline
	Grade 4*	Discontinue	Treatment resumption is not allowed
Cardiac dysfunction	Grade 3	Withhold	Resolve to grade 0-1 or baseline
	Grade 4	Discontinue	Treatment resumption is not allowed
Posterior reversible encephalopathy syndrome (PRES)/ reversible posterior leukoencephalopathy syndrome (RPLS)	Any grade	Withhold	Consider resumption of treatment at a lower dose if the event resolves to grade 0-1
Hepatotoxicity	Grade 3	Withhold	Resolve to grade 0-1 or baseline
	Grade 4*	Discontinue	Treatment resumption is not allowed
Arterial thromboembolism	Any grade	Discontinue	Treatment resumption is not allowed
Bleeding	Grade 3	Withhold	Resolve to grade 0-1
	Grade 4	Discontinue	Treatment resumption is not allowed
Gastrointestinal perforation or gastrointestinal fistula	Grade 3	Withhold	Resolve to grade 0-1 or baseline
	Grade 4	Discontinue	Treatment resumption is not allowed
Non-gastrointestinal fistula	Grade 4	Discontinue	Treatment resumption is not allowed
QT interval prolongation	>500 msec	Withhold	Resolve to ≤ 480 msec or baseline
Diarrhea	Grade 3	Withhold	Resolve to grade 0-1 or

Adverse Reaction	Severity	Intervention	Dose reduction and restoration of lenvatinib mesylate
			baseline
	Grade 4 (despite medical management)	Discontinue	Treatment resumption is not allowed

*Adverse reactions of grade 4 laboratory abnormality, if judged as not life-threatening, can be managed as grade 3 adverse reaction.

a.Dose withhold is not required at the first occurrence.

Table 6.6.2.2-2 Recommended Management of Hypertension in Subjects Taking Lenvatinib

Blood Pressure	Recommended Measures
140 mmHg ≤ SBP <160 mmHg, or 90 mmHg ≤ DBP < 100 mmHg	Continue lenvatinib treatment and start anti-hypertension treatment (for antihypertensive therapy-naive patients), or continue lenvatinib and increase the dose of the current antihypertensive drugs or start to add other antihypertensive therapy
SBP remains ≥ 160 mmHg or DBP remains ≥ 100 mmHg despite the best anti-hypertension therapy	1. Withhold lenvatinib 2. If the SBP is ≤ 150 mmHg and DBP ≤ 95 mmHg, and the patient has been on stable-dose anti-hypertensive therapy for 48 hours or longer, lenvatinib can be restarted at a lower dose.
Life-threatening hypertension (malignant hypertension, neurological disorder or hypertension crisis)	Emergent intervention is needed. Lenvatinib therapy is stopped and adequate intervention should be given.

6.6.3 TREATMENT BEYOND DISEASE PROGRESSION

For immune therapies such as CS1003, pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. Accumulated data have shown that these patients may still benefit clinically despite preliminary evidence of PD according to RECIST v1.1. For disease progression suspected as pseudo-progression, investigators should repeat radiologic examination at least 4 weeks later or at the next scheduled imaging assessment to confirm disease progression. (Note: the repeated radiologic examination must be performed no later than 9 weeks after the first recorded disease progression.)

Between the first documentation of PD and confirmation of PD, if in the investigator's judgment, subject can benefit from the study treatment and all of the following criteria are met, the subject may continue receiving study treatment after being re-consented and study treatment continuation decision should be notified to the sponsor.

a) There is clinical benefit as assessed by investigator, such as absence of clinical symptoms and signs of disease progression (including worsening of laboratory values);
b) The study treatment is tolerable to the subject;
c) Stable ECOG performance status (PS);
d) Absence of rapid progression of disease or tumor at critical anatomical sites (e.g., spinal cord compression) that requires urgent medical intervention.

6.7 CONCOMITANT TREATMENT

Concomitant treatment includes any medication (e.g., prescription, over-the-counter, herbal or homeopathic therapy, nutritional supplements) used by the subject from 28 days prior to the first dose of study treatment to the safety follow-up period. All concomitant medications should be reported to the investigator and recorded in the concomitant medication sheet in the eCRF.

Any unscheduled treatment or surgery that occurs during the study is also considered concomitant treatment and must be recorded. Information about concomitant medications and treatment should include the dose, administration, route, indication, start date, end date, and any relevant clinical outcome of the medication history and concomitant medications.

In addition, when an adverse event occurs in the study, they should be closely monitored, and appropriate treatment should be provided. These drugs used should be recorded following the same rule as stated above.

6.7.1 PERMITTED TREATMENT

In this study, the permitted treatment includes

- Inactivated or attenuated influenza vaccine that doesn't require wash-out. The use of other inactivated or attenuated preventive vaccines will be determined according to the actual condition after discussion between the investigator and Sponsor's medical monitor.
- Topical, ophthalmic, intra-articular, nasal and inhaled corticosteroid (with very little systemic absorption) are permitted. Adrenal replacement with ≤ 10 mg prednisone per day or equivalents is permitted. Short-course (< 3 weeks) of corticosteroid as prophylaxis (for contrast allergy) or treatment for non-autoimmune conditions (e.g., delayed-type hypersensitivity caused by allergen contact).
- Symptomatic and supportive treatment for AEs during the study treatment is permitted.

Permitted Medications, Precautions and Other Restrictions of Lenvatinib Treatment:

- If nausea, vomiting or diarrhea occurs, effective treatment must be taken.
- In the event of hand-foot syndrome or other dermatological reaction, effective treatment must be taken.

- Hypertension, if any, should be managed by effective measures based on local or professional guideline (e.g., China's Guideline on the Prevention and Management of Hypertension) and documented.

- According to local guideline or other guidelines (e.g. ASCO guidelines), hematopoietic growth factors (HGFs) can be used to treat febrile neutropenia but should not be used as a primary or secondary prophylactic treatment for neutropenia. The use of any HGF must be recorded in the subject's record during the study treatment.

- Erythropoietin can be used in accordance with guidelines for chemotherapy-related anemia (e.g. ASCO guideline).

6.7.2 PROHIBITED TREATMENT

Treatments that the investigator considers necessary for a subject's welfare may be administered except for the following prohibited therapies. If any of the following therapies is required by a subject as per the investigator's assessment, the subject's eligibility for continuing investigational treatment will be at the investigator's discretion in consultation with the Sponsor's medical monitor.

- Anti-tumor therapies: no other anti-cancer therapy than the study treatment is permitted. This includes but is not limited to chemotherapy, radiotherapy, immune therapy, biological targeted therapy, hepatic interventional therapy, locoregional therapy and traditional Chinese medicines with anti-cancer indications.

  Note:

  a) Palliative, local treatment (including surgery and radiotherapy) for extrahepatic non-target lesions is allowed.

  b) Interferon treatment for hepatitis is not permitted during the treatment period.

  All interventions must be discussed with the investigator and medical monitor before being implemented.

- Concurrent investigational drug (unapproved medications) other than CS1003.

- Immunosuppressant, including but not limited to systemic corticosteroid (of a dose higher than prednisone 10 mg/d or equivalent), is not permitted, unless it is used for treating AE or for other special conditions. In the latter case, the investigator must discuss with the Sponsor's medical monitor.

- Live vaccines are prohibited during the study. Live vaccines including but not limited to: measles, mumps, rubella, chickenpox / shingles (varicella), yellow fever, rabies, BCG and typhoid vaccines. Seasonal influenza vaccines for injections are generally permitted because they are inactivated virus vaccines; however, intranasal influenza vaccines (for example, FluMist®) is live attenuated vaccines thus prohibited.

- Other prohibited treatment as specified in the inclusion/exclusion criteria.

Prohibited Medications or Restrictions During Lenvatinib Treatment:

The following medications should be avoided during lenvatinib treatment.

- Medications with known potential to prolong QT/QTc interval.
- Be cautious to use this product with concomitant P-glycoprotein (P-gp) inhibitor (e.g., ketoconazole, quinidine), because the product's plasma concentration can be increased.
- Be cautious of using this product with concomitant CYP3A or P-gp inducer (e.g., phenytoin sodium and carbamazepine) because the product's plasma concentration can be decreased.
- Anticoagulants or X factor inhibitors that require monitoring of the international standardized ratio (INR)., such as warfarin or similar, Treatment with low molecular weight heparin is permitted.

6.8 SPECIAL PRECAUTIONS

The subject's condition will be closely monitored during CS1003 or placebo infusion and for 30 minutes after the end of infusion.

CS1003 or placebo infusion will be withheld if grade ≥ 2 hypersensitivity, inflammatory reaction or infusion-related reaction occurs. Treatment recommendations for infusion-related reactions and severe hypersensitivities by NCI are listed in Section 6.8.1 and 6.8.2, respectively.

6.8.1 INFUSION-RELATED REACTION

The symptoms of infusion-related reactions include fever, chills, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Subjects should be closely monitored for such reactions. If a subject experiences any infusion reaction-like symptom caused by CS1003, treatment adjustment should be made according to Table 6.8.1-1.

Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions in the study sites. The study treatment must be suspended when a grade ≥ 2 infusion-related reaction, anaphylaxis or anaphylactoid reaction occurs.

If a hypersensitivity occurs, the subject will be treated using the best available treatment. According to the Emergency Treatment of Anaphylactic Reactions by Resuscitation Council (UK), subjects should be told to report any delayed hypersensitivity to the investigator immediately when the event occurs.

Table 6.8.1-1. Treatment Adjustment in the Event of Investigational Product-Related Infusion Reaction Symptoms

NCI-CTCAE Grade	Treatment Modification Investigational Product Treatment
Grade 1 - Mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	The infusion rate is decreased by 50% and subject is closely monitored for any worsening. Medication treatment as needed.
Grade 2 - Moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Discontinue infusion of investigational product. Infusion is resumed at 50% of previous rate once infusion related reactions has resolved or decreased to grade ≤1 in severity and any worsening is closely monitored. Adequate medication treatment is administered as stated below.
Grade 3 - Severe Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated due to clinical sequelae.	Subjects must permanently discontinue study treatment. Adequate medication treatment is administered as stated below.
Grade 4 – life-threatening Grade 4: Life-threatening consequences; urgent intervention indicated.	Subjects must permanently discontinue study treatment. Adequate medication treatment is administered as stated below.

Abbreviation: NCI-CTCAE = National Cancer Institute Common Terminology Classification for Adverse Events; NSAID = non-steroidal anti-inflammatory drugs.

Once the investigational product infusion rate has been decreased by 50% or suspended due to an infusion related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction (grade ≥ 2) on the slower infusion rate, infusion should be discontinued and the subject should be permanently discontinued from study treatment.

CTCAE grade 1 or 2 infusion reaction: Proper medical management should be administered, as indicated per type of the reaction. This includes but is not limited to an antihistamine (e.g. diphenhydramine or equivalent), anti-pyretic (e.g. paracetamol or equivalent), and if considered indicated oral or i.v. corticosteroids, epinephrine, bronchodilators, and oxygen. In the following treatment cycles, subjects should receive oral premedication with an antihistamine (e.g. diphenhydramine or equivalent) and an anti-pyretic (e.g. paracetamol or equivalent) at least 30 minutes before start of the infusion, and they should be closely monitored for clinical signs and symptoms of any infusion reaction.

CTCAE grade 3 or 4 infusion reaction: The study treatment must be discontinued permanently. Proper medical management should be administered, as indicated per type and severity of the reaction. This includes but is not limited to oral or i.v. anti-histamine, anti-pyretic, corticosteroids, epinephrine, bronchodilators, and oxygen.

6.8.2 SEVERE HYPERSENSITIVITY AND INFLUENZA-LIKE SYMPTOMS

If a hypersensitivity occurs, the subject will be treated using the best available treatment recommended by the Emergency Treatment of Anaphylactic Reactions by Resuscitation Council (UK). Subjects should be told to report any delayed hypersensitivity to the investigator immediately when the event occurs.

When a systemic anaphylaxis/ anaphylactoid reaction (featured by respiratory distress, laryngeal edema and/or severe bronchospasm that occur in minutes after the dosing/antigen administration, followed by circulatory failure or shock before dyspnea occurs; dermatological symptoms include pruritus and urticaria with or without edema; gastrointestinal symptoms include nausea, vomiting, spasmodic colic and diarrhea) occurs, the infusion must be stopped immediately and the subject is discontinued from participating the study.

When a hypersensitivity is observed, the subject will be treated using epinephrine and dexamethasone infusion, and then monitored. Meanwhile, the Intensive Care Unit (ICU) will be notified to get prepared for a possible subject transfer.

To prevent influenza-like symptoms, 25 mg indometacin or equivalent NSAID (e.g., 600 mg ibuprofen or 500 mg naproxen sodium) will be used 2 hours before and 8 hours after the start the investigational product infusion. The investigator may decide if any other anti-pyretic treatment (e.g., paracetamol) is needed.

6.8.3 IMMUNE-RELATED ADVERSE EVENTS

CS1003 may be associated with the risks of immune-related adverse events (irAEs) based on its mechanism of action, such as immune-related pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hypothyroidism, hyperthyroidism, dermatitis, neuromuscular toxicity, ocular toxicity, arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency.

When a suspected irAE occurs, the investigator should perform adequate evaluation of the subject, identify the etiology and rule out other causes. The following criteria are recommended to identify irAEs:

- Temporal relationship of AE with CS1003 administration;
- If the AE belongs to immune-related class effect of PD-1/PD-L1;
- If the AE need be treated with corticosteroid or other immunosuppressant therapy, and if the AE is improved upon immunosuppressive treatment (for endocrine disorders: if the AE need be treated with hormone replacement or immunosuppressive treatment);

- If there is the histopathology/biopsy result which is consistent with the manifestation of irAEs;
- If there are the other clear etiologies, such as other pathogens, medical history, disease progression, or other concomitant medications.

Generally, for grade ≥ 3 irAEs or grade 2 irAEs that require suspension or discontinuation of study treatment, the investigator should report the event to the Sponsor as soon as possible and consult the Sponsor when necessary. The investigational product may be suspended and corticosteroid administered as per the severity of the AE. When the event resolves to grade ≤ 1, corticosteroid dose will be gradually tapered in over 1 month. Tumor necrosis factor (TNF) antagonist, mycophenolate mofetil or other medication may be used for temporary immune suppression treatment if needed. If the AE maintains at grade ≤ 1, the study treatment may resume. For any persistent, worsened or recurrent grade 3 irAE or any grade 4 irAE, the study treatment will be permanently discontinued (refer to Section 6.6.1). Identification, diagnosis, management and dose modification of irAEs are detailed in Section 14.3.

6.8.4 ADVERSE REACTIONS TO LENVATINIB TREATMENT

Refer to the prescription information.

7 STUDY PROCEDURE SCHEDULE

7.1 SAFETY ASSESSMENTS

The safety assessment will consist of monitoring and reporting of adverse events, including serious adverse events; laboratory safety assessments as specified in the protocol; and protocol-specified other safety-relevant important examinations, such as vital signs, physical examination, ECOG performance status, ECG, echocardiogram, and safety laboratory tests (e.g. PT/aPTT, urinalysis, hematology, serum chemistry and thyroid function, etc.).

In case subjects are unable to visit the site due to COVID-19 related local travel restrictions, alternate arrangements may be made to complete safety assessments per local guidelines.

Subject's medical history will be taken at screening for understanding the underlying condition information. Immune-related adverse events (e.g., gastrointestinal, skin, pulmonary, hepatic, renal, endocrine organs) should be paid special attention.

In the whole study, AEs and laboratory test results will be graded according to NCI-CTCAE v5.0. The investigator is responsible for ensuring that all adverse events (as defined in Sections 8.1, 8.2 and 8.3) are documented on the adverse event eCRF and reported to the sponsor in accordance with the instructions provided in this section and Section 8.4 and 8.5.

For each adverse event recorded on the adverse event eCRF, the investigator will evaluate its seriousness (see Section 8.3 for seriousness criteria), severity (Section 8.4.5), and causality (Section 8.4.6).

7.1.1 VITAL SIGNS

Vital signs include temperature, blood pressure, pulse and respiratory rate. Additional vital sign monitoring will be at the discretion of investigator as clinically indicated.

Not all vital sign abnormalities are adverse events. If the vital signs meet one or more of the following criteria, it should be reported as an adverse event:

- Symptomatic
- Leading to changes in study treatment (e.g. dose adjustment, dose interruption or dose discontinuation)
- Leading to medical intervention or altering concomitant therapy
- Clinically significant in the judgment of investigators

Investigators are responsible for reviewing all abnormal vital signs. Medical and scientific methods should be used to determine whether vital sign abnormality alone is an adverse event. If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g. elevated blood pressure), the diagnosis (i.e., hypertension) should be recorded in the adverse event eCRF.

Vital sign abnormalities of the same clinical significance should not be reported repeatedly on adverse event eCRF unless the cause changes. The initial severity of the event should be recorded and the severity and seriousness should be updated once the event is aggravated.

7.1.2 PHYSICAL EXAMINATION AND ECOG PERFORMANCE STATUS

Physical examination and the Eastern Cooperative Oncology Group (ECOG) performance status will be evaluated at screening and within 72 hours prior to each scheduled visit. Abnormal changes in physical examination and ECOG PS will be assessed by the investigator.

7.1.3 ELECTROCARDIOGRAPHY (ECG) AND ECHOCARDIOGRAM

All eligible subjects will be tested for 12-lead ECG and echocardiogram as specified in the protocol (see Table 1.2-1). Extra ECG can be conducted if clinically indicated.

ECG measurements are taken using standard equipment after 5 minutes of rest in the supine position. ECG parameters including heart rate, P-R interval, QRS interval, QT interval, QTc interval, QRS wave and T wave evaluation and investigator's assessment for ECG should be recorded.

7.1.4 LABORATORY TESTS

Blood and urine samples for laboratory tests will be collected as per this protocol. Refer to Section 14.1 for details.

For laboratory test findings with unknown cause or unexpected findings, if clinically significant judged by the investigator, the tests are recommended to be retaken in 24 hours and followed up till test results return to normal range and/or cause found.

Abnormal laboratory results that meet one or more of the following criteria should be documented as adverse events:

- Symptomatic or clinically significant
- Leading to changes in study treatment administration (e.g. dose adjustment, dose interruption or permanent discontinuation)
- Resulting in changes in the combination therapy (i.e., adding, interrupting, or discontinuing combined medication or treatment, or make any other changes to the combined medication or treatment)

Use clinical terms instead of laboratory terms (such as anemia, not low hemoglobin value), if possible.

7.2 EFFICACY ASSESSMENTS

The investigators and the BICR will carry out efficacy assessments independently based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Refer to Appendix 14.2 for detailed evaluation criteria.

Tumor imaging will be conducted by using computed tomography (CT) or magnetic resonance imaging (MRI) according to the investigator's decision. The same imaging method, equipment and technical parameters should be used throughout the study, if possible. Contrast agent should be used if not contraindicated. The same investigator or radiologist should perform the imaging evaluation throughout the study, if possible.

Baseline tumor evaluation should be performed by using CT or MRI within 14 days prior to the randomization. In addition to the brain, chest, abdomen, and pelvis, other sites will also be evaluated at baseline as clinically indicated at the discretion of the investigator. Subsequent evaluations should include all sites evaluated at baseline and should be taken with the same imaging method as used at baseline. Subjects that are without brain metastasis as confirmed by brain imaging at screening are not required to receive regular brain imaging in the following visits. Brain imaging will be ordered by the investigator as clinically indicated. For unscheduled tumor assessment while the subject hasn't progressed, the following tumor assessment will still be done as planned.

The tumor imaging will be performed at 6 weeks (±7 days) after the randomization, every 6 weeks (±7 days) in the first 48 weeks, and every 12 weeks (± 7 days) thereafter, regardless of treatment schedule, until progression of disease (PD) confirmed by radiological examination , subject withdraws informed consent, lost to follow-up, end of study, or death, whichever occurs first. Subjects who discontinue study treatment due to causes other than PD will continue to receive radiological assessments at pre-determined time points until PD, subject withdraws informed consent, lost to follow-up, end of study, or death, whichever occurs first.

In case subjects are unable to visit the site due to COVID-19 related local travel restrictions, alternate arrangements may be made to complete efficacy assessments per local guidelines.

All radiological images will be transferred to the Central Radiology Laboratory for storage and review by the BICR committee (refer to BICR Guidance for details) till the number of PFS events for PFS analysis has been reached. Independent central radiology evaluation will be used as evidence to support the investigator's evaluation, but not used to support any subject eligibility decision or any treatment decision. Clinical management of subjects (including treatment continuation or discontinuation) will be based on investigator's evaluation of tumor imaging and investigator's clinical judgment.

