# CLINICAL STUDY PROTOCOL

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| **Protocol Title:** | A Phase 2 Study to Investigate the Preliminary Antitumor Activity, Safety and Tolerability of Tislelizumab in Combination with Lenvatinib in Patients with Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma |
| **Protocol Identifier:** | BGB-A317-211 |
| **Phase:** | 2 |
| **Investigational Products:** | Tislelizumab (BGB-A317) |
| **Indication:** | Hepatocellular Carcinoma |
| **Sponsor:** | BeiGene (Shanghai) Co., Ltd.<br>Floor 4, Building D<br>No. 780, Cailun Road<br>Pilot Free Trade Zone<br>Shanghai 201203, P.R. China |
| **Sponsor Medical Monitor:** | [redacted]<br>BeiGene Co., Ltd.<br>26th Floor, Tower D<br>Central International Trade Center<br>6A Jianguomenwai Avenue<br>Chaoyang District 100022<br>Beijing, China<br>Phone number: [redacted]<br>Email: [redacted] |
| **Original Protocol:** | 26 October 2019 |
| **Amendment 1.0:** | 25 December 2019 |
| **NCT Number:** | NCT04401800 |

**FINAL PROTOCOL APPROVAL SHEET**

**BGB-A317-211:** A Phase 2 Study to Investigate the Preliminary Antitumor Activity, Safety and Tolerability of Tislelizumab in Combination with Lenvatinib in Patients with Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma

**BeiGene (Shanghai) Co., Ltd., Approval:**

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26-Dec-2019 | 02:02:14 PST
[redacted]

26-Dec-2019 | 02:02:18 PST

Sponsor Medical Monitor

Date

BeiGene Co., Ltd.

**INVESTIGATOR SIGNATURE PAGE**

**Protocol Title:** A Phase 2 Study to Investigate the Preliminary Antitumor Activity, Safety and Tolerability of Tislelizumab in Combination with Lenvatinib in Patients with Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma

**Protocol Identifier:** BGB-A317-211

This protocol is a confidential communication of BeiGene (Shanghai) Co., Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene (Shanghai) Co., Ltd., or one of its subsidiaries.

**Instructions for Investigator:** Please SIGN and DATE this signature page. PRINT your name, title, and the name and address of the center in which the study will be conducted. Return the signed copy to BeiGene or its designee

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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**PROTOCOL AMENDMENT 1.0 (25DEC2019)**

The primary purpose of this amendment is to revise the inclusion criteria and exclusion criteria to clarify the eligible patient population in the study.

| Applicable Section | Description of Revision |
|---|---|
| **Change: Non-content related changes made throughout the document**<br>**Reason: To provide consistency with other BeiGene tislelizumab protocols and to clarify some confusions** | |
| All Sections | • Administrative updates, correcting typos, editorial changes, and/or style and formatting revisions have been made to improve clarity and consistency throughout the document. |
| **Change: Modifications to the definition and responsibility of Safety Monitoring Committee (SMC)**<br>**Reason: To clarify the definition and responsibility of SMC and keep consistency with other BeiGene tislelizumab protocols** | |
| Section 1.5<br>Section 3.1.1<br>Section 3.8.2 | • Removed the requirement of efficacy data review<br>• Clarified the definition and responsibility of SMC |
| **Change: Revised the criteria of Concomitant Therapy**<br>**Reason: To clarify the criteria of Prohibited Concomitant Medications/Procedures** | |
| Section 6.1.2 | • Added new criterion of "anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring" in Section 6.1.2<br>• In Section 6.1.2 removed criterion of "All of the herbal remedies not recommend for use during the study treatment. Patients must notify the investigator of all herbal remedies used during the study", because there is similar criterion in Section 6.1.3 (Restricted Concomitant Medications/Procedures) |
| **Change: Updated the background information of tislelizumab**<br>**Reason: To keep consistency with the latest stage of clinical development/product launch** | |
| Section 1.2.1<br>Section 8.1 | • Modified the description of clinical development stage from "under clinical development for the treatment of several human malignancies" to "under clinical development for the treatment of HCC" |

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| **Change: Revised the references in Assessment of Causality**<br>**Reason: To provide new reference in Assessment of Causality** | |
| Section 8.3.3 | • Added "Pharmaceutical Instructions of lenvatinib" as a new reference in Section 8.3.3 |
| **Change: Updated the content of mRECIST criterion**<br>**Reason: To clarify the main assessment method** | |
| Appendix 12 | • Deleted the section of "AASLD-JNCI Guidelines for Trial Design in HCC" from mRECIST criterion |
| **Change: Revised the administration of contrast agent**<br>**Reason: To clarify the details on administration of contrast agent** | |
| Section 7.4 | • Removed the detail administration of contrast agent for contrast-enhanced computed tomography (CT) scans. |
| **Change: Updated the descriptions of PK analysis method and PK analysis set**<br>**Reason: To clarify the definition of PK analysis set and the analysis method** | |
| Synopsis<br>Section 9.1.1 | • Modified the PK analysis set into "The PK analysis set includes patients who received at least 1 dose of tislelizumab (lenvatinib) study drug and contributed at least 1 post-baseline quantifiable tislelizumab (lenvatinib) PK sample." |
| **Change: Updated definition of hypertension grade**<br>**Reason: Added the detail definition of hypertension grade in Section 3.8.2 and keep consistency with other content of this protocol** | |
| Synopsis<br>Section 3.8.2 | • Added "Hypertension will be graded using NCI-CTCAE v 5.0, based on BP measurements only (and not on the number of antihypertensive medications). Each assessment of BP and BP elevation confirmation (systolic and diastolic) should follow Section 7.3.1." as a note into Section 3.8.2 to keep consistency with other content of this protocol |
| **Change: Revised the inclusion criteria of HCC confirmed diagnosis**<br>**Reason: To clarify inclusion criteria and exclude the non-HCC histology patients** | |

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| Section 4.1<br><br>Appendix 1 | • Changed the criteria of HCC confirmed diagnosis as following: unresectable locally advanced or metastatic HCC, which must be confirmed by histologically or cytologically. Fibrolamellar, sarcomatoid, or mixed cholangiocarcinoma histology confirmed by histologically or cytologically is excluded. |

**Change: Revised the exclusion criteria**

**Reason: To specify the exclusion criteria on Exclusion Criterion #2, #3, #16 and prior #20**

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| Section 4.2 | • Change the exclusion criterion #2 as "Any clearly known invasion or tumor thrombus on first grade/second grade intrahepatic bile duct or extrahepatic bile duct"<br>• Change the exclusion criterion #3 as "Patients underwent surgical of transjugular intrahepatic portosystemic shunt (TIPS) or other forms of portosystemic shunt"<br>• Merged #16 and prior #20, removed the prior #20 |

**Change: Updated the Structure of Discontinuation from Study Treatment**

**Reason: For more clarification on criterion of discontinuation from study treatment**

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| Section 3.6.1 | • Merged section of patient discontinuation from study treatment and section of sponsor discontinuation from study treatment<br>• Added following content "loco-regional therapy" to clarify the criterion of discontinuation from study treatment |

**Change: Updated the Recommendation Priority on Method of Cardiac Function Evaluations**

**Reason: To keep consistency with clinical practice and reduce difficulties of operation**

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| Section 7.3.8<br><br>Appendix 1 | • Changed the recommendation priority as "investigator will decide the method (MUGA or echocardiograms) for evaluation of cardiac function" |

**Change: Removed Ophthalmologic Examination from safety assessment**

**Reason: Consistency with other BeiGene study protocols for tislelizumab**

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| Prior Section 7.3.3<br><br>Appendix 1 | • Deleted contents for Ophthalmologic Examination |

**Change: Revised the Further Decision of Treatment After Progression via investigator assessed based on RECIST v1.1**

**Reason: To clarify the further treatment for patient who continue study drugs beyond investigator-assessed PD based on RECIST v1.1**

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| Section 7.4<br><br>Appendix 1<br><br>Synopsis | • Removed the requirement of judgment by investigator on suspected pseudo progression, revised the treatment of investigator-assessed initial PD based on RECIST v1.1 as "all patients with initial PD via investigator assessed based on RECIST v1.1 should continue study drugs, until iCPD (investigator assessed based on iRECIST) is confirmed by repeated imaging ≥ 4 weeks later"<br>• Clarified the further treatment for patient who continue study drugs beyond investigator-assessed initial PD based on RECIST v1.1 as following:<br>o Tumor assessments are still required to be performed on original schedule plan via investigator and central site imaging facility based on RECIST v1.1, mRECIST and iRECIST respectively<br>o Unless investigator-assessed iCPD based on iRECIST, patients will continue study drugs, until the patient meet other criterion of discontinuation from study treatment (see Section 3.6.1 for details)<br>• Added the recommended time of repeated imaging after initial documentation of PD via investigator based on RECIST v1.1 |

**Change: Updated the Criterion of Discontinuation from Study Treatment**

**Reason: To keep consistency with above modification (further treatment after investigator-assessed progression based on RECIST v1.1) and keep all subjects with similar treatment duration**

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| Synopsis<br><br>Section 3.1<br><br>Section 3.3<br><br>Section 3.6.1<br><br>Section 5.3<br><br>Section 9.2.1 | • Clarify that the progression in criterion of discontinuation from study treatment:<br>o Confirmed progressive disease (iCPD) assessed by investigator based on iRECIST<br>• Revised the study drugs max treatment duration for each patient in criterion of discontinuation from study treatment:<br>o 12-month treatment duration completion |

**Change: Updated the Treatment for Patients Who Are Still Under Response or Disease Stable beyond 12-Month Treatment Duration Completion**

**Reason: To provide more benefit and clarify the treatment for patients who are still under response or disease stable beyond 12-month treatment duration completion**

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| Synopsis<br>Section 3.6.1<br>Section 5.3<br>Section 9.2.1 | • Changed the treatment as "If patients don't meet any discontinuation criterion, such as investigator-assessed iCPD based on iRECIST, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor, lenvatinib and tislelizumab will be administered until patient completes his/her 12-month treatment duration of study drugs. After 12-month treatment duration completion, if the patients are still under the response (CR, PR) or stable disease (SD) assessed by investigator based on RECIST v1.1 or under the response (complete response [iCR], partial response [iPR]), stable disease (iSD) and unconfirmed progression (iUPD) assessed by investigator based on iRECIST, and may continue receiving benefit based on investigator's assessment, tislelizumab could be further provided by sponsor, this decision must be agreed with medical monitor and documented in the study records, patients are also required to be reconsented." |
| **Change: Revised the Name of Urinalysis**<br>**Reason: To keep consistency with clinical practice** | |
| Section 4.2<br>Section 8.8.3 | • Changed the name of urine dipstick testing as "urinalysis" |
| **Change: Revised the Visit Window of D1C2**<br>**Reason: Clarify the D1C2 visit window** | |
| Section 7.3.4<br>Appendix 1 | • Modified the D1C2 visit window as "± 1" day<br>• Removed the requirement of "After Cycle 1, laboratory safety results should be reviewed within 48 hours before study drugs administration" |

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## SYNOPSIS

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| **Name of Sponsor:** | BeiGene (Shanghai) Co., Ltd |
| **Investigational Products:** | Tislelizumab (BGB-A317) |
| **Title of Study:** | A Phase 2 Study to Investigate the Preliminary Antitumor Activity, Safety and Tolerability of Tislelizumab in Combination with Lenvatinib in Patients with Unresectable Locally Advanced or Metastatic Hepatocellular Carcinoma |
| **Protocol Identifier:** | BGB-A317-211 |
| **Phase of Development:** | Phase 2 |
| **Number of Patients:** | Planned 60-66 patients will be enrolled for part 1 and part 2 (6-12 for part 1 and 54 for part 2) |
| **Study Centers:** | Approximately 10 centers in China |

**Study Objectives:**

**Primary:**

- To assess the preliminary antitumor activity as indicated by overall response rate (ORR) assessed by central site imaging facility for tumor assessment per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

**Secondary:**

- To characterize the safety and tolerability of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To assess the preliminary antitumor activity as indicated by ORR assessed by investigators per RECIST v1.1 of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To assess the preliminary antitumor activity as indicated by ORR assessed by investigators and central site imaging facility for tumor assessment per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and Immune-related Response Evaluation Criteria in Solid Tumors(iRECIST) respectively of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To assess the preliminary antitumor activity as indicated by duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) assessed by investigators and central site imaging facility for tumor assessment per RECIST v1.1, mRECIST and iRECIST respectively of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

**Exploratory:**

- To characterize the pharmacokinetic (PK) and immunogenicity of tislelizumab when given in combination with lenvatinib in Part I
- To assess OS

**Study Endpoints:**

**Primary Endpoint:**

- ORR assessed by central site imaging facility for tumor assessment based on RECIST v1.1

**Secondary Endpoints:**

- The safety and tolerability of tislelizumab in combination with lenvatinib will be evaluated by the incidence, nature, and severity of adverse events (AEs) and serious AEs (SAEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, clinical laboratory abnormalities, relevant physical exam, ECGs, vital signs and DLTs.
- ORR assessed by investigators based on RECIST v1.1
- ORR assessed by investigators and central site imaging facility respectively based on mRECIST and iRECIST
- DOR, DCR, and PFS assessed by investigators and central site imaging facility respectively based on RECIST v1.1, mRECIST and iRECIST

**Exploratory Endpoints:**

- Serum concentrations of tislelizumab and incidences of anti-tislelizumab-antibodies (ADA) in Part I
- OS

**Study Population**

Patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HCC.

**Key Eligibility Criteria**

Adult patients (≥ 18 years of age at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed unresectable locally advanced or metastatic HCC. Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease that is not amenable to or has progressed after loco-regional therapy and is not amenable to a curative treatment approach without any prior systemic treatment. All patients are also required to an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 1, and Child-Pugh A classification for liver function. No tumor thrombus involving main trunk of portal vein or inferior vena cava. At least one measurable site of disease as defined by RECIST v1.1 per radiologically. Life expectancy⩾3 months.

**Study Design**

This is an open-label, multicenter Phase 2 clinical study for patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HCC. All patients will receive study treatments until confirmed progressive disease (iCPD) assessed by investigator based on iRECIST, unacceptable toxicity, 12-month treatment duration completion, death, withdrawal of consent, study termination by sponsor or patients meet any discontinuation criterion which will be described in protocol (see Section 3.6 and Section 3.7 for details), whichever comes first. Patients will be closely monitored for safety and tolerability throughout the study. This study consists of the following two parts:

**Part 1** (Safety run-in part [21-day DLT assessment] for lenvatinib in combination with tislelizumab): Approximately 6-12 patients with unresectable locally advanced or metastatic HCC will be enrolled in this part.

- The safety and tolerability of starting dose for lenvatinib in combination with tislelizumab will be evaluated. 3 patients with baseline body weight≥60 kg and 3 patients with baseline body weight <60 kg will be enrolled. These patients will be administered with lenvatinib orally once a day and tislelizumab (200mg) by intravenous injection (IV), on Day 1 of each 21-day cycle (once every 3 weeks, Q3W). The starting dose for lenvatinib in safety run-in part will be based on baseline body weight. 12 mg lenvatinib will be administered once daily if baseline body weight of patient≥60 kg. 8 mg lenvatinib will be administered once daily if baseline body weight of patient <60 kg.
- If ≤1 of 6 patients experience a dose limiting toxicity (DLT) in lenvatinib starting dose cohort, this dose level is determined as RP2D (Recommended Phase 2 Dose). The part 2 will be started to enroll at RP2D.
- If >1 of 6 patients experience a DLT in this cohort, sponsor will decide to terminate the study or to start a new cohort to investigate lenvatinib at reduced dose. Lenvatinib dose in the dose reduced cohort may be set as 8 mg or 4 mg once daily based on baseline body weight≥60 kg or <60 kg, respectively. 6 eligible patients, 3≥60 kg and 3<60 kg will be enrolled in this cohort. Tislelizumab dose is the same, 200 mg IV Q3W.
- If≤1 of 6 patients experience a DLT in lenvatinib dose reduced cohort, this dose level is determined as RP2D. The part 2 will start to enroll at RP2D.
- If>1 of 6 patients experience a DLT in lenvatinib dose reduced cohort, the part 1 will be stopped, and part 2 won't be proceeded.

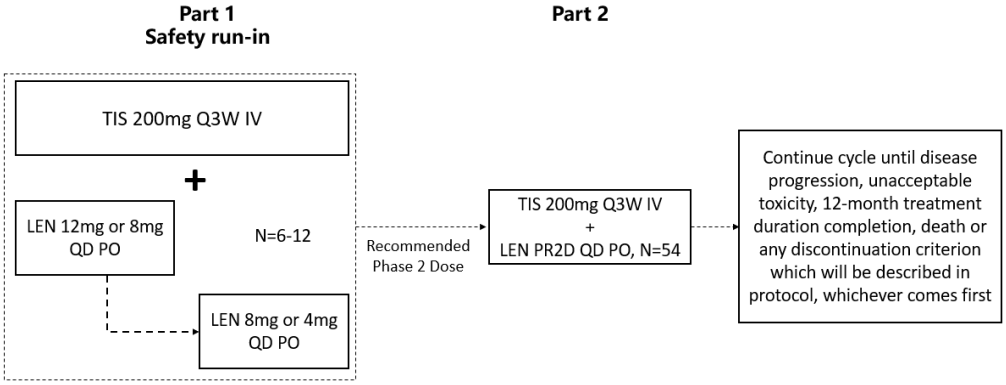
The Safety Monitoring Committee (SMC) will determine RP2D of combination treatment based on all available safety data.

**Part 2**: The planned 54 patients will be enrolled in this part. Each eligible patient will be administered by lenvatinib in combination with tislelizumab. Lenvatinib in accordance with recommended dose determined in part 1 will be administered orally, once daily continuously, tislelizumab will be administered sequentially starting on Cycle 1 Day 1 and every 21 days thereafter.

The planned 60-66 patients will be enrolled in whole study, including 6-12 patients in part 1 and 54 patients in part 2. A Simon's 2 stage design will be used to test the superiority of studied combination treatment vs. the historical control. When 30 patients dosed at RP2D level (including patients from both part 1 and part 2) are enrolled and all reach their best overall response (BOR) assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the preliminary efficiency and safety of those 30 patients will be assessed as interim analysis.

- If within these 30 patients, ≤6 patients achieve response including complete response (CR) and partial response (PR) as their BOR assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will be terminated.
- If within these 30 patients, >6 patients achieve response including CR and PR as their BOR assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will continue.
- The enrollment won't be interrupted after 30 patients were enrolled.
- If patients don't meet any discontinuation criterion, such as investigator-assessed iCPD based on iRECIST, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor, lenvatinib and tislelizumab will be administered until patient completes his/her 12-month treatment duration of study drugs. After 12-month treatment duration completion, if the patients are still under the response (CR, PR) or stable disease (SD) assessed by investigator based on RECIST v1.1 or under the response (complete response [iCR], partial response [iPR]), stable disease (iSD) and unconfirmed progression (iUPD) assessed by investigator based on iRECIST, and may continue receiving benefit based on investigator's assessment, tislelizumab could be further provided by sponsor, this decision must be agreed with medical monitor and documented in the study records, patients are also required to be reconsented.

**Study Schema**




Abbreviations: QD, once a day; Q3W, every 3 weeks; PO, orally; IV, intravenous injection; LEN, Lenvatinib; TIS, Tislelizumab.