For immune therapies such as CS1003, pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. Therefore, subjects with suspected pseudo-progression should receive further tumor imaging for confirmation. The confirmatory assessment is based on the next tumor imaging at least 4 weeks later or at the next regularly scheduled imaging time point to confirm disease progression. (Note that the repeated radiologic examination must be performed no later than 9 weeks after the first recorded disease progression.)

7.3 PATIENT REPORTED OUTCOMES

In addition, PROs are collected. PROs are collected through EORTC QLQ-C30, EORTC QLQ-HCC18 and EQ-5D-5L questionnaires completed by subjects. Before subject leaves

the site, the investigator should review completeness of all questionnaires. During survival follow-up, all PROs are collected every 3 months unless the subject withdraws the informed consent or the Sponsor ends this study. During survival follow-up, PRO could be collected at the site when subject comes for a visit or by phone calls.

7.4 PHARMACOKINETIC EVALUATION AND IMMUNOGENICITY

See Table 1.2-2 for details of sampling for PK evaluation and immunogenicity analysis.

Pharmacokinetics (PK): Blood samples will be collected within 60 minutes prior to CS1003 or placebo infusion as pre-treatment samples at Cycle 1, 2, 3, 4, 8, and every 4 cycles thereafter (e.g. Cycle 12, 16) and within 30 minutes after infusion at Cycle 1 and 4 in treatment phase and at EOT visit.

Anti-drug antibody (ADA): Pre-treatment blood samples are collected (within 60 minutes prior to dosing of CS1003 or placebo) at Cycle 1, 2, 3, 4, 8 and every 4 cycles thereafter (e.g. Cycle 12, 16, and so on), EOT visit and safety follow-up 3.

ADA and PK sampling: 3.5 mL whole blood sample each collected into a serum blood collection tube. In this study, all subjects will have blood sample collection as required above. See Central Laboratory Manual for detailed sample collection, handling, storage and transportation.

The PK and immunogenicity serum samples of CS1003 will be transported to the bioassay laboratory for analysis. PK analysis of CS1003 will be performed using a validated electrochemical luminescence assay. Neutralizing antibody of CS1003 will be tested as per the actual need if the neutralizing antibody test method is established for CS1003.

7.5 BIOMARKER EVALUATION

After the approval from local health authorities obtained (if applicable), baseline tumor tissue samples will be collected from subjects with proper informed consent for PD-L1 expression analysis.

a) Archival tumor tissue can be formalin-fixed paraffin embedded (FFPE) tissue block collected previously within 5 years before randomization (preferably within 12 months), or 3-5 freshly sectioned unstained slides (freshly sectioned within 6 months). Tissue block is preferred over unstained slides.

b) Acceptable tissue sample include core needle punctured, resected or incisional biopsy, or surgical sample. (Note: Fine needle aspirational cytology (FNAC), ascites and pleural effusion samples are not acceptable. Tumor tissue from bone metastases is not evaluable for determination of PD-L1 expression and is therefore also not acceptable).

c) Fresh biopsy should not be obtained from any RECIST-defined target lesions if possible. Consult the Sponsor when no other lesions are suitable for biopsy.

The potential correlation between PD-L1 expression levels and clinical efficacy will be analyzed. Detailed instructions for the collection, handling, and shipping of tumor samples are outlined in the applicable study Laboratory Manual.

7.6 STUDY PROCEDURES

Study procedures and assessments should be performed at the planned time points as stated below and in the SoA table.

7.6.1 SCREENING

The written ICF from subject must be firstly obtained before any screening evaluation or any study-related evaluation.

After signing the ICF, the subject will be screened for eligibility according to the criteria listed in Section 5.2 and 5.3. Subjects who meet all inclusion criteria and do not meet any of the exclusion criteria are eligible for randomization.

Screening evaluations should be completed within 28 days prior to the first dose of study treatment, unless otherwise specified. Items for screening include:

- Inclusion/exclusion criteria evaluations
- Demographics
- Past medical history and present history
- Diagnosis and confirmation of tumors, include but are not limited to histopathology, cytological diagnosis, date of first diagnosis, clinical stage and tumor-related symptoms, etc.
- History of anti-cancer treatment
- Tumor tissue sample collection (newly obtained samples or archived for < 12 months) after obtaining the approval from local health authorities (if applicable) for PD-L1 expression analysis
- Height, body weight and vital signs
- ECOG performance status and complete physical examination
- 12-Lead electrocardiography (ECG) and echocardiogram. ECG is performed within 14 days before the first dose, and the results of this evaluation will be used as a baseline. ECG should be performed before any planned vital sign measurement and blood sampling, if possible.
- Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), anti-hepatitis C virus (HCV) antibody and anti-human immunodeficiency virus (HIV) antibody tests. Subjects with positive HBsAg or positive HBcAb must receive further hepatitis B virus (HBV) DNA titer test. Subjects with positive HCV antibody must receive further HCV RNA test.

- Clinical laboratory tests (hematology, chemistry and urinalysis)
- AFP
- Coagulation function
- Thyroid function
- Esophagogastroduodenoscopy (EGD); patients who have undergone an EGD within 6 months prior to the initiation of study treatment do not need to repeat the procedure.
- Serum pregnancy test must be performed within 7 days prior to the first dose.
- Review adverse events and concomitant medications
- Tumor radiology examination must be completed within 14 days prior to randomization. If the subject takes a CT/MRI scanning within 14 days prior to randomization, but before signing the ICF, this scanning can be used as the baseline tumor evaluation if accepted by the investigator.
- PRO (prior to any examinations scheduled at this visit)

7.6.2 RANDOMIZATION

A subject can be randomized when eligibility is confirmed according to all the inclusion/exclusion criteria. First dose of study treatment will be administered on the day of randomization if possible, and no later than 3 days after randomization.

Continuous documentation of concomitant medications and adverse events.

7.6.3 TREATMENT

Subjects to receive CS1003 or placebo infusion will be administered CS1003 200 mg or placebo i.v. infusion every 21 days (3 weeks ± 3 days). The interval between two doses must be no less than 18 days. All visits will be conducted at the planned time points specified in the protocol. If there is any new or worsened clinically significant change compared to baseline or the last examination, it should be reported as an adverse event or serious adverse event.

Procedures to be completed in the treatment phase include:

Cycle 1 Day 1

- Body weight and vital signs (if vital signs at screening are taken within 3 days prior to the first dose of study treatment, the measurements don't need to be repeated before the first dose)
- ECOG performance status and complete physical examination
- ECG (if conducted within 7 days prior to the first dose of study treatment, there is no need to repeat the measurement.)
- Echocardiogram (as indicated clinically)

- Hematology, clinical chemistry and urinalysis: when laboratory test and administration of IP or lenvatinib are to be on the same day (e.g., the first day [D1] of each treatment cycle), test result must be available before dosing. If laboratory test at screening is performed within 7 days prior to the first dose of study treatment, the laboratory test of first cycle before the first dose is not required to be repeated.
- Coagulation function: When laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing. If the test at screening is performed within 7 days prior to the first dose of study treatment, the laboratory test of the first cycle before the first dose will not be required
- Thyroid function: (If the test at screening is performed within 7 days prior to the first dose of study treatment, the laboratory test of the first cycle before the first dose will not be required). Every 2 cycles thereafter.
- Review adverse events and concomitant medications
- PK blood sample and immunogenicity blood sample (collected at time points specified in Table 1.2-2)
- PRO (prior to any examinations scheduled at this visit)
- Study treatment

Cycle 2 Day 1

- Body weight and vital signs
- ECOG performance status and complete physical examination
- ECG and echocardiogram, as indicated clinically
- Hematology, clinical chemistry and urinalysis: when laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.
- Coagulation function: When laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.
- Urine pregnancy test
- Review adverse events and concomitant medications
- PK blood sample and immunogenicity blood sample (collected at time points specified in Table 1.2-2)
- Patient-reported outcome (prior to any examinations scheduled at this visit; time window of -7 days)
- Study treatment
- Review treatment compliance

Cycle 3 Day 1

- Body weight and vital signs
- ECOG performance status and complete physical examination
- ECG
- Echocardiography (as indicated clinically)
- Hematology, clinical chemistry and urinalysis: when laboratory test and administration of IP or lenvatinib are to be on the same day (e.g., the first day [D1] of each treatment cycle), test result must be available before dosing.
- Coagulation function: When laboratory test and administration of IP or lenvatinib are to be on the same day (e.g., the first day [D1] of each treatment cycle), test result must be available before dosing.
- Thyroid function
- Urine pregnancy test for EU countries
- Review adverse events and concomitant medications
- PK blood sample and immunogenicity blood sample (collected at time points specified in Table 1.2-2)
- Tumor imaging (time window of ±7 days)
- Patient-reported outcome (prior to any examinations scheduled at this visit; time window of -7 days)
- Study treatment
- Review treatment compliance

Cycle 4 Day 1

- Body weight and vital signs
- ECOG performance status and complete physical examination
- ECG and echocardiogram, as indicated clinically
- Hematology, clinical chemistry and urinalysis: when laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.
- Coagulation function: When laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.
- Urine pregnancy test
- Review adverse events and concomitant medications
- PK blood sample and immunogenicity blood sample (collected at time points specified in Table 1.2-2)

- Patient-reported outcome (prior to any examinations scheduled at this visit; time window of -7 days)
- Study treatment
- Review treatment compliance

Cycle 5 Day 1

- Body weight and vital signs
- ECOG performance status and complete physical examination
- ECG
- Echocardiogram (as indicated clinically)
- Hematology, clinical chemistry and urinalysis: when laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.
- Coagulation function: When laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.
- AFP
- HBV DNA titer test (if HBsAg or HBcAb is positive at baseline), HCV RNA test (if anti-HCV antibody is positive at baseline) start at Cycle 5
- Thyroid function
- Urine pregnancy test for EU countries
- Review adverse events and concomitant medications
- Tumor imaging (time window of ±7 days)
- Patient-reported outcome (prior to any examinations scheduled at this visit; time window of -7 days)
- Study treatment
- Review treatment compliance

Cycle 6 Day 1

- Body weight and vital signs
- ECOG performance status and complete physical examination
- ECG and echocardiogram, as indicated clinically
- Hematology, clinical chemistry and urinalysis: when laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.

- Coagulation function: When laboratory test and administration of IP or lenvatinib are to be on the same day, test result must be available before dosing.
- Urine pregnancy test
- Review adverse events and concomitant medications
- Patient-reported outcome (prior to any examinations scheduled at this visit; time window of -7 days)
- Study treatment
- Review treatment compliance

Cycle 7 Day 1 and the first day of the following treatment cycles

- Body weight and vital signs
- ECOG performance status and complete physical examination
- ECG (every 2 cycles or as clinically indicated) and echocardiogram (as clinically indicated)
- Hematology, clinical chemistry and urinalysis: when laboratory test and administration of IP or lenvatinib are to be on the same day (e.g., the first day [D1] of each treatment cycle), test result must be available before dosing.
- AFP (at Cycle 9 and every 4 cycles thereafter)
- HBV DNA titer test (if HBsAg or HBcAb is positive at baseline), HCV RNA test (if anti-HCV antibody is positive at baseline) at Cycle 9 and every 4 cycles thereafter
- Coagulation function: When laboratory test and administration of IP or lenvatinib are to be on the same day (e.g., the first day [D1] of each treatment cycle), test result must be available before dosing.
- Thyroid function, every 2 cycles thereafter
- Urine pregnancy test, at Cycle 8 and every 2 cycles thereafter (for EU countries at Cycle 7 and every cycle thereafter); additional pregnancy tests may also be undertaken if requested by Institutional Review Board/Ethics Committees (IRB/ECs) or local regulations.
- Review adverse events and concomitant medications
- PK blood sample and immunogenicity blood sample (collected at Cycle 8, and every 4 cycles thereafter. Refer to Table 1.2-2 for time points of sample collection)
- Patient-reported outcome (prior to any examinations scheduled at each visit; time window of -7 days) at Cycle 8, and every 2 cycles thereafter

- Tumor imaging (time window of ±7 days) and every 6 weeks (± 7 days) for the first 48 weeks, every 12 weeks (± 7 days) thereafter (refer to Table 1.2-1 Study Assessments and Procedures Schedule for details)
- Study treatment
- Review treatment compliance

7.6.4 END-OF-TREATMENT (EOT) VISIT

End-of-treatment visit is defined as the visit subjects take within 7 days after the investigator confirms end of study treatment that is discontinued due to any cause. Note: The date when the investigator confirms end of treatment may not necessarily be the date of the last dose.

Every effort should be made to have the subjects complete the EOT visit within the planned time window. If end of treatment visit is within the time window of safety follow-up, it will be done according to the safety follow-up, same test items will not be repeated.

Procedures to be completed at the EOT visit include:

- Body weight and vital signs
- ECOG performance status and complete physical examination
- Clinical laboratory tests (hematology, chemistry and urinalysis). No need to repeat the tests if there's available result obtained within 7 days prior to the visit
- ECG, no need to repeat the measurement if there's available result obtained within 7 days prior to the visit
- Echocardiogram (as indicated clinically)
- AFP, no need to repeat the test if there's available result obtained within 7 days prior to the visit
- HBV DNA titer test (if HBsAg or HBcAb is positive at baseline), HCV RNA test (if anti-HCV antibody is positive at baseline), no need to repeat the tests if there are available results obtained within 7 days prior to the visit
- Coagulation function: no need to repeat the tests if there's available result obtained within 7 days prior to the visit
- Thyroid function: no need to repeat the tests if there's available result obtained within 7 days prior to the visit
- Urine pregnancy test: no need to repeat if a pregnancy test is completed within 7 days prior to the visit
- Patient-reported outcome; If PROs are assessed within 7 days prior to the end-of-treatment visit, it is not required to repeat at this visit
- Tumor imaging (no need to repeat the evaluation if it has been evaluated within 28 days prior to the end of treatment visit)

- PK blood sample and immunogenicity blood sample
- Review treatment compliance
- Review adverse events and concomitant medications
- Subsequent anti-cancer treatment (if applicable)

7.6.5 FOLLOW-UP

Follow-up visit includes safety follow-up and survival follow-up.

The safety follow-up visit continues until 90 days ± 7 days after the last dose of IP or lenvatinib whichever is later, or the subject starts a new anti-cancer treatment, whichever occurs first.

Three visits are scheduled in the safety follow-up:

Safety follow-up visit 1 (at 30±7 days after the last dose of study treatment)

- Body weight and vital signs
- ECOG performance status and (symptom-specific) physical examination
- HBV DNA (if HBsAg or HBcAb is positive at baseline), HCV RNA (if anti-HCV antibody is positive at baseline), no need to repeat the tests if there are available results obtained within 7 days prior to the visit
- ECG, no need to repeat the measurement if there's available result obtained within 7 days prior to the visit
- Echocardiogram (as indicated clinically)
- Clinical laboratory tests (hematology, chemistry and urinalysis). No need to repeat the tests if there's available result obtained within 7 days prior to the visit
- AFP, no need to repeat the test if there's available result obtained within 7 days prior to the visit
- Coagulation function: no need to repeat the tests if there's available result obtained within 7 days prior to the visit
- Thyroid function: no need to repeat the tests if there's available result obtained within 7 days prior to the visit
- Urine pregnancy test: no need to repeat if a pregnancy test is completed within 7 days prior to the visit
- Patient-reported outcome; If PROs are assessed within 7 days prior to the safety follow-up visit, it is not required to repeat at this visit
- Tumor imaging (if applicable)
- Review adverse events and concomitant medications

- Subsequent anti-cancer treatment (if applicable)

Safety follow-up visit 2 (at 60±7 days after the last dose)

- Review adverse events and concomitant medications
- Tumor imaging (if applicable)
- Urine pregnancy test (for EU only)
- Subsequent anti-cancer treatment (if applicable)

Safety follow-up visit 3 (at 90±7 days after the last dose)

- Review adverse events and concomitant medications
- Immunogenicity blood sample
- Tumor imaging (if applicable)
- Urine pregnancy test (for EU only)
- Subsequent anti-cancer treatment (if applicable)

Survival Follow-up:

Subjects will be assessed for survival status by telephone follow-up or site visit every 12 weeks after the last dose of study treatment till death, lost to follow-up or end of study. The following data will be collected in these telephone visits/follow-up visits:

- Survival status of the subject
- Subsequent anti-cancer treatment (if applicable)
- Tumor imaging (if applicable)
- Review drug-related SAE
- Review patient-reported outcome every 12 weeks ± 7 days. PRO could be collected at the site when the subject comes for a visit or by phone calls.

7.6.6 UNSCHEDULED VISIT

The physicians may perform symptom-specific clinical assessments in the unscheduled visits. These assessments may include symptom-specific physical examination, ECOG PS evaluation, clinical laboratory tests, echocardiogram, immunogenicity test and radiological tumor evaluation. Newly identified abnormality that indicates a change from baseline should be recorded in subject's medical record. New or worsened finding will be recorded in the eCRF AE sheet as an AE.

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Principal investigator is responsible for ensuring this chapter well understood by all study staff.

8.1 DEFINITION OF AN ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject after signing the informed consent. An AE does not necessarily have a causal relationship with the investigational product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug discontinuation;
- Drug abuse;
- Drug misuse;
- Drug-drug interaction;
- Drug dependence;
- Extravasation;
- Pregnancy.

An AE can be a serious adverse event (SAE) or non-serious AE.

8.2 ABNORMAL TEST RESULT

The criteria for determining whether an abnormal objective test result should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or;
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or;
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or;
- Test result is considered to be an adverse event by the investigator or Sponsor.
- Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any test result that is determined to be an error does not require reporting as an adverse event. Clinical diagnosis would be reported as an AE and corresponding lab abnormality would not be reported as a separate AE.

8.3 DEFINITION OF A SERIOUS ADVERSE EVENT

A serious adverse event as defined by ICH is any untoward medical occurrence of the following conditions:

- Results in death;
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization (Cause of hospitalization is made clear to be adverse event, not elective surgery, or non-medical reasons, refer to the text below);
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly or birth defect (in the child of a subject);
- Medically significant events.

Medically significant events that may not result in death or be life-threatening may be considered serious, if they may jeopardize the participant and may require intervention to prevent one of the outcomes listed in this definition based upon appropriate medical judgment.

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 subject hospitalization, or the development of drug dependency or drug abuse. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact. Medically significant events as judged by the investigator according to medical data or clinical experience should be reported according to the rule of expedited reporting of SAE. In addition, suspected transmission of any infectious agent via a medicinal product is also considered as medically significant event.

Unlisted (Unexpected) Adverse Event

An unlisted AE refers to the event of which the nature or severity not consistent with the applicable product reference safety information. For CS1003, the expectedness of an AE will be determined by referring to IB.

Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/ intensive care unit (e.g., from the pediatric unit to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as out-patient/ same day/ ambulatory procedures).

Hospitalization or prolongation of hospitalization with following reasons will not be reported as a serious adverse event:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Pre-planned treatments and/or surgical procedures should be noted in the baseline documentation;
- Admission exclusively for the use of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example,

an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.4 DOCUMENTATION OF ADVERSE EVENTS

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit/ you were last asked?” or revealed by observation will be collected and recorded. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, then each sign or symptom will be recorded separately.

Confirmed SARS-CoV-2 infection and COVID-19 will be recorded in the adverse event CRF. AE monitoring for COVID-19 will follow local regulations and guidelines.

8.4.1 TIME OF AE COLLECTiON

AEs and SAEs should be recorded from the time of subject signing the informed consent, throughout the treatment period and during the safety follow-up period, after which time, only related SAEs need to be recorded and reported*. AEs that occur after safety follow-up visit 1 can be collected at safety follow-up visit 2 and 3 by phone calls.

*Note: If the investigator becomes aware of any SAE (including death) that occurs after safety follow-up or a subject withdraws from the study, and believes that this event is possibly related to the investigational product, the investigator should notify the Sponsor's pharmacovigilance team or its representative.

8.4.2 FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. Any AEs that are unresolved at the subject’s last visit in the study are followed up by the investigator as long as medically indicated.

The sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 EVENTS THAT OCCUR AFTER SUBJECT WITHDRAWS FROM STUDY

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring after the safety follow-up period. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently discontinued from study, and he/she considers there is a reasonable possibility that the event is related to the investigational product, the investigator should notify the Sponsor’s pharmacovigilance team or its representative.

8.4.4 COLLECTION OF ADVERSE EVENT INFORMATION

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator's causality attribution against the investigational product
- Actions taken with regard to the investigational product
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date when the AE met the criteria of SAE
- Date when the investigator became aware of the SAE
- AE is serious due to
- Date of discharge (if applicable)
- Primary cause of death (if applicable)
- Date of death (if applicable)
- Autopsy findings (if applicable)
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of SAE

8.4.5 SEVERITY ANALYSIS

It is important to distinguish between serious and severe AEs. An AE of severe intensity may not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mile stroke but would be a SAE.

- The investigator will make an assessment of intensity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

8.4.6 CAUSALITY ASSESSMENT

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). The investigator must record the causal relationship in the eCRF and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event.

If the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

For SAEs causal relationship will also be assessed for other medication and study procedures. This includes non-treatment-emergent SAEs (e.g., SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
- Not protocol related: The event is related to an etiology other than the procedure/intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

8.4.7 DISEASE PROGRESSION

Disease progression refers to a worsening of subject's condition attributable to the disease for which the investigational product is being studied. Disease progression-related deterioration of symptoms and/or signs should not be reported as an AE. According to NCI CTCAE Version 5.0, death caused by disease progression during the reporting period should be reported as SAE.

8.4.8 NEW CANCERS

The development of a new cancer should be regarded as a SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the subject's inclusion in this study.

8.5 REPORTING OF ADVERSE EVENTS

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.5.1 REQUIREMENTS FOR SERIOUS ADVERSE EVENT REPORTING

All serious adverse events occurring during clinical study must be reported to the sponsor or its designated representative by investigational staff immediately but ***no later than 24 hours*** of when he/she becomes aware of it. This time frame also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of pregnancy cases.

The Sponsor's representative works with the investigator to ensure that all the necessary information is provided within above timeline.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided.

In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated sponsor representative.

In case EDC is down, facsimile transmission/encrypted email of paper SAE form is the preferred backup method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the paper SAE report sent later in an encrypted mail. Initial notification via the telephone does not replace the need for the investigator to complete and sign the paper SAE form within 24 hours when he/she aware of the event.

The contact information for assistance with SAE reporting, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE report form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

The Sponsor's representative will advise the investigator/study site personnel how to proceed.

The sponsor has a legal responsibility to notify, as appropriate, both the local Health Authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB) /Independent Ethics Committee (IEC).

Abnormal Liver Function Tests

Hy's law is essentially a translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. Elevations in liver biochemistry that meet Hy's Law criteria are defined and reported as SAEs, using the important medical event serious criterion if no other criteria are applicable. In this study, the following occurrence should be reported as SAE:

- For subjects with normal baseline of AST or ALT and total bilirubin: Treatment-emergent AST or ALT ≥ 3 × ULN in combination with total bilirubin ≥ 2 × ULN, with no evidence of hemolysis and no evidence of ALP ≥ 2 × ULN or not available;
- For subjects with preexisting ALT or AST or total bilirubin above the ULN: Treatment-emergent AST or ALT ≥ 2 ×baseline values and ≥ 3 × ULN, or ≥ 8 × ULN (whichever is smaller) in combination with total bilirubin level increased by at least 1 × ULN from baseline or if the total bilirubin level reaches ≥ 3 × ULN (whichever is smaller).

8.5.2 REQUIREMENTS FOR NON-SERIOUS ADVERSE EVENT OF REPORTING

All adverse events will be reported on the adverse event page(s)/module of the eCRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the relevant forms must be completed in a consistent manner. For example, the AE term should be the same in the two forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.6 OVERDOSE

Overdose is defined as: the subject has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol. Subjects with a suspected overdose should be managed with appropriate supportive therapy as determined by the investigator in consultation with the medical monitor.

Any overdose should be informed to the medical monitor, and also reported as a protocol deviation. Additionally, any AE occurring as a result of overdose should be included in standard AE recording; and for overdoses associated with SAE, standard SAE reporting timeline and procedure apply.

8.7 PREGNANCY

To ensure subject's safety, the investigator or other site staff must inform the sponsor's representative of any pregnancy that occurs during the study immediately but no later than 24 hours after getting aware of this event. The sponsor's representative and the investigator should make sure all relevant information is reported to the sponsor's pharmacovigilance representative. Every pregnancy and its outcome of a subject who has received study treatment must be reported. An abnormal pregnancy outcome is considered SAE and reported in the SAE Report Form following the standard reporting timeline of SAE.

Therefore mentioned time limit also applies to a pregnancy outcome learned of.

8.7.1 MATERNAL EXPOSURE

For a female who becomes, or is found to be, pregnant either receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, the investigational product should be discontinued immediately, and the pregnancy should be reported to the Sponsor. For a female who becomes or is found to be pregnant after discontinuation of investigational product treatment and/or prior exposure to the investigational product, the pregnancy should be reported to the Sponsor.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, the investigator or other site personnel should inform the appropriate the Sponsor representative within 24 hours after getting aware of it.

The same timeline applies when pregnancy outcome information is available.

The Pregnancy report module in the CRF is used to report the pregnancy. (When EDC is down, the sponsor-provided Pregnancy Report Form can be used for reporting, and data should be entered into EDC system when it recovers.) The Pregnancy Outcome Report is used to report the outcome of the pregnancy.

Pregnancies that occur within up to 180 days after the completion of study treatment must also be reported to the Sponsor.

8.7.2 PATERNAL EXPOSURE

A male has been exposed, either due to treatment or environmental factors, to the investigational product prior to or around the time of conception and/or is exposed during his partner’s pregnancy.

Information on the pregnancy of a subject’s partner must be obtained directly from the subject’s partner. Therefore, prior to obtaining information on the pregnancy, the investigator must obtain the consent of the subject’s partner.

Male subjects should refrain from fathering a child or donating sperm during the study and for 180 days following the last dose.

Pregnancy of the subject’s partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be followed up and documented.

To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome. A consent form specific to this situation must be used. The outcome of any conception occurring from the date of the first dose until 180 days after the last dose should be followed up and documented.

9 QUALITY CONTROL, QUALITY ASSURANCE AND DATA MANAGEMENT

In the conduct of this trial, CStone and/or its agent (e.g., Contract research organization CRO) will conduct periodic quality control (e.g. monitoring and quality visit) and quality assurance (e.g. auditing) activities.

This quality control and quality assurance visits may review source documents and other study-related documents, study facilities and materials, etc. to ensure the accuracy, consistency, integrity and reliability, and compliance with protocol and Good Clinical Practice (GCP). The investigator and site must allow the Sponsor's representative and regulatory authorities the access to all study-related documents including medical history record and concomitant medication record, etc.

The site may be subject to review by IRB/IEC, and/or to Quality Assurance audits performed by CStone and/or CStone's partners or delegates, and/or inspections by appropriate regulatory authorities. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

9.1 CLINICAL MONITORING

In accordance with applicable regulations, GCP, and Sponsor procedures, the Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. Monitors will work in accordance with the Sponsor or CRO's standard operating procedures (SOPs). Monitors will establish and maintain regular contact between the investigator and the Sponsor.

During these contacts, the monitor will:

- Check the progress of the study;
- Review study data collected;
- Conduct source document review and verification;
- Manage IP and lenvatinib;
- Identify any issues and address them.

This will be done in order to verify that:

- Data are authentic, accurate, and complete;
- Safety and rights of subjects are being protected;
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

9.2 DATA MANAGEMENT AND CODING

Data Management will be performed by the Sponsor delegated Data Management Vendor.

An electronic data capture (EDC) system will be used for this study. All eCRF data will be entered in electronic forms at the study center. Data collection, including all entries, corrections and alterations are to be made by investigator or authorized study center personnel designated by the investigator.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate. All entries to the study database and changes will be fully recorded in a protected audit trail.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. The monitor will review the eCRFs and evaluate them for completeness and consistency by source document verification.

The data will be validated as defined in the Data Management Plan. Data queries will be raised for inconsistent, impossible or missing data. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

Adverse events and medical/ surgical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-Drug). All codings will be performed by the vendor.

9.3 QUALITY ASSURANCE AUDITS/INSPECTIONS

Authorized representatives of the Sponsor/CRO, a regulatory authority, or an IEC/IRB may perform audits or inspections. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities are conducted and data are recorded, analyzed, and accurately reported according to the protocol, GCP, ICH guidelines, and any applicable regulatory requirements. Such audits/inspections can occur at any time during or after completion of the study.

In an event of COVID-19 pandemic restrictions or events, any contingency measurements undertaken to ensure quality of data generated/study integrity or patient safety should be highlighted.

In case planned on-site monitoring visits were no longer possible, details regarding sponsors consideration of optimizing use of central and remote monitoring programs to maintain oversight of clinical sites will be provided in the monitoring plan.

Monitoring visits at site will be limited to a minimum required as deemed appropriate during COVID-19 pandemic.

As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration to protect subjects, site staff and society as a whole.

Measures to mitigate the additional risks caused by COVID-19 are:

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Subjects will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat and fatigue throughout the study. Once clinical signs of infection are reported by subjects, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurements during outpatient visits will be implemented.
- Confirmation of COVID-19 infection by optional laboratory assessment may be conducted based on availability (test capacity and turnaround time) of approved tests and on Investigator's discretion and local requirement.
- The probability of virus transmission will be controlled as much as possible by:
    - Advice for subject to adhere to local requirements for reduction of the public exposure while ambulatory.
    - Physical distancing and person-to-person contact restrictions will be applied during site visits by following local requirements.
    - Where physical distancing is not possible, personal protective equipment (PPE) is used by study participant (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the investigators and site staff and guided by local requirements.

10 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

10.1 SAMPLE SIZE DETERMINATION

The primary endpoint of this study is: OS

Number of events and sample size are estimated based on the following hypotheses:

- Randomization ratio is 2:1.
- Type I error is controlled for two-sided test at 0.05.
- OS will be tested with log-rank test.
- CCI [redacted]
- One interim analysis of OS will be conducted. Type I error will be controlled using Lan-DeMets approximation to the O'Brien-Fleming boundary.
- Survival times are exponentially distributed.
- CCI [redacted].
- CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

10.2 SUMMARIES OF CONDUCT OF STUDY

10.2.1 ANALYSIS SETS

Intent-to-treat (ITT) set: all randomized subjects; these subjects will be grouped by the assigned treatment at randomization. Subject disposition, demographics, and other baseline characteristics, OS, ORR, PFS, and DCR analyses will be based on the ITT set. DoR analysis

will be based on patients in the ITT set who achieve an objective response. TTD analysis is for ITT subjects with baseline PRO and at least one post-baseline PRO assessment.

Safety analysis set (SAS): subjects who have received at least one dose of either study drug. Randomized subjects who haven't received any dose of study treatment will not be included in the SAS. For safety analysis, subjects will be grouped according to the actually received treatment (patients who receive any dose of CS1003 incorrectly will be counted in CS1003-treated group). The safety analyses will be based on the SAS.

10.2.2 DEMOGRAPHICS AND BASELINE

Demographics and baseline characteristics, e.g., age, sex, baseline disease characteristics, medical history, and ECOG performance status will be summarized based on the ITT set. Baseline measurement is defined as the last measurement before the first dose of either study drug.

Continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.

10.3 EFFICACY ANALYSES

10.3.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint of this study is: OS

Overall survival (OS): defined as the time interval between the date of randomization to the date of death from any cause. Subjects who are alive at the time of analysis will be censored at the last known date of alive. Subjects without any data after baseline will be censored on the randomization day.

The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment, withdrawing further participation in the study but not the informed consent to further information disclosure, and starting of new anti-cancer treatment.

OS comparison will be based on stratified log-rank test. Stratified Cox regression model will be used to estimate the HR (and its 95% CI). Unstratified HR will also be provided. The stratification factors from IVRS/IWRS will be those used for randomization. If the number of subjects in any stratified group doesn't meet the requirement of the analytical method, for example, less than 10 subjects, the associated stratification factors will be combined. Kaplan-Meier method will be used to estimate the median OS, OS rate at various time points, and their 95% confidence intervals (by Brookmeyer Crowley method) of each group. Kaplan-Meier curves may also be constructed to provide a visual description of the OS rate change over time.

10.3.2 KEY SECONDARY EFFICACY ENDPOINTS

The key secondary efficacy endpoints of this study include ORR and PFS assessed by BICR based on RECIST v1.1.

- **Objective response rate (ORR) assessed by BICR based on RECIST v1.1**: the number and proportion of subjects who achieve objective response (CR or PR) assessed by BICR will be summarized. Patients without any measurable disease at baseline or any tumor assessment after baseline will be considered non-responders. The analysis will be based on the ITT set. Stratified Mantel-Haenszel test will be used to compare the ORR between groups. Normal approximation to binomial distribution will be used to calculate 95% CI for ORR difference between groups. Clopper Pearson method will be used to calculate the ORR and its 95% CI of each group.

- **PFS assessed by BICR based on RECIST v1.1:** defined as the time from the date of randomization to disease progression assessed by BICR or death, whichever occurs first. Subjects without event (no disease progression or death) will be censored at the date of the last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day. PFS will be analyzed according to the above methods in section 10.3.1.

10.3.3 MULTIPLE COMPARISONS

The primary and key secondary endpoints will be tested at an overall 2-sided Type I error rate at 5% level based on the fixed sequence testing procedure at the time of primary analysis. These endpoints will be tested in the following order:

- OS
- ORR assessed by BICR
- PFS assessed by BICR

Two analyses are planned for OS – one interim analysis and one final analysis (refer to section 10.8 for more details). ORR and PFS will be sequentially tested if OS is statistically significant, and the data cutoff date of the ORR and PFS will be the date when 387 PFS events are observed.

10.3.4 OTHER SECONDARY EFFICACY ENDPOINTS

The other secondary efficacy endpoints of this study include ORR and PFS assessed by investigators based on RECIST v1.1, DCR, and DoR assessed by BICR and investigators, and TTD.

- **ORR assessed by investigators based on RECIST v1.1**: the number and proportion of subjects who achieve objective response (CR or PR) assessed by investigators will be summarized. Patients without any measurable disease at baseline or any tumor assessment after baseline will be considered as non-responders. The analysis will be based on ITT set. Stratified Mantel-Haenszel test will be used to compare the ORR between groups. Normal approximation to binomial distribution will be used to calculate 95% CI for ORR difference between groups. Clopper Pearson method will be used to calculate the ORR and its 95% CI of each group.

- **PFS assessed by investigators based on RECIST v1.1** is defined as the time from the date of randomization to the first documented disease progression assessed by investigators or death, whichever occurs first. Subjects without event (no disease

progression or death) will be censored at the date of the last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day.

- **Duration of response (DoR)** is defined as, among responders (CR or PR), the time interval between the date of the first occurrence of a complete or partial response and the date of PD or death due to any cause, whichever occurs first. Patients who have not progressed and still survive at the time of analysis will be censored at the date of the last tumor assessment day. DoR analysis will be based on ITT subjects with complete or partial responses.

- **Disease Control Rate (DCR)** is defined as the proportion of subjects who achieve CR, PR, and SD based on RECIST v1.1. It will be analyzed similarly as ORR.

- **Time to deterioration (TTD)** is defined as the time from randomization to the first worsening of EORTC QLQ-C30 scale. Deterioration will be measured based on the minimal clinically important change specified in the statistical analysis plan. When TTD is calculated, patients without deterioration will be censored at the date of the last PRO assessment. TTD analysis is for ITT patients with baseline PRO and at least one post-baseline PRO assessment.

PFS and DoR will all be analyzed according to the above methods in section 10.3.1, and DCR will be analyzed using the same method as ORR. The other secondary efficacy endpoints except TTD will be analyzed using the same data cutoff date as the key secondary endpoints.

10.3.5 HANDLING OF MISSING DATA

Subjects without any assessment after baseline will be considered non-responders for ORR analysis.

For PFS analysis, patients who have not progressed and who have not died at the time of analysis will be censored at the date of the last tumor assessment date. Patients without post-baseline tumor assessment will be censored on the randomization day.

For OS analysis, patients without death reported at the time of analysis will be censored at the last known date of alive. Patients without any data after will be censored on the randomization day.

For DoR analysis, patients who have not progressed and who have not died at the time of analysis will be censored at the date of the last tumor assessment date. If no tumor assessments are performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of CR or PR.

For TTD analysis, subjects without events will be censored at the date of the last PRO assessment.

More details about missing data handling will be provided in the SAP.

10.4 SAFETY ANALYSES

Safety analysis will be performed on the safety analysis set.

The exposure of study drugs will be summarized according to the number of cycles, duration of treatment, number of doses and dose level, etc.

All adverse events will be verbatim described according to MedDRA and graded based on NCI CTCAE v5.0. Treatment-emergent AEs (TEAEs) will be summarized by preferred term, system organ class, NCI-CTCAE grade of severity, and relationship to the study treatment. In addition, serious adverse events, severe adverse events (grade ≥ 3), drug-related adverse events, and adverse events causing discontinuation or suspension of study drug administration will be summarized separately. Multiple occurrences of the same event will be only counted once for the most severe event.

A TEAE is defined as (regardless of severity):

- Any AE that occurs on or after treatment initiation
- An AE that is present at the time of treatment initiation but gets worsened on or after treatment initiation

Vital signs, clinical laboratory findings, and ECG, along with their change from baseline will be summarized descriptively by treatment groups. Shifts from baseline at various post-baseline time points will also be presented if applicable. All deaths reported during the treatment or follow-up period after the last dose/discontinuation of study drugs will be summarized by treatment groups.

10.5 PHARMACOKINETIC ANALYSES

The PK data in this study will be pooled with other CS1003 clinical trials-data to develop a population PK model. This model will be used to evaluate internal and external variables and their influence on the PK of CS1003. Furthermore, exposure-response analysis will be performed on specific pharmacodynamic and safety endpoints. Results of the above population PK and exposure-response analyses will be recorded in separate reports.

10.6 IMMUNOGENICITY ANALYSES

Immunogenicity evaluation results will be reported for the following parameters. The analyses include number and percentage of subjects who have positive ADA at baseline; and number and percentage of subjects with at least one positive ADA test result at any time point following the first dose of study treatment.

10.7 EXPLORATORY ANALYSES

Subjects will be sub-grouped based on their demographics (e.g., age, gender) and baseline characteristics (e.g., serum AFP at baseline, ECOG PS, histology, etc.) for evaluating the consistency among all subgroups.

PD-L1 expression level in tumor tissues including tumor cells and immune cells, and its correlation with the efficacy endpoints will be investigated depending on PD-L1 data availability.

The descriptive statistics (e.g., mean, median, standard deviation, and range) of the absolute scores will be calculated for EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D-5L by treatment group.

10.8 INTERIM ANALYSES

CCI [redacted]

The OS will be tested using log-rank test with the following boundaries:

CCI [redacted]

IDMC

An independent data monitoring committee (IDMC) will review the safety data collected in the trial regularly about every 3 months for the first two meetings from the first subject enrollment, and the following frequency will be adjusted based on the available safety data, e.g. every 6 months. The IDMC will also monitor the data for OS interim analysis and make recommendations to the Sponsor according to the pre-defined boundaries. Members of IDMC are from outside the Sponsor, who must follow the charter about duties and responsibilities. Any safety monitoring result that may affect the conduct of this trial must be notified to the investigator so that Ethics Committee (EC) will be informed. Membership, roles and responsibilities and implementation details of IDMC will be described in the IDMC charter.

10.9 SENSITIVITY ANALYSIS

The stratification factors collected by EDC are used in the sensitivity analysis for OS. OS will also be analyzed using an unstratified Cox regression model.

The following sensitivity analysis of OS will also be performed: patients who used PD-1/PD-L1 checkpoint inhibitors subsequent anti-cancer treatment prior to death will be censored on the day they receive PD-1/PD-L1 checkpoint inhibitors subsequent anti-cancer treatment.

Refer to Section 10.3.1 for sensitivity analysis methods.

11 ETHICAL, REGULATORY AND OTHER REQUIREMENTS

11.1 REGULATORY AUTHORITY APPROVAL

The Sponsor will obtain approval to conduct the study from the appropriate regulatory authorities in accordance with any applicable country specific regulatory requirements before any site in that country is activated.

11.2 ETHICAL CONDUCT OF THE STUDY AND ETHICS APPROVAL

This study will be conducted in accordance with ICH / GCP and all applicable regulatory requirements, including, where applicable, current version of the Declaration of Helsinki. The investigator (or the Sponsor, where applicable) is responsible for ensuring that this protocol, the informed consent form for the site, and any other information that will be presented to potential subjects (e.g. advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate Ethics Committee. The investigator agrees to permit the Ethics Committee direct access to all relevant documents. The Ethics Committee must be constituted in accordance with all applicable regulatory requirements. The Sponsor will provide the investigator with relevant documents/data that are needed for the Ethics Committee's review and approval of this study.

If the protocol, informed consent form, or any other information that the Ethics Committee has approved for presentation to potential subjects is amended during the study, the investigator is responsible for making sure the Ethics Committee reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining approval of the amended form from the Ethics Committee before new subjects consent to take part in the study using this version of the form. Copies of the Ethics Committee’s approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the Sponsor promptly.