**Note:** The dose level of tislelizumab is fixed in the entire study. In part 1 whether to proceed to the lenvatinib dose reduced cohort will depend on safety observations in lenvatinib starting dose cohort and sponsor's decision.

**Investigational Products, Dose, and Mode of Administration:**

- Tislelizumab will be administered by intravenous injection, on Day 1 of each 21-day cycle (once every 3 weeks). The dose of tislelizumab will be fixed as 200 mg.
- Lenvatinib was approved for 1st line HCC treatment in China. It will be administered orally, once daily, in a continuous manner. The starting dose and administration of lenvatinib in safety run-in part will follow Lenvatinib Package Insert strictly. Lenvatinib dose will be based on baseline body weight: 12 mg lenvatinib will be administered once daily if baseline body weight of patient

≥ 60 kg, and 8 mg lenvatinib will be administered once daily for patients with baseline body weight＜60 kg. The reduced lenvatinib dose is set as 8 mg or 4 mg once daily for patients with baseline body weight of ≥ 60 kg or＜60 kg, respectively.

**Study Assessments**

A table of study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study.

**Assessment of Dose-Limiting Toxicity**

Dose-limiting toxicity (DLT) will be assessed among evaluable patients within 21 days after the first dose administration of lenvatinib plus tislelizumab at each dose level. For DLT assessment decision, only DLTs occurring within 21 days will be evaluated. The following patients will not be considered evaluable for DLT, and will be replaced if needed to meet the minimum patient number required for safety evaluation:

- Patients who withdraw or are withdrawn from the study before completing the DLT assessment window for reasons other than a DLT.
- Patients receiving combination therapy who do not receive ≥ 75% of scheduled lenvatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window, unless they experience a DLT.

**Definition of DLT**

A DLT is defined as any of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to lenvatinib and/or tislelizumab.

**Hematologic**

- Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 3 days and requiring transfusion, or any decreased platelet count < 15,000/$mm^3$ or < 15.0 x $10^9$/ L
- ≥ Grade 4 anemia

**Non-Hematologic**

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days of initiating optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement;

- Grade 3 of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors);
- Grade 3 rash;
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset);
- Grade 3 hypertension that is resolving within 7 days of optimal supportive care;

  Note: Hypertension will be graded using NCI-CTCAE v 5.0, based on BP measurements only (and not on the number of antihypertensive medications). Each assessment of BP and BP elevation confirmation (systolic and diastolic) should follow Section 7.3.1.
- Clinically insignificant or transient abnormal laboratory findings, including but not limited to following:
  - Grade 3-4 alanine aminotransferase elevation, aspartate aminotransferase elevation or hyperbilirubinemia without significant related clinical symptoms and judged by investigators and medical monitors as non-fatal risk;
  - Grade 3-4 hyperamylasemia or hyperlipasemia that is not associated with symptoms or clinical manifestations of pancreatitis and judged by investigators and medical monitors as non-fatal risk;
  - Grade 3 proteinuria that is resolving within 7 days of optimal supportive care.

**Tumor Assessments**

Radiological assessment of tumor-response status will be performed approximately every 6 weeks (± 7 days) in the first year, then every 9 weeks (± 7 days) thereafter.

Tumor response will be assessed by investigators and central site imaging facility for tumor assessment respectively based on mRECIST, RECIST v1.1 and iRECIST.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment time point.

If radiographic initial PD is observed by the investigator based on RECIST 1.1, patients should continue treatment with tislelizumab until iCPD (investigator assessed based on iRECIST) is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 8 weeks from the date of initial documentation of PD, repeated imaging on next scheduled tumor assessment visit date, around 6 weeks from the date of initial documentation of PD is recommended). The criteria which must be met in order to treat patients to continue study drugs beyond initial PD via investigator assessed based on RECIST v1.1 will be described in protocol (see Section 7.4 for details).

The decision to continue study drug(s) beyond investigator-assessed progression must be agreed with the medical monitor and documented in the study records. In such cases, patients are also required to be reconsented.

**Central site imaging facility for tumor assessment**

Central site imaging facility for tumor assessment is composed of 3 radiology experts at the leading site or the site where the leading PI is located, specialized in tumor radiological assessment. The selection of these experts will be confirmed by leading PI and medical monitor, documented in study records. The executive plan will be described in protocol (see Section 7.4.2 for details).

**Statistical Methods**

**Analysis Sets**

- The safety analysis set includes all patients who received at least 1 dose of any study drug(s) (any component for the combination therapy). This analysis set will be used for all safety analyses.
- The efficacy evaluable analysis set includes all patients within the safety analysis set and with both measurable disease at baseline per RECIST v 1.1 and had at least 1 post treatment evaluable tumor assessment unless treatment was discontinued due to clinical progression or death before the first post treatment tumor assessment. This analysis set will be used for all efficacy analyses.
- DLT evaluable analysis set includes patients who received ≥ 75% of scheduled lenvatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window. This analysis set will be used for the DLT analyses.
- The PK analysis set includes patients who received at least 1 dose of tislelizumab (lenvatinib) and contributed at least 1 post-bassline quantifiable tislelizumab (lenvatinib) PK sample.

**DLT Analysis:**

DLTs during the DLT assessment window will be used to determine RP2D of lenvatinib in combination with tislelizumab. The DLT events will be summarized descriptively for each combination dosing level in the DLT evaluable analysis set.

**Efficacy Analysis:**

The efficacy endpoints (i.e., ORR, DOR, PFS, and DCR) will be assessed by investigators and central site imaging facility for tumor assessment respectively based on RECIST v1.1/mRECIST/iRECIST and will be summarized to evaluate the antitumor activities of Lenvatinib in combination with tislelizumab.

- ORR is defined as the proportion of patients who had complete response (CR) or partial response (PR) as their best overall response (BOR) based achieved during the study.
- DOR is defined as the time interval between the date of the earliest qualifying response (CR or PR) and the date of PD or death (whichever occurs earlier).
- DCR is defined as the proportion of patients with BOR of CR, PR or SD.
- PFS is defined as the time from the date of the first dose of study drug(s) to the date of the confirmed documentation of PD or death, whichever occurs first.
- OS is defined as the time from the date of the first dose of study drug(s) to the date of death.

Observed rates and the binomial exact 95% CI will be calculated for the proportions (ORR, DCR and each category of BOR). Hypothesis testing will be done for ORR evaluated based on RECIST v1.1 by central site imaging facility for tumor assessment according to the specified Simon's 2 stage design.

Time-to-event variables, DOR, PFS, and OS, will be estimated using the Kaplan-Meier (KM) method and be plotted over time. Median DOR, PFS, and OS, will be presented by assessor and response evaluation criteria along with their 95% CIs, if estimable. PFS rate and OS rate at 6-month and 12-month will also be provided.

**Safety Analysis:**

Safety will be determined by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECG findings will also be used in determining the safety profile. The severity of AEs will be graded according to the CTCAE v5.0. The incidence of DLT events and treatment-emergent adverse events (TEAEs) will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics (i.e., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) will be provided for above safety parameters. In addition, changes from baseline will also be provided for laboratory and vital signs parameters.

**Sample Size Considerations:**

The planned 60-66 patients will be enrolled in whole study, including 6-12 patients in part 1 and 54 patients in part 2.

Part 1 (lenvatinib in combination with tislelizumab safety run-in): Approximately 6 to 12 patients with unresectable locally advanced will be enrolled.

With total of 60 patients at RP2D from both part 1 and part 2, based on Simon's 2 stage design, we have about 95% power to detect a statistical significant difference between ORR (assessed based on RECIST v1.1) in studied combination treatment (assumed to be around 40%) to a historical of 18.8% with 1-sided alpha as 0.025. Within first 30 pts (including the 6 patients from part 1 and 24 patients from part 2) in the efficacy analysis set, if we observe$\leqslant$6 responders, study will be terminated. Otherwise, study will continue. If within the final 60 patients in the efficacy analysis set, we observe$\geqslant$18 responders, we will claim we are statistically superior than a historical control of 18.8% under the settings. Participants withdraw due to personal reason or AE before first assessment will be replaced (refer to Analysis Set), which might need 4-6 extra participants.

## LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| AASLD | American Association For The Study Of Liver Disease |
| ADA | Antidrug Antibody |
| ADCC | Antibody-Dependent Cellular Cytotoxicity |
| AEs | Adverse Events |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| APHE | Arterial Phase Hyperenhancement |
| aPTT | Activated Partial Thromboplastin Time |
| ASCO | American Society Of Clinical Oncology |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under The Curve |
| BCLC | Barcelona Clinic Liver Cancer |
| BOR | Best Overall Response |
| BP | Blood Pressure |
| CBC | Complete Blood Count |
| CDC | Complement-Dependent Cytotoxicity |
| CEC | Circulating Endothelial Cells |
| CEP | Circulating Progenitor Cells |
| CI | Confidence Interval |
| CK | Creatine Kinase |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| c-KITR | C-KIT Receptor |
| CK-MB | Creatine Kinase Mb |
| CL | Systemic Plasma Clearance |
| $C_{max}$ | Maximum Plasma Concentration |
| CP-A | Child–Pugh Classes A |
| CP-B | Child–Pugh Classes B |
| CR | Complete Response |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CYP | Cytochrome P450 Proteins |
| DCR | Disease Control Rate |
| DLT | Dose Limiting Toxicity |
| DOR | Duration Of Response |
| ECG | Electrocardiogram |
| ECHO | Echocardiography |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EFF | Efficacy Evaluable Analysis Set |
| EOT | End Of Treatment |
| ESMO | European Society For Medical Oncology |
| Fc | Fragment Crystallizable |
| FcγRIIIA | Gamma Fragment Crystallizable Region Receptor Iiia |

| Abbreviation | Definition |
|---|---|
| FDA | US Food And Drug Administration |
| FGFR | Fibroblast Growth Factor Receptors |
| FRS2α | FGF-Receptor Substrate 2A |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| GLP | Good Laboratory Practice |
| HBcAb | Hepatitis B Core Antibody |
| HBsAg | Hepatitis B Surface Antigen |
| HBV | Hepatitis B Virus |
| HCC | Hepatocellular Carcinoma |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| HUVEC | Human Umbilical Vein Endothelial Cells |
| ADL | Activity Of Daily Living |
| ICF | Informed Consent Form |
| ICH | International Council For Harmonization |
| ICU | Intensive Care Unit |
| IECs | Independent Ethics Committees |
| IgG4 | Immunoglobulin G4 |
| IND | Investigational New Drug |
| INR | International Normalized Ratio |
| irAE | Immune-Related Adverse Event |
| IRBs | Institutional Review Boards |
| iRECIST | Immune-Related Response Evaluation Criteria In Solid Tumors |
| IRRC | Independent Radiologic Review Committee |
| IV | Intravenous Injection |
| KIT | KIT Proto-Oncogenes |
| KM | Kaplan-Meier |
| LFT | Liver Function Testing |
| LPI | Last Patient In |
| LVEF | Left Ventricular Ejection Fraction |
| MedDRA® | Medical Dictionary For Regulatory Activities |
| mRECIST | Modified Response Evaluation Criteria In Solid Tumors |
| MRI | Magnetic Resonance Imaging |

| Abbreviation | Definition |
|---|---|
| MTD | Maximum Tolerated Dose |
| MUGA | Multigated Acquisition |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria For Adverse Events |
| NK cell | Natural Killer Cell |
| NMPA | National Medical Products Administration |
| NSAIDs | Non-Steroid Anti-Inflammatory Drugs |
| NSCLC | Programmed Cell Death Protein Ligand-1 |
| NYHA | New York Heart Association Classification |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PD-1 | Programmed Cell Death Protein-1 |
| PDGF-BB | PDGF-Homodimer BB |
| PD-L1 | Programmed Cell Death Protein Ligand-1 |
| PD-L2 | Programmed Cell Death Protein Ligand-2 |
| PET | Positron Emission Tomography |
| PFS | Progression-Free Survival |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PO | Orally |
| PPE | Palmar Plantar Erythrodysesthesia |
| PPES | Palmar-Plantar Erythrodysesthesia Syndrome |
| PR | Partial Response |
| PRES | Posterior Reversible Encephalopathy Syndrome |
| PT | Preferred Term |
| PT | Prothrombin Time |
| Q3W | Every 3 Weeks |
| QD | Once A Day |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| RET | RET Proto-Oncogenes |
| RP2D | Recommended Phase 2 Dose/Doses |

| Abbreviation | Definition |
|---|---|
| RPLS | Reversible Posterior Leukoencephalopathy Syndrome |
| RSI | Reference Safety Information |
| RTK | Receptor Tyrosine Kinases |
| RTKs | Receptor Tyrosine Kinases |
| SADR | Serious Adverse Drug Reaction |
| SAEs | Serious Adverse Events |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SCF | Stem Cell Factor |
| SD | Stable Disease |
| SMC | Safety Monitoring Committee |
| SOC | System Organ Class |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| sVEGFR | Soluble VEGFR |
| t1/2 | Half-Life |
| TACE | Transarterial Chemoembolization |
| TAM | Tumor Associated Macrophages |
| TC-99m | Technetium-99m |
| TEAE | Treatment Emergent Adverse Events |
| TFTs | Thyroid Function Tests |
| TKI | Tyrosine Kinase Inhibitors |
| TME | Tumor Microenvironment |
| TSH | Thyroid-Stimulating Hormone |
| ULN | Upper Limit Of Normal |
| UPCR | Urine Protein-To-Creatinine Ratio |
| Vd | Volume Of Distribution |
| VEGF | Vascular Endothelial Growth Factor |

# 1. INTRODUCTION AND RATIONALES

## 1.1. Background Information on Hepatocellular Carcinoma

Liver cancer was the sixth most common type of cancer in 2012, with 782,000 new cases worldwide, the fifth most common cancer in men (554,000 cases, 7.5% of the total number of 7410,400) and the ninth in women (228,000 cases, 3.4% of the total number of 6657,500) (Ferlay et al 2015). It was also the second most common cause of cancer-related mortality worldwide, according to the World Health Organization's GLOBOCAN 2012 database, responsible for an estimated 746,000 deaths in 2012 (Ferlay et al 2015). In 2015, there was an estimated 466,100 new liver cancer cases and 422,100 liver cancer deaths in China (Chen et al 2016), accounting for approximately 50% of the total number of cases and deaths worldwide (Torre et al 2015). In 2018, it is estimated that there will be 2215 newly diagnosed liver cancer cases in Australia, and 2088 deaths from liver cancer (AIHW 2017). HCC accounts for 80% to 90% of primary liver cancer.

A variety of risk factors are known to cause HCC. These include infection with hepatitis viruses, aflatoxin B, tobacco, vinyl chloride, heavy alcohol intake, nonalcoholic fatty liver disease, hemochromatosis, and diabetes. Together, hepatitis B virus (HBV) and hepatitis C virus (HCV) account for 80% to 90% of all HCC cases worldwide (Bosch et al 2005). Chronic HBV infection is the dominant risk factor for the disease in most areas of Asia, with the exception of Japan (El-Serag 2012), while chronic infection with HCV is the leading cause of HCC in Western countries and in Japan (Choo et al 2016).

So far, there are only 2 approved first-line systemic treatment for advanced unresectable HCC by US Food and Drug Administration (FDA): sorafenib and lenvatinib. Regorafenib has also been approved by FDA as the second line of systemic treatment (Bruix et al 2017). However, sorafenib and regorafenib are difficult for patients to tolerate. The most common side effects include hypertension, hemorrhage, hand-foot skin reaction, diarrhea, sensory neuropathy, weight loss, rash, alopecia, anorexia, and pain in abdomen. Additional its efficacy is also unsatisfied, SHARP study shows that in sorafenib group just 7 patients (2%) had a partial response according to RECIST (NEXAVAR prescribing information). Even though lenvatinib shows noninferiority to sorafenib, it still has no decrease of adverse events (AEs) rate. Even lenvatinib shows better ORR and PFS, those are still unsatisfied on efficacy for clinical practice. (Kudo et al 2018).

Oxaliplatin in FOLFOX4 chemotherapy is approved in China for unresectable HCC (Chinese hepatocellular carcinoma guideline 2017), but more frequent/severe hematological toxicity has been observed, including neutropenia, leukopenia, and thrombocytopenia (Qin et al 2013), thus limits Oxaliplatin usage in Chinese HCC patients.

Immune check point-inhibitory receptor, PD-1 is mainly expressed in activated T-cells, plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. Many clinical trial results in solid tumor shows its promising efficacy with good tolerability in cancer treatment. So far, only Nivolumab (OPDIVO updated label, 2018, El-Khoueiry et al 2017) and pembrolizumab (KEYTRUDA updated label, 2018, Zhu AX et al 2018) are approved in US as second-line monotherapy for advanced HCC after treatment failure with sorafenib. There were one-third of patients developing progressive disease (PD) , and the median

progression-free survival (PFS) of nivolumab is 4.0 months (2.9 to 5.4) in nivolumab CheckMate040 trial (El-Khoueiry et al 2017), one-third of patients developing progressive disease (PD) , and the median PFS of pembrolizumab is 4.9 months (95% CI 3.4 to 7.2) in pembrolizumab KEYNOTE224 trial ( Zhu AX et al 2018) . In pembrolizumab KEYNOTE240 trial in previously treated patients with advanced HCC, KEYNOTE-240 did not meet its co-primary endpoints of OS and PFS compared with placebo plus best supportive care (First presentation of data from KEYNOTE-240, 2019). In CheckMate-459, a randomized Phase 3 study evaluating nivolumab versus sorafenib as a first-line treatment in patients with unresectable HCC, this trial did not achieve statistical significance for its primary endpoint of OS per the pre-specified analysis (HR=0.85 [95% CI: 0.72-1.02]; p=0.0752) (Bristol-Myers Squibb Announces Results from CheckMate -459 Study, 2019).

In China as of now there are only 4 therapies approved by National Medical Products Administration (NMPA) for patients with patients with unresectable locally advanced or metastatic hepatocellular carcinoma, including sorafenib, lenvatinib, FOLFOX4 chemotherapy for first line systemic therapy and regorafenib for second line systemic therapy. As mentioned above, these 4 therapies are still unsatisfied on efficacy and safety for clinical practice.

It is believed immunotherapy in combination with TKI could achieve a synergistic effect (see section 1.4 for details) and due to limited efficacy and poor tolerability of current available monotherapy in HCC treatment, , combination therapy is becoming a hot clinical research area in cancer treatment (Masafumi Ikeda, et al. 2018 ASCO Annual Meeting).

Recently, 3 combination treatment studies showed the promising activity in HCC: lenvatinib and pembrolizumab combination trial for unresectable HCC (NCT03006926) showed 36.7% ORR in 30 evaluable patients (0/30 CR, 11/30 PR) based on RECIST1.1 per independent imaging review. Another combination trial in HCC, atezolizumab and bevacizumab (NCT02715531), presents 27% ORR by independent review facility assessment in 73 evaluable patients (4/73 CR, 16/73 PR). The median PFS was 14.9 months. (M.J. Pishvaian, et al 2018). SHR1210 combination treatment with apatinib showed the similar result. Of the 16 evaluable HCC patients, the ORR was 43.8% (Xu et al 2018). Although the results are promising and suggestive of synergistic effects, optimal anti PD-1/PD-L1 combination treatment option are still under investigation.