11.3 INFORMED CONSENT PROCESS

The primary investigators at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each patient is notified that he or she is free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed informed consent forms are kept in the investigator's Study File.
- Ensure a copy of the signed ICF is given to the patient.

11.4 CHANGES TO THE PROTOCOL AND INFORMED CONSENT FORM

Study procedures will not be changed without the mutual agreement of the PI and the Sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the clinical study protocol. The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols. The Sponsor will distribute any subsequent amendments and new versions of the protocol to each PI(s).

If a protocol amendment requires a change to a site's ICF, the Sponsor and the Ethics Committee of the site are to approve the revised ICF before the revised protocol is used. If local regulations require, any administrative change will be communicated with and approved by each Ethics Committee.

11.5 PROTOCOL ADHERENCE AND DEVIATION

Read through the whole study protocol and follow the instructions. An immediate emergent intervention judged by the investigator or a trained study personnel as necessary for the subject's protection, safety and health considerations may be regarded as an exception.

However, the investigator or designated personnel must communicate any major protocol deviation due to an emergency, accident or error to the medical monitor by telephone. And as such the decision regarding the subject's eligibility to further participate in the trial will be jointly determined and recorded by the investigator, Sponsor and medical monitor.

Protocol deviations (e.g. missing assessments/visits) related to COVID-19 will be listed separately.

11.6 SITE CLOSURE

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the Sponsor.
- Data queries.
- Accountability, reconciliation, and arrangements for used/unused IP and lenvatinib.
- Review of study records for completeness.
- Return of treatment codes to the Sponsor.

- Shipment of PK and ADA samples to central laboratories.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the Sponsor determines such action is needed, the Sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform all other investigators and/or sites conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the Ethics Committee promptly and provide the reason for the suspension or termination.

If the study is prematurely ended, all study data must be returned to the Sponsor. In addition, arrangements will be made for all unused IP and lenvatinib in accordance with the applicable Sponsor procedures for the study.

Financial compensation to investigators and/or sites will be in accordance with the agreement established between the investigator and the Sponsor.

11.7 RECORDS RETENTION

Following closure of the study, the investigator must maintain all study records in a safe and secure location. Where permitted by local laws/regulations or site policy, some or all of these records can be maintained in a format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The Sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any site-specific requirements or local laws or regulations, or the Sponsor’s standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.8 CLINICAL STUDY REPORT

A final clinical study report (CSR) will be made in accordance with the principles on the structure and content of clinical study reports in ICH and local regulations. A final CSR will be made regardless of whether this study is completed or early terminated. The Sponsor will provide a copy of the final CSR to all investigators for reference.

11.9 CONFIDENTIAL AND PRIVACY

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor and their treatments. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidentiality. No information concerning the study, or the data will be released to any unauthorized third party without written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, authorized representatives of the Sponsor, representatives of the Ethics Committee, regulatory agencies or pharmaceutical company supplying investigational product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing Ethics Committee, site policies, or Sponsor requirements.

11.10 PUBLICATION PRIVACY

Upon study completion, the study results will be co-submitted by the investigators and Sponsor for publication. Investigators must make a promise that any data obtained under this protocol will not be submitted for publication without prior permission from CStone Pharmaceuticals (Suzhou) Co., Ltd.

For multi-center studies, the first publication or disclosure of study results shall be a complete, joint multi-center publication or disclosure coordinated by the Sponsor.

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the study center (collectively, a "Publication"), the investigator shall provide the Sponsor with a copy of the proposed publication and allow the Sponsor a period of at least 30 days (or, for abstracts, at least 5 working days) to review the proposed publication. Proposed publications shall not include any Sponsor information other than the study results or any personal data on any subject, such as name or initials.

At the Sponsor's request, the submission or other disclosure of a proposed publication will be delayed a sufficient time to allow the Sponsor to seek patent or similar protection of any inventions, know how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

11.11 INSURANCE, REIMBURSEMENT AND COMPENSATION

CStone Pharmaceuticals (Suzhou) Co., Ltd. will maintain an adequate insurance policy for the study.

Avoid the situation of protocol deviation (especially unplanned dose, other method of administration, or other indications) which is not covered by the subject's compulsory insurance.

11.12 TERMINATION OF STUDY

The Sponsor may terminate the study. When it's in the best interest of the subjects and due to medical or ethical considerations, the study may be terminated at any time upon agreement of investigators and the Sponsor. CStone Pharmaceuticals (Suzhou) Co., Ltd., the CROs and investigators must ensure the full consideration about securing subjects' rights at the study termination.

Reasons for study termination may include but are not limited to:

- Unanticipated, major or unacceptable risk occurred in enrolled subjects;
- The Sponsor determines to suspend or stop the development of the study treatment.

12 ABBREVIATIONS

Abbreviation	Definition
AACR	American Association of Cancer Research
AASLD	American Association for the Study of Liver Diseases
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Review adverse events
AFP	Alpha fetoprotein
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Alanine aminotransferase
AUC	Area under the plasma concentration curve
BCLC	Barcelona clinic liver cancer staging system
BICR	Blinded Independent Central Review Committee
BUN	Blood urea/urea nitrogen
C_0	Plasma concentration at time zero
CDC	Antibody-dependent cytotoxicity
CI	Confidence interval
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum observed plasma concentration
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
CR	Complete remission
CrCl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen-4
DCR	Disease control rate
DLT	Dose limiting toxicity

Abbreviation	Definition
dMMR	Mismatch repair gene deficiency
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	ETHICS COMMITTEE
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGD	Esophagogastroduodenscopy
ELISA	Enzyme-Linked Immuno Sorbent Assay
EOI	End of infusion
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment visit
EQ-5D-5L	European quality of life 5-dimensions using 5-level scale
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FIH	First-in-Human
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practices
GHS	Global health status
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGV	Hematopoietic growth factor
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICF	Informed consent
ICH	International Conference on Harmonization
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN-γ	Interferon-γ

Abbreviation	Definition
IgG	Immunoglobulin G, for example IgG1, IgG2, IgG3 and IgG4; other immunoglobulins include IgM, IgD, etc.
INR	International Normalized Ratio
IO	Immuno-oncology
IP	Investigational product
irAE	Immune-related adverse events
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
LAG-3	Lymphocyte activation gene-3
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mmHg	millimeter of mercury
mPFS	Median Progression-free survival
MRI	Magnetic resonance imaging
msec	Millisecond
MSI-H	High microsatellite instability
MTD	Maximum tolerable dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
NMPA	National Medical Product Administration in China
NOAEL	No observed adverse effect level
NSAID	Non-steroid anti-inflammation drug
NSAID	Non-steroid anti-inflammation drug
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Disease progression
PD-1	Programmed death receptor-1
PD-L1	Programmed death ligand-1
PET	Positron emission tomography
PFS	Progression-free survival

Abbreviation	Definition
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPE	Personal protective equipment
PPK	Population pharmacokinetics
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
PT	Prothrombin Time
Q3W	Every 3 weeks
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-HCC18	Quality of Life Questionnaire for Hepatocellular Carcinoma 18
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
RPLS	Reversible posterior leukoencephalopathy syndrome
RTK	Receptor Tyrosine Kinase
RT-PCR	Real-time Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety analysis set
SD	Stable disease
SMC	Safety Monitoring Committee
SMP	Safety Management Plan
SOP	Standard operating procedure
TACE	Transarterial chemoembolization
T3	Free triiodothyronine
T4	Thyroxine
TEAE	Treatment emergent adverse event
TIM-3	T cell immunoglobulin-and mucin-domain-containing molecule-3
T_{max}	Time to maximum observed plasma concentration
TSH	Thyroid stimulating hormone
TTD	Time to deterioration
TTP	Time to progression
ULN	Upper limit of normal
VEGFi	Vascular endothelial growth factor inhibitor
WHO	Word Health Organization

Abbreviation	Definition
WHO-Drug	World Health Organization Drug Dictionary

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14 APPENDICES

14.1 APPENDIX 1: SAFETY ASSESSMENTS

Table 14.1. List of Safety Assessment Items

Tests	Items
Physical examination	Head, eyes, ears, nose, pharynx and larynx, respiratory, cardiovascular, gastrointestinal, musculoskeletal, nervous system, skin, blood/lymphatics, endocrine system, genitourinary (for previously symptomatic subjects)
Vital signs	Temperature (tympanic approaches may be used), pulse, respiratory rate and blood pressure
Pregnancy test	Blood/urine human chorionic gonadotrophin pregnancy test (female with child bearing potential only)
Hematology	complete blood count (CBC) and hemoglobin
Serum chemistry	Blood urea or urea nitrogen (BUN), creatinine, sodium, potassium, magnesium, chloride, calcium, phosphate, blood glucose, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), total cholesterol, total protein and albumin
Urinalysis	Specific gravity, pH, urine glucose, protein, cast, ketones, urinary occult blood and white blood cells, 24-hour urine protein as clinical indicated
Coagulation function	PT, aPTT, or INR
HBV, HCV, HIV	Anti-HIV antibody, HBsAg, anti-HCV antibody, HBV DNA test (HBsAg positive or HBcAb positive subjects only), HCV RNA test (anti-HCV antibody positive subjects only)
Thyroid function	FT3, FT4 and TSH (if FT3 or FT4 is not available, total T3/T4 value is obtained)

14.2 APPENDIX 2: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: REVISED RECIST GUIDELINE (VERSION 1.1)

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1)

14.2.1 ELIGIBILITY

To assess subject's response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a reference for subsequent measurements. To be eligible for enrollment, subject should have at least one measurable lesion, or one evaluable lesion, if not measurable.

14.2.2 DEFINITION

Measurable disease: At least one measurable lesion. Must be accurately measured in at least 1 dimension with a minimum size of: ≥10 mm in longest diameter, or ≥15 mm in shortest diameter if it's a lymph node, measured by 5-mm thin-section CT; ≥20 mm by chest X ray with good contrast; ≥10 mm on a color photo with a scale on it (for a superficial skin nodule), but imaging is preferred if applicable.

Non-measurable disease: All other lesions, including small lesions (longest diameter <10 mm or shortest diameter ≥10 to <15 mm if it's a lymph node) and other lesions that are indeed not measurable. Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not reproducible by imaging techniques.

Special cases of measurable disease: bone lesions, cystic lesions and lesions with prior local treatment are included. Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. If non-cystic lesions and cystic lesions are both present in the same patient, non-cystic lesions are preferred for selection as target lesions. Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

14.2.3 METHOD OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of ≤10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

When the primary endpoint of the study is objective response evaluation, **ultrasound** should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared. To meet the requirement of disease progression, elevation of tumor marker level must be associated with visible disease progression.

Cytology and **histology** can be used to differentiate between PR and CR in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

When a measurable lesion meets the criteria of response or stable disease, cytology must be used to confirm the source of any exudate that appears or worsens during treatment, in order to differentiate between response, stable disease or progression.

14.2.4 EVALUATION OF TUMOR RESPONSE

14.2.4.1 TARGET AND NON-TARGET LESIONS RECORDED AT BASELINE

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

14.2.4.2 CRITERIA OF RESPONSE EVALUATION

14.2.4.2.1 TARGET LESION

1. Evaluation criteria of target lesions

Refer to Table 14.2.4-1.

Table 14.2.4-1 Evaluation criteria for target lesions

Complete Response (CR):	Disappearance of all target lesions; the short diameter of any pathologic lymph node must be < 10 mm (regardless of target or non-target lesion).
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Progression of Disease (PD):	At least a 20% and 5 mm increase in the sum of the LD of target lesions, taking as reference the smallest sum of LD recorded since the treatment started or baseline sum of LD if it's the smallest value. (Note: Appearance of a new lesion is also considered to be progressive disease.)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

2. Special notes on the assessment of target lesions

a) Lymph nodes

Lymph nodes require special attention because normal lymph nodes can be radiologically detected despite the absence of tumor. Lymph nodes identified as measurable nodal lesions and even target lesions must meet the following criteria: **short axis measurement ≥ 15 mm**. Baseline sum of lesions only include the short axis measurements of these nodes. While the lymph nodes measured < 10 mm in short axis don't belong to the scope of pathologic nodes, and are not necessarily recorded or followed up.

b) Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). If the radiologist can give an exact measurement of the lesion, although it may be smaller than 5 mm, it still needs to be recorded.

However, if these lesions become so faint that it's difficult to identify or precisely measure them:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: If a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness).

c) Lesions that split or coalesce on treatment

- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.

- As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

14.2.4.2.2 NON-TARGET LESIONS

1. Evaluation criteria of non-target lesions

Refer to Table 14.2.4-2.

Table 14.2.4-2 Evaluation criteria of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathologic in terms of size (with the short diameter < 10 mm).
Non-CR/Non-PD (NN):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progression of Disease (PD):	Appearance of ≥ one new lesions and/or unequivocal progression of existing non-target lesions.*

*Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel.

2. Special notes on the assessment of non-target lesions

a) When the patient also has measurable disease.

- In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

b) When the patient has only non-measurable disease.

- In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e.an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'.
- If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

14.2.4.2.3 TUMOR BIOMARKERS

Tumor biomarkers will not be used to assess objective response of tumor.

14.2.4.2.4 NEW LESIONS

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (e.g.,,,.,, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

14.2.4.3 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the study treatment till the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

14.2.4.3.1 TIME POINT RESPONSE

It is assumed that at each protocol specified time point, a response assessment occurs. Table 14.2.4.3.1-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 14.2.4.3.1-2 is to be used.

Table 14.2.4.3.1-1 Time point response: patients with target (+/– non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

Table 14.2.4.3.1-2 Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = not evaluable.

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

14.2.4.3.2 MISSING ASSESSMENTS AND INEVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

14.2.4.3.3 CONFIRMATION SCANNING

Response confirmation: Complete or partial responses can be determined only if the repeat scanning confirms the change in tumor measurement at a subsequent time point ≥ 4 weeks later. In this study, the next scheduled tumor evaluation meets this criterion.

Confirmation of progression: In the case of equivocal progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), disease progression should be confirmed. If the repeat scan confirms that disease progression has occurred, that is, progression has been determined, the date of progression is the date of the first scanning showing progression. If the repeat scan cannot confirm the disease progression, the subject is considered to have no disease progression.

14.2.4.3.4 BEST OVERALL RESPONSE: ALL TIME POINTS

Best response is defined as the best response across all time points (confirmed later). Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

In this circumstance, the best overall response can be interpreted as in Table 14.2.4.3.4-1. When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Special notes on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to ‘normal’ size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of ‘zero’ on the case report form (CRF).

Deterioration of overall condition that requires discontinuation of treatment, but with no objective evidence of disease progression should be reported as “symptomatic worsening”. Objective progression will be confirmed despite discontinuation of treatment. Symptomatic worsening is not an objective description of response status, but a cause of treatment discontinuation. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 14.2.4.3.1-1, 14.2.4.3.1-2 and

14.2.4.3.4-1.

Table 14.2.4.3.4-1 Best overall response when confirmation of CR and PR required

Overall response at first time point	Overall response at subsequent time points	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[b] The duration of SD is required to be 6 weeks at minimum.

14.3 APPENDIX 3: GUIDANCE FOR IMMUNE-RELATED ADVERSE EVENT MANAGEMENT

Identification, diagnosis, management and dose modification for irAEs are detailed below:

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Pneumonitis	Symptomatic: dyspnea, cough, pleuritic chest pain, hypoxia Asymptomatic: lung infiltrates that mimic severe bacterial pneumonia	• Radiographic imaging of chest • Tissue and lavage samples from bronchoscopy to rule out infectious pathogens and pathologic evaluation	Moderate (grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1003 until event resolved to grade ≤ 1
			Severe (grade 3) or worse: high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; in-subject hospitalization; consultation with a respiratory physician; additional immunosuppression with infliximab can be considered	Permanent discontinuation of CS1003 treatment
Colitis	Watery diarrhea, mucus or blood in stool, abdominal pain, nausea/vomiting, dehydration, peritoneal signs, bowel perforation	• Stool cultures • Endoscopy or colonoscopy to rule out infection • Biopsy to rule out alternative etiology	Moderate (grade ≥ 2) diarrhea: antidiarrheal medication, oral hydration, electrolyte supplement	Continue dosing
			Persistent grade 2 diarrhea: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1003 until event resolves to grade ≤ 1
			Severe (grade 3) diarrhea: high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; infliximab can be considered for steroid refractory diarrhea	Withhold CS1003 until ≤ Grade 1

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			Recurrent severe (grade 3) or life-threatening (grade 4) diarrhea: high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; infliximab can be considered for steroid refractory diarrhea; in-subject hospitalization	Permanent discontinuation of CS1003 treatment
			If bowel perforation is suspected, steroid should be withheld and surgical opinion should be explored; in-subject hospitalization; Infliximab should not be administered	Permanent discontinuation from the study
Hepatitis	Symptomatic: fever, fatigue, nausea, abdominal pain, jaundice, hepatomegaly Asymptomatic: elevation of liver function tests (hepatic aminotransferases, bilirubin)	• Chemistry: elevated levels of hepatic aminotransferases • Serologic testing: should be performed to rule out viral hepatitis (including hepatitis A and B), cytomegalovirus, and Epstein-Barr virus • Ultrasonograms of the liver • Biopsy or radiologic imaging to distinguish from other etiologies of hepatic injury, such as neoplastic disease progression in the liver, infections, and effects of other medications or alcohol intake	• Moderate (grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents • For a subject with metastatic or primary hepatocellular carcinoma who has been diagnosed with moderate (grade 2) AST/ALT elevation (by ≥50% over baseline) at enrollment, CS1003 treatment will be withheld.	Withhold CS1003 until event resolves to grade ≤ 1
			• Severe (grade 3) or worse: administration of high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); if not improved after 48-72 hours, alternative immunosuppression	Permanent discontinuation of CS1003 treatment

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			agents (mycophenolate mofetil) should be considered; in-subject hospitalization; consultation with a hepatologist • For a subject with metastatic or primary hepatocellular carcinoma who has been diagnosed with moderate (Grade 2) AST/ALT elevation (by ≥50% over baseline and persists for one week or longer) at enrollment, CS1003 treatment will be permanently discontinued. • Total serum bilirubin >3 times upper limit of normal	
Hypophysitis	Headache refractory to nonsteroidal anti-inflammatory drugs or other analgesics; weakness; fatigue, weight gain or weight loss; changes in mood or behavior; hypotension; electrolyte disturbances; abdominal pain; loss of libido; adrenal crisis; hypogonadism	• Clinical chemistry tests • Endocrinological laboratory test, ACTH, thyroid function test • Magnetic resonance imaging (MRI) of the brain: enlargement of the pituitary with variable contrast enhancement characteristics	Moderate (grade 2) without adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); initiate appropriate hormone replacement therapy; consultation with an endocrinologist	Withhold CS1003 until event resolves to grade ≤ 1
			grade ≥ 3 or adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); consultation with an endocrinologist	Permanent discontinuation of CS1003 treatment

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Nephritis	Hematuria, peripheral edema, elevated serum creatinine	• Clinical chemistry tests • Urine test • Biopsy if necessary	Moderate (Grade 2): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1003 until event resolves to grade ≤ 1
			Severe (grade 3) or worse: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Permanent discontinuation of CS1003 treatment
Hypothyroidism /hyperthyroidism	Typically asymptomatic and is identified by lab tests	Triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH) test results	Asymptomatic ≤ moderate (grade 2) hypothyroidism: thyroxine replacement therapy	Continue dosing
			Asymptomatic moderate (grade 2) or milder hyperthyroidism: consider beta blockade	Continue dosing
			Severe (grade 3) or worse hypothyroidism: replacement therapy	Withhold CS1003 until event resolved to grade ≤ 1 or baseline
			Severe (grade 3) hyperthyroidism lasting ≥ 6 weeks despite active management: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1003 until event resolves to grade ≤ 1
			Life-threatening (grade 4) hyperthyroidism	Permanent discontinuation of CS1003 treatment
Dermatitis	Maculopapular rash or erythroderma, pruritus, skin ulceration, bullous dermatitis, Stevens-Johnson syndrome	• Unless an alternative etiology is identified, it should be considered immune-related • Pathologic evaluation of skin biopsy can be performed to rule out alternative etiology	Moderate (grade 2) or better (up to 30% of body surface area): topical corticosteroids and oral over-the-counter antihistamines and systemic corticosteroids if no improvement within 7 days	Continue dosing

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			Severe (grade 3, > 30% of body surface area): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1003 until event resolves to grade ≤ 2
			Life-threatening (grade 4, for example Stevens-Johnson syndrome, toxic epidermal necrosis, full-thickness dermal ulceration, necrosis or hemorrhage): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); in-subject hospitalization; consultation with a dermatologist	Permanent discontinuation of CS1003 treatment
Neuromuscular toxicity	Peripheral sensory neuropathy, muscle weakness, Guilliain-Barre syndrome, transverse myelitis, myasthenia gravis	• Physical exam of sensory change, loss of deep-tendon reflexes • Neuroimaging, nerve conduction exam • Nerve/muscle biopsy	Moderate (grade 2) or better: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold CS1003 until event resolves to grade ≤ 1
			Severe (grade 3) or worse: high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone)	Permanent discontinuation of CS1003 treatment
Ocular toxicity	Photosensitivity, pain or dryness of the eyes, blurred vision, uveitis, iritis, episcleritis	• Ophthalmic exam	Moderate (grade 2) or better: topical steroids (1% prednisolone)	Withhold CS1003 until event resolved to grade ≤ 1; if not resolved grade ≤ 1 within 14 days with topical steroids or initiation of systemic treatment, permanent discontinuation of CS1003 treatment
			≥ Severe (Grade 3): high dose corticosteroids (2-4 mg/kg/day IV methylprednisolone)	permanent discontinuation of CS1003 treatment

Potential irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Other irAEs, such as arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency, myasthenic syndrome, and rhabdomyolysis			Moderate (grade 2)	Withhold CS1003 until event resolves to grade ≤ 1
			Severe (grade 3) or worse	permanent discontinuation of CS1003 treatment

14.4 APPENDIX 4: ECOG PERFORMANCE STATUS

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Results in death;

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

14.5 APPENDIX 5: NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

When there is a reasonable uncertainty that the symptoms or signs are not of cardiac origin, the diagnosis should be *No heart disease.*

Functional Capacity	**Objective Assessment**
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

*The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*.9th ed. Boston, Mass:Little, Brown & Co; 1994:253-256.