### 1.2. Tislelizumab as a PD-1 Blocker

Immune check point-inhibitory receptor, PD-1 is mainly expressed in activated T-cells including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes (Topalian et al 2012, Bersanelli and Buti 2017). It is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor and attenuate T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes, while the expression of PD-1 ligand, PD-L1, is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as IFN-γ and IFN-α in the tumor microenvironment. Furthermore, the increased PD-1 expression in tumor-infiltrating lymphocytes and/or PD-L1 expression in tumor and tumor-associated stromal cells is observed in many types of solid human

tumors including, but not limited to, melanoma, squamous cell carcinoma, uveal melanoma, NSCLC, head and neck squamous cell carcinoma , triple-negative breast cancer, renal cell carcinoma, bladder cancer, and ovarian cancer (Jin and Yoon 2016, ONO 2017, Patel and Kurzock 2015, Van Der Kraak et al 2016, McDaniel 2016, Gong et al 2011, Liu et al 2017, Saito et al 2013). Several anti-PD-1 agents have been approved for the treatment of several cancers. Thus, PD-1 is an established target for cancer immunotherapy.

### 1.2.1. Pharmacology

Tislelizumab is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 under clinical development for the treatment of HCC.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [KD]=0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T-cells and preactivated, primary peripheral blood mononuclear cells. In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were coinjected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to gamma fragment crystallizable region (Fc) receptor IIIA (FcγRIIIA) and complement 1q, a subunit of complement 1, by in vitro assays, suggesting either low or no antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009).

Please refer to the tislelizumab IB for additional details regarding nonclinical studies of tislelizumab.

### 1.2.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys. The pivotal toxicology studies were conducted following GLP regulations. The single-dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat-dosing regimens spanned to 3-fold higher than the maximum of the intended human doses.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in human whole-blood assay. The toxicokinetics profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The NOAEL of tislelizumab in the 13-week monkey toxicity study was to be considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study of BGB-A317-211.

Please refer to the tislelizumab IB for more detailed information on the toxicology of tislelizumab.

### 1.2.3. Clinical Pharmacology

In the Phase 1 BGB-A317_Study_001 and Study BGB-A317-102, interim PK analysis (data cutoff date 28 August 2017) was conducted using noncompartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, and 2.0 mg/kg, 5.0 mg/kg, and 200 mg once every 3 weeks. The $C_{max}$ and the AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg, both after single-dose administration at steady state. Preliminary PK data from 27 patients who were administered 1 dose of 200 mg once every 3 weeks showed tislelizumab concentrations between the range of concentrations observed for patients who were administered 2 mg/kg and 5 mg/kg doses.

Preliminary population PK analysis using a 2-compartment model with first-order elimination shows a systemic plasma clearance (CL) of tislelizumab of 0.173 L/day, volume of distribution ($V_d$) in the central and peripheral compartments of 2.89 L and 1.76 L, respectively, and half-life ($t_{1/2}$) of approximately 19 days. Race, gender, and body weight were not significant covariates on the CL of tislelizumab, which supports fixed-dosing across different ethnic groups.

### 1.2.4. Clinical Experience With Tislelizumab

As of 20 May 2019, there are 22 ongoing studies with tislelizumab. Of these, 13 have available preliminary data available: 7 monotherapy studies (BGB-A317_Study_001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGBA317-207, BGB-A317-208, and BGB-A317-209); 2 chemotherapy combination therapy studies (BGB-A317-205 and BGB-A317-206); and 4 investigational agent combination therapy studies (BGB-A317/BGB-290_Study_001 [tislelizumab in combination with BGB-290 (also known as pamiparib, a poly [ADP-ribose] polymerase [PARP] inhibitor)], BGB-3111_BGBA317_Study_001 [tislelizumab in combination with zanubrutinib (also known as BGB-3111, a Bruton's tyrosine kinase inhibitor)], BGB-900-101 [BGB-A333 (an anti-PD-L1 monoclonal antibody) alone and in combination with tislelizumab], and BGB-900-103 [tislelizumab in combination with sitravatinib (also known as MGCD516, a receptor tyrosine kinase inhibitor)]).

Additionally, there are 9 ongoing studies that do not have available clinical data yet, including 7 pivotal Phase 3 studies (Studies BGB-A317-301, BGB-A317-302, BGBA317-303, BGB-A317-304, BGB-A317-305, BGB-A317-306, and BGB-A317-307) and Studies BGB-900-102 and BGB-900-104 that have insufficient data.

Of the ongoing studies, BGB-A317_Study_001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGBA317-207, BGB-A317-208, BGB-A317-209 and BGB-900-103 are considered to be relevant to BGB-A317-211 study, available data from BGB-A317_Study_001, BGB-A317-102, BGB-A317-203, BGB-A317-204, BGBA317-207, BGB-A317-208, BGB-A317-209 and BGB-900-103 are summarized below.

Please refer to the tislelizumab IB for more detailed information on efficacy and safety of tislelizumab.

#### 1.2.4.1. Study BGB-A317_Study_001 (Monotherapy)

BGB-A317_Study_001 is a 2-stage study. Phase 1a consists of a dose escalation and dose-finding component to establish the maximum tolerated dose (MTD), if any, and recommended Phase 2 dose/doses

(RP2D). The primary objective of Phase 1a is to assess the safety and tolerability of tislelizumab in patients with advanced tumors. Phase 1b investigates efficacy in select tumor types and further evaluates the safety and tolerability of tislelizumab at the selected dose. The primary objective of Phase 1b is to assess the antitumor activity of tislelizumab in select tumor types.

This study was fully enrolled as of 27 October 2017. The MTD was not reached. Data are available from 451 patients treated on study (116 patients in Phase 1a and 335 patients in Phase 1b).

Safety results for Study BGB-A317_Study_001 are part of the pooled monotherapy analysis shown in Section 1.3.4.8. Preliminary efficacy results are summarized in Section 1.3.4.9.

#### 1.2.4.2. Study BGB-A317_Study_102 (Monotherapy)

Study BGB-A317-102 is a two-phase, non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. The dose verification substudy of Phase 1 assessed the safety and tolerability of tislelizumab in patients with advanced solid tumors and confirmed the MTD and RP2D in Chinese patients. The PK substudy of Phase 1 assesses the PK of the products derived from 2 manufacturing processes and scales (500L-FMP and 2000L-FMP), and safety and tolerability. An indication-expansion Phase 2 study involving 11 groups of indications of interest assesses the efficacy, safety, and tolerability of tislelizumab in Chinese patients with malignant solid tumors. This Phase 2 study utilizes the 200 mg IV Q3W dose and schedule, as it has been confirmed as a tolerable dose in the Chinese population.

This study was fully enrolled as of 31 May 2018. Data are available from 300 patients treated on study.

Safety results for Study BGB-A317-102 are part of the pooled monotherapy analysis shown in Section 1.3.4.8. Preliminary efficacy results are summarized in Section 1.3.4.9. PK data are not yet available.

#### 1.2.4.3. Study BGB-A317_Study_ 203 (Monotherapy)

Study BGB-A317-203 is a single-arm, multicenter, Phase 2 study of tislelizumab monotherapy in patients with relapsed or refractory classical Hodgkin lymphoma in China. The primary objective of this study is to evaluate the efficacy of tislelizumab in this population. Additionally, safety, PK, and immunogenicity are being assessed. Approximately 68 patients were planned to be enrolled into the study to receive tislelizumab at a dose of 200 mg IV Q3W. This study was fully enrolled as of 22 November 2017. Data are available from the 70 patients treated on study.

Safety results for Study BGB-A317-203 are part of the pooled monotherapy analysis shown in Section 1.3.4.8. Efficacy and PK data are currently under evaluation in a marketing application.

#### 1.2.4.4. Study BGB-A317_Study_ 204 (Monotherapy)

Study BGB-A317-204 is a single-arm, open-label, multicenter, Phase 2 study of tislelizumab monotherapy in patients with previously treated, program death ligand-1 positive (PD-L1+), locally advanced, or metastatic urothelial bladder cancer. The primary objective of this study is to determine the efficacy of tislelizumab in this population. Additionally, safety, PK, immunogenicity, and potential predictive biomarkers are being assessed. Tislelizumab 200 mg was administered by IV infusion Q3W at

a fixed dose. Approximately 110 patients were to be enrolled in this study. This study was fully enrolled as of 31 August 2018. Data are available from all 113 patients treated on study.

Safety results for Study BGB-A317-204 are part of the pooled monotherapy analysis shown in Section 1.3.4.8. Efficacy and PK data are currently under evaluation in a marketing application.

#### 1.2.4.5. Study BGB-A317_Study_ 207 (Monotherapy)

Study BGB-A317-207 is an open-label, non-randomized, multicenter, prospective, Phase 2 study of tislelizumab monotherapy in patients with relapsed or refractory mature T- and natural killer (NK)-cell neoplasms. The primary objective of this study is to determine the efficacy of tislelizumab in this patient population. Additionally, safety, PK, immunogenicity, potential predictive biomarkers, and circulating Epstein Barr virus DNA levels are being assessed.

There are three cohorts of patients: Cohort 1 includes patients with relapsed or refractory extranodal NK/T-cell lymphoma (nasal or non-nasal type), with aggressive NK leukemia excluded; Cohort 2 includes patients with relapsed or refractory mature T-cell neoplasms limited to peripheral T-cell lymphomas not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large-cell lymphoma; and Cohort 3 includes relapsed or refractory patients with stage IB-IVB cutaneous T-cell lymphomas, limited to mycosis fungoides or Sèzary syndrome. Tislelizumab 200 mg is administered IV Q3W at a fixed dose.

As of 20 May 2019, Cohort 1 was closed to enrollment with 22 patients treated. Up to 50 patients are planned for enrollment into Cohort 2, and up to 10 patients are planned for enrollment into Cohort 3, for a total sample size of up to approximately 80-85 patients. Enrollment for this study is ongoing. As of 20 May 2019, data are available from 66 patients treated on study.

Safety results for Study BGB-A317-207 are part of the pooled monotherapy analysis shown in Section 1.3.4.8. Preliminary efficacy and PK data are not yet available.

#### 1.2.4.6. Study BGB-A317_Study_ 208 (Monotherapy)

Study BGB-A317-208 is an open-label, single-arm, multicenter Phase 2 study of tislelizumab monotherapy in patients with previously treated unresectable hepatocellular carcinoma (HCC). The primary objective of this study is to evaluate efficacy in patients previously treated unresectable HCC. Additionally, safety, tolerability, PK, immunogenicity, and potential predictive biomarkers are being assessed. Tislelizumab 200 mg is administered IV Q3W at a fixed dose.

This study was fully enrolled as of 27 February 2019. Data are available from all 249 patients treated on study.

Safety results for Study BGB-A317-208 are part of the pooled monotherapy analysis shown in Section 1.3.4.8. Preliminary efficacy and PK data are not yet available.

#### 1.2.4.7. Study BGB-A317_Study_ 209 (Monotherapy)

Study BGB-A317-209 is an open-label, single-arm, multicenter, Phase 2 study of tislelizumab monotherapy in patients with previously treated locally advanced unresectable or metastatic microsatellite

instability-high or mismatch repair deficient solid tumors. The primary objective of this study is to evaluate the efficacy of tislelizumab in patients with previously treated locally advanced unresectable or metastatic solid tumors that are centrally confirmed as microsatellite instability-high or mismatch repair deficient. Additionally, duration of response, time to response, disease control rate, progression-free survival, safety, tolerability, PK, immunogenicity, and potential predictive biomarkers are being assessed. Tislelizumab 200 mg is administered IV Q3W at a fixed dose.

Approximately 60 subjects were planned to be enrolled in this study. Enrollment for this study is ongoing. As of 20 May 2019, data are available from 24 patients treated on study.

Preliminary safety results for Study BGB-A317-209 are part of the pooled monotherapy analysis shown in Section 1.3.4.8. Preliminary efficacy and PK data are not yet available

### 1.2.4.8. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy. To enhance the analysis and interpretation of the monotherapy safety profile, safety results from the relevant studies are presented based on the underlying tumor types included in the study, either as solid tumors or hematologic malignancies. The monotherapy studies within the pooled safety analysis are shown in Table 1.

**Table 1 Pooled Monotherapy Studies of tislelizumab**

| | Study | Total Enrollment (as of 20 May 2019) | Study Design |
|---|---|---|---|
| Monotherapy-Solid Tumors | BGB-A317-001 | 451 (enrollment complete) | Section 1.3.4.1 |
| | BGB-A317-102 | 300 (enrollment complete) | Section 1.3.4.2 |
| | BGB-A317-204 | 113 (enrollment complete) | Section 1.3.4.4 |
| | BGB-A317-208 | 249 (enrollment complete) | Section 1.3.4.6 |
| | BGB-A317-209 | 24 (enrollment complete) | Section 1.3.4.7 |
| Monotherapy-Hematology | BGB-A317-203 | 70 (enrollment complete) | Section 1.3.4.3 |
| | BGB-A317-207 | 66 (enrollment complete) | Section 1.3.4.5 |
| | Total | 1273 | |

The relevant pooled studies are presented based on the underlying tumor types included in the study, either as solid tumors or hematologic malignancies, and as a total pooled population.

There were 1137 patients treated in the 5 pooled solid tumor monotherapy studies. Of the 1137 enrolled, 439 patients (38.6%) remained on study as of 20 May 2019; 208 patients (18.3%) were still receiving

tislelizumab treatment, and 231 patients (18.6%) were in follow-up. At the time of data cut-off, 678 patients had a dosing period of ≥ 2 months, ie, evaluable for treatment assessment beyond 2 months. Among them, 201 patients (29.6%) continued to receive tislelizumab treatment.

There were 136 patients treated in the 2 pooled hematologic malignancies monotherapy studies. Of the 136 enrolled, 105 patients (77.2%) remained on study as of 20 May 2019; 64 patients (47.1%) were still receiving tislelizumab treatment, and 41 patients (30.2%) were in follow-up. At the time of data cut-off, 107 patients had a dosing period of ≥ 2 months, ie, evaluable for treatment assessment beyond 2 months. Among them, 60 patients (56.1%) continued to receive tislelizumab treatment.

Overall, there were 1273 patients in the Pooled Monotherapy studies. Of the 1273 enrolled, 544 patients (42.7%) remained on study as of 20 May 2019; 272 patients (21.4%) were still receiving tislelizumab treatment, and 272 patients (21.4%) were in follow-up. At the time of data cut-off, 785 patients had a dosing period of ≥ 2 months, ie, evaluable for treatment assessment beyond 2 months. Among them, 261 patients (33.2%) continued to receive tislelizumab treatment.

#### 1.2.4.8.1. Dose-Escalation DLTs and Determination of the MTD

**Study BGB-A317-001**

A DLT is defined as an AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, occurring in the first 28 days, and meeting any of the criteria listed in the study protocol.

The maximum administered dose in the dose escalation part of the study was 10 mg/kg Q2W. The MTD was not identified. Only 1 DLT of Grade 3 colitis occurred with 5 mg/kg Q2W. Based on the results of 103 patients in the dose-escalation and dose-expansion part of the Phase 1a study, 5 mg/kg Q3W was selected to explore tislelizumab activity in multiple tumor types in the Phase 1b study. An additional cohort (Phase 1a, Part 3) was added to evaluate fixed dosing at 200 mg Q3W.

**Study BGB-A317-102**

The occurrence of any of the toxicities listed in the study protocol during Cycle 1 were considered a DLT, if judged by the Investigator to be possibly, probably, or definitely related to study drug administration.

No DLTs occurred in Phase 1 dose verification portion of Study BGB-A317-102. The dose of 200 mg Q3W was confirmed as the RP2D.

#### 1.2.4.8.2. Treatment-Emergent Adverse Events Assessed as Related to Treatment with in Monotherapy Studies

As of 20 May 2019, Of the 1137 total patients in the solid tumor group within the Pooled Monotherapy studies, 734 (64.6%) experienced at least one treatment-related TEAE. The most common treatment-related TEAEs were list in table 2 below.

**Table 2 The most common treatment-related TEAEs in the solid tumor group of Tislelizumab Pooled Monotherapy studies**

| Adverse Event | Tislelizumab |
|---|---|
| The most common treatment-related TEAEs | |
| AST increased | 117 (10.3%) |
| ALT increased | 110 (9.7%) |
| Fatigue | 90 (7.9%) |
| Rash | 88 (7.7%) |
| Hypothyroidism | 85 (7.5%) |
| ≥ 1 Treatment-related TEAEs of grade ≥ 3 | 141 (12.4%) |
| Treatment-related TEAEs of grade ≥ 3 occurring in ≥1% patients | |
| AST increased | 19 (1.7%) |
| ALT increased | 15 (1.3%) |

As of 20 May 2019, within the 136 patients in the hematology group within the Pooled Monotherapy studies, 112 (82.4%) experienced at least one treatment-related TEAE. The most common treatment-related TEAEs were list in table 3 below.

**Table 3 The most common treatment-related TEAEs in the hematology group of Tislelizumab Pooled Monotherapy studies**

| Adverse Event | Tislelizumab |
|---|---|
| The most common treatment-related TEAEs | |
| Pyrexia | 46 (33.8%) |
| Hypothyroidism | 28 (20.6%) |
| Pruritus | 16 (11.8%) |
| ALT increased | 13 (9.6%) |
| AST increased | 11 (8.1%) |

| | |
|---|---|
| ≥ 1 Treatment-related TEAEs of grade ≥ 3 | 21 (15.4%) |
| Treatment-related TEAEs of grade ≥ 3 occurring in ≥1% patients | |
| Neutrophil count decreased | 3 (2.2%) |
| Lipase increased | 2 (1.5%) |
| Anemia | 2 (1.5%) |
| Neutropenia | 2 (1.5%) |
| Pneumonitis | 2 (1.5%) |
| Pneumonia | 2 (1.5%) |

As of 20 May 2019, of the 1,273 total patients treated in the Pooled Monotherapy studies, 846 (66.5%) experienced at least one treatment-related TEAE. The most common treatment-related TEAEs were list in table 4 below.

**Table 4 The most common treatment-related TEAEs in total patients of Tislelizumab Pooled Monotherapy studies**

| Adverse Event | Tislelizumab |
|---|---|
| The most common treatment-related TEAEs | |
| AST increased | 128 (10.1%) |
| ALT increased | 123 (9.7%) |
| Hypothyroidism | 113 (8.9%) |
| Rash | 96 (7.5%) |
| Pyrexia | 94 (7.4%) |
| ≥ 1 Treatment-related TEAEs of grade ≥ 3 | 163 (12.8%) |
| Treatment-related TEAEs of grade ≥ 3 occurring in ≥1% patients | |
| AST increased | 19 (1.5%) |
| ALT increased | 15 (1.2%) |

#### 1.2.4.8.3. Special Categories of Immune-Related Adverse Events with in Monotherapy Studies

As of 20 May 2019, of the 1,137 patients in the solid tumor group for the Pooled Monotherapy studies, 521 (45.8%) experienced at least one irAE of any grade. The most common irAEs were list in table 5 below.