14.6 APPENDIX 6: CHILD-PUGH CLASSIFICATION AND BCLC STAGING

Child-Pugh classification[a, b]: Class A: 5-6 points; Class B: 7-9 points; Class C: ≥ 10 points

Clinical chemistry	**1 point**	**2 points**	**3 points**
Presence of hepatic encephalopathy	None	Grade I-II	Grade III-IV
Presence of ascites	None	Mild	Moderate to severe
Total bilirubin (μmol/L)	< 34	34-51	> 51
Albumin (g/L)	> 35	28-35	< 28
Prothrombin Time prolongation (seconds)	< 4	4-6	> 6

BCLC Staging[c]

Stage	**Performance status (PS)**	**Tumor status**		**Functional status**
		Number	**Size**	
Stage 0: very early stage	0	Single	<2 cm	No portal hypertension
Stage A: early stage	0	Single	Any	Child-Pugh A-B
		Up to 3 lesions	<3cm	Child-Pugh A-B
Stage B: intermediate stage	0	Multifocal disease	Any	Child-Pugh A-B
Stage C: advanced stage	1-2	Portal vascular invasion and/or N1 and/or M1	Any	Child-Pugh A-B
Stage D: end-stage disease	3-4	Any	Any	Child-Pugh C

[a] Child CG, Turcotte JG. Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders 1964:50-64. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni

[b] MC, Williams R. Transection of the esophagus in bleeding oesophageal varices. Br J Surg 1973;60:648-52

[c] Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Sem Liver Dis 1999;19:329–38.

14.7 APPENDIX 7: CONTRACEPTION GUIDANCE

In this study, male subjects and female subjects with childbearing potential will receive CS1003 that may have adverse effects on a fetus in utero in combination with lenvatinib, which may be embryotoxic and teratogenic. Female subjects with childbearing potential and male subjects with female partners of childbearing potential should follow the guidance below for contraceptive measures.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

The contraceptive methods that can achieve a failure rate of less than 1% per year alone or in combination, when used consistently and correctly are considered as highly effective contraceptive methods.

For female subjects with childbearing potential, they must agree to use highly effective, low user dependent contraceptive methods during the protocol required period, the examples include[a]:

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomy of a female subject's male partner (highly effective provided that partner is the sole sexual partner of the female subject with childbearing potential, and that the vasectomised partner has received medical assessment of the surgical success.)
- bilateral tubal occlusion
- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation

For male subjects with female partners of childbearing potential, they must remain abstinent or use a condom plus an additional contraceptive method[a] that together result in a failure rate of <1% per year during the protocol required period. For male subjects with pregnant female partners, male subjects must remain abstinent or use a condom during the protocol required period. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

a. If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

14.8 APPENDIX 8: RESPONSIBILITY FOR MEDICATION MANAGEMENT

1. Each investigational product should have a label and package provided by CStone Pharmaceuticals (Suzhou) Co., Ltd. The sponsor can provide qualification certificate, investigational product assay report to each site, and coordinate the transportation of investigational products to each site. The investigational product will be stored in a specific area;

2. Some specifically authorized personnel at the site will manage the investigational product, receive, dispense and return the medication by strictly following applicable SOPs and drug administrative requirements.

3. The investigational product is only for use in this trial, but not any other circumstance.

4. The transport, receiving, dispensing and return of the investigational product must be recorded by an authorized personnel. The use of investigational product will be carefully recorded in the Investigational Product Use Log, signed and dated by the operator.

5. The investigator must not destroy and package or label or the residual unused medication without prior notification and permission of the Sponsor.

6. Unused investigational products will be destroyed at a third party designated by the sponsor. Used investigational products can be destroyed at site or by a third party delegated by Sponsor. Study personnel should ensure, develop and record adequate process of investigational product handling in compliance with applicable regulations, guidelines and policies. The investigational product will be destroyed per Sponsor’s approval.

14.9 APPENDIX 9: EORTC QLQ-C30/EORTC QLQ-HCC18/EQ-5D-5L SCALES

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ – HCC18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Did you feel thirsty?	1	2	3	4
32. Have you had problems with your sense of taste?	1	2	3	4
33. Have you lost muscle from your arms or legs?	1	2	3	4
34. Have you had abdominal swelling?	1	2	3	4
35. Have you been concerned by the appearance of your abdomen?	1	2	3	4
36. Have you been concerned by your skin or eyes being yellow (jaundiced)?	1	2	3	4
37. Have you had itching?	1	2	3	4
38. Have you had pain in your shoulder?	1	2	3	4
39. Have you had abdominal pain?	1	2	3	4
40. Have you had fevers?	1	2	3	4
41. Have you had chills?	1	2	3	4
42. Have you worried about getting enough nourishment?	1	2	3	4
43. Have you felt full up too quickly after beginning to eat?	1	2	3	4
44. Have you worried about your weight being too low?	1	2	3	4
45. Have you been less active than you would like to be?	1	2	3	4
46. Have you found it difficult to finish things?	1	2	3	4
47. Have you needed to sleep during the day?	1	2	3	4
During the past four weeks:				
48. Has the disease or treatment had any effect on your sex life?	1	2	3	4

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

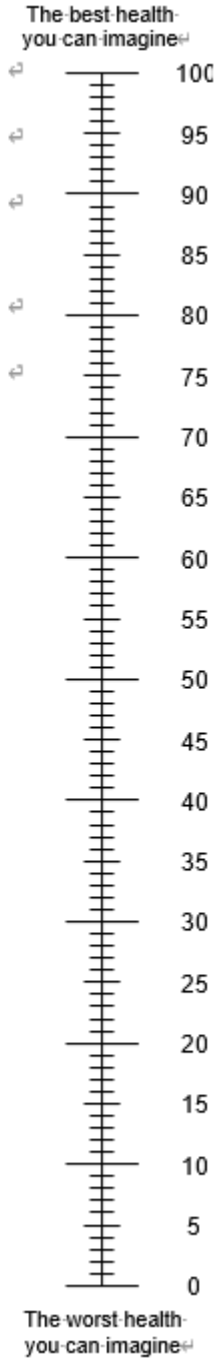
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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14.10 APPENDIX 10: AASLD LI-RADS 5 CRITERIA

Size	Criteria	Comments
≥20 mm	APHE (nonrim) **AND** one or more of following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5B or 5X
10-19 m	APHE (nonrim) **AND** the following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5A
	APHE (nonrim) **AND** "Washout" (nonperipheral)	Equivalent to 2010 AASLD criteria
	APHE (nonrim) **AND** threshold growth	Equivalent to OPTN 5A-5G

Threshold growth = size increase of a mass by ≥ 50% in ≤ 6 months; "Washout" = washout appearance; "Capsule" = capsule appearance.
Abbreviation: APHE, arterial phase hyperenhancement.

Reference: Marrero JA, Kulik LM, Sirlin CB, et al. (2018) Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 68(2):723-50

15 CHANGES TO THE PROTOCOL

Version 5.0 (Amendment 04)

Protocol CS1003-305, A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC), has been amended to version 5.0.

The main purpose of this protocol amendment is to change the dual primary endpoints of PFS and OS to a single primary endpoint of OS. This amendment is based on recently and historically disclosed data in the first-line treatment of advanced HCC. Additional updates to keep consistent within protocol and further clarification are described in the table below.

Section	Header	Summary of changes of Amendment 04 (Protocol version 5.0)	Rationale
Section 1.1	Synopsis	Approximately 7480 sites globally	Updated according to the latest enrollment.
Section 1.1/3.1	Synopsis/ Primary objective, estimand and endpoint	~~• Primary endpoint: Progression-free survival (PFS) evaluated by Blinded Independent Central Review Committee (BICR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1~~ ~~• Estimand: The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment before BICR assessed disease progression and starting of non-protocol anti-cancer treatment before disease progression. The population-level summary for PFS evaluated by Blinded Independent Central Review Committee (BICR) will be estimated by the HR from stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set.~~	Removed the PFS from the primary endpoint based on recently and historically disclosed data in the first-line treatment of advanced HCC.
Section 1.1/3.2	Synopsis/Secondary objectives, estimands and endpoints	Key secondary endpoints: • Objective response rate (ORR) assessed by Blinded Independent Central Review Committee (BICR) • Estimand: ORR assessed by BICR will be evaluated under the modified while-on-treatment strategy using tumor assessments prior to initiating non-protocol anti-cancer treatment to reflect the effect of the initially assigned randomized study treatment. The population-level summary for ORR evaluated by BICR will be presented by the rate difference between the two groups and the corresponding 95% CI using normal approximation to the binomial distribution, and p-value calculated by Stratified Mantel-Haenszel test for the ITT set. • Progression-free survival (PFS) assessed by BICR based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 • Estimand: PFS assessed by BICR will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment before BICR assessed disease progression and starting of non-protocol anti-cancer treatment before disease progression. The population-level summary for PFS evaluated by BICR will be estimated by the hazard ratio (HR) from stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set.	Designated ORR and PFS evaluated by BICR as the key secondary endpoints while designating ORR and PFS evaluated by investigators, DOR/DCR evaluated by BICR and investigators as the other secondary endpoints due to the clinical importance and likelihood of success; Removed TTP due to less importance

		Other secondary endpoints: • ~~Progression-free survival (~~PFS~~)~~ evaluated by investigator based on RECIST v1.1 • ~~Objective response rate (~~ORR~~)~~ evaluated by ~~BICR and~~ investigators based on RECIST v1.1 • Duration of response (DoR) and disease control rate (DCR) evaluated by BICR and investigators based on RECIST v1.1 • ~~Time to progression (TTP) evaluated by BICR and investigators based on RECIST v1.1~~	
Section 1.1/10.1	Synopsis/Sample size determination	Sample size determination: The primary endpoint~~s~~ of this study ~~are~~ is~~PFS assessed by BICR based on RECIST v1.1 and~~ OS. Number of events and sample size are estimated based ~~up~~on the following hypotheses: • Randomization ratio is 2:1. • Type I error is controlled for two-sided test at 0.05~~. with Bonferroni and Fallback methods.~~ • ~~PFS will be tested at a two-sided significance level of 0.01 with log-rank test.~~ • OS will be tested ~~at a two-sided significance level of 0.04~~ with log-rank test. • ~~85% power to detect the hazard ratio (HR) of 0.68 for PFS, corresponding to an improvement in median PFS from 7 months to 10.3 months.~~ • 8~~3~~0% power to detect the hazard ratio (HR) of 0.~~72~~74 for OS, corresponding to an improvement of median OS from ~~13~~19 months to ~~18~~25.7 months. • One interim analysis of OS will be conducted. Type I error will be controlled using Lan-DeMets approximation to the O'Brien-Fleming boundary. • Survival times are exponentially distributed • Assuming a recruitment period of approximately 32 months, with an average accrual rate of 3.2 subjects per month during the first 6 months and 19.8 subjects per month thereafter.~~Average enrollment rate is 26 subjects per month~~ • Dropout rate for OS is 2% per 12 months • ~~Dropout rate for PFS is 5% per 12 months~~ Based ~~up~~on the above hypotheses, approximately ~~525~~534 subjects are planned to be enrolled in this study. Approximately 3~~87 PFS~~90 OS events are needed for ~~PFS~~OS analysis, with the corresponding maximum detectable HR of 0.~~76~~809. ~~Approximately 378 death events are needed for OS analysis, with the corresponding maximum detectable HR of 0.799.~~	To re-calculate the OS events number and the overall sample size due to the change of OS assumption according to the most recently disclosed clinical data, the change of the significance level, and the change of the accrual rate.
Section 10.1	Sample size determination	ORR and PFS will be sequentially tested if OS is statistically significant. Assuming an 18% ORR in the placebo+lenvatinib arm and a 30% ORR in the CS1003+lenvatinib arm, a total sample size of 534 will provide approximately 87% power to detect a difference of ORR between the two groups under a 2-sided alpha of 0.05. Assuming an HR of 0.68 for PFS (median PFS of 7 months in the placebo+lenvatinib arm vs. 10.3 months in the CS1003+lenvatinib arm)	To clarify the statistical power of the key secondary endpoints ORR and PFS as well as the events number needed to do PFS analysis.

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<tr><td></td><td></td><td>and exponentially distributed event times, a total of 387 PFS events will provide approximately 95% power under a 2-sided alpha of 0.05.</td><td></td></tr>
<tr><td>Section 1.1/10.8</td><td>Synopsis/Interim analyses</td><td>~~The final PFS analysis will be carried out when approximately 387 PFS events are observed, which is estimated to be around 30 months after the first subject enrollment.~~
~~The~~An interim OS analysis will be carried out ~~at the same time with the final analysis of PFS. A~~when approximately ~~284~~293 death events (75% information) are ~~expected to be~~ observed, which is estimated to be around 47 months after the first subject is enrolled. ~~at that time.~~It is anticipated to have approximately ~~378~~390 death events for the final OS analysis at approximately 67~~42~~ months after the first subject is enrolled. ~~If PFS analysis result is statistically significant, the level of 0.01 will be recycled to OS analysis.~~ The interim and final OS analyses will use Lan-DeMets ~~method~~ approximation to the O’Brien-Fleming boundary to control the ~~two-sided~~ type I error rate.
Log-rank test will be used for OS hypothesis, with its analysis boundaries shown in the table below:
<table>
<tr><td></td><td>Sample size</td><td>Number of events</td><td>Time (months)</td><td>Boundary of hazard ratio</td><td>Median difference for hazard ratio boundary (months)</td><td>Boundary of P value</td></tr>
<tr><td colspan="7">~~OS (two-sided alpha = 0.04, PFS result is not statistically significant)~~</td></tr>
<tr><td>~~Interim Analyses~~</td><td>~~525~~</td><td>~~284~~</td><td>~~30~~</td><td>~~0.741~~</td><td>~~4.5~~</td><td>~~0.014~~</td></tr>
<tr><td>~~Final analysis~~</td><td>~~525~~</td><td>~~378~~</td><td>~~42~~</td><td>~~0.799~~</td><td>~~3.3~~</td><td>~~0.036~~</td></tr>
<tr><td colspan="7">OS (two-sided alpha = 0.05~~, PFS result is statistically significant~~)</td></tr>
<tr><td>Interim Analyses</td><td>534~~525~~</td><td>293~~284~~</td><td>47~~30~~</td><td>0.754~~0.751~~</td><td>~~4.3~~6.2</td><td>0.019</td></tr>
<tr><td>Final analysis</td><td>534~~525~~</td><td>390~~378~~</td><td>67~~42~~</td><td>0.809~~0.807~~</td><td>~~3.1~~4.5</td><td>0.044</td></tr>
</table>
~~One optional interim efficacy analysis for the primary endpoint of OS might be conducted to adapt to information that may emerge during the course of this study.~~
~~The interim analysis will be conducted by an external statistical group and reviewed by the iDMC.~~</td><td>To update the events number, analysis timing as well as the analysis boundaries for interim and final analyses due to the changes of overall events number and the OS assumptions. Meanwhile, the PFS-related information was deleted.</td></tr>
</table>

		IDMC An ~~I~~independent data monitoring committee (IDMC) will review the safety data collected in the trial regularly about every 3 months for the first two meetings from the first subject enrollment, and the following frequency will be adjusted based on the available safety data, e.g. every 6 months. The IDMC will also monitor the data for OS interim analysis and make recommendations to the Sponsor according to the pre-defined boundaries. Membership, roles and responsibilities, and implementation details of the IDMC will be described in the IDMC charter.	
Section 1.2/7.2	Schedule of Activities/Efficacy Assessments	Section 1.2: All the images will be transferred to central radiology laboratory for blinded independent central review (BICR, refer to BICR Guidance for details) till the number of PFS events for PFS analysis has been reached. Section 7.2: All radiological images will be transferred to the Central Radiology Laboratory for storage and review by the BICR committee (refer to BICR Guidance for details) till the number of PFS events for PFS analysis has been reached.	To further clarify the cut-off time of the radiological images transmission.
Section 2.2	Mechanism of action and background	Updated with the latest disclosed clinical data.	Updated with the latest disclosed clinical data.
Section 2.3.2	Pharmacokinetics	Updated with the latest available clinical data from CS1003-101 and CS1003-102 studies. In the 10 mg/kg multiple dose group, no systemic exposure of CS1003 was detected in any of the mice after 3rd dosing due to ADA formation. In the 6 mg/kg multiple dose group, systemic exposure of CS1003 after 4th dosing ~~was not detected~~ decreased in some ~~in any~~ of the monkeys due to ADA formation.	Updated with the latest available data to be consistent with the data in Investigator Brochure.
Section 2.4	Clinical studies	Updated with the latest available clinical data from CS1003-101 and CS1003-102 studies.	Updated with the latest available data to be consistent with the data in Investigator Brochure.
Section 4.1.3	Independent data monitoring committee (IDMC)	The Independent Data Monitoring Committee (IDMC) will be established for the purpose of monitoring the safety of investigational treatment and OS interim analysis. All data provided to IDMC for official safety and/or efficacy ~~analysis~~analyses will be kept blinded to the Sponsor.	To further clarify the process of IDMC monitoring.

Section 4.2.2	Rational for CS1003 and lencatinib combination therapy	Updated with the latest disclosed clinical data.	Updated with the latest disclosed clinical data.
Section 5.7.2	Follow-up of subjects who discontinue study treatment	Lost-to-follow up is defined as being unable to contact the subject or having insufficient data to determine subject's status after specified contact attempts by site. In this study, at least three attempts at each scheduled visit till scheduled survival follow up visit 3 should be made before determining it as a lost-to-follow up. A subject that refuses to receive survival follow-up is ~~categorized as withdrawing informed consent but~~ not lost-to-follow up. Study sites will contact subject who is not reachable~~lost to follow up~~, if possible, to determine the reason ~~for lost to follow up~~ and try best to rearrange follow-up visit. ~~At least three attempts should be made to contact each subject.~~ The process, date and means of contacting the subject will be recorded in the source documents~~study file~~.	To further clarify the process of lost-to-follow up.
Section 5.7.3	Study withdrawal	A subject who withdraws the informed consent of study treatment, assessment ~~participation~~ and information disclosure will not receive study treatment or receive any follow-up assessment or have any follow-up~~ing~~ survival data collected. The Sponsor will keep the data and information obtained before the informed consent withdrawal. If a subject only withdraws the informed consent of study treatment and assessment ~~further participation in the study~~ but not the ~~informed consent to further~~ information disclosure, the survival-related data of the subject will still be collected till the end of the study, if possible.	To further clarify the process of withdraws the informed consent.
Section 6.7.1	Permitted treatment	Adrenal replacement with ⩽ 10 mg prednisone ~~corticosteroid~~ per day or equivalents is permitted.	To specify corticosteroid and keep consistent within the protocol.
Section 6.8.1	Infusion-related reaction	**Table 6.8.1-1. Treatment Adjustment in the Event of Investigational Product-Related Infusion Reaction Symptoms**	To keep information consistent with Section 6.6.1.

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<tr><th>NCI-CTCAE Grade</th><th>Treatment Modification Investigational Product Treatment</th></tr>
<tr><td>Grade 3 ~~or 4~~ Severe ~~or life threatening~~
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated due to clinical sequelae.
~~Grade 4: Life-threatening consequences; urgent intervention indicated.~~</td><td>Subjects must permanently discontinue study treatment.~~Study treatment is immediately discontinued and infusion tube disconnected. Continuation of study treatment is at the discretion of investigator.~~Adequate medication treatment is administered as stated below.

~~Subjects must permanently discontinue study treatment. Adequate medication treatment is administered as stated below.~~</td></tr>
<tr><td>Grade 4 – life-threatening
Grade 4: Life-threatening consequences; urgent intervention indicated.</td><td>Subjects must permanently discontinue study treatment. Adequate medication treatment is administered as stated below.</td></tr>
</table>
CTCAE grade 3 or 4 infusion reaction: The study treatment must be discontinued permanently. ~~Immediately withhold the infusion.~~ Proper medical management should be administered, as indicated per type and severity of the reaction. This includes but is not limited to oral or i.v. anti-histamine, anti-pyretic, corticosteroids, epinephrine, bronchodilators, and oxygen.
~~If a subject experiences a grade 4 infusion related reaction at any time, the study treatment must be discontinued permanently.~~
~~In the event of a grade 3 infusion reaction, continuation of study treatment is at the discretion of the investigator after consultation with the Sponsor's medical monitor. If continued, the infusion time of investigational product in the next cycle should be at least 1 hours. The subject should receive oral prophylactic treatment with an antihistamine (e.g., diphenhydramine or equivalent) and an anti-pyretic (e.g., paracetamol or equivalent) and intravenous methylprednisolone 100 mg or equivalent corticosteroid before start of the infusion. Subjects should be closely monitored for clinical signs and symptoms of an infusion reaction.~~
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<tr>
<td>Section 8.4.4</td>
<td>Collection of adverse event information</td>
<td>Primary ~~Possible~~cause of death (if applicable)</td>
<td>To clarify collection of SAEs information</td>
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Section 8.4.6	Causality assessment	If the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes~~, as defined by the sponsor~~.	To avoid misunderstanding.
Section 10.3.1	Primary efficacy endpoint	The primary efficacy endpoint~~s~~ of this study ~~are~~is: ~~(1) PFS assessed by BICR based on RECIST v1.1~~ ~~(2)~~ OS **~~PFS assessed by BICR based on RECIST v1.1:~~** ~~defined as the time from the date of randomization to disease progression assessed by BICR or death, whichever occurs first. Subjects without event (no disease progression or death) will be censored at the date of last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day.~~ ~~The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment before BICR-assessed disease progression, starting of new anti-cancer treatment before disease progression.~~	Removed the PFS assessed by BICR based on RECIST v1.1 from the primary endpoint based on recently and historically disclosed data in the first-line treatment of advanced HCC. The definition of PFS assessed by BICR based on RECIST v1.1 was also removed to section 10.3.2.
Section 10.3.2	~~Multiple comparisons~~	~~Type I error rate is controlled by using Bonferroni and Fallback method in this study. Using Bonferroni method, the two-sided significance level of 0.01 is assigned to PFS (assessed by BICR based on RECIST v1.1) and 0.04 to OS. When the PFS analysis is statistically significant, the level of 0.01 will be recycled to OS analysis, then OS will be tested at the two-sided significance level of 0.05. Refer to the following graph for details.~~ **~~Figure 10.3.2-1 Type I Error Rate Allocation and Recycling~~** 	Deleted the whole section because it is not applicable anymore and change this section to 10.3.3.
Section 10.3.2	Key secondary efficacy endpoints	The key secondary efficacy endpoints of this study include ORR and PFS assessed by BICR based on RECIST v1.1. • **Objective response rate (ORR) assessed by BICR based on RECIST v1.1**: the number and proportion of subjects who achieve objective response (CR or PR) assessed by BICR will be summarized. Patients without any measurable disease at baseline or any tumor assessment after baseline will be considered non-responders. The analysis will be based on the ITT set. Stratified Mantel-Haenszel test will be used to compare the ORR between groups. Normal approximation to binomial distribution will be used to calculate 95% CI for	To further clarify the definition of ORR and PFS assessed by BICR based on RECIST v1.1.

		ORR difference between groups. Clopper Pearson method will be used to calculate the ORR and its 95% CI of each group. • **PFS assessed by BICR based on RECIST v1.1:** defined as the time from the date of randomization to disease progression assessed by BICR or death, whichever occurs first. Subjects without event (no disease progression or death) will be censored at the date of the last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day. PFS will be analyzed according to the above methods in section 10.3.1.	
Section 10.3.3	Multiple comparisons	The primary and key secondary endpoints will be tested at an overall 2-sided Type I error rate at 5% level based on the fixed sequence testing procedure at the time of primary analysis. These endpoints will be tested in the following order: · OS · ORR assessed by BICR · PFS assessed by BICR Two analyses are planned for OS – one interim analysis and one final analysis (refer to section 10.8 for more details). ORR and PFS will be sequentially tested if OS is statistically significant, and the data cutoff date of the ORR and PFS will be the date when 387 PFS events are observed.	To further clarify the method to address multiplicity issues.
Section 10.3.4	Other secondary efficacy endpoints	The other secondary efficacy endpoints of this study include ORR and PFS assessed by investigators based on RECIST v1.1, ~~and ORR,~~ DCR, and DoR ~~and TTP~~ assessed by BICR and investigators, and TTD. • **ORR assessed by investigators based on RECIST v1.1**: the number and proportion of subjects who achieve objective response (CR or PR) assessed by investigators will be summarized. Patients without any measurable disease at baseline or any tumor assessment after baseline will be considered as non-responders. The analysis will be based on ITT set. Stratified Mantel-Haenszel test will be used to compare the ORR between groups. Normal approximation to binomial distribution will be used to calculate 95% CI for ORR difference between groups. Clopper Pearson method will be used to calculate the ORR and its 95% CI of each group. • **PFS assessed by investigators based on RECIST v1.1** is defined as the time from the date of randomization to the first documented disease progression assessed by investigators or death, whichever occurs first. Subjects without event (no disease progression or death) will be censored at the date of the last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day.	To further clarify the definition of other secondary efficacy endpoints and the analysis methods.

		~~• **Objective response rate (ORR)**: the number and proportion of subjects who achieve objective response (CR or PR) will be summarized. Patients without any measurable disease at baseline or any tumor assessment after baseline will be considered as a non-responder. The analysis will be based upon ITT analysis set. Stratified Mantel-Haenszel test will be used to compare the ORR between groups. Normal approximation to binomial distribution will be used to calculate 95% CI for ORR difference between groups. Clopper Pearson method will be used to calculate the ORR and its 95% CI of each group.~~ • **Duration of response (DoR)** is defined as, among responders (CR or PR), the time interval between the date of the first occurrence of a complete or partial response and the date of PD or death due to any cause, whichever occurs first. Patients who have not progressed and still survive at the time of analysis will be censored at the date of the last tumor assessment day. DoR analysis will be based on ITT subjects with complete or partial responses. • **Disease Control Rate (DCR)** is defined as the proportion of subjects who achieve CR, PR, and SD based on RECIST v1.1. It will be analyzed similarly as ORR. ~~• **Time to progression (TTP)** is defined as interval from randomization to the first documented disease progression. Patients without progression will be censored at the date of last tumor assessment. Patients without tumor assessment after baseline will be censored on the randomization day.~~ • **Time to deterioration (TTD)** is defined as the time from randomization to the first worsening of EORTC QLQ-C30 scale. Deterioration will be measured based on the minimal clinically important change specified in the statistical analysis plan. When TTD is calculated, patients without deterioration will be censored at the date of last PRO assessment. TTD analysis is for ITT patients with baseline PRO and at least one post-baseline PRO assessment. PFS and DoR will all be analyzed according to the above methods in section 10.3.1, and DCR will be analyzed using the same method as ORR. The other secondary efficacy endpoints except TTD will be analyzed using the same data cutoff date as the key secondary endpoints. ~~TTP, PFS, DoR and TTD will all be analyzed according to the above methods in section 10.3.1.~~	
Section 10.3.5	Handling of missing data	~~For TTP analysis, patients who have not progressed at the time of analysis will be censored at the date of last tumor assessment date. For patients without post-baseline tumor assessment will be censored on the randomization day.~~	TTP has been removed. It is not applicable anymore

Section 10.5	Pharmacokinetic analyses	~~Statistics will be performed for serum concentration of CS1003 samples taken in planned sampling time points.~~The PK data in this study will be pooled with other CS1003 clinical trials-data to develop a population PK model.	To further clarify pharmacokinetic analyses.
Section 10.8.2	Optional internal analysis	~~To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for the primary endpoint of OS beyond what is specified in Section 10.8.1. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.~~ ~~The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.~~	No optional interim efficacy analysis is required.
Section 10.9	Sensitivity analysis	~~The impact of non-protocol anti-cancer treatment on PFS (assessed by BICR based on RECIST v1.1) will be assessed. Subjects who have used any non-protocol specified anti-cancer treatment before PFS event (assessed by BICR based on RECIST v1.1) will be censored on the last tumor assessment date before the use of non-protocol specified anti-cancer treatment. Subjects without any tumor assessment after the baseline will be censored on the randomization day.~~ ~~Sensitivity analysis will be carried out to evaluate the impact of missing tumor assessment on PFS (assessed by BICR based on RECIST v1.1). Subjects who have missed two or more consecutive tumor assessments before PFS event (assessed by BICR based on RECIST v1.1) will be censored on the last tumor assessment date prior to PFS (assessed by BICR based on RECIST v1.1) event. Subjects without any tumor assessment after the baseline will be censored on the randomization day.~~ The stratification factors collected by EDC are used in the sensitivity analysis for ~~PFS (assessed by BICR based on RECIST v1.1) and~~ OS. OS will also be analyzed using an unstratified Cox regression model~~Unstratified analysis will also be provided.~~ The following sensitivity analysis of OS will also be performed: patients who used PD-1/PD-L1 checkpoint inhibitors subsequent anti-cancer treatment prior to death will be censored on the day they receive PD-1/PD-L1 checkpoint inhibitors subsequent anti-cancer treatment. Refer to Section 10.3.1 for sensitivity analysis methods.	Deleted PFS related sensitivity analyses since PFS has been removed from the primary endpoint. Added one sensitivity analysis on OS that patients who used PD-1/PD-L1 checkpoint inhibitors subsequent anti-cancer treatment prior to death will be censored on the day they receive PD-1/PD-L1 checkpoint inhibitors subsequent anti-cancer treatment to further demonstrate the robustness of efficacy.

Section 14.2.4.2.2	Non-target lesions	Non-CR~~Incomplete Response~~ /Non-PD~~Stable Disease (SD)~~	To be consistent with RECIST v1.1.
Throughout the protocol		Minor modifications to correct typos, errors, adjust paragraph order, or clarifications are not shown in this table. Modifications to keep the consistency throughout the protocol.	Editorial changes

Version 4.0 (Amendment 03)

Protocol CS1003-305, A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC), has been amended to version 4.0.

The main purpose of this protocol amendment was to follow recommendations received from US Food and Drug Administration (FDA) and Italian Medicines Agency Agenzia Italiana del Farmaco (AIFA) in order to comply with local or regional guidelines, where applicable, and to protect patients' safety through minimizing any potential risks that may have impact on the patients.

Section	Header	Summary of changes of Amendment 03 (Protocol version 4.0)	Rationale
Section 1.1	Synopsis	Changes were made in accordance with those made to the protocol.	To keep information consistent whthin the protocol.
Section 1.2	Schedule of Activities (SoA)	Added the assessment and footnote of EGD: h. EGD All patients must undergo an EGD and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Added "Additional pregnancy tests may also be undertaken if requested by Institutional Review Board/Ethics Committees (IRB/ECs) or local regulations." to footnote m.	To reflect the changes in exclusion criterion #3 (footnote h) and comply with CTFG guideline on Recommendations related to contraception and pregnancy testing in clinical trials (version 1.1) (footnote m), as well as keep information consistent within the protocol.
Section 5.2	Inclusion criteria	Inclusion criterion 19 was updated. Female subjects with childbearing potential must have negative serum pregnancy test result at screening. Female subjects with childbearing potential ~~except those with documented sterilization operation or post-menopausal subjects~~, and male subjects and their female partners with childbearing potential must agree to use an ~~effective~~ contraceptive method(s) (detailed contraception guidance is provided in Section 14.7 Appendix 7) from the day of signing informed consent form (ICF), during the study and till at least 6 months after the last dose of study treatment. ~~(effective contraception methods are listed in Section 14.7 appendix 7.)~~	To comply with CTFG guideline on Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (version 1.1).
Section 5.3	Exclusion Criteria	Exclusion Criterion #3 was updated. A prior bleeding event due to esophageal or gastric varices within 6 months or other gastrointestinal bleeding events within 28 days prior to screening. Untreated or incompletely treated esophageal or gastric varices that are considered by the	To add EGD assessment during patient enrollment to minimize potential GI bleeding risk.

		investigator to be at high-risk for bleeding~~.~~ (Note: Patients must undergo an esophagogastroduodenoscopy [EGD], and all size of varices [small to large] must be assessed and treated per local standard of care prior to enrollment; patients who have undergone an EGD within 6 months of prior to initiation of study treatment do not need to repeat the procedure). Active gastric or duodenal ulcer.	
Section 5.3	Exclusion criteria	Exclusion crierion #15 was clarified. Presence of interstitial pneumonitis~~a~~ or non-infectious pneumonitis~~a~~, which might confound the evaluation or management of pulmonary toxicity associated with study treatment.	To improve the accuracy of the criterion.
Section 5.7.1	Criteria for Study Treatment Discontinuation	Criterion #3 was updated. 3. Progression of disease. ~~Treatment can be discontinued based on investigator's assessment if this is for the best interests of subjects in the judgment of the investigator~~. ~~Subject who meets the criteria for treatment beyond pseudo-progression may continue treatment till confirmation of disease progression by imaging evaluation or the subject would not receive any further clinical benefit in the judgment of the investigator~~.	To further clarify the criterion for treatment discontinuation due to disease progression and keep information consistent within the protocol.
Section 6.6.1	CS1003 or Placebo Dose Adjustment	Added clarifications for CS1003 dose adjustment for G2 hypothyroidism and hyperthyroidism. 6.6.1.1 CRITERIA OF CS1003 OR PLACEBO DOSING WITHHOLDING • Any grade 2 drug-related adverse event (non-dermal event) other than: Grade 2 drug-related fatigue or abnormal laboratory test result that doesn't require postponing study treatment Grade 2 drug-related hypothyroidism or hyperthyroidism does not require a treatment delay	To provide more details on CS1003 dose adjustment and keep consistent with guidance for irAE management in Appendix 3.

Section 6.6.3	Treatment beyond Disease Progression	The section was updated. Between the first documentation of PD and ~~tumor assessment~~ confirmation of PD, if in the investigator's judgment, subject can benefit from the study treatment and all of the following criteria are met, the subject may continue receiving study treatment after being re-consented and study treatment continuation decision should be notified to the sponsor. a) There is clinical benefit as assessed by investigator, such as absence of clinical symptoms and signs of disease progression (including worsening of laboratory values); b) The study treatment is tolerable to the subject; c) Stable ECOG performance status (PS); d) Absence of rapid progression of disease or tumor at critical anatomical sites (e.g., spinal cord compression) that requires urgent medical intervention. ~~In rare cases, subjects may continue study treatment despite disease progression confirmed by the repeated tumor imaging if in the investigator's judgment the subject may benefit from further treatment.~~ ~~The investigator has the obligation to determine if the subject will benefit from treatment beyond pseudo-progression. The investigator should make a prudent decision, providing treatment to potentially benefited subjects while avoiding long-term noneffective treatment. Written consent for continuing study treatment must be obtained from the subject prior any further study treatment provided beyond disease pseudo-progression. Any decision on continuing study~~	To remove the option for study treatment beyond confirmed disease progression to avoid noneffective treatment.

		~~treatment beyond pseudo-progression may be discussed with the medical monitor and must be recorded in the study file.~~	
Section 6.8.3	Immune-related Adverse Evetns	The section was updated to provide recommendations on identifying irAEs. CS1003 may be associated with the risks of immune-related adverse events (irAEs) based on its mechanism of action, such as immune-related pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hypothyroidism, hyperthyroidism, dermatitis, neuromuscular toxicity, ocular toxicity, arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency. When a suspected irAE occurs, the investigator should perform adequate evaluation for the subject, identify the etiology and rule out other causes. The following criteria are recommended to identify irAEs: • Temporal relationship of AE with CS1003 administration; • If the AE belongs to immune-related class effect of PD-1/PD-L1; • If the AE need be treated with corticosteroid or other immunosuppressant therapy, and if the AE is improved upon immunosuppressive treatment (for endocrine disorders: if the AE need be treated with hormone replacement or immunosuppressive treatment);	To add method for classifying adverse events as irAEs.

		• If there is the histopathology/biopsy result which is consistent with the manifestation of irAEs; • If there are the other clear etiologies, such as other pathogens, medical history, disease progression, or other concomitant medications. ~~When a suspected immune-related adverse event (irAE) occurs, the investigator should perform adequate evaluation for the subject, identify the etiology and rule out other causes.~~ Generally, ~~F~~for grade ≥ 3 irAEs or grade 2 irAEs that require suspension or discontinuation of study treatment, the investigator should report the event to the Sponsor as soon as possible and consult the Sponsor when necessary. The investigational product may be suspended and corticosteroid may be administered as per the severity of the AE. When the event resolves to grade ≤ 1, corticosteroid dose will be gradually tapered in over 1 month. Tumor necrosis factor (TNF) antagonist, mycophenolate mofetil or other medication may be used for temporary immune suppression treatment if needed. If the AE maintains at grade ≤ 1, the study treatment may resume. For any persistent, worsened or recurrent grade 3 irAE or any grade 4 irAE, the study treatment will be permanently discontinued (refer to Section 6.6.1). Identification, diagnosis, management and dose modification of irAEs are detailed in Section 14.3.	

Section 7.6	Study Procedures	Changes were made in accordance with SoA table.	To clarifty the requirements for study procedures/assessments and keep information consistent within the protocol.
Section 8.4.1	Time of AE collection	AEs and SAEs should be recorded from the time of subject signing the informed consent, throughout the treatment period and during the safety follow-up period, ~~or the subject starts a new anti-cancer treatment, whichever occurs earlier,~~ after which time, only ~~treatment~~ related SAEs need to be recorded and reported*. AEs that occur after safety follow-up visit 1 can be collected at safety follow-up visit 2 and 3 by phone calls. *Note: If the investigator becomes~~gets~~ aware of any SAE (including death) that occurs after safety follow-up or a subject withdraws from the study, and believes that this event is possibly related to the investigational product, the investigator should notify the Sponsor's pharmacovigilance team or its representative.	To further clarify the time for AE collection period and keep consistent throughout the protocol.
Section 10.8	Interim Analysis	The contents in this section were moved under new subsection 10.8.1 Planned Interim Analyses. A new subsection 10.8.2 Optional Interim Analysis was added: 10.8.2 Optional Interim Analysis To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for the primary endpoint of OS beyond what is specified in Section 10.8.1. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed. The interim analysis will be conducted by an external statistical	10.8.2 was added to allow optional interim analysis based on information that may emerge during the study conduct.

		group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.	
Section 14.7	~~Effective~~ Contraception Guidance ~~Methods~~	The section was updated with detailed contraception guidance provided. ~~The following measures are considered to be effective contraception methods:~~ ~~• Diaphragm~~ ~~• Intrauterine device~~ ~~• Cervical cap~~ ~~• Female condom~~ ~~• Condom~~ ~~• Spermicide~~	To comply with with CTFG guideline on Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (version 1.1).

		~~• Sexual abstinence~~ In this study, male subjects and female subjects with childbearing potential will receive CS1003 that may have adverse effects on a fetus in utero in combination with lenvatinib, which may be embryotoxic and teratogenic. Female subjects with childbearing potential and male subjects with female partners of childbearing potential should follow the guidance below for contraceptive measures. A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The contraceptive methods that can achieve a failure rate of less than 1% per year alone or in combination, when used consistently and correctly are considered as highly effective contraceptive methods. For female subjects with childbearing potential, they must agree to use highly effective, low user dependent contraceptive methods during the protocol required period, the examples include[a]: • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • vasectomy of a female subject's male partner (highly effective provided that partner is the sole sexual partner of the female subject with childbearing potential, and	

		that the vasectomised partner has received medical assessment of the surgical success.) • bilateral tubal occlusion • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation For male subjects with female partners of childbearing potential, they must remain abstinent or use a condom plus an additional contraceptive method[a] that together result in a failure rate of <1% per year during the protocol required period. For male subjects with pregnant female partners, male subjects must remain abstinent or use a condom during the protocol required period. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. a. If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.	
Through out the protocol		Minor modifications to correct typos, errors, adjust paragraph order, or clarifications are not shown in this table	Editorial changes

Version 3.0 (Amendment 02)
Protocol CS1003-305, A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC), has been amended to version 3.0.