**Table 5 The most common irAEs in the solid tumor group of Tislelizumab Pooled Monotherapy studies**

| Adverse Event | Tislelizumab |
|---|---|
| The most common irAEs of any grade | |
| AST increased | 118 (10.4%) |
| ALT increased | 111 (9.8%) |
| Rash | 88 (7.7%) |
| Hypothyroidism | 85 (7.5%) |
| Blood bilirubin increased | 66 (5.8%) |
| ≥ 1 irAEs of grade ≥ 3 | 106 (9.3%) |
| The most common irAEs of grade ≥ 3 | |
| AST increased | 21 (1.8%) |
| Gamma-glutamyltransferase increased | 17 (1.5%) |
| ALT increased | 16 (1.4%) |
| Pneumonitis | 7 (0.6%) |

As of 20 May 2019, of the 136 patients in the hematology group for the Pooled Monotherapy studies, 81 (59.6%) experienced at least one irAE of any grade. The most common irAEs were list in table 6 below.

**Table 6 The most common irAEs in the hematology group of Tislelizumab Pooled Monotherapy studies**

| Adverse Event | Tislelizumab |
|---|---|
| The most common irAEs of any grade | |
| Hypothyroidism | 28 (20.6%) |

| | |
|---|---|
| Pruritus | 16 (11.8%) |
| ALT increased | 13 (9.6%) |
| AST increased | 11 (8.1%) |
| Rash | 9 (6.6%) |
| ≥ 1 irAEs of grade ≥ 3 | 15 (11.0%) |
| The most common irAEs of grade ≥ 3 | |
| Pneumonitis | 2 (1.5%) |
| Pneumonia | 2 (1.5%) |
| Lipase increased | 2 (1.5%) |
| Blood creatine phosphokinase increased | 2 (1.5%) |

As of 20 May 2019, of the 1,273 total patients for the Pooled Monotherapy studies, 602 (47.3%) experienced at least one irAE of any grade. The most common irAEs were list in table 7 below.

**Table 7 The most common irAEs in total patients of Tislelizumab Pooled Monotherapy studies**

| Adverse Event | Tislelizumab |
|---|---|
| The most common irAEs of any grade | |
| AST increased | 129 (10.1%) |
| ALT increased | 124 (9.7%) |
| Hypothyroidism | 113 (8.9%) |
| Rash | 97 (7.6%) |
| Pruritus | 78 (6.1%) |
| ≥ 1 irAEs of grade ≥ 3 | 121 (9.5%) |
| The most common irAEs of grade ≥ 3 | |
| AST increased | 21 (1.6%) |

| | |
|---|---|
| Gamma-glutamyltransferase increased | 17 (1.3%) |
| ALT increased | 16 (1.3%) |
| Pneumonitis | 9 (0.7%) |
| Pneumonia | 9 (0.7%) |

#### 1.2.4.8.4. Fatal Adverse Events with in Monotherapy Studies

As of 20 May 2019, 68 patients (5.3%) had a TEAE leading to death. A total of 105 patients (8.2% of the total population) died within 30 days of the last study drug dose in the Pooled Monotherapy studies. Of these 105 patients, there were 21 patients (1.6% of the total population) who had an AE with a fatal outcome within 30 days of the last study drug dose. Of the 536 patients (42.1% of the total population) who died more than 30 days after the last study drug dose, 14 patients (1.1% of the total population) died as a result of an AE.

### 1.2.4.9. Pooled Efficacy Assessment of Monotherapy Studies

**Study BGB-A317-001**

BGB-A317_Study_001 is a two-stage study. Phase 1a consists of a dose escalation and dose-finding component, and Phase 1b investigates efficacy and safety in select tumor types.

There were 451 patients treated in the study and 441 patients were included in the efficacy evaluable set. Responses were assessed by the Investigator per RECIST v1.1 criteria.

Across all disease cohorts, there were 5 patients (1.1%) with a CR. A total of 55 patients (12.5%) had a confirmed PR. The resulting overall clinical response rate was 13.6%. Additionally, there were 142 patients (32.2%) with a best overall response of stable disease (SD). A total of 199 patients (45.1%) had a best response of PD in this study.

**Study BGB-A317-102**

Study BGB-A317-102 is a two-phase, non-randomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. Phase 1 includes a dose verification substudy and a substudy of PK evaluation of the products derived from 2 manufacturing processes and scales. Phase 2 is an indication expansion study.

Responses were assessed by the Investigator per the RECIST v1.1 criteria.

Overall, of the 300 patients treated in Study BGB-A317-102, 249 patients were included in the Efficacy Evaluable Analysis Set. The Efficacy Evaluable Analysis Set includes all treated patients who had at least 1 measurable baseline target lesion and had at least 1 evaluable post-baseline tumor assessment.

Across all disease cohorts and study phases, there was 1 patient (0.4%) with a CR. A total of 44 patients (17.7%) had a confirmed PR. The resulting overall clinical response rate was 18.1%. Additionally, there

were 91 patients (36.5%) with a best overall response of SD. A total of 113 patients (45.4%) had a best response of PD in this study.

#### 1.2.4.10. Study BGB-900-103 (Combination Therapy)

Study BGB-900-103 is an open-label, multicenter, non-randomized, Phase 1b study to assess the safety, tolerability, PK, and preliminary antitumor activity of sitravatinib in combination with tislelizumab in patients with advanced solid tumors. Additionally, potential pharmacodynamic biomarkers, biomarkers of efficacy or resistance, immunogenicity of tislelizumab, and overall survival are being assessed.

Approximately 140 patients were planned to be enrolled in this study. Enrollment for this study is ongoing. As of 20 May 2019, data are available from 38 patients treated on study.

Preliminary efficacy and PK data are not yet available.

**Preliminary Safety**

Of the 38 patients treated, 36 patients (94.7%) remained on study as of 20 May 2019; 31 patients (81.6%) were still receiving tislelizumab treatment, and 5 patients (13.2%) were in follow-up. At the time of data cut-off, 21 patients had a dosing period ≥ 2 months, ie, evaluable for treatment assessment beyond 2 months. Among them, 19 patients (90.5%) continued to receive tislelizumab treatment.

As of 20 May 2019, the median treatment exposure duration for tislelizumab for patients in Study BGB-900-103 was 2.15 months (range: 0.1 to 6.6), and the median study follow-up duration was 2.68 months (range: 0.1 to 6.6).

Of the 38 total patients treated in Study BGB-900-103, 19 (50.0%) experienced at least 1 TEAE assessed as related to tislelizumab by the investigator. The most common treatment-related TEAEs were summarized in table 8 below.

**Table 8 The most common treatment-related TEAEs in Study BGB-900-103**

| Adverse Event | Tislelizumab + sitravatinib |
|---|---|
| Treatment-related TEAEs | |
| ALT increased | 5 (13.2%) |
| AST increased | 3 (7.9%) |
| transaminases increased | 3 (7.9%) |
| fatigue | 3 (7.9%) |
| hypothyroidism | 3 (7.9%) |
| ≥ 1 treatment-related TEAEs of grade ≥ 3 | 4 (10.5%) |

| | |
|---|---|
| Treatment-related TEAEs of grade ≥ 3 occurring in ≥ 2 patients | |
| transaminases increased | 2 (5.3%) |
| Treatment-related TEAEs of grade ≥ 3 occurring in 1 patients | |
| ALT increased | 1 (2.6%) |
| platelet count decreased | 1 (2.6%) |
| intestinal obstruction | 1 (2.6%) |

**Special Categories of Immune-Related Treatment-Emergent Adverse Events**

Of the 38 total patients treated in Study BGB-900-103, 11 (28.9%) experienced at least 1 potential irAE. The potential irAEs occurring in 2 or more patients were ALT increased (5 patients, 13.2%; 1 patient with an event ≥ Grade 3); AST increased, transaminases increased, and hypothyroidism (3 patients each, 7.9%; 2 patients with transaminases increased events ≥ Grade 3); and diarrhea (2 patients, 5.3%). All other events occurred in single patients and no additional events ≥ Grade 3 were reported.

**Fatal Adverse Events**

As of 20 May 2019, there had been no fatal AEs reported in Study BGB-900-103. There was 1 patient who died more than 30 days after the last dose of study medication.

This death was attributable to the patients underlying disease under study.

### 1.2.5. Clinical Safety of Tislelizumab

According to available clinical studies data (as of 20 May 2019), the safety profile of tislelizumab is consistent with the therapeutic class of the drug with a relatively low rate of treatment-related Grade 3 or above toxicity.

Across the monotherapy studies, the safety profile was consistent in the Phase 1 and Phase 2 studies. Over half of the patients in these studies experienced a treatment-related TEAE, though related ≥ Grade 3 events were low (12.7%). Immune-related AEs of any grade were reported in approximately 50% of patients but were primarily low grade (9% ≥ Grade 3). These irAEs, however, have well-established algorithms for treatment and are therefore considered manageable.

In studies with tislelizumab plus chemotherapy, the AE profile is consistent with the now well-established profile of an immune checkpoint inhibitor in combination with the established AE profile of the standard chemotherapy agent. Over 70% of patients in these studies experienced a treatment-related TEAE, though ≥ Grade 3 events were lower (13% to 33%).

When combined with another investigational agent, the safety profile of the combination is generally consistent with the safety profiles of each drug given as monotherapy and with other agents in the checkpoint and PARP inhibitor classes. In these studies, over 50% of patients experienced a treatment-

related TEAE, though ≥ Grade 3 events were lower (10% to 38%). These data should be interpreted with some caution as the sample sizes are relatively small for these ongoing studies.

**Serious Adverse Events and Serious Adverse Events with a Fatal Outcome**

Across the monotherapy studies, the treatment-emergent SAE rate was 33.3% in patients with a variety of different disease characteristics. Treatment-related treatment-emergent SAEs were notably lower with a rate of 9.6%. In studies with tislelizumab plus chemotherapy, the treatment-emergent SAE rate ranged from 30% to 43%. Treatment-related treatment-emergent SAEs were notably lower with a rate ranging from 13% to 20%. When combined with another investigational agent, the treatment-emergent SAE rate ranges from 33% to 58%, but the treatment-related treatment-emergent SAE rate was 5% to 29%. These data should be interpreted with some caution as the sample sizes for some of these individual studies are relatively small.

There have been 83 TEAEs leading to death (4.9% of the total population [n=1705]) reported as of 20 May 2019 across all of the active studies with clinical data available. The incidence of TEAEs leading to death was low overall across studies, and the AEs associated with an outcome of death were consistent with what has been reported for the pharmaceutical class.

Please refer to the tislelizumab IB for more detailed information on safety of tislelizumab.

### 1.2.6. Rationale for Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The flat dose of 200 mg intravenously (IV) once every 3 weeks was selected for further evaluation. The MTD was not identified and only 1 DLT was reported in the first-in-human study.

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg once every 2 weeks ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg once every 3 weeks.

According to PK data from BGB-A317_Study_001, Phase 1a, the CL of tislelizumab was found to be independent of body weight, ethnicity, and gender, and the observed serum exposure of a 200-mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

Additionally, no unexpected treatment-related AEs occurred in the 200-mg fixed dose cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n = 13), 3 patients (23%) had a BOR of PR, 4 patients (31%) had a BOR of stable disease (SD), and 6 patients (46%) had a BOR of PD. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks.

In conclusion, tislelizumab 200 mg once every 3 weeks is the recommended initial dose for combination with lenvatinib.

### 1.3. Lenvatinib as a Receptor Tyrosine Kinase Inhibitor

Receptor tyrosine kinases (RTKs) are essential components of signal transduction pathways that mediate cell-to-cell communication (Hubbard and Miler 2007). They are a subclass of cell-surface growth-factor receptors with an intrinsic, ligand-controlled tyrosine-kinase activity. These single-pass transmembrane receptors, which bind polypeptide ligands-mainly growth factors-play key roles in processes such as cellular growth, differentiation, metabolism, and motility. In cancer, constitutive and aberrant activations of components of those pathways result in increased proliferation, survival, and metastasis. Therefore, these signaling pathways became prime targets for cancer therapy.

Lenvatinib (E7080) is an oral small molecule, multikinase inhibitor, which was discovered in an exploratory study for an angiogenesis inhibitor, mainly inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2, and VEGFR3), fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3, and FGFR4), KIT, and RET (Tohyama O, et al. J Thyroid Res. 2014). Lenvatinib is an extremely effective inhibitor of tumor angiogenesis that simultaneously interferes with these tumors angiogenesis-related molecular and suppresses growth signals mediated by VEGFRs and FGFRs (Yamamoto Y, et al. Vasc Cell. 2014). Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation (FDA updated label of lenvatinib capsules, 2018 ). In vivo study where human cancer cells are transplanted in immune deficient mouse models, lenvatinib also demonstrated high anticancer effect in a wide variety of cancers including HCC. In addition, safety results in non-clinical studies showed lenvatinib was well tolerated within the therapeutic range. In addition to targeting genetically altered oncogenic drivers, lenvatinib targets are expressed in a number of immune cell types and promote an immunosuppressive tumor microenvironment (TME), providing rationale for combining with PD-1 checkpoint inhibitor therapy. For example, lenvatinib may significantly decreased the percentage of tumor associated macrophages (TAM) in mice model with hepatocellular carcinoma cell, in addition immune inhibitory molecules were downregulated in tumors. And in the same preclinical trial lenvatinib significantly increased the percentage of IFNγ-secreting CD8+ T cells (Kato Y, et al. Molecular Cancer Therapeutics 2015 ). In another preclinical trial, in mouse models PD-1 inhibitor increased both Th1 and Th2 cytokines, LEN decreased Th2 cytokines, and combination treatment increased Th1 cytokines but decreased Th2 cytokines. In the same preclinical trial combination of LEN with PD-1 inhibitor showed more potent inhibitory activity against tumor growth compared with each single agent (Kato Y, et al. Annals of Oncology 2016).

Lenvatinib was approved for several solid tumor by FDA including differentiated thyroid cancer at a dose of 24 mg once daily, renal cell carcinoma at a dose of 18 mg in combination with 5 mg everolimus once daily and hepatocellular carcinoma at a body weight-dependent doses (12 mg for patients greater than or equal to 60 kg or 8 mg for patients less than 60 kg) once daily (Lenvatinib Pharmaceutical Instruction. 2018.), and approved by National Medical Products Administration (NMPA) for hepatocellular carcinoma at a body weight-dependent doses (12 mg for patients greater than or equal to 60 kg or 8 mg for patients less than 60 kg) once daily (Lenvatinib Pharmaceutical Instruction. 2018.).

### 1.3.1. Pharmacology

There are multiple studies to reported analyses on the pharmacodynamic properties of lenvatinib following administration in patients with cancer. A preclinical trial with human thyroid cancer models (Tohyama O et al. 2014) shown the half-maximal concentration (IC50) values of lenvatinib for its targets are shown following: IC50 for VEGFR1, VEGFR2, VEGFR3, RET proto-oncogenes (RET), fibroblast growth factor receptor (FGFR) 1, FGFR 2, FGFR 3, FGFR 4, platelet-derived growth factor receptor (PDGFR) alpha and KIT proto-oncogenes (KIT) is 4.7 nmol/L, 3.0 nmol/L, 2.3 nmol/L, 6.4 nmol/L, 61 nmol/L, 27 nmol/L, 52 nmol/L, 43 nmol/L, 29 nmol/L and 85 nmol/L respectively.

In vitro angiogenesis model, lenvatinib inhibits both VEGF-driven and FGF-driven tube formation of Human Umbilical Vein Endothelial Cells (HUVEC) at almost similar dose (IC50 values are 2.1 nmol/L and 7.3 nmol/L, respectively). Next, the effects of lenvatinib on in vivo angiogenesis, which was enhanced by overexpressed VEGF or FGF in human pancreatic cancer KP-1 cells, were examined in the mouse dorsal air sac assay. In vivo angiogenesis induced by overexpressed VEGF (KP-1/VEGF transfectants) or FGF (KP-1/FGF4 transfectants) was significantly suppressed with oral treatments of lenvatinib at 10 and 30 mg/kg. In addition, lenvatinib significantly inhibited bFGF-induced angiogenesis in matrigel plug assay, which is driven by recombinant human bFGF and stromal-derived mouse VEGF, at even 3 mg/kg. Increase of plasma FGF23 level is PD biomarker for an inhibition of FGFR1 signaling and it has been known that plasma FGF23 level is up-regulated by administration of FGFR inhibitors in mice. Lenvatinib at 10 mg/kg significantly elevated mice FGF23 levels 24 hours after lenvatinib treatment in a dose dependent manner. In conclusion, lenvatinib has potent both VEGF and FGF driven-antiangiogenic activity in vitro and in vivo. Inhibition of FGFR signaling pathway with lenvatinib was also supported by increase of plasma FGF23 levels at the same dose to show an inhibition in FGF-driven in vivo angiogenesis model (Ichikawa K, et al. 2015).

A preclinical trial demonstrated that lenvatinib has potent preclinical antitumor activity in human HCC xenograft models with or without amplification/overexpression of fibroblast growth factor 19, furthermore, the maximum antitumor effect of lenvatinib was greater than that of sorafenib in this study (Matsuki M, et al. 2017).

### 1.3.2. Toxicology

Carcinogenicity studies have not been conducted with lenvatinib. Lenvatinib mesylate was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Lenvatinib was not clastogenic in the in vitro mouse lymphoma thymidine kinase assay or the in vivo rat micronucleus assay (Lenvatinib Pharmaceutical Instruction. 2018.).

No specific studies with lenvatinib have been conducted in animals to evaluate the effect on fertility; however, results from general toxicology studies in rats, monkeys, and dogs suggest there is a potential for lenvatinib to impair fertility. Male dogs exhibited testicular hypocellularity of the seminiferous epithelium and desquamated seminiferous epithelial cells in the epididymides at lenvatinib exposures approximately 0.02 to 0.09 times the AUC at the recommended clinical dose of 24 mg once daily for differentiated thyroid cancer. Follicular atresia of the ovaries was observed in monkeys and rats at exposures 0.2 to 0.8 times and 10 to 44 times the AUC at the recommended clinical dose of 24 mg once

daily for differentiated thyroid cancer, respectively. In addition, in monkeys, a decreased incidence of menstruation was reported at lenvatinib exposures lower than those observed in humans at the recommended clinical dose of 24 mg once daily for differentiated thyroid cancer (Lenvatinib Pharmaceutical Instruction. 2018.).

### 1.3.3. Clinical Pharmacology

After oral administration of lenvatinib, time to peak plasma concentration (Tmax) typically occurred from 1 to 4 hours post-dose. Administration with a high fat meal did not change bioavailability of lenvatinib, but delayed the median Tmax from 2 hours to 4 hours. In patients with solid tumors administered single and multiple doses of lenvatinib QD, the maximum lenvatinib plasma concentration (Cmax) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 to 32 mg with a median accumulation index varying between 0.96 (20 mg) and 1.54 (6.4 mg). At clinically relevant doses (≥12 mg QD), mean accumulation ratios of lenvatinib ranged between 0.96 and 1.28. Plasma lenvatinib concentrations declined bi-exponentially following Cmax. The terminal elimination half-life of lenvatinib was approximately 28 hours (Lenvatinib FDA Approval Package. 2014).

In vitro binding of lenvatinib to human plasma proteins ranged from 97.9% to 98.6% (0.3-30 µg/mL). The contributions of albumin, α1-acid glycoprotein, and γ-globulin to the human plasma protein binding of lenvatinib were estimated to be 93.2%, 6.1%, and 0.7%, respectively. In vitro, the lenvatinib blood-to-plasma concentration ratio ranged from 0.59 to 0.61 (0.1-10 µg/mL) (Lenvatinib FDA Approval Package. 2014).

### 1.3.4. Pharmacodynamic Properties

In a Phase 1 dose-escalation study of lenvatinib, investigators utilized biomarker analysis of circulating endothelial cells (CEC) and circulating progenitor cells (CEP), which reflect active vascular turnover and angiogenesis, to conduct lenvatinib pharmacodynamic analyses in patients with advanced solid tumors (Yamada K et al. 2011). Furthermore, this study also evaluated whether the CEC and CEP were c-KIT positive (+) or c-KIT negative (-). The c-KIT receptor (c-KITR) is expressed on endothelial, mast, and cancer cells, and it is believed that activation of c-KITR via its ligand, stem cell factor (SCF), induces signal transduction pathways that may promote angiogenesis (Marech I et al. 2014). After 14 days of oral lenvatinib treatment, c-KIT(+) CEPs and CECs significantly decreased, but c-KIT(-) CEPs and CECs did not (Yamada K et al. 2011). Change from baseline in c-KIT(+) CEC ratio in cycle 1 (14-day treatment) and baseline stromal cell-derived factor 1-alpha (SDF1a), c-KIT(+) CEPs, and c-KIT(+) CEP ratio was significantly associated with the therapeutic effect of lenvatinib.

A separate Phase 1 dose-escalation trial of lenvatinib evaluated correlations between pharmacodynamic biomarkers and patient clinical outcomes (Koyama N et al. 2014). Plasma pharmacodynamic biomarkers measured in this study included the angiogenic proteins IL-6, IL-8, and IL-10, VEGF, PDGF, HGF, SCF, and SDF1a. Soluble VEGFR1 (sVEGFR1) and sVEGFR2 were also quantified. Lenvatinib was orally administered twice daily in 3-week cycles (2 weeks of treatment, then 1 week without treatment), and blood samples were collected on days 1 (baseline), 8, and 15 of cycle 1, and days 1, 8, and 15 of cycle 2. Increasing lenvatinib exposure was significantly associated with increased levels of VEGF and SDF1 alpha, decreased sVEGFR2 levels, and tumor shrinkage. Tumor shrinkage was also associated with

decreased sVEGFR2 levels; however, maximum tumor shrinkage was specifically correlated with increased levels of SDF1 alpha.

An expansion of a Phase 1 study of lenvatinib in patients with solid tumors evaluated pharmacodynamics of lenvatinib (escalating doses given in 28-day cycles) in patients with melanoma (Hong DS, et al. 2015). Serum samples were tested for angiogenesis-related (PDGF-homodimer BB [PDGF-BB], soluble Tie-2, angiopoietin-1, soluble E-selectin, and soluble c-KIT) and apoptosis-related markers (cytochrome C and M30 neoantigen). High baseline cytochrome C levels and a higher ratio of M30 on cycle 1, day 8 to baseline were associated with greater tumor shrinkage. Decreased angiopoietin-1 ratio (2 h to baseline) was associated with prolonged PFS.

### 1.3.5. Clinical Experience with Lenvatinib in Patients with HCC

Due to limited data accessibility, lenvatinib monotherapy in patients with HCC have been assessed in 3 completed clinical studies, including one Phase 1 clinical study (Ikeda M et al. 2016), one Phase 2 clinical study (Ikeda M et al. 2017) and one Phase 3 clinical study (Kudo M et al. 2018), and there is one on-going clinical studies of lenvatinib in combination with pembrolizumab in patients with HCC, which has released data before (Masafumi Ikeda, et al. 2018 ASCO Annual Meeting), will be briefed in Section 1.4.2.2.

#### 1.3.5.1. Lenvatinib Monotherapy Phase 1 Clinical Study for Patients with HCC

This Phase 1, open-label, dose-escalation study of lenvatinib study (Ikeda M et al. 2016) was determine the maximum tolerable dose (MTD), safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of lenvatinib in patients with advanced HCC stratified by Child–Pugh (CP) classes A and B (Llovet JM, et al. 2008).

A total of 20 patients, 9 in the CP-A and 11 in the CP-B group, were enrolled in this study between August 3, 2009,and November 22, 2011; all patients received the study treatment and completed the study. Most patients (65%) had undergone targeted therapy/systemic chemotherapy, predominantly with sorafenib. The MTD was12 and 8 mg once daily in CP-A and CP-B, respectively; DLTs included proteinuria, hepatic encephalopathy, and hyperbilirubinemia. The most frequent treatment-emergent AEs were list in table 9 below. Serious AEs(SAE) were reported in 4 patients in the CP-A and 6 in the CP-B group. There were 2 deaths in the CP-B group that occurred due to hematemesis (8mg) or hepatic failure (12mg) as a result of progression of HCC after discontinuation of the study drug. Both deaths were considered unrelated to the study drug by the investigator. Other SAEs were hyperbilirubinemia (1 patient in the CP-A group and 1 patient in the CP-B group), tumor hemorrhage (2 patients in the CP-B group), and hepatic encephalopathy (1patient in the CP-A and 1 patient in the CP-B group).

**Table 9 The most frequent treatment-emergent AEs in the HCC patients of lenvatinib monotherapy (Phase 1 Clinical Study)**

| Adverse Event | Lenvatinib | |
|---|---|---|
| | All grades | Grade 3–4 |

| | | |
|---|---|---|
| Diarrhea | 90% | 10% |
| Fatigue | 90% | 5% |
| Decreased appetite | 80% | 10% |
| Hypertension | 75% | 50% |
| Hyperbilirubinemia | 60% | 20% |
| Palmar-plantar erythrodysesthesia syndrome (PPES) | 65% | 5% |
| Nausea | 60% | 0% |
| Vomiting | 50% | 0% |

There was no complete response. Partial response was observed in 1 patient in each of the CP-A 12-mg, CP-A 16-mg, and CP-B 8-mg groups. The ORR was 22.2% (2/9) in the CP-A and 9.1% (1/11)in the CP-B. Overall, 10 patients (50.0%) had a best overall tumor response of stable disease: 4 in the CP-A group (2 each in the 12-mg and 16-mg cohorts) and 6 in the CP-B group (4 in the 8-mg and 2 in the 12-mg cohorts). Progressive disease occurred in 2 (22.2%), 4 (36.4%), and 6 (30.0%) patients in the CP-A group, CP-B group, and in the overall study, respectively. The DCR was 66.7% in the CP-A and 63.6% in the CP-B group. The overall ORR and DCR were 15.0% (95% CI, 3.2–37.9) and 65.0% (95% CI, 40.8–84.6), respectively. Any tumor shrinkage from baseline was observed in 14 patients, 7 each in the CP-A and CP-B groups.

#### 1.3.5.2. Lenvatinib Monotherapy Phase 2 Clinical Study for Patients with HCC

This Phase 2, open-label study of lenvatinib study (Ikeda M et al. 2017) was to assess the antitumor activity and safety of lenvatinib in patients with advanced HCC. Patients in CP class A, with histologically/clinically confirmed advanced HCC who did not qualify for surgical resection or local therapies received lenvatinib at a dosage of 12 mg once daily (QD) in 28-day cycles. Dose interruption and sequential reduction of lenvatinib (to 8- and 4-mg QD) were permitted for drug-related adverse events. The study drug was discontinued if patient recovery time was beyond 2 weeks.

Overall, 46 patients were enrolled and received lenvatinib at 14 sites across Japan and Korea between July 2010 and June 2011. All patients were included in the safety and efficacy analyses. Median TTP was 7.4 months (95 % CI: 5.5–9.4) as assessed by independent radiologic review committee (IRRC) per mRECIST. Median TTP was 12.8 months (95 % CI: 7.2–14.7) by investigator assessment. Seventeen patients (37 %) achieved a partial response and 19 patients (41 %) had stable disease with a DCR of 78 % by IRRC based on mRECIST. Eleven patients (24 %) achieved a partial response and 25 patients (54 %) had stable disease with a DCR of 78 % by IRRC based on RECIST 1.1. Median OS was 18.7 months (95 % CI: 12.7–25.1).

All 46 patients experienced at least one AE. The most common AEs were summarized in table 10 below.

**Table 10 The most common AEs in the HCC patients of lenvatinib monotherapy (Phase 2 Clinical Study)**

| Adverse Event | Lenvatinib |
|---|---|
| The most common any-grade AEs | |
| Hypertension | 76% |
| Palmar-plantar erythrodysesthesia syndrome (PPES) | 65% |
| Decreased appetite | 61% |
| Proteinuria | 61% |
| Serious AEs (SAEs) | 48% |
| The most frequently reported SAE | |
| Hepatic encephalopathy | 11% |
| Treatment-related deaths | 0% |

In an exploratory analysis of differences in baseline characteristics between patients who did and did not require an early dose withdrawal or reduction, body weight and minimum concentration of lenvatinib ($C_{trough}$) were identified as potential differentiators. Median body weight was lower for patients who experienced an early dose withdrawal or reduction (54.1 kg) than for those who did not (67.6 kg).

### 1.3.5.3. Lenvatinib Monotherapy Phase 3 Clinical Study for Patients with HCC

This an open-label, Phase 3, multicenter, non-inferiority trial (Kudo M et al. 2018) to compare the efficacy and safety of lenvatinib versus sorafenib as a first-line treatment for unresectable HCC. This study recruited patients with unresectable HCC, who had not received treatment, in CP class A. Patients were randomly assigned (1:1) to receive oral lenvatinib (12 mg/day for bodyweight ⩾60 kg or 8 mg/day for bodyweight <60 kg, QD) or sorafenib 400 mg twice-daily in 28-day cycles.

Between March 1, 2013, and July 30, 2015, 1492 patients were recruited. 954 eligible patients from 20 countries were randomly assigned to receive lenvatinib (n=478) or sorafenib (n=476). At the time of data cutoff (Nov 13, 2016, at 701 deaths), the median duration of follow-up was 27.7 months (IQR 23.3–32.8) in the lenvatinib group and 27.2 months (22.6–31.3) in the sorafenib group. Lenvatinib showed non-inferiority in terms of overall survival compared with sorafenib, 13.6 vs 12.3 months with HR 0.92 (95% CI 0.79–1.06). Median time to progression was 8.9 months (95% CI 7.4–9.2) for patients in the lenvatinib group compared to 3.7 months (3.6–5.4) for patients in the sorafenib group. Lenvatinib also showed a greater objective response rate than did sorafenib (Odds Ratio 3.34; 2.17–5.14, p＜0.0001). In lenvatinib group 90 patients (18·8%, 15.3–22.3) achieved objective response and 348 patients (72.8%, 68.8–76.8)

had disease control by independent imaging review based on RECIST 1.1. In sorafenib group 31 patients (6.5%, 4.3–8.7) achieved objective response and 281 patients (59.0%, 54.6–63.5) had disease control by independent imaging review based on RECIST 1.1. In lenvatinib group and sorafenib group mPFS was 7.3 (5.6–7.5) and 3.6 (3.6–3.9) with HR 0.65 (0.56–0.77, $p<0.0001$).

The median duration of study treatment for patients in the lenvatinib group was 5.7 months (IQR 2.9–11.1), compared with 3.7 months (1.8–7.4) in the sorafenib group. Total treatment-emergent adverse events in lenvatinib group and sorafenib group was 470 (99%) and 472 (99%) respectively. The most common treatment-emergent adverse events were shown in table 11 below.

**Table 11 The most common treatment-emergent adverse events in the HCC patients of lenvatinib monotherapy (Phase 3 Clinical Study)**

| Adverse Event | Lenvatinib |
|---|---|
| The most common treatment-emergent adverse events of any grade | |
| Hypertension | 42% |
| diarrhoea | 39% |
| Decreased appetite | 34% |
| decreased weight | 31% |
| Palmar-plantar erythrodysesthesia | 27% |
| Total treatment-emergent adverse events of grade ≥ 3 | 75% |
| The most common treatment-emergent adverse events of grade ≥ 3 | |
| Hypertension | 23% |
| Decreased weight | 8% |
| Increased blood bilirubin | 7% |
| Proteinuria | 6% |
| Decreased appetite | 5% |
| Decreased platelet count | 5% |
| Elevated aspartate aminotransferase | 5% |

| | |
|---|---|
| Total treatment-emergent fatal adverse events | 2% |
| Hepatic failure | 0.6% |
| Cerebral haemorrhage | 0.6% |
| Respiratory failure | 0.4% |

### 1.3.6. Rationale for Lenvatinib Dose Selection in HCC Patients

In the Phase 2 study (Ikeda M et al. 2017), a uniform daily dose of 12 mg irrespective of body weight and surface area led to dose reduction in a large proportion of patients: dose adjustment in 34 of 46 patients (74%) because of treatment-related adverse events and withdrawal in 10 patients (22%) because of toxicity. Close examination of patient characteristics indicated that body weight and serum lenvatinib levels were likely to be associated with dose reduction or early withdrawal. More precisely, patients who had dose reduction or early therapy withdrawal within 30 days of lenvatinib treatment were significantly lighter (median weight, 54.1 vs. 67.6 kg) and had a significantly higher minimum plasma concentration of lenvatinib (trough concentration [C1D15Ctrough], 62.4 vs. 33.9 ng/mL).

In a pooled data analysis study (Toshiyuki Tamai et al. 2017), which aimed to identify the lenvatinib optimal dose for subjects with advanced HCC Child-Pugh class A. Pooled data from Phase 1 studies in healthy adults and in subjects with mixed tumor types, were analyzed using a population pharmacokinetic approach, the conclusion of this study is that the relationship between the lenvatinib area under the plasma concentration–time curve (AUC) at steady state and body weight demonstrated an increase in AUC as body weight decreased in subjects with HCC. An exposure–response relationship was observed, with higher lenvatinib AUC and lower body weight resulting in earlier drug withdrawal or dose reduction. The best cutoff values for body weight and lenvatinib AUC were 57.8 kg and 2430 ng·h/mL, respectively, to predict the group at high risk for early drug withdrawal or dose reduction. Therefore 12 mg and 8 mg starting doses for subjects ≥ 60 kg and < 60 kg, respectively, in subjects with HCC Child-Pugh class A is recommended in this study.

Based on the available data described above, 12 mg and 8 mg starting doses for subjects ≥60 kg and <60 kg respectively is recommended for patients with HCC Child-Pugh class A.

## 1.4. Combination of Lenvatinib and Tislelizumab

### 1.4.1. Rationale for Combination of Lenvatinib and Tislelizumab in the Treatment of Advanced Solid Tumors

Cancer cells face selective pressures while being treated and mutations occurring in individual cancer cells represent continuous evolution of the original cancer. Almost all malignancies develop resistance to anticancer therapies eventually. This is also the case for checkpoint blockade agents where acquired resistance occurs in a large portion of treated patients who achieved an initial meaningful response. (Syn et al 2017).

Monoclonal antibodies that target either PD-1 or PD-L1, checkpoint inhibitors, can block binding and boost the immune response against cancer cells. These drugs have been shown to be helpful in treating several types of cancer, including melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma. Cancer cells in most nonresponders to single-agent checkpoint inhibitors escape through innate mechanisms that allow the cancer cells to grow and survive. However, unlike intrinsic resistance, late relapses are now emerging in patients with prior clinical benefit after longer follow-up of clinical trials, suggesting the emergence of acquired resistance (Jenkins et al 2018). Strategies to improve the clinical efficacy of checkpoint inhibitors by overcoming innate or acquired resistance are needed.

Combining an immunotherapeutic PD-1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could enhance the antitumor efficacy observed with either agent alone. The use of TKIs to treat cancer is well established based on robust clinical efficacy achieved with well tolerated inhibitors directed toward oncogenic tyrosine kinases. Together, lenvatinib and tislelizumab may elicit greater antitumor activity, as lenvatinib is predicted to enhance several steps in the cancer immunity cycle that may augment the efficacy of tislelizumab. First, the antitumor activity of lenvatinib may promote the release of tumor antigens by killing tumor cell. Second, lenvatinib may significantly decreased the percentage of tumor associated macrophages (TAM) in mice model with hepatocellular carcinoma cell, in addition immune inhibitory molecules were downregulated in tumors. And in the same preclinical trial lenvatinib significantly increased the percentage of IFNγ-secreting CD8+ T cells (Kato Y, et al. Molecular Cancer Therapeutics 2015 ). Third, in mouse models, PD-1 inhibitor increased both Th1 and Th2 cytokines, lenvatinib decreased Th2 cytokines, and combination treatment increased Th1 cytokines but decreased Th2 cytokines. In the same preclinical trial combination of LEN with PD-1 inhibitor showed more potent inhibitory activity against tumor growth compared with each single agent (Kato Y, et al. Annals of Oncology 2016).

Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy is a rational approach to improving outcomes in patients. In summary, selective RTKs inhibit key molecular and cellular pathways strongly implicated in checkpoint inhibitor resistance and therefore represent reasonable strategies to enhance or restore antitumor immunity when combined with anti-PD-1 or anti-PD-L1 monoclonal antibodies.

### 1.4.2. Clinical Experience with Lenvatinib in Combination with PD-1 Inhibitor

As of 01 September 2019, there are 18 ongoing studies with lenvatinib in combination with PD-1 inhibitors or PD-L1 inhibitors searched via clinicaltrials.gov. 2 ongoing studies with available preliminary data: pembrolizumab combination therapy studies NCT03006887 and NCT03006926.

Of the ongoing studies, available data from NCT03006887 and NCT03006926 are summarized below.

#### 1.4.2.1. NCT03006887 study (pembrolizumab combination study) (Data Cutoff 02 November 2017)

NCT03006887 study is an Open-Label Phase Ib trial to confirm the tolerability and safety of lenvatinib in combination with pembrolizumab in participants with selected solid tumors (non-small cell lung cancer,

predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma). Participants will receive oral lenvatinib capsules at a starting dose of 20 mg once a day in combination with intravenous infusion of pembrolizumab 200 mg every 3 weeks on a 21-day treatment cycle (NCT03006887_ clinicaltrials.gov).

As of 2 November 2017, all the 6 pts (3 Urothelial, 3 NSCLC) received lenvatinib 20 mg QD in combination with fixed dose of pembrolizumab 200 mg Q3W and completed Cycle 1 without DLT. The most common TEAEs (all grade, > or = 3 of pts) were AST increased (6 pts), hypertension (6 pts), ALT increased (5 pts), fatigue (5 pts), hypothyroidism (5 pts), decreased appetite (4 pts), nausea (4 pts), proteinuria (3 pts), lipase increased (3 pts), thrombocytopenia (3 pts), and WBC decreased (3 pts). Grade 3 TEAEs (> or = 2 of pts) were AST increased, ALT increased, and gamma-GTP increased (each 2 pts). No Grade 4 or 5 TEAEs were observed. Grade 5 AE was pneumonitis (1 pt). One complete and 1 partial response were observed in pts with urothelial carcinoma. Pharmacokinetic evaluation is not available as of now (Shigehisa Kitano, et al. 2018 JSMO Annual Meeting).