Protocol Amendment Summary of Changes and Overall Rationale for Amendment.
The primary purpose of this amendment is to include text in adherence to the newly issued Food and Drug Administration (FDA) and European Medicine Agency (EMA) Guidance on the conduct of clinical trials of drugs and biological products during the Coronavirus disease 2019 (COVID-19) pandemic public health emergency and to introduce changes in specific sections of the protocol in order to minimize the impact of this pandemic on study conduct and data integrity. Other major changes include updates in inclusion/exclusion criteria and criteria for study treatment discontinuation to further clarify the requirements for patient enrollment and discontinuation from study. Statistical analyses information was updated to address regulatory agencies' comments and provide clarifications on analyses timing and methods.

Section	Header	Summary of changes of Amendment 02 (Protocol version 3.0)	Rationale
Section 1.1	Synopsis	Changes were made in accordance with those made to the protocol.	To keep information consistent whthin the protocol.
Section 1.2	Schedule of Activities (SoA)	The SoA (Table 1.2-1) was updated.	To clarify study conduct information and keep them consistent within the protocol.
		Footnote a was updated.	To clarify that there might be assessment before obtaining informed consent.
		Footnote b was updated.	To reflect changes made in the eligibility criteria.
		Footnote c was updated.	To further clarify the schedules of HBV/HCV tests.
		Footnote d was updated.	To provide more clear guidance on physical examinations.
		Footnote e for vital signs were updated to specify temperature measurement method (tympanic body temperature).	To avoid contact to participant's mouths/saliva under the COVID-19 situation.
		Footnote f, g, h, i, j, k and l were updated.	To make the requirements for lab tests clearer.

		Footnote n was updated.	To further clarify the requirements for collection of subsequent anti-cancer treatment.
		Footnote o was updated.	To further clarify the requirements for tumor imaging.
		Footnote q was added.	To refer the Table 1.2-2.
		Footnote r was updated.	In order to make the PRO procedure clearer.
Section 2.4.2	Clinical Studies	The data were updated from 15 June 2019 to 21 Mar 2020, where applicable.	To include the data in the latest CS1003 IB (v4.0).
Section 2.5	Benefit/Risk Assessment	Benefit/Risk assessment was updated.	To show that the COVID-19 is expected to have limited impact on the benefit risk assessment of the study drug. In order to safeguard the subjects' and study team's safety while ensuring procedures are done within local restrictions due to virus curbing efforts by government, several measures have been put in place.
Section 3.1	Primary objective, estimands and endpoints	Added estimand information according to ICH E9(R1). Primary endpoint: PFS Estimand: The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment,	To address regulatory agencies' (US FDA and TFDA) review comments and to be in compliance with ICH E9 requirements.

		irrespective of intercurrent events such as discontinuing treatment before BICR assessed disease progression and starting of non-protocol anti-cancer treatment before disease progression. The population-level summary for PFS evaluated by BICR will be estimated by the hazard ratio (HR) from stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set. Primary endpoint: Overall survival (OS) Estimand: The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment, withdraw or dropout the study and starting of non-protocol anti-cancer treatment. The population-level summary for OS will be estimated by the hazard ratio (HR) from stratified Cox regression model together with its corresponding 95% CI and stratified logrank p-value for the ITT set.	
Section 4.2.5	Rationale of dose selection	The results for ongoing dose expansion part in two clinical studies (CS1003-101, CS1003-102) were added.	To include the data in latest CS1003 IB (v4.0).
Section 5.2	Inclusion criteria	Inclusion criterion #1 was updated. Age ≥18 years ~~-75 years of age~~ on the day of signing informed consent (For Taiwan, the lower limit of age is 20 years).	To remove the upper limit of age for patient enrollment which is more inclusive for patient population and consistent with with regulatory agency's (US FDA) recommendation.
Section 5.2	Inclusion criteria	Inclusion criterion #3 was updated. Subjects with ~~histologically or cytologically confirmed~~ unresectable advanced HCC that is not eligible for surgery and/or locoregional therapy (Stage B or Stage C based on Barcelona Clinic Liver Cancer [BCLC] staging	To update HCC diagnosis criteria for patient enrollment.

		system indicated in Appendix 14.6), and meets either one of the following criteria: 1) histologically or cytologically confirmed diagnosis of HCC, 2) clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria. Patients without cirrhosis require histological confirmation of diagnosis. The curative treatment and/or locoregional therapy must have been completed ≥ 4 weeks prior to the baseline scan for subjects who experienced disease progression.	
Section 5.2	Inclusion criteria	Inclusion criterion #4 was updated. At least one measurable lesion can be assessed by the investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 14.2) within 14 days prior to randomization. Target lesions in the past radiation fields or that underwent locoregional therapy (~~including~~ e.g., ~~interventional therapy~~ transarterial chemoembolization [TACE] or ablation), if confirmed as radiographic progression, are considered as measurable lesions.	To update examples given to locoregional therapy.
Section 5.2	Inclusion criteria	Inclusion criterion #9 was updated. Subjects with hepatitis B virus (HBV) infection must have HBV DNA < 2000 IU/mL prior to randomization~~enrollment~~. Subjects with positive HBsAg and/or detectable HBV DNA must be treated with antiviral therapy for at least 2 weeks prior to the first dose of study treatment and must remain on antiviral therapy during the study.	To clarify time frame requirement for HBV DNA.
Section 5.2	Inclusion criteria	Inclusion criterion #18 was updated.	To clarify the requirement for coagulation parameter.

		Coagulation: International normalized ratio (INR) or~~and~~ prothrombin time (PT) ≤ 1.5 × ULN	
Section 5.3	Exclusion Criteria	Exclusion criteria #1 and #20 were updated. #1 Fibrolame~~me~~llar HCC, sarcomatoid HCC, cholangiocellular carcinoma or mixed cholangiocarcinoma and HCC. #20 Current or prior use of systemic corticosteroid (> 10 mg/day prednisone or equivalent) or other immunosuppressive medication within 14 days before the first dose of study treatment. Note: Inhaled or topical steroid, or adrenal replacement with ~~≤~~ 10 mg prednisone or equivalent is permitted if there~~,~~ is no active autoimmune disease. Short-term (≤ 7 days) steroid for prophylactic treatment (e.g., for contrast allergy) or for non-autoimmune conditions (e.g., delayed hypersensitivity caused by contrast allergy) is allowed. Corticosteroid, if required by a subject, should be taken at least two days prior to or after CS1003 or placebo infusion.	Typo error correction.
Section 5.3	Exclusion Criteria	Exclusion criterion #3 was updated. ~~Gastrointestinal bleeding (e.g., hematemesis, melena) that is active or documented within the past 6 months prior to screening.~~ A prior bleeding event due to esophageal or gastric varices within 6 months or other gastrointestinal bleeding events within 28 days prior to screening. Untreated or incompletely treated esophageal or gastric varices that are considered by the investigator to be at high-risk for bleeding. Active gastric or duodenal ulcer.	To further clarify bleeding events to be excluded.
Section 5.3	Exclusion Criteria	Exclusion criterion #4 was updated.	To further clarify location of tumor thrombus to be excluded.

		Radiographic evidence of tumor thrombus in the main trunk ~~or contralateral branch~~ of portal vein ~~(VP4)~~, vena cava or heart involvement on baseline imaging.	
Section 5.3	Exclusion Criteria	Exclusion criterion #7 was updated. ~~Palliative~~ S~~s~~urgery, or locoregional therapy for palliative purpose (e.g., to treat bone metastases or metastases causing nerve impingement) ~~(including interventional therapy, ablation, ethanol injection, etc.)~~ within 4 weeks prior to study treatment~~screening~~. Palliative radiotherapy within 2 weeks prior to study treatment~~screening~~. Minor surgery (i.e, simple excision) within 7 days prior to study treatment~~study entry~~.	To clarify the palliation therapy including timeframe requirement.
Section 5.3	Exclusion Criteria	Exclusion criterion #16 was updated. Any active infection (except for hepatitis virus infection) requires systemic treatment ~~via intravenous infusion~~ within 2 weeks prior to the first dose of study treatment.	To provide further clarification on treatments for infections.
Section 5.3	Exclusion Criteria	Exclusion criterion #19 was updated. Any use of traditional Chinese medicine preparation with anti-tumor~~HCC~~ indication (e.g., Ban Mao capsule, elemene, Kanglaite, Cinobufacini, Xiaoaiping, Huai'er granule, Ganfule tablet, Jinlong capsule and Aidi) within 14 days prior to the first dose of study treatment.	To include additional example for traditional Chinese medicine with anti-tumor indication.
Section 5.3	Exclusion Criteria	Exclusion criterion #24 was updated. Known history of drug abuse that would interfere with cooperation with the requirements of the trial.	To clarify the drug abuse history that needs to be excluded.
Section 5.7.1	Criteria for Study Treatment Discontinuation	Criteria for participant discontinuation/withdrawal from the study was updated. #3 Progression of disease ~~per BICR assessment~~.	To delete "per BICR assessment" to avoid confusion. To discontinue patients from the study infected with COVID-19 based on

		If a subject develops fever or symptoms suspected of being a result of COVID-19 infection during the study they will be instructed to follow-up with their regular healthcare provider or follow the instructions for suspected COVID-19 cases per their local health authority. Withdrawal of a subject under such conditions is at the discretion of the Investigator, following discussion with Sponsor or Medical Monitor to protect the safety of the subject, other study participants or study site staff.	Investigator's discretion and to include new individual discontinuation criteria related to COVID-19.
Section 5.7.2	Follow-up of subjects who discontinue study treatment	Tumor imaging collection requirement was updated.	To further clarify the requirements for tumor assessment and keep consistent with other sections in the protocol.
Section 6.1	Investigational products (IPs)	Removed "(preferred diluent)".	To follow CMC instructions based on data support.
Section 6.6.1	CS1003 or Placebo Dose Adjustment	Added text concerning enrolled participants with confirmed active COVID-19 infection or participants who may have come in contact with someone infected with COVID-19.	To specify interruption of study treatments for participants with active COVID-19 infection or participants who has come in contact with someone infected after discussion with sponsor.
Section 6.6.2	Lenvatinib	Footnote d in Table 6.6.2.1-1 was updated. Footnote a was added in Table 6.6.2.2-1.	To clarify requirements for lenvatinib dose adjustment.
Section 7.1	Safety assessments	Added: In case subjects are unable to visit the site due to COVID-19 related local travel restrictions, alternate arrangements may be made to complete safety assessments per local guidelines.	To include considerations for subject visitis that may be impacted by COVID-19.
Section 7.2	Efficacy assessment	Tumor imaging collection timeframe requirements for different situations were updated. The tumor imaging will be performed at 6 weeks (±7 days) after the randomization, every 6 weeks (±7 days) in the first 48 weeks, and every 12 weeks (± 7 days)	To clarify the imaging collection requirements and keep information consistent within the protocol.

		thereafter, regardless of treatment schedule, until ~~BICR assessed~~ progression of disease (PD) confirmed by radiological examination, subject withdraws informed consent, lost to follow-up, end of study, or death, whichever occurs first. Subjects who discontinue study treatment due to causes other than PD will continue to receive radiological assessments at pre-determined time points until PD, subject withdraws informed consent, lost to follow-up, end of study, or death, whichever occurs first. ~~subject withdraws informed consent or death, whichever occurs first. For all subjects except those who discontinue treatment due to disease progression assessed by imaging, radiological assessment should be performed at pre-determined time points.~~ In case subjects are unable to visit the site due to COVID-19 related local travel restrictions, alternate arrangements may be made to complete efficacy assessments per local guidelines. All radiological images will be transferred to the Central Radiology Laboratory for storage and review by the Blinded Independent Central Review (BICR) committee (refer to BICR Guidance for details). Independent central radiology evaluation will be used as evidence to support the investigator's evaluation, but not used to support any subject eligibility decision or any treatment decision. Clinical management of subjects (including treatment continuation or discontinuation) will be based on investigator's evaluation of tumor imaging and investigator's clinical judgment. ~~to determine if a subject~~	To allow flexibility in tumor imaging for COVID-19 impacted regions/countries. To clarify that BICR assessment is used as evidence to support the investigator's evaluation.

		~~has experienced progression of disease that need treatment intervention. Refer to section 5.7.1 for criteria for study treatment discontinuation.~~	
Section 7.5	Biomarker evaluation	Tumor tissue collection for biomarker analysis was updated. Archival tumor tissue can be formalin-fixed paraffin embedded (FFPE) tissue block collected previously within 5 years before randomization (preferably within 12 months), ~~(preferably collected within 12 months before randomization)~~ or 3-5 freshly sectioned unstained slides (freshly sectioned within 6 months).	To clarify tumor tissue sample collection requirements.
Section 7.6	Study procedure	Changes were made in accordance with SoA table and protocol clarification letter.	To clarifty the requirements for study procedures/assessments and keep information consistent within the protocol.
Section 8.4	Documentation of adverse events	Text added include confirmed SARS-CoV-2 infection and COVID-19 as adverse events.	To ensure that collection and recording of adverse events of confirmed SARS-CoV-2 infection and COVID-19 will be done.
Section 9.3	Quality assurance audits/inspections	Text was added to include instruction to maintain data quality and patient safety.	Contingency measures were put in place to ensure that patient safety, quality of study data, and overall study integrity.
		Text added to indicate that site monitoring visits are to be done remotely or to be kept minimum required.	To account for minimum required or remote site-monitoring visits during local restrictions applicable during COVID-19 pandemic.

		Measures to mitigate additional risk of COVID-19 were outlined.	To ensure safety of study participants from of public exposure during site visits.
Section 10.1	Sample size determination	Based upon the above hypotheses, approximately 525 subjects are planned to be enrolled in this study. Approximately 378 death events are needed for OS analysis, with the corresponding maximum~~minimum~~ detectable HR of 0.799. Approximately 387 PFS events assessed by BICR are needed for PFS analysis, with the corresponding ~~minimum~~ maximum detectable HR of 0.76. The final PFS analysis will be carried out when approximately 387 PFS events assessed by BICR are observed ~~or when the last subject is recruited, whichever occurs later,~~ which is estimated to be around 30 months after the first subject is enrolled. The interim OS analysis will be carried out at the same time with the final analysis of PFS. ~~when a~~Approximately 284 death events (75% information) are expected to be observed at that time~~or last patient is enrolled, whichever occurs later. The interim analysis of OSThe above analysis is estimated to be carried out at approximately 30 months after the first patient is enrolled; therefore this analysis may possibly will be carried out at the same time with the final analysis of PFS.~~ It's anticipated to have 378 death events for the final OS analysis at approximately 42 months after the first subject is enrolled.	To further clarify the timing of final analysis and address US FDA comments, as well as other statistical analysis clarifications.

Section 10.3.1	Primary efficacy endpoints	PFS: The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment before BICR assessed disease progression, starting of new anti-cancer treatment before disease progression. ~~The analysis method of PFS is consistent with that of OS except for the significance level. If PFS analysis shows statistically significant, the type I error rate will be recycled to OS analysis.~~ OS: The primary objective will be evaluated under the treatment policy strategy to reflect the effect of the initially assigned randomized study treatment, irrespective of intercurrent events such as discontinuing treatment, withdraw further participation in the study but not the informed consent to further information disclosure, and starting of new anti-cancer treatment. OS and PFS comparison will be based on stratified log-rank test. ~~If the primary PFS analysis is not statistically significant, the two-sided significance level of OS test is 0.04, otherwise, it's 0.05.~~ Stratified Cox regression model will be used to estimate the HR (and its 95% CI). Unstratified HR will also be provided. The stratification factors from IVRS/IWRS will be those used for randomization.	**To clarify analyses for primary** efficacy **endpoints.**
Section 10.3.3	Secondary efficacy endpoints	DoR: ~~For patients with no tumor assessment performed after the first documentation of CR or PR, the subject will be censored at the date of the first occurrence of CR or PR.~~	To clarify analyses for secondary endpoints.

Section 10.8	Interim analyses	The final PFS analysis will be carried out when approximately 387 PFS events are observed ~~or when the last subject is recruited, whichever occurs later,~~ which is estimated to be around 30 months after the first subject enrollment. The interim OS analysis will be carried out at the same time with the final analysis of PFS. ~~when a~~Approximately 284 death events (75% of data) are expected to be observed at that time, but the information fraction and the p-value boundary will be calculated based on the acutal number of deaths at that time. ~~or last patient is enrolled, whichever occurs later~~. ~~The analysis is estimated to be carried out at approximately 30 months after the first patient enrollment; therefore thisthe interim analysis of OS may will possibly be carried out at the same time with the final analysis of PFS.~~ Independent data monitoring committee (IDMC) will review the safety data collected in the trial regularly about every 3 months for the first two meetings from the first subject enrollment~~.~~, and the following frequency will be adjusted based on the available safety data, e.g. every 6 months.~~The frequency of meeting will be adjusted based on the available safety data.~~	To further clarify the statistical analysis and address US FDA comments. To clarify iDMC meeting frequency.
Section 10.9	Sensitivity analysis	~~Based on number of subjects using non-protocol specified anti-cancer treatment t~~The impact of ~~that~~ non-protocol ~~specified~~ anti-cancer treatment on PFS (assessed by BICR based on RECIST v1.1) ~~is~~ will be assessed. ~~Sensitivity analysis will be performed when more than 5% of subjects in either treatment group use anti-cancer treatment not specified in the protocol.~~	To clarify the sensitivity analysis.

Section 11.5	Protocol adherence and deviations	Text was added to include protocol deviations related to COVID-19 pandemic.	To ensure protocol deviation data with respect to COVID-19 are captured to account for analysis of study data at the time of reporting.
Section 12	Abbreviations	The list was updated to include all abbreviations added in text.	Administrative update.
Section 13	References	The list was updated to include additional references added to the text.	Administrative update.
Section 14.1	Appendix 1: safety assessments	Details of safety assessments were updated in Table 14.1.	Minor updates to keep information consistent within the protocol.
Section 14.10	Appendix 10 AASLD LI-RADS 5 crieria	New appendix was added.	To provide reference for AASLD criteria on HCC diagnosis which is included in updated Inclusion Crterion #3.
Throughout the protocol		Minor modifications to correct typos, errors or clarifications are not shown in this table	Editorial changes

Amendment 01

Protocol CS1003-305, A Multi-Center, Double-Blind, Randomized, Phase III Study to Investigate the Efficacy and Safety of CS1003 in Combination with Lenvatinib Compared to Placebo in Combination with Lenvatinib as First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma (HCC), has been amended to version 2.0.

The primary purpose of this amendment is to change the **primary endpoint from investigator assessed PFS to BICR assessed PFS** to comply with the health authority request. Additional updates in patients' eligibility criteria and other operational aspects of the protocol are being implemented in this amendment as described in the table below. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Note:
Deletions have been identified by ~~strikethroughs~~.
Additions have been identified by the use of underscore.
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Section	Header	Summary of changes of Amendment 01 (Protocol version 2.0)	Rationale
Front cover	Front cover	Added the EudraCT number. Updated the Principle investigator information.	To reflect the change of the trial information and principle investigator list.
1.1	synopsis	Changed the co-primary endpoint of investigator assessed PFS to BICR assessed PFS. Put investigator assessed PFS to secondary endpoint. * Statistical analysis plan was updated accordingly.	To comply with the health authority's request.
1.1	synopsis	Inclusion criteria 3: Subjects with ~~pathohistologically~~histologically or cytologically confirmed unresectable advanced HCC, not eligible for surgery and/or locoregional therapy (Stage B ~~or~~[that is not eligible for locoregional therapy] or Stage C based on Barcelona Clinic Liver Cancer [BCLC] staging system indicated in Appendix 14.6 ~~not eligible for radical surgery~~). The curative treatment and/or locoregional therapy~~,~~ ~~or~~ must have been completed ≥ 4 weeks prior to the baseline scan for subjects who experienced ~~progressive~~ disease ~~after surgery and/or locoregional therapy).~~ progression.	Clarify the requirements of diagnosis of study indication and prior treatment history
1.1	synopsis	Inclusion criteria 4: At least one measurable lesion can be assessed by the investigator based on RECIST 1.1 with in 14 days prior to ~~the first dose of study treatment~~ randomization	Clarify the window of baseline tumor assessment to be consistent through the protocol.
1.1	synopsis	Inclusion criteria 8: a) Interferon is only allowed for hepatitis treatment with a washout period of no less than 5 half-lives prior to the initiation of study treatment.	To clarify the use of interferon for study entry. Prior interferon use is allowed for hepatitis treatment with a washout period.
1.1	synopsis	Inclusion criteria 9: Subjects with hepatitis C virus (HCV) infection (active or past infection) are allowed to be enrolled and HCV RNA detectable subjects are allowed to receive approved anti-HCV treatment during the study.	To comply with the health authority's request to clarify that HCV patient can be enrolled and can receive approved treatment.