#### 1.4.2.2. NCT03006926 study (pembrolizumab combination study) (Data Cutoff 23 August 2018)

NCT03006926 study is an open-label, Phase Ib trial to determine safety, efficacy, tolerability and pharmacokinetic profile of lenvatinib with pembrolizumab in patients with BCLC stage B or C Hepatocellular Carcinoma. Patients receive lenvatinib 12 mg (body weight > or = 60 kg) or 8 mg (body weight < 60 kg) orally once daily and pembrolizumab 200 mg intravenously once every 3 weeks. Tolerability was evaluated by assessing DLTs during the first cycle in patient for whom no other appropriate therapy (including sorafenib) was available (3+3 design part 1). Once tolerability of lenvatinib plus pembrolizumab was confirmed, additional patients with no prior systemic therapy of unresectable HCC were enrolled (part 2). Tumor assessments of complete or partial response (CR or PR) were confirmed > or 4 weeks after initial response (Masafumi Ikeda, et al. 2018 ASCO Annual Meeting).

As of 23 August 2018, 30 pts were enrolled and received lenvatinib plus pembrolizumab (Part 1, n=6; Part 2, n=24) (Masafumi Ikeda, et al. 2019 AACR Annual Meeting). Patients had BCLC stage B (n=9) or C (n=21), Child-Pugh scores of 5 (n=26) or 6 (n=4). At data cutoff (Aug 23, 2018), 18 (60%) pts were still on study treatment; median duration of follow-up was 9.7 months. Any-grade TEAEs occurred in 28 patients (93%); the most common any-grade TEAEs were decreased appetite (63%) and hypertension (60%). 7 (23%) pts discontinued treatment due to TEAEs, and no new safety signals were identified. Efficacy outcomes reported below.

Efficacy data for this study are based on a data-cut-off of 23 August 2018 and include part 1 and part 2 patients.

- For all the patients in part 1 and part 2 (n = 30), there were 11 patients with a confirmed response and 16 patients with a best overall response (BOR) of stable disease (SD) based on RECIST 1.1 per independent imaging review.

### 1.5. Benefit-Risk Assessment

Combination therapy with a small molecule inhibitor of the VEGFR pathway may improve the clinical efficacy of immunotherapies and overcome resistance to checkpoint inhibitor therapy (refer to

Section 1.4.1). For patients with HCC, combination therapy may improve the clinical efficacy of single-agent immunotherapies (Section 1.1). Based on available tislelizumab and lenvatinib data and the publication from other PD-1 or PD-L1 inhibitors and other small molecule inhibitors of the VEGFR pathway, the combination of lenvatinib and tislelizumab may elicit greater antitumor activity and have a manageable safety profile. However, the risk benefit for this combination has not yet been established.

**Tislelizumab**

As of 20 May 2019, there are currently 22 ongoing studies with tislelizumab monotherapy or combination therapy for several tumors. The safety profile is consistent with known class effects of anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3 or Grade 4 irAEs have been observed, which are generally reversible and manageable with study drug interruption and/or steroid treatment. For further discussion on the safety profile of tislelizumab, please refer to the tislelizumab IB.

**Lenvatinib monotherapy or in combination with pembrolizumab**

Lenvatinib has been evaluated as monotherapy in patients with advanced HCC through 3 clinical studies, which has demonstrated the antitumor efficacy, safety and tolerance of lenvatinib in that patients. Lenvatinib was approved for hepatocellular carcinoma by FDA(Lenvatinib Pharmaceutical Instruction. 2018.).

As of 01 September 2019, there are 18 ongoing studies with lenvatinib in combination with PD-1 inhibitors or PD-L1 inhibitors. 2 ongoing studies with available preliminary data are NCT03006887 and NCT03006926. Based on updated interim results from the NCT03006926 study, FDA has granted Breakthrough Therapy designation for pembrolizumab in combination with lenvatinib for the potential first-line treatment of patients with advanced unresectable hepatocellular carcinoma (HCC) not amenable to locoregional treatment (Third Breakthrough Therapy Designation from FDA 2019).

Due to the safety assessment of dosage in combination therapy setting with lenvatinib and pembrolizumab has been implemented in NCT03006926 study, and no DLTs has been found during the first cycle in patient (3+3 design part 1) , when all patients received regular dosages of lenvatinib for HCC as the label approved by FDA ( depended on weight, lenvatinib 12 mg if body weight > or = 60 kg, lenvatinib 8 mg if body weight < 60 kg, orally once daily), in combination with regular dosages of pembrolizumab for HCC as the label approved by FDA (pembrolizumab 200 mg intravenously once every 3 weeks), and no new safety signals were identified as well.

**Benefit-risk assessment of tislelizumab in combination with lenvatinib**

According to above analysis, it may be tolerable when patients with HCC receive regular dosages of lenvatinib for HCC in combination with regular dosages of tislelizumab for HCC. Considering of safety, safety run-in part for combination dosages of lenvatinib and tislelizumab will be performed.

Based on the efficacy data of pembrolizumab in combination with lenvatinib for the first-line treatment of HCC patients, it is believed Tislelizumab in combination with lenvatinib is also an efficious treatment option, benefit-risk assessment favors the implementation of this study.

A Safety Monitoring Committee (SMC) will be established consisting of the sponsor's clinical, safety, and medical team representatives (eg, medical monitor, Clinical Pharmacology, Statistician, and Drug

Safety) and investigators, will monitor the preliminary safety of lenvatinib in combination with tislelizumab and determine the RP2D of lenvatinib in combination with tislelizumab based on the available data in this study.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Study Objectives

### 2.1.1. Primary Objectives

- To assess the preliminary antitumor activity as indicated by overall response rate (ORR) assessed by central site imaging facility for tumor assessment per Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1 of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

### 2.1.2. Secondary Objectives

- To characterize the safety and tolerability of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To assess the preliminary antitumor activity as indicated by ORR assessed by investigators per RECIST v1.1 of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To assess the preliminary antitumor activity as indicated by ORR assessed by investigators and central site imaging facility for tumor assessment per modified Response Evaluation Criteria in Solid Tumors (mRECIST) and Immune-related Response Evaluation Criteria in Solid Tumors(iRECIST) respectively of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma
- To patients assess the preliminary antitumor activity as indicated by duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) assessed by investigators and central site imaging facility for tumor assessment per RECIST v1.1, mRECIST and iRECIST respectively of tislelizumab in combination with lenvatinib in patients with unresectable locally advanced or metastatic hepatocellular carcinoma

### 2.1.3. Exploratory Objectives

- To characterize the pharmacokinetic (PK) and immunogenicity of tislelizumab when given in combination with lenvatinib in Part 1
- To assess overall survival (OS)

## 2.2. Study Endpoints

### 2.2.1. Primary Endpoints

- ORR assessed by central site imaging facility for tumor assessment based on RECIST v1.1

### 2.2.2. Secondary Endpoints

- The safety and tolerability of tislelizumab in combination with lenvatinib will be evaluated by the incidence, nature, and severity of adverse events (AEs) and serious AEs (SAEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, clinical laboratory abnormalities, relevant physical exam, ECGs, vital signs and DLTs.
- ORR assessed by investigators based on RECIST v1.1
- ORR assessed by investigators and central site imaging facility for tumor assessment respectively based on mRECIST and iRECIST
- DOR, DCR, and PFS assessed by investigators and central site imaging facility for tumor assessment respectively based on RECIST v1.1, mRECIST and iRECIST

### 2.2.3. Exploratory Endpoints

- Serum concentrations of tislelizumab and incidences of anti-tislelizumab-antibodies in Part 1
- OS

## 3. STUDY DESIGN

### 3.1. Summary of Study Design

This is an open-label, multicenter Phase 2 clinical study for patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HCC. All patients will receive study treatments until confirmed progressive disease (iCPD) assessed by investigator based on iRECIST, unacceptable toxicity, 12-month treatment duration completion, death, withdrawal of consent, study termination by sponsor or patients meet any discontinuation criterion which will be described in protocol (see Section 3.6 and Section 3.7 for details), whichever comes first. There will be approximately 10 centers in China.

This study consists of the 2 parts.

#### 3.1.1. Part 1 (Safety run-in part for lenvatinib in combination with tislelizumab)

Since there is no safety data on lenvatinib in combination with tislelizumab in HCC patient, considering patient's safety, a safety run-in part for combination dosages of lenvatinib and tislelizumab will be performed.

**DLT Observation Period and Safety Run-in Scheme**

For part 1 safety run-in, a 21-day DLT assessment window will be utilized for each dose of lenvatinib confirmation recommendations in combination with tislelizumab. DLTs will be assessed among evaluable patients within 21 days after the first dose of study drugs. Only DLTs occurring within 21 days will be evaluated. Approximately 6-12 patients with unresectable locally advanced or metastatic HCC will be enrolled in this part.

Dose safety run-in for lenvatinib in combination with tislelizumab will occur in accordance with the following procedures.

- The safety and tolerability of starting dose for lenvatinib in combination with tislelizumab will be evaluated. 3 patients with baseline body weight≥60 kg and 3 patients with baseline body weight <60 kg will be enrolled. These patients will be administered with lenvatinib orally once a day and tislelizumab (200mg) by intravenous injection (IV), on Day 1 of each 21-day cycle (once every 3 weeks, Q3W). The starting dose for lenvatinib in safety run-in part will be based on baseline body weight. 12 mg lenvatinib will be administered once daily if baseline body weight of patient≥60 kg. 8 mg lenvatinib will be administered once daily if baseline body weight of patient <60 kg.
- If ≤1 of 6 patients experience a dose limiting toxicity (DLT) in lenvatinib starting dose cohort, this dose level is determined as RP2D (recommended phase 2 dose). The part 2 will start to enroll at RP2D.
- If >1 of 6 patients experience a DLT in this cohort, sponsor will decide to terminate the study or to start a new cohort to investigate lenvatinib at reduced dose. Lenvatinib dose in the dose reduced cohort may be set as 8 mg or 4 mg once daily based on baseline body weight≥60 kg or <60 kg, respectively. 6 eligible patients, 3≥60 kg and 3<60 kg will be enrolled in this cohort. Tislelizumab dose is the same, 200 mg IV Q3W.
- If≤1 of 6 patients experience a DLT in lenvatinib dose reduced cohort, this dose level is determined as RP2D. The part 2 will start to enroll at RP2D.
- If>1 of 6 patients experience a DLT in lenvatinib dose reduced cohort, the part 1 will be stopped, and part 2 won't be proceeded. Depend on incidence, nature, and severity of DLTs, sponsor may decide to implement additional test to characterize the pharmacokinetic (PK) of lenvatinib in combination with tislelizumab, to determine the potential influence of lenvatinib PK profile in combination with tislelizumab. So, samples of plasma will be collected at specified times points within a reasonable variation windows for a potential test of lenvatinib PK profile. (refer to Appendix 1 and Appendix 2).

A Safety Monitoring Committee (SMC) will be established consisting of the sponsor's clinical, safety, and medical team representatives (eg, medical monitor, Clinical Pharmacology, Statistician, and Drug Safety) and investigators. A planned formal SMC review of safety data will be performed after at least 6 evaluable patients have completed 21-day DLT assessment in each lenvatinib dose level. The SMC will monitor the preliminary safety of lenvatinib in combination with tislelizumab and determine the RP2D of lenvatinib in combination with tislelizumab based on the available data (eg, safety and PK data) in this study. Study accrual will be held pending data review and lenvatinib RP2D determination by the SMC.

Note: the definition of evaluable patients for DLT assessment and DLT assessment window please see Section 3.8.1.

### 3.1.2. Part 2

Target 54 patients will be enrolled in this part. Each eligible patient will be administered by lenvatinib in combination with tislelizumab. Lenvatinib in accordance with RP2D determined in part 1 will be administered orally, once daily continuously, tislelizumab will be administered sequentially starting on

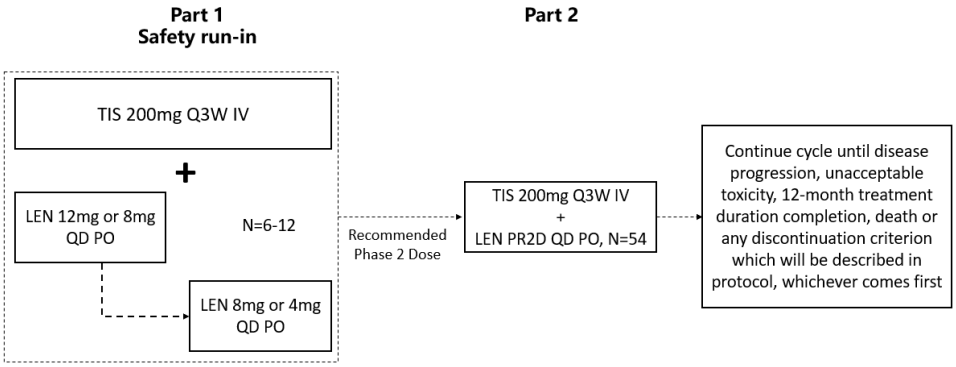
Cycle 1 Day 1 and every 21 days thereafter. The study drug(s) will be administered until they meet a discontinuation criterion. (The enrollment won't be interrupted after 30 patients were enrolled.

Figure 1).

Target 60-66 patients will be enrolled in whole study, including 6-12 patients in part 1 and 54 patients in part 2. A Simon's 2 stage design will be used to test the superiority of studied combination treatment vs. the historical control. When 30 patients dosed at RP2D level (including patients from both part 1 and part 2) are enrolled and all reach their best overall response (BOR) assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the preliminary efficiency and safety of those 30 patients will be assessed as interim analysis. (refer to Section 9.7 for details)

- If within these 30 patients, ≤6 patients achieve response including complete response (CR) and partial response (PR) as their BOR assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will be terminated.
- If within these 30 patients, >6 patients achieve response including CR and PR as their BOR assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will continue.
- The enrollment won't be interrupted after 30 patients were enrolled.

**Figure 1. Study Schema**




Abbreviations: QD, once a day; Q3W, every 3 weeks; PO, orally; IV, intravenous injection; LEN, Lenvatinib; TIS, Tislelizumab.

**Note:** The dose level of tislelizumab is fixed in the entire study. In part 1 whether to proceed to the lenvatinib dose reduced cohort will depend on safety observations in lenvatinib starting dose cohort and sponsor's decision.

### 3.2. Screening Period

Screening evaluations will be performed within 28 days prior to the first dose of study drug(s). Patients who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure. Refer to Section 7.1 for additional details.

### 3.3. Treatment Period

After completing all screening activities, patients confirmed to be eligible by the sponsor or designee will be enrolled to receive lenvatinib in combination with tislelizumab. All patients will receive study

treatments until confirmed progressive disease (iCPD) assessed by investigator based on iRECIST, unacceptable toxicity, 12-month treatment duration completion, death, withdrawal of consent, study termination by sponsor or patients meet any discontinuation criterion which will be described in protocol (see Section 3.6 and Section 3.7 for details), whichever comes first.

Study procedures of each clinic visit are outlined in Appendix 1 and Appendix 2.

On days with PK assessments, tislelizumab should be administered in the clinic in accordance with the schedule for the PK samples. Assessments should be obtained before study drugs administration unless stated otherwise in Appendix 1 and Appendix 2 and should be performed in order of least invasive to most invasive assessment. All safety-related assessments must be reviewed and dose modifications, if necessary, must be made by the investigator or sub-investigator before study drugs administration.

### 3.4. End-of-Treatment Visit and Safety Follow-up Phone Calls

Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit within 30 days after last dose of the study drugs or before initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, clinical chemistry) were performed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If the study drugs were initially interrupted due to AEs and then permanently discontinued, the EOT Visit may occur later, but no later than the permitted time of dose delay plus 7 days.

See Appendix 1 for assessments to be performed for the EOT Visit.

Telephone contact with patients should be conducted to assess irAEs and concomitant medications (if appropriate; eg, if associated with an irAE or is a new anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. If patient reports a suspected irAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.6.

Patients who discontinue study treatment prior to iCPD will have their tumors assessed as outlined in Section 7.4.

### 3.5. Survival Follow-Up

All patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor.

## 3.6. Discontinuation from Study Treatment or from the Study

### 3.6.1. Patient Discontinuation from Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than iCPD assessed by investigator based on iRECIST, should be followed for assessments of antitumor activity (Section 7.4), safety (Section 7.3) and survival (Section 3.5), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF). Patients may discontinue study treatment for reasons which include, but are not limited to, the following:

- Patient withdrawal of consent
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent antineoplastic therapy (ie, loco-regional therapy, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese or other Country herbal medicine and Chinese or other Country patent medicines] for the treatment of cancer)
- Patient noncompliance
- iCPD assessed by investigator based on iRECIST
- 12−month treatment duration completion

If patients don't meet any discontinuation criterion, such as investigator-assessed iCPD based on iRECIST, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor, lenvatinib and tislelizumab will be administered until patient completes his/her 12-month treatment duration of study drugs. After 12-month treatment duration completion, if the patients are still under the response (CR, PR) or stable disease (SD) assessed by investigator based on RECIST v1.1 or under the response (complete response [iCR], partial response [iPR]), stable disease (iSD) and unconfirmed progression (iUPD) assessed by investigator based on iRECIST, and may continue receiving benefit based on investigator's assessment, tislelizumab could be further provided by sponsor, this decision must be agreed with medical monitor and documented in the study records, patients are also required to be reconsented.

### 3.6.2. Patient Discontinuation from Study (End of Study for an Individual Patient)

Patients may discontinue study for reasons which include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Lost to follow up
- Sponsor termination of study

### 3.7. End of Study

The end of study is defined as the date when the last patient's last visit (LPLV) occurs or the date at which the last data point required for statistical analysis or safety follow-up is collected for the last patient, whichever occurs later.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- In part 1, ＞1 of 6 patients experience a DLT in lenvatinib initial dose cohort
- In part 1, ＞1 of 6 patients experience a DLT in lenvatinib dose reduced cohort
- In interim analysis, within these 30 patients, ≤6 patients achieve response including complete response (CR) and partial response (PR) as their best overall response (BOR) assessed by central site imaging facility for tumor assessment based on RECIST v1.1 (refer to Section 9.7 for details)
- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

The sponsor has the right to close a site at any time. The decision will be notified to the site in advance. Reasons for closing a site may include, but are not limited, to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with Good Clinical Practice (GCP), applicable laws, and regulations
- Study activity is completed (ie, all patients have been completed and all obligations have been fulfilled)

### 3.8. Dose-Limiting Toxicities

#### 3.8.1. Assessment of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) will be assessed among evaluable patients within 21 days after the first dose of study drugs. For dose reduction decision, only DLTs occurring within 21 days will be evaluated. The following patients will not be considered evaluable for DLT, and will be replaced if needed to meet the minimum patient number required for dose escalation:

- Patients who withdraw or are withdrawn from the study before completing the DLT assessment window for reasons other than a DLT.
- Patients receiving combination therapy who do not receive ≥ 75% of scheduled lenvatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window, unless they experience a DLT.

### 3.8.2. Definition of Dose-Limiting Toxicity

A DLT is defined as any of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to lenvatinib and/or tislelizumab.

**Hematologic**

- Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 3 days and requiring transfusion, or any decreased platelet count < 15,000/mm3 or < 15.0 x 109/L
- ≥ Grade 4 anemia

**Non-Hematologic**

- ≥ Grade 4 toxicity
- Grade 3 toxicity that is clinically significant and does not resolve to baseline or ≤ Grade 1 within 7 days of initiating optimal supportive care

Note: The following AEs will not be considered DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement;
- Grade 3 of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors);
- Grade 3 rash;
- Grade 3 infusion-related AE that is transient (resolving within 6 hours of onset);
- Grade 3 hypertension that is resolving within 7 days of optimal supportive care;

  Note: Hypertension will be graded using NCI-CTCAE v 5.0, based on BP measurements only (and not on the number of antihypertensive medications). Each assessment of BP and BP elevation confirmation (systolic and diastolic) should follow Section 7.3.1.
- Clinically insignificant or transient abnormal laboratory findings, including but not limited to following:
  - Grade 3-4 alanine aminotransferase elevation, aspartate aminotransferase elevation or hyperbilirubinemia without significant related clinical symptoms and judged by investigators and medical monitors as non-fatal risk;

- Grade 3-4 hyperamylasemia or hyperlipasemia that is not associated with symptoms or clinical manifestations of pancreatitis and judged by investigators and medical monitors as non-fatal risk;
- Grade 3 proteinuria that is resolving within 7 days of optimal supportive care.

All available safety data, including AEs, laboratory assessments, and PK analyses (as available), will be reviewed with input from other functional representatives as appropriate.

A Safety Monitoring Committee (SMC) will be established consisting of the sponsor's clinical, safety, and medical team representatives (eg, medical monitor, Clinical Pharmacology, Statistician, and Drug Safety) and investigators. A planned formal SMC review of safety data will be performed after at least 6 evaluable patients have completed 21-day DLT assessment in each lenvatinib dose level. The SMC will monitor the preliminary safety of lenvatinib in combination with tislelizumab and determine the RP2D of lenvatinib in combination with tislelizumab based on the available data (eg, safety and PK data) in this study. Study accrual will be held pending data review and lenvatinib RP2D determination by the SMC.

## 4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

### 4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Age ≥ 18 but ≤ 70 years on the day of signing the ICF
3. Unresectable locally advanced or metastatic HCC, which must be confirmed by histologically or cytologically. Fibrolamellar, sarcomatoid, or mixed cholangiocarcinoma histology confirmed by histologically or cytologically is excluded.
4. Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease (see Appendix 15 for details) that is not amenable to or has progressed after loco-regional therapy and is not amenable to a curative treatment approach
5. Did not receive any systemic treatment before and is unwilling to accept standard of care treatment or not suitable for standard of care treatment as judged by investigators
6. No loco-regional therapy to the liver (ie, transarterial chemoembolization [TACE], transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation) within 28 days before the first dose of study drugs
7. At least 1 measurable lesion as defined by RECIST v1.1

   **Note:** Selected target lesion(s) must meet 1 of 2 criteria: 1) not previously treated with local therapy or 2) within the field of prior local therapy but with documented subsequent progression as per RECIST v1.1
8. ECOG Performance Status ≤ 1 (Appendix 4)

9. Child-Pugh A classification for liver function (Appendix 5) assessed within 7 days of first dose of study drugs
10. No tumor thrombus involving main trunk of portal vein or inferior vena cava
11. No prior history of ≥ Grade 2 hepatic encephalopathy before the first dose of study drugs
12. No clinical evidence of portal hypertension with bleeding esophageal or gastric varices within 6 months before the first dose of study drugs
13. Adequate organ function as indicated by the following laboratory values ≤ 7 days before the first dose of study drugs:
    a. Patients must not have required a blood or platelet transfusion or growth factor support ≤ 14 days before sample collection at screening for the following
       i. ANC ≥ 1.5 x $10^9$/L
       ii. Platelets ≥ 75 x $10^9$/L
       iii. Hemoglobin ≥ 90 g/L
    b. Estimated glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 $m^2$ by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Appendix 9)
    c. AST, ALP and ALT ≤ 5 x ULN
    d. Serum total bilirubin ≤ 51.3 µmol/L (3 mg/dl)
    e. International normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 x ULN
    f. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
    g. Serum albumin ≥ 30 g/L
    h. Amylase and lipase ≤ 1.5 x ULN
14. Adequately controlled blood pressure with or without the use of antihypertensive agents (defined as systolic blood pressure ≤ 150 mmHg and diastolic blood pressure ≤ 90 mmHg) at screening and no change in antihypertensive therapy within 1 week prior to the first dose of study drugs
15. If patient has HBV or HCV infection, meets the following criteria as applicable to the infection type:

    <u>For patients with inactive/asymptomatic carrier, chronic, or active HBV:</u>

    - Has HBV deoxyribonucleic acid (DNA) < 500 IU/mL (or 2500 copies/mL) at Screening
      **NOTE:** Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks prior to first dose of study drugs and should continue treatment on study.

    <u>For patients with HCV:</u>

    - Infection is evidenced by detectable HCV ribonucleic acid (RNA), which is not eligible to enroll
16. Survival expectation of 3 months or longer after study enrollment
17. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and ≥ 120 days after the last dose of study drugs, and have a negative serum pregnancy test ≤ 7 days of first dose of study drugs (see Appendix 7 for details)

18. Males participant of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drugs (see Appendix 7 for details)

### 4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll:

1. Any known brain or leptomeningeal metastases
2. Any clearly known invasion or tumor thrombus on first grade/second grade intrahepatic bile duct or extrahepatic bile duct
3. Patients underwent surgical of transjugular intrahepatic portosystemic shunt (TIPS) or other forms of portosystemic shunt
4. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 6).

   **Note:** Patients with the following diseases are not excluded and may proceed to further screening:

   a. Controlled Type I diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors

5. Any active malignancy ≤ 2 years before the first dose of study drugs except for specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).
6. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drugs.

   **Note:** Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a nonautoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

7. Uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management, or ≥ Grade 3 hypoalbuminemia ≤ 14 days before the first dose of study drugs
8. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled diseases including pulmonary fibrosis, acute lung diseases, etc
9. Severe chronic or active infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal, or antiviral therapy within 14 days prior to first dose of study drugs. Note: antiviral therapy is permitted for patients with viral hepatitis
10. Subjects having ≥ 1+ proteinuria on urinalysis will undergo a 24-hour urine collection for quantitative assessment of proteinuria. Subjects with a urine protein ≥1 g/24 hours will be ineligible
11. Known history of human immunodeficiency virus (HIV) infection
12. Any major surgical procedure requiring general anesthesia ≤ 28 days before the first dose of study drugs
13. Prior allogeneic stem cell transplantation or organ transplantation
14. Any of the following cardiovascular criteria
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drugs
    b. Symptomatic pulmonary embolism ≤ 28 days before the first dose of study drugs
    c. Any history of acute myocardial infarction ≤ 6 months before the first dose of study drugs
    d. Any history of heart failure meeting New York Heart Association Classification (NYHA) III or IV (Appendix 8) ≤ 6 months before the first dose of study drugs
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drugs
    f. Any history of cerebrovascular accident ≤ 6 months before the first dose of study drugs
    g. QT corrected (QTc) interval (corrected by Fridericia's method) > 480 ms

       Note: If QTc interval is > 480 ms on initial ECG, a follow up ECG will be performed to exclude result
    h. Current left ventricular ejection fraction (LVEF) < institutional lower limit of normal as assessed by echocardiography (ECHO). The same modality used at baseline must be applied for subsequent evaluations
    i. Any episode of syncope or seizure ≤ 28 days before the first dose of study drugs
15. Hypersensitivity to tislelizumab or lenvatinib, to any ingredient in the formulation, or to any component of the container

16. Thrombotic disorders or use of anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring within 6 months before the first dose of study drugs, or requiring use of antiplatelet agents during whole study
17. Clinically significant hemoptysis, tumor hemorrhage or other significant bleeding for any cause within 2 weeks prior to the first dose of study drugs
18. Any systemic chemotherapy within 28 days of the first dose of study drugs or immunotherapy (eg, interleukin, interferon, thymosin, etc.), hormone therapy, targeted therapy, or any investigational therapies within 14 days or 5 half-lives (whichever is shorter) of first dose of study drugs
19. Any Chinese herbal or Chinese patent medicine with anticancer activity approved by the China National Medical Product Administration (NMPA) (regardless of the type of cancer) used within 14 days before the first administration of study drugs
20. Toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
21. Administration of live vaccine ≤ 4 weeks before the first dose of study drugs

    **Note:** seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed
22. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drugs or affect the explanation of drug toxicity or AEs or result in insufficient or might impair compliance with study conduct
23. Concurrent participation in another therapeutic clinical study
24. Inability to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the complete stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
25. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage or medical intervention (clinically significant recurrence requiring an additional intervention within 2 weeks of intervention; cytological confirmation of any effusion permitted) within 7 days before first dose of study drugs
26. Patients with gastrointestinal perforation or any fistula formation (e.g. gastrointestinal fistula formation, tracheal fistula, tracheoesophageal fistula, esophageal fistula, skin fistula, female genital fistula) ≤ 6 months before the first dose of study drugs
27. Patients with serious non-healing wound, ulcer, or bone fracture
28. Patients with medical contraindications that preclude all forms of contrast enhanced imaging(both CT and MRI)
29. Pregnant or breastfeeding woman

# 5. STUDY TREATMENT

## 5.1. Formulation, Packaging, and Handling

### 5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, United States Pharmacopeia type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the Investigator's Brochure for other details regarding tislelizumab.

### 5.1.2. Lenvatinib

Management (ie, handling, storage, administration, and disposal) of Lenvatinib will be in accordance with relevant local guidelines, package insert/summary of product characteristics.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

## 5.2. Dosage and Administration

On days when lenvatinib and tislelizumab dosing are both scheduled, the daily dose of lenvatinib should precede tislelizumab infusion.

### 5.2.1. Tislelizumab

Tislelizumab (200 mg) will be administered on Day 1 of each 21-day cycle (once every 3 weeks). Tislelizumab will be administered by intravenous infusion through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

Guidelines Pharmacy Manual for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 8.7 and Appendix 10.

### 5.2.2. Lenvatinib

In part 1, lenvatinib capsules will be administered orally, once daily, in a continuous regimen in 21-day cycles. The starting dose for lenvatinib in part 1 will depended on patients' weight in baseline, 12 mg lenvatinib will be administered once daily if baseline body weight of patient≥60 kg, 8 mg lenvatinib will be administered once daily if baseline body weight of patient＜60 kg. Depending on safety observations and sponsor's decision, the lenvatinib dose in the subsequent cohort of patients may be reduced as following, 8 mg lenvatinib will be administered once daily if baseline body weight of patient≥60 kg, 4 mg lenvatinib will be administered once daily if baseline body weight of patient＜60 kg.

In part 2, SMC will confirm RP2D of the combination treatment dosing of lenvatinib, which can be withheld for up to approximately 28 days consecutively.

Dose modifications of lenvatinib should be performed based on the Section of Management of Lenvatinib-Specific Adverse Events (See Section 8.8 for details). Specific instructions for product administration are provided in the Pharmacy Manual.

## 5.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or appropriately delegated study personnel at each patient visit and information provided by the patient. Patients enrolled in the study will be provided with patient diaries. The patient is responsible for maintaining the patient diary and will record the number of capsules of lenvatinib taken and if any were missed. The site personnel responsible for drug accountability will record the quantity of drug dispensed and quantity of drug received after the cycle visit. The patient diaries and the pharmacist record of drug will be assessed by the investigator/study personnel at each visit.

The study drugs (lenvatinib and tislelizumab) required for this study, before the data of discontinuation from study treatment or from the study (see Section 3.6 for details) will be provided by the sponsor, as required by local or country-specific guidance. If patients don't meet any discontinuation criterion, such as investigator-assessed iCPD based on iRECIST, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor, lenvatinib and tislelizumab will be administered until patient completes his/her 12-month treatment duration of study drugs. After 12-month treatment duration completion, if the patients are still under the response (CR, PR) or stable disease (SD) assessed by investigator based on RECIST v1.1 or under the response (complete response [iCR], partial response [iPR]), stable disease (iSD) and unconfirmed progression (iUPD) assessed by investigator based on iRECIST, and may continue receiving benefit based on investigator's assessment, tislelizumab could be further provided by sponsor, this decision must be agreed with medical monitor and documented in the study records, patients are also required to be reconsented.

The investigational site will acknowledge receipt of study drugs. Any damaged shipments will be replaced.

Accurate records of all study drugs received, dispensed, returned, and disposed should be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of study drugs management.

### 5.4. Overdose

#### 5.4.1. Tislelizumab

Any overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) or incorrect administration of tislelizumab should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.6.2. Supportive care measures should be administered as appropriate.

#### 5.4.2. Lenvatinib

Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multiorgan dysfunction occurred in a patient who received a single dose of lenvatinib 120 mg orally. (Lenvatinib Pharmaceutical Instruction. 2018.) Any overdose or incorrect administration of lenvatinib should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.6.2. Supportive care measures should be administered as appropriate.

### 5.5. Modification and Dose Delay

#### 5.5.1. Dose Modification

There will be no dose reductions for tislelizumab in this study. Dose reductions for lenvatinib are presented in table 12. Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis. If the administration of lenvatinib is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose. Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to lenvatinib are presented in Section 8.8.

**Table 12 Lenvatinib Dose Reductions**

| Weight in baseline | ≥60 kg [a] | < 60 kg [a] |
|---|---|---|
| Dose Level-1 | 12 mg once daily | 8 mg once daily |
| Dose Level-2 | 8 mg once daily | 4 mg once daily |
| Dose Level-3 | 4 mg once daily | 4 mg every other day |
| Dose Level-4 | 4 mg every other day | Discontinue |

a. Based on the previous dose levels, the dose was gradually reduced in the order of 12 mg once a day, 8 mg once a day, 4 mg once a day or 4 mg every other day.

If one study drug is interrupted or discontinued, administration of the other study drug may continue at the discretion of the investigator.

### 5.5.2. Dose Delay

Every effort should be made to administer the study drugs according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to study drugs and requires a dose to be withheld. Patients should resume study drugs as soon as possible after the AEs recover to baseline or Grade 1 (whichever is less severe) and within 4 weeks (28 days) for lenvatinib or 12 weeks for tislelizumab after last dose of the respective study drug. Lenvatinib should be resumed at a reduced dose level as outlined in table 12. If the administration of lenvatinib is interrupted for reasons other than toxicity, then treatment with the study drugs may be resumed at the same dose.

The following dose delays or interruptions will be permitted:

- Tislelizumab can be delayed or interrupted for up to 12 weeks. If a dose is delayed for ≤ 10 days before a planned dosing cycle (eg, Cycle 3, Day 1), tislelizumab should be administered (on the same day with lenvatinib, if applicable) and all assessments should be conducted according to the original cycle (ie, Cycle 3). If the delay is > 10 days, the patient should skip the tislelizumab, and tislelizumab will be administered on Day 1 of the next planned cycle (ie, Cycle 4, Day 1).
- Lenvatinib can be interrupted for up to approximately 28 days consecutively. If treatment with lenvatinib is delayed for ≥ 14 days, then resumption at a reduced dose should be considered. If drug is planned to be interrupted ≥ 28 days, the medical monitor should be contacted before permanent patient discontinuation from the study drug.

The tumor assessment schedule will not be altered even if the administration of study drugs is delayed.

If the patient is unable to resume lenvatinib or tislelizumab within the permitted timeframe after the last dose of study drugs, then the patient should be discontinued from the study drugs.

Dose modification related to irAEs and infusion-related reactions for tislelizumab are described in Appendix 10 and Section 8.7, respectively.

## 6. PRIOR AND CONCOMITANT THERAPY

### 6.1. Concomitant Therapy

### 6.1.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary in keeping with the local standards of medical care at the discretion of the investigator for supportive care (eg, antiemetics, antidiarrheals) and in a patient's interest are allowed.

Proton pump inhibitors and H2 antagonists should be avoided during treatment on study but are not exclusionary. Switching from use of proton pump inhibitors or $H_2$ antagonists to use of antacids is

preferred. Use of antacids should be avoided 4 hours before and 2 hours after administration of investigational study treatment.

Systemic corticosteroids given for the control of irAEs must be tapered gradually (see Appendix 10) and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next administration of tislelizumab. The short-term use of steroids as prophylactic treatment (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

If patients are known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before first dose of study drugs, and investigators should therefore ensure that patients enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry.

Patients with active hepatitis B, defined as either detectable HBsAg or HBV DNA at baseline, must initiate treatment 2 weeks prior to first dose of study drugs and continue until 6 months after the last dose of study drugs. Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel, 2015). The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the Investigator; however, reason(s) must be provided in the CRF if a patient with active hepatitis B is not treated with antiviral prophylaxis, and this case should be discussed with the medical monitor and the medical monitor agrees.

Palliative (limited-field) radiation therapy is permitted for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline. The lesion being considered for palliative radiation should not be a target lesion for RECIST v1.1. The case should be discussed with the medical monitor; the therapy will be used if the medical monitor agrees that the conditions required to receive palliative radiation are met. Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the medical monitor. Whenever possible, these patients should undergo a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out PD.

### 6.1.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, loco-regional therapy, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicine] for the treatment of cancer) is not allowed. Chinese herbal and Chinese patent medicines with anticancer activity are defined as medication with approval by the China NMPA for use as anticancer treatment (regardless of the type of cancer).
- Live vaccines within 28 days before first dose of study drugs and 60 days following the last dose of study drugs.
- Any antiplatelet agents are prohibited.
- Anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring.

### 6.1.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should avoid alcohol completely and should avoid other addictive drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.1.1.
- Herbal remedies are not recommended for use during the study treatment. Patients must notify the investigators of all herbal remedies used during the study.
- Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

## 6.2. Potential Interactions Between the Study Drugs and Concomitant Medications

Effect of Other Drugs on Lenvatinib

Chemotherapeutic drugs: There was no significant effect on pharmacokinetics of any of the three drugs by combination of lenvatinib, carboplatin and paclitaxel.

Effect of Lenvatinib on Other Drugs

No data showed that lenvatinib could be excluded from the risk of being an inducer of CYP3A4 or P-gp in the gastrointestinal tract. That may lead to a decrease in the exposure of oral drugs with CYP3A4/P-gp as the substrate. Therefore, this should be fully taken into account when taking drugs with CYP3A4/P-gp as the substrate in combination with lenvatinib, in order to ensure the efficacy. So CYP3A4 substrates with known narrow therapeutic windows should be used with caution in patients receiving lenvatinib, for example, asmidazole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine and dihydroergotamine).

Oral contraceptive

It is not clear whether lenvatinib reduces the effectiveness of hormonal contraceptives, so women who are using oral hormonal contraceptives should increase barrier contraception.

Drugs That Prolong the QT Interval

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia

and III antiarrhythmics. Withhold and resume at reduced dose of lenvatinib upon recovery based on severity ( see Section 8.8 for more details).

Per the International Council for Harmonisation (ICH) E14 guidance, it is recommended to avoid medications with potential to prolong QT/QTc or cause Torsades. Please refer to Appendix 14 for a list of medications or substances to be avoided or used with caution during treatment with lenvatinib.

**Potential Interaction with Tislelizumab**

Lenvatinib administered in combination with tislelizumab is unlikely to result in clinically relevant drug-drug interactions based on absorption, metabolism, elimination, or protein binding. Tislelizumab is a monoclonal antibody and is administered intravenously, whereas lenvatinib is a small molecule therapeutic administered orally. Like most therapeutic proteins, tislelizumab is not expected to be metabolized by CYP or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

## 7. STUDY ASSESSMENTS AND PROCEDURES

The study-specific assessments and procedures with allowed time windows are outlined in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment unless otherwise noted. Laboratory results are required to be reviewed prior to dosing. Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date, with subsequent visits conducted according to the planned schedule every 3 weeks from Cycle 1 Day 1.