1.1	synopsis	Inclusion criteria 10: After the approval from local health authorities is obtained (if applicable), ~~all~~at screening, subjects must agree to provide ~~unstained~~, if available, tumor tissue ~~sections of adequate quality and the corresponding pathology report~~ for biomarker analysis ~~before randomization. During the screening, subjects only with imaging diagnosis must be confirmed by histology before enrollment. The~~. When archival tumor tissue ~~sections are prepared using~~is not available, it is optional for the subject to undergo a fresh ~~or archived sample that has been archived for < 12 months.~~ biopsy to collect tumor tissue if deemed medically safe by the Investigator (details are in section 7.5)	Clarify the requirement of tumor sample collection.
1.1	synopsis	Exclusion criteria 3: ~~Gastrointestinal bleeding (e.g., hematemesis, melena) that is active or documented within the past 6 months.~~ A prior bleeding event due to esophageal or gastric varices within 6 months prior to screening. Untreated or incompletely treated esophageal or gastric varices that are considered by the Investigator to be at high-risk for bleeding. Active gastric or duodenal ulcer.	Update the exclusion criteria for patients with risk of bleeding to mitigate the bleeding risk during study treatment.
1.1	synopsis	Exclusion criteria 4: Radiographic evidence of ~~portal vein~~ tumor thrombus in the main trunk or contralateral branch of portal vein (VP4), vena cava or heart involvement on baseline imaging.	Clarify VP4 subject will be excluded.
1.1	synopsis	Exclusion criteria 7: screening (palliative radiotherapy must be completed at least 2 weeks prior to screening). Minor surgery (i.e, simple excision) within 7 days prior study entry.	Clarify the washout window for palliative treatments.
1.1	synopsis	Exclusion 10: diastolic blood pressure > ~~100~~90 mmHg	Revised the diastolic blood pressure to >90 mmHg to comply with the clinical practice for assessment of patient with risk of hypertension.

1.1	synopsis	Exclusion 30: Major surgery ~~ortrauma~~ within 4 weeks prior to the first dose of study treatment or planned major surgery during this study. (mediastinoscopy, insertion of a central venous access device and insertion of a feeding tube are not considered major surgery).	Clarify that subjects have planned major surgery during the study treatment period is excluded.
1.1	synopsis	Exclusion 31: Serious non-healing wound, ulcer, or bone fracture.	Added the restriction to patients with risk of non-healing as inhibition of the vascular endothelial growth factor receptor (VEGFR) signaling pathway impairs angiogenesis and can disrupt wound healing.
1.1	synopsis	Exclusion 32: Urine protein≥1 g/24-hours (routine urine test, urine protein>1+ will have 24-hour urine collected to assess proteinuria).	Added the restriction to patients with risk of proteinuria consider it is a common reported adverse event of VEGFR tyrosine kinase inhibitors (TKI).
1.2	schedule of activities	Bullet "b": During ~~the~~ screening, subjects ~~only~~ with radiological diagnosis only must be confirmed by histology or cytology before ~~the first dose of study treatment. After obtaining the approval from local health authorities (if applicable), all~~ randomization. Subjects must agree to provide freshly acquired or archival tumor tissue ~~sections (3-5 unstained sections) archived~~ for ~~no more than~~ biomarker analysis (after applicable regulatory approval obtained). Archival tumor tissue can be formalin-fixed paraffin-embedded tissue block collected previously within 5 years before randomization (preferably within 12 months), or 5 freshly sectioned unstained slides (freshly sectioned) . When archival tissue is not available, it is optional for ~~PD-L1 expression test~~ the subjects to have a fresh biopsy to collect tumor tissue collection if deemed medicinally safe by the investigator. Refer to section 7.5 and Lab Manual for	Clarify the requirements for tumor sample collection.

		detailed requirements for tumor sample collection.	
1.2	schedule of activities	Bullet "l": Update the pregnancy test to be performed at each cycle and follow up in EU countries. The test window has been shortened to ±3 days and pregnant test result must be obtained before dosing of each cycle for EU countries.	To comply with the Health authority's request.
1.2	schedule of activities	Bullet "o": Tumor assessment performed within 14 days prior to the ~~first dose of study treatment~~randomization can be used as the baseline tumor evaluation if accepted by investigators… Independent central radiology evaluation will be used ~~as evidence to support the investigator's evaluation, but not used to support any~~to determine if a subject ~~eligibility decision or any~~has experienced progression of disease that need treatment ~~decision. Clinical management of subjects (including treatment continuation or discontinuation) will be based on the investigator'sevaluationaccording to tumor imagingandinvestigator'sclinicaljudgment~~.intervention.	To unify the calculation approach of tumor evaluation schedule through the protocol. To reflect the change of use BICR assessed PFS as co-primary endpoint.
1.2	schedule of activities	Bullet "s": ~~It's allowed to dispense CS1003 or placebo within 3 days at maximum prior to each day of medication administration.~~	Dispense of CS1003 is suggested to be on the same day as dose administration.
2.4	Clinical studies	Update with the latest available clinical data from CS1003-101 and CS1003-102 studies.	Update with the latest available data to be consistent with the data in Investigator Brochure per health authorities requirement.
3.1	primary objectives and endpoints	Changed the co-primary endpoint of investigator assessed PFS to BICR assessed PFS. Put investigator assessed PFS to secondary endpoint.	To comply with the health authority's request.

4.1.3	independent data monitoring committee (idmc)	The Independent Data Monitoring Committee (IDMC) will be established for the purpose of monitoring the safety ~~andefficacy~~ of investigational treatment.	IDMC monitor safety only.
4.1.5	Treatment	All subjects will receive assigned treatment until progression of disease, unacceptable toxicity, subject withdraws informed consent, death, other causes specified in the protocol~~,~~ ~~treatmentdurationreaches2~~ ~~years~~ or the end of study, whichever occurs first.	Remove the 2-year treatment limitation in the entire protocol.
4.1.6	Follow-up	Survival follow-up: Subjects will receive a follow-up visit every 12 weeks during survival follow-up, and subject without documented radiographic disease progression ~~data~~as assessed by BICR will ~~be collected~~ continued to collect tumor assessment until ~~loss~~ disease progression, lost to follow-up, death or end of study, whichever occurs first. Telephone follow-up is acceptable.	To comply with ICH E 9 that tumor assessment will be continued if a subject discontinued on study treatment without documented PD assessed by BICR.
4.2.5	Does selection rationale	Updated and expanded the dose selection rationales.	To comply with the health authority's request, clarified the rationales for the dose selection from both clinical and pre-clinical perspectives.
5.2	Inclusion criteria	Updated to be consistent with synopsis	Reflect the changes of inclusion criteria made in the synopsis
5.3	Exclusion criteria	Update to be consistent with synopsis	Reflect the changes of inclusion criteria made in the synopsis
5.5.1	Screening	4. To ensure only those who are qualified for the clinical trial to be enrolled in the study, CStone (or contracted CRO) will implement the eligibility review process for all subjects to be enrolled. Study sites will complete the study specific eligibility review form and send this form along with other	Further clarify the eligibility review process.

		redacted supporting documents deemed as necessary to CStone (or contracted CRO) for review and approval before randomization, if the process does not contradict with local regulations. A detailed guideline will be developed to ensure compliance with relevant data protection, privacy legislation and local regulations.	
5.7.1	Criteria for study treatment discontinuation	3. Progression of disease~~. (~~per BICR assessment. Treatment can be discontinued based on Investigator's assessment if this is for the best interests of subjects in the judgement of the investigator.	Clarify that PD is determined per BICR assessment to reflect the change of switching investigator assessed PFS to BICR assessed PFS while treatment decision can be made based on investigator's overall assessment of patient risk and benefit..
5.7.2	follow-up of subjects who discontinue study treatment	Apart from subjects who discontinue study treatment due to BICR assessed disease progression, radiological assessment should be performed at pre-determined time points until BICR assessed disease progression, Subject withdraws informed consent, ~~the start of new anti-cancer treatment,~~ death or the end of this study whichever occurs first…	To comply with ICH E9 when a subject discontinued from the study treatment not for the reason of PD, the tumor assessment should be continued until PD.
6.1	Investigational product	CS1003 is a monoclonal antibody drug which is liquid for single use and diluted with normal saline (0.9% sodium chloride injection) or 5% dextrose (preferred diluent) prior to i.v. administration.	To clarify the CS1003 preparation process.
6.3.3	preparation and administration of investigational product	The first infusion must be administered ~~over~~ no less than 90 minutes. In the absence of infusion-related toxicity, the second infusion ~~can~~ must be administered ~~over~~ no less than 60 minutes. And in the absence of infusion-related toxicity during second infusion, the subsequent infusions ~~can~~ must be administered ~~over~~ no less than 30 minutes.	Correction of the CS1003 infusion guideline.

6.3.3	preparation and administration of investigational product	From dilution to end of infusion, at room temperature ~~(20°C to 25°C)~~	Removed exact room temperature interpretation.
6.4.1	unblinding for expedited reporting to regulatory authorities	Unless approved for unblinding exemption, the sponsor will unblind all suspected unexpected serious adverse reaction (SUSAR) ~~in the clinical study report.~~ for the expedited reporting to regulatory authorities.	Clarify the reporting process of unblinded SUSARs during study.
6.5	Compiance to study treatment	Overdose is defined as: the subject has taken (accidentally or intentionally) a dose exceeding the protocol defined dose ~~prescribed~~ in the protocol ~~by 20%.~~.	Remove 20% here because overdose is calculated according to the prescription information which is not a fixed percentage for all medications.
6.6.1.3	criteria for permanent discontinuation of cs1003 or placebo	Continuation of lenvatinib treatment is allowed if the subject permanent discontinued with CS1003 or placebo.	Clarify any of the study treatment is allowed to be continued if the other is discontinued,
6.6.2.2	Lenvatinib Withholding and Permanent Discontinuation	Continuation with CS1003 or placebo is allowed if the subject permanent discontinued with lenvatinib.	Clarify any of the study treatment is allowed to be continued if the other is discontinued.
6.7.2	Prohibited treatment	b) Interferon treatment for hepatitis is not permitted during the treatment period.	Clarify that interferon is not allowed in the treatment period for hepatitis

6.7.2	Prohibited treatment	• Live vaccines are prohibited during the study. Live vaccines including but not limited to: measles, mumps, rubella, chickenpox / shingles (varicella), yellow fever, rabies, BCG and typhoid vaccines. Seasonal influenza vaccines for injections are generally permitted because they are inactivated virus vaccines; however, intranasal influenza vaccines (for example, FluMist®) is live attenuated vaccines thus prohibited.	Safety management plan updated to prohibit the use of live vaccine during the study.
6.7.2	Prohibited treatment	Anticoagulants or X factor inhibitors that require monitoring of the international standardized ratio (INR)., such as warfarin or similar, Treatment with low molecular weight heparin is permitted.	Safety management plan updated to prohibit the use of anticoagulants that require monitoring of INR.
7.2	Efficacy assessments	Baseline tumor evaluation should be performed by using CT or MRI within 14 days prior to the ~~first dose of study treatment.~~randomization. The tumor imaging will be performed at 6 weeks (±7 days) after the ~~first dose of study treatment~~randomization, every 6 weeks (±7 days) in the first ~~12 months~~48 weeks, and every 12 weeks (± 7 days) thereafter, regardless of treatment schedule, until BICR assessed progression of disease (PD), ~~the start of new anti-cancer treatment,~~ subject withdraws informed consent or death, whichever occurs first. Independent central radiology evaluation will be used ~~as evidence to support the investigator's evaluation, but not used to support any~~to determine if a subject ~~eligibility decision or any~~has experienced progression of disease that need treatment ~~decision. Clinical management of subjects (including~~intervention. Refer to section 5.7.1 for criteria for study treatment ~~continuation or~~ discontinuation~~) will be based on investigator's evaluation of tumor imaging and investigator's clinical judgment~~.	Clarify the window of baseline tumor assessment to be consistent through the protocol. And update the tumor assessment endpoint to reflect the changes of using BICR assessed PFS as primary endpoint.

7.5	Biomarker evaluation	After the approval from local health authorities ~~is~~ obtained (if applicable), ~~any subject who has signed the ICF must provide 3-5 evaluable unstained~~ baseline tumor tissue ~~sections at screening~~samples will be collected from subjects with proper informed consent for PD-L1 ~~tests~~expression analysis. a) Archival tumor tissue can be formalin-fixed paraffin embedded (FFPE) tissue block (preferably collected within 12 months before randomization) or 5 freshly sectioned unstained slides. Tissue block is preferred over unstained slides. b) Acceptable tissue sample include core needle punctured, resected or incisional biopsy, or surgical sample. (Note: Fine needle aspirational cytology (FNAC), ascites and pleural effusion samples are not acceptable. Tumor tissue from bone metastases is not evaluable for determination of PD-L1 expression and is therefore also not acceptable). c) Fresh biopsy should not be obtained from any RECIST-defined target lesions if possible. Consult the Sponsor when no other lesions are suitable for biopsy. The potential correlation between PD-L1 expression status and clinical efficacy will be analyzed. Detailed instructions for the collection, handling, and shipping of tumor samples are outlined in the applicable study Laboratory Manual.	The section is expanded with the detailed guideline for collecting acceptable tumor tissue for biomarker expression analysis.

7.6.1	Study procedure	•Tumor radiology examination must be completed within 14 days prior to ~~the first dose.~~randomization. If the subject takes a CT/MRI scanning within 14 days prior to ~~the first dose~~randomization, but before signing the ICF, this scanning can be used as the baseline tumor evaluation if accepted by the investigator.	Clarify the window of baseline tumor assessment to be consistent through the protocol.
7.6.3	Treatment	Urine pregnancy test ~~(time window of ± 7 days),~~ Urine pregnancy test for EU countries	Remove the ±7 day window for urine pregnancy test and add urine pregnancy test for EU countries to comply with the health authority's request.
7.6.5	Follow-up	Urine pregnancy test (for EU only)	Add urine pregnancy test in safety follow-up period to comply with the health authority's request.
7.6.6	Unscheduled visit	These assessments may include symptom-specific physical examination, ECOG PS evaluation, clinical laboratory tests, echocardiogram, immunogenicity test and radiological tumor evaluation.	Add unscheduled immunogenicity test to comply with the health authority's requirement.
8.2	Abnormal test result	Clinical diagnosis would be reported as an AE and corresponding lab abnormality would not be reported as a separate AE.	Clarify AE reporting criteria.
8.4.1	Time of AE collection	AEs and SAEs should be recorded from the time of subject signing the informed consent, throughout the treatment period and during the safety follow-up period ~~(90 days after the last dose of investigational product).~~, or the subject starts a new anti-cancer treatment, whichever occurs earlier, after which time, only treatment-related SAEs need to be recorded and reported. AEs that occur after safety follow-up visit 1 can be collected at safety follow-up visit 2 and 3 by phone calls.	Clarify the AE reporting period.

8.5.1	requirements for serious adverse event reporting	~~For details, please refer to the study specific Safety Management Plan (SMP).~~	No SMP is applicable for reference.
8.5.1	requirements for serious adverse event reporting	For subjects with normal baseline of AST or ALT and total bilirubin: Treatment-emergent AST or ALT ≥ 3 × ULN in combination with total bilirubin ≥ 2 × ULN, with no evidence of hemolysis and no evidence of ALP ≥ 2 × ULN or not available	Correction: Hy's law interpretation.
8.6	Overdose	Overdose is defined as: the ~~subject~~patient has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol ~~by 20%. Subjects~~. Patients with a suspected overdose should be managed with appropriate ~~symptomatic and~~ supportive therapy~~.~~ as determined by the investigator in consultation with the medical monitor. Any overdose should be ~~reported~~informed to the medical monitor~~. Any adverse event caused by overdose is included in standard AE documentation~~, and also reported as a protocol deviation. ~~For overdose~~Additionally, any AE occurring as a result of overdose should be included in standard AE recording; and for overdoses associated with SAE, ~~the~~ standard SAE reporting ~~method and~~ timeline ~~of SAE applies~~and procedure apply.	Remove 20% here because overdose is calculated according to the prescription information which is not a fixed percentage for all medications. Section reworded.

10.1	Sample size determination	(1) PFS assessed by ~~investigators~~BICR based on RECIST v1.1	To comply with the health authority's request to use BICR assessed PFS as co-primary endpoint and investigator assessed PFS as secondary endpoint.
10.3.1	Primary efficacy endpoint	**PFS assessed by BICR based on RECIST v1.1:** defined as the time from the date of randomization to objective disease progression assessed by BICR or death, whichever occurs first. Subjects without event (no disease progression or death) will be censored at the date of last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day. The analysis method of PFS is consistent with that of OS except for the significance level. ~~**PFS assessed by investigators based on RECIST v1.1** is defined as the time from the date of randomization to first documented disease progression assessed by investigators or death whichever occurs first. Subjects without event (no disease progression or death) will be censored at the date of last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day. The analysis method of PFS is consistent with that of OS except for the significance level.~~ If PFS analysis shows statistically significant, the ~~consumed~~ type I error rate will be recycled to OS analysis.	To comply with the health authority's request to use BICR assessed PFS as co-primary endpoint and investigator assessed PFS as secondary endpoint.
10.3.2	Multiple comparisons	Using Bonferroni method, the two-sided significance level of 0.01 is assigned to PFS (assessed by ~~investigators~~BICR based on RECIST v1.1) and 0.04 to OS.	To comply with the health authority's request to use BICR assessed PFS as co-primary endpoint and investigator assessed PFS as secondary endpoint.

10.3.3	Secondary efficacy endpoints	**~~PFS assessed by BICR based on RECIST v1.1~~** **~~is~~PFS assessed by investigators based on RECIST v1.1** is defined as the time from the date of randomization to first documented disease progression assessed by investigators or death whichever occurs first. Subjects without event (no disease progression or death) will be censored at the date of last tumor assessment. Subjects without tumor assessment after baseline will be censored on the randomization day.	To comply with the health authority's request to use BICR assessed PFS as co-primary endpoint and investigator assessed PFS as secondary endpoint.
10.3.3	Secondary efficacy endpoints	**Disease Control Rate (DCR)** is defined as the proportion of subjects who achieve CR, PR, and SD based on RECIST v1.1. It will be analyzed similarly as ORR.	DCR definition has been added to the secondary endpoint list.
10.3.3	Secondary efficacy endpoints	TTP, PFS, DoR and TTD ~~assessed by the investigator~~ will all be analyzed according to the above methods in section 10.3.1.	To comply with the health authority's request to use BICR assessed PFS as co-primary endpoint and investigator assessed PFS as secondary endpoint.
10.9	Sensitivity analysis	Based on number of subjects using non-protocol specified anti-cancer treatment the impact of that non-protocol specified anti-cancer treatment on PFS (assessed by ~~investigators~~BICR based on RECIST v1.1) is assessed. Sensitivity analysis will be performed when more than 5% of subjects in either treatment group use anti-cancer treatment not specified in the protocol. Subjects who have used any non-protocol specified anti-cancer treatment before PFS event (assessed by ~~investigators~~BICR based on RECIST v1.1) will be censored on the last tumor assessment date before the use of non-protocol specified anti-cancer treatment. Subjects without any tumor assessment after the baseline will be censored on the randomization day. Sensitivity analysis will be carried out to evaluate the impact of missing tumor assessment on PFS (assessed by	To comply with the health authority's request to use BICR assessed PFS as co-primary endpoint and investigator assessed PFS as secondary endpoint.

		~~investigators~~BICR based on RECIST v1.1). Subjects who have missed two or more consecutive tumor assessments before PFS event (assessed by ~~investigators~~BICR based on RECIST v1.1) will be censored on the last tumor assessment date prior to PFS (assessed by ~~investigators~~BICR based on RECIST v1.1) event. Subjects without any tumor assessment after the baseline will be censored on the randomization day. The stratification factors collected by EDC are used in the sensitivity analysis for PFS (assessed by ~~investigators~~BICR based on RECIST v1.1) and OS. Unstratified analysis will also be provided.	
14.7	Appendix 7: effective contraception methods	• Sexual abstinence	Sexual abstinence is considered to be effective contraception method and has been added to the protocol.
14.9	Appendix 9: EORTC QLQ - C30/EORTC QLQ - HCC18/EQ-5D-5L SCALES	EQ-5D-5L table exchange	US version is used to replace UK version.
Other sections		Minor modifications to correct typos, errors or clarifications are not shown in this table	Editorial changes.