### 7.1. Screening

Screening evaluations will be performed within 28 days prior to the first dose of study drugs. Patients who agree to participate will sign the ICF prior to undergoing any screening procedure. The screening period begins on the first day a screening procedure is conducted. Patients who are suspected or known to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drugs may be used for the purposes of screening rather than repeating the standard of care tests unless otherwise indicated.

Procedures conducted during the Screening Visit only are described in this section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.3), Tumor and Response Evaluations (Section 7.4). The PK sampling schedule is shown in Appendix 2.

Rescreening under limited conditions may be allowed after consultation with BeiGene, eg, when a patient narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

### 7.1.1. Demographics and Medical History

Demographic data will include gender, year of birth and age, and race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before the first dose of study drug.

Cancer history will include an assessment of prior surgery, prior radiotherapy, and prior drug therapy, including start and stop dates, best response, and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator. If applicable, histologically and cytologically of cancer will include assessment result, date of assessment and assessment agency.

### 7.1.2. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 7 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential"

### 7.1.3. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. ICFs for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first dose of study drugs. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 7.1.4. Pulmonary Function Tests

Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will undergo pulmonary function testing, which

may include, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study.

## 7.2. Enrollment

The investigator will assess, and the sponsor or designee will confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete an Eligibility Authorization Packet and send it to the medical monitor or designee to approve the enrollment. Study site personnel should ensure that a medical monitor's confirmation has been received before the study drug administration.

## 7.3. Safety Assessments

### 7.3.1. Vital Signs

Vital signs will include measurements of temperature (˚C), pulse rate, and blood pressure (BP, including systolic and diastolic) while the patients keep resting for 10 minutes.

Each BP assessment and BP elevation confirmation should be performed as following processes:

- First BP measurement should be performed after the patients keep resting for at least 10 minutes.
- The second BP measurement should be repeated at least 10 minutes later, while patients keep resting for at least 10 minutes as well.
- The mean value of 2 measurements at least 10 minutes apart is defined as one BP assessment
- If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 10 minutes apart) is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 10 minutes apart) to yield a mean value.

### 7.3.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v 5.0 and recorded on the eCRF with appropriate disease/condition terms.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed. Changes from baseline will be recorded. New or worsened clinically significant abnormalities are to be recorded as AEs on the Adverse Event eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

### 7.3.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (refer to Appendix 4) will be assessed during the study.

### 7.3.4. Laboratory Safety Test

Local laboratory assessments of hematology, serum chemistry, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 1.

If laboratory tests at screening are not performed within 7 days prior to the administration of study drugs on Cycle 1 Day 1, these tests should be repeated and reviewed before study drugs administration. Hematology, as specified in Appendix 1, should be performed weekly for the first 2 cycles and at the beginning of subsequent cycles in patients who are enrolled in part 1 and be performed for patients enrolled in part 2 at the beginning of each cycles. Urinalysis and serum chemistry should be performed weekly for the first 2 cycles and at the beginning of subsequent cycles in patients who are enrolled in part 1 and part 2.

Urinalysis on routine urinalysis, if urine protein is ≥ 2+ (≥ 1+ in screening) by dipstick, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio (refer to Section 8.8.3 for detection and confirmation of proteinuria). In 24-hour protein assessment, to achieve the result prior to study drugs administration on the day of each scheduled assessment, the urine sample may be collected 24 hours ahead of schedule in 24-hour protein assessment, as specified in Appendix 1.

Instruction manuals and supply kits will be provided for all central laboratory assessments.

Investigators may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decision.

In addition, the following tests will be conducted in this study:

- Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to administration of study drugs. Urine or serum pregnancy tests will be performed during treatment before study drugs administration at each cycle and at the EOT Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
- Thyroid function tests (TFTs) (thyroid-stimulating hormone [TSH], free T3, free T4) will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the EOT Visit.
- Patients receiving tislelizumab will receive CK and CK-MB testing. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients with a history of cardiological disease or after discontinuation of tislelizumab, may receive CK and CK-MB testing if clinically indicated. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

### 7.3.5. Hepatitis B and C Testing

Testing will be performed by the local laboratory at screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).

Patients who have detectable HBV DNA at screening will receive a viral load test every 4 cycles, at the EOT Visit.

### 7.3.6. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's study file at the site.

When coinciding with blood draws, ECG assessment should be performed prior to blood draws. Patients should rest in semirecumbent supine position for at least 10 minutes prior to ECG collection.

### 7.3.7. Multigated Acquisition (MUGA) Scans or Echocardiograms

Evaluations of cardiac function will be performed at screening and every 12 weeks during treatment. Investigator will decide the method (MUGA or echocardiograms) for evaluation of cardiac function. The method used for individual patients should be consistent throughout study participation.

### 7.3.8. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0 (NCI-CTCAE 2017). Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.6.

## 7.4. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days prior to the first dose of study drugs. Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drugs may be used for the purposes of screening rather than repeating the standard of care tests. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) in the first year and thereafter approximately every 9 weeks (± 7 days).

Screening assessments and each subsequent assessment must include contrast-enhanced computed tomography (CT) scans or contrast-enhanced magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc).

Tumor assessments must include contrast-enhanced CT scans or contrast-enhanced MRI, with preference for contrast-enhanced CT, of the chest (if choose MRI as tumor assessment, for chest, a noncontrast or contrast-enhanced CT of the chest should be performed instead of MRI of chest), abdomen, and pelvis. Unless contraindicated, contrast-enhanced CT scans are recommended in tumor assessments. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc). The same radiographic procedure used to assess disease sites at screening is required to be used throughout the

study (eg, the same contrast protocol for contrast-enhanced CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

- Imaging of the brain (MRI or CT) at baseline (≤ 28 days of informed consent) is required for all screened patients. Unless contraindicated or not readily available, MRI scans of brain are recommended at screening.
- Unless contraindicated, contrast-enhanced CT scans are recommended in tumor assessments.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a noncontrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a contrast-contrast diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans afterwards, or clinically indicated, TC-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

Tumor response will be assessed using RECIST v1.1, mRECIST and iRECIST respectively (refer to Appendix 11, Appendix 12 and Appendix 13).

After the first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment time point.

If radiographic initial PD is observed by the investigator based on RECIST 1.1, patients should continue treatment with tislelizumab until iCPD (investigator assessed based on iRECIST) is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 8 weeks from the date of initial documentation of PD, repeated imaging on next scheduled tumor assessment visit date, around 6 weeks from the date of initial documentation of PD is recommended). The following criteria must be met in order to treat patients to continue study drugs beyond initial PD via investigator assessed based on RECIST v1.1:

- Absence of clinical symptoms and signs of PD (including clinically significant worsening of laboratory values)
- Stable ECOG Performance Status ≤ 1
- Absence of rapid PD or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic PD and inform patients that this practice is not considered standard in the treatment of cancer

The decision to continue study drugs beyond investigator-assessed progression must be agreed with the medical monitor and documented in the study records. After decision to continue study drugs beyond investigator-assessed progression based on RECIST v1.1, the further decision of treatment will follow below criterion:

- Tumor assessments are still required to be performed on original schedule plan via investigator and central site imaging facility based on RECIST v1.1, mRECIST and iRECIST respectively
- Unless investigator-assessed iCPD based on iRECIST, patients will continue study drugs, until the patient meet other criterion of discontinuation from study treatment (see Section 3.6.1 for details)

Patients who discontinue study treatment early for reasons other than iCPD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, withdraws consent, is lost to follow-up, death, or until the study terminates, whichever occurs first.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held.

### 7.4.1. Investigator Assessment

For investigator assessment, the same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

### 7.4.2. Central Site Imaging Facility for Tumor Assessment

Central site imaging facility for tumor assessment is composed of at least 3 radiology experts at the leading site or the site where the leading PI is located, specialized in tumor radiological assessment. The selection of these experts will be confirmed by leading PI and medical monitor, documented in study records. The executive plan will be described in Protocol of Central Site Imaging Facility.

## 7.5. Pharmacokinetic Assessment

The PK concentrations will be determined using serum (tislelizumab) samples collected at specified time points within a reasonable variation window. When each PK sample is collected for tislelizumab. (refer to Appendix 1 and Appendix 2). The actual collection date and time of each sample collection will be recorded on the source document and eCRF.

Samples of plasma will be collected at specified times points within a reasonable variation windows for a potential test for lenvatinib PK profile. (refer to Appendix 1 and Appendix 2).

In the event of a DLT or significant toxicity, it is recommended that an unscheduled PK serum (tislelizumab) sample be drawn as soon as possible.

Shipping, storage, and handling of samples will be managed through a central laboratory. Analysis of samples will be performed using specific validated bioanalytical methods. Instruction manuals and supply kits will be provided for all central laboratory assessments.

### 7.6. Antidrug Antibody Testing

Tislelizumab may elicit an immune response. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints throughout the study (Appendix 1). The immunogenicity evaluation will use a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to tislelizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. (refer to Appendix 1 and Appendix 2).

Shipping, storage, and handling of samples will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

### 7.7. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from Cycle 1 Day 1.

### 7.8. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/focused physical examination; ECOG Performance status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected PD, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

## 8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

### 8.1. Risks Associated with Lenvatinib and Tislelizumab

Lenvatinib is a post-market agent in China which has been approved by NMPA for hepatocellular carcinoma once daily (Lenvatinib Pharmaceutical Instruction. 2018.). Tislelizumab are investigational agents that are currently in clinical development for the treatment of HCC. Limited safety data for lenvatinib in combination with tislelizumab in patients are available, and the full safety profiles have not

been characterized. The following recommendations are based on results from nonclinical and clinical studies of lenvatinib or tislelizumab and published data on other molecules within the same biologic classes.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.

The guidelines for management of potential AEs more specific to treatment with lenvatinib or agents in the same class of cancer treatment are presented in Section 8.8.

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures for suspected irAEs are provided in Appendix 10.

## 8.2. General Plan to Manage Safety Concerns

### 8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies of lenvatinib and tislelizumab, clinical data with lenvatinib and tislelizumab, as well as the nonclinical/clinical data from other RTK inhibitors and PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation, and patients who have received a live vaccine within 28 days before the first dose of study drugs are excluded from the study (see Section 4.2).

### 8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed prior to the start of each cycle.

**Note:** Hypertension will be graded using NCI-CTCAE v 5.0, based on BP measurements only (and not on the number of antihypertensive medications).

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, chemistry, etc.), and other assessments. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn for determination of antidrug antibody (ADA) to tislelizumab in patients who are enrolled in part 1. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2).

All AEs will be recorded during the study (AE from the time of the first dose of study drugs and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. At the EOT, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Immune-related AEs will be recorded until up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

Investigators are instructed to report all AEs (including pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

## 8.3. Adverse Events

### 8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drugs or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drugs administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drugs or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

### 8.3.2. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note:

1. The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, Grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.
2. Hypertension will be graded using NCI-CTCAE v 5.0, based on BP measurements only (and not on the number of antihypertensive medications).

### 8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drugs and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drugs should be considered and investigated. The investigator should refer to the Investigator's Brochures of tislelizumab, information regarding lenvatinib in this protocol and Pharmaceutical Instructions of lenvatinib (Lenvatinib Pharmaceutical Instruction. 2018) in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every SAE prior to transmission of the SAE report to the sponsor, since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). Several factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified

- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered "related" to study drug if any of the following criteria are met, otherwise the event should be assessed as not related:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

### 8.3.4. Following Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow up, or the patient withdraws consent. The investigator will ensure that follow up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.2.

### 8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count [CBC], coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or
- further diagnostic investigation.

Abnormalities in liver function tests (ALT, AST, total bilirubin) that are Grade 3 or higher need to be reported to the sponsor within 24 hours of occurrence via SAE reporting process as described in Section 8.6.2.1. Repeat liver function testing (LFT) should be performed according to the schedule in Appendix 10.

### 8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe
- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting
- Results in disability/incapacity

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

### 8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the Investigator's Brochure or related information in this protocol) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Investigator's Brochure.

### 8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

#### 8.6.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drugs or initiation of new anticancer therapy, whichever occurs first. Immune-related AEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab, regardless of if the patient starts a new anticancer therapy.

The investigator should report any SAEs that are assessed as related to study drug treatment, at any time after treatment discontinuation.

#### 8.6.2. Reporting Serious Adverse Events

##### 8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in table 13.

**Table 13 Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee**

| | Timeframe for Making Initial Report | Documentation Method | Timeframe for Making Follow-up Report | Documentation Method | Reporting Method |
|---|---|---|---|---|---|
| All SAEs | Within 24 h of first knowledge of the SAE | SAE report | As expeditiously as possible | SAE report | Email or fax SAE form |

Abbreviations: h, hours; SAE, serious adverse event.

##### 8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.6.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

#### 8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1 and Section 8.6.2.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

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 IRB/IEC.

All SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for lenvatinib and tislelizumab studies.

When a study center receives an initial or follow-up report or other safety information (eg, revised investigator's book) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

### 8.6.3. Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

### 8.6.4. Progressive Disease

Progressive disease (including fatal PD), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the AE term(s).

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of PD. If a patient experienced a fatal multiorgan failure due to PD, the term "multiorgan failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression."

### 8.6.5. Deaths

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg, "death," "death of unknown cause," or "death unexplained."

### 8.6.6. Pregnancies

If a female patient or the partner of a male patient receiving investigational therapy becomes pregnant within 120 days after the last dose of tislelizumab or lenvatinib, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow up will be no longer than 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drugs should be recorded and reported as an SAE.

### 8.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drugs experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information (RSI) documents:

- tislelizumab IB
- all information of lenvatinib presented in Pharmaceutical Instructions of lenvatinib (Lenvatinib Pharmaceutical Instruction. 2018.)

### 8.6.8. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related (see Section 8.7.3) should be classified as irAEs and identified as such in the eCRF AE page until 90 days after the last dose of study treatment.

Investigators should consult the guidance on diagnostic evaluation and management of irAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 10.

An extensive list of potential irAEs appears in table 15. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 10.

### 8.7. Management of Adverse Events of Special Interest of Tislelizumab

As a routine precaution, after infusion of tislelizumab on Cycle 1 and Cycle 2 Day 1, patients must be monitored for at least 1 hour afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management of infusion-related reactions, severe hypersensitivity reactions and irAEs according to the NCI-CTCAE criteria are outlined below.

#### 8.7.1. Infusion-Related Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, 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. Patients should be closely monitored for such reactions. 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.

Treatment modification for symptoms of infusion-related reactions due to tislelizumab is provided in table 14.

**Table 14 Treatment Modification for Symptoms of Infusion-Related Reactions Due to Tislelizumab**

| NCI-CTCAE Grade | Treatment Modification for Tislelizumab |
|---|---|
| **Grade 1 - mild**<br>Mild transient reaction; infusion interruption not indicated; intervention not indicated. | Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed.<br>Subsequent infusions should be given after premedication and at the reduced infusion rate. |
| **Grade 2 - moderate**<br>Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h. | Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions have resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below.<br>Subsequent infusions should be given after premedication and at the reduced infusion rate. |

| | |
|---|---|
| **Grade 3 – severe**<br>Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. | Immediately stop the infusion. Proper medical management should be instituted as described below.<br>The patient should be withdrawn from study drugs treatment. |
| **Grade 4 – life threatening**<br>Life-threatening consequences; urgent intervention indicated. | Immediately stop the infusion. Proper medical management should be instituted as described below.<br>The patient should be withdrawn from study drugs treatment.<br>Hospitalization is recommended |

Abbreviations: h, hours; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions with premedication. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from tislelizumab treatment.

**NCI-CTCAE Grade 1 or 2 infusion reaction:** Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

**NCI-CTCAE Grade 3 or 4 infusion reaction:** Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

### 8.7.2. Severe Hypersensitivity Reactions and Flu-like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK). Patients should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen, and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea), the infusion must be immediately stopped and the patient discontinued from the study.

The patients will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and ICU should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drug infusion. Alternative treatments for fever (ie, paracetamol) may be given to patients at the discretion of the investigator.

### 8.7.3. Immune-related Adverse Events

While lenvatinib may have immunostimulatory effects, autoimmune AEs have not been reported in clinical trials, including to date in combination with pembrolizumab. However, the potential for lenvatinib to exacerbate or promote these AEs when administered in combination with a PD-1 inhibitor should be noted.

Immune-related AEs are of special interest in this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, PD, metabolic, toxin, or other neoplastic causes) with appropriate diagnostic tests which may include but are not limited to serologic, immunologic, and histologic (if available) data. If alternative causes have been ruled out; the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune mediated mechanism of action, the irAE indicator in the eCRF AE page should be checked. A clinically relevant overlap in toxicity may arise between an irAE attributed to tislelizumab and the nonspecific, most often mild to moderate AE (eg, rash, colitis and abnormalities in ALT, AST and total bilirubin) observed with lenvatinib. The time to onset may be helpful in distinguishing an AE that may be attributed to autoimmune effects versus nonspecific toxicity.

A list of potential irAEs is shown below in table 15. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-related.

Recommendation for diagnostic evaluation and management of irAEs is based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017, Brahmer et al 2018) and common immune-related toxicities are detailed in Appendix 10. For any AEs not included in Appendix 10 please refer to ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-related toxicities.

**Table 15 Immune-Related Adverse Events**

| Body System Affected | Events |
|---|---|
| Skin (mild-common) | pruritus or maculopapular rash; vitiligo |
| Skin (moderate) | follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome |
| Skin (severe-rare) | full-thickness necrolysis/Stevens-Johnson syndrome |
| Gastrointestinal | colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation |
| Endocrine | thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency |
| Respiratory | pneumonitis/diffuse alveolitis |
| Eye | episcleritis; conjunctivitis; iritis/uveitis |
| Neuromuscular | arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis |
| Blood | anemia; leukopenia; thrombocytopenia |
| Renal | interstitial nephritis; glomerulonephritis; acute renal failure |
| Cardiac | pericarditis; myocarditis; heart failure |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Recommendations for managing irAEs are detailed in Appendix 10.

In the event of an immune-related AE during study treatment, administration of lenvatinib and tislelizumab should be interrupted until the event stabilizes to ≤ Grade 1, unless otherwise noted. If a toxicity does not resolve to ≤ Grade 1 within 4 weeks for lenvatinib or 12 weeks for tislelizumab, study drugs should be discontinued after consultation with the sponsor. Patients who experience a recurrence of the any event at the same or higher severity grade with re-challenge should permanently discontinue treatment.

## 8.8. Management of Lenvatinib-Specific Adverse Events

The management of lenvatinib-specific adverse events almost refer to Pharmaceutical Instructions of lenvatinib (Lenvatinib Pharmaceutical Instruction. 2018.). And patients will be closely monitored for any toxicities.

### 8.8.1. Management of Non-Hematological Toxicities and Hematological Toxicities of Lenvatinib

Non-hematological and hematological toxicities ≥ Grade 3 or Grade 2 intolerable non-hematological and hematological toxicities which have underwent active treatment, considered to be related to lenvatinib treatment may be managed by lenvatinib interruption, lenvatinib dosage reduction or lenvatinib discontinuing treatment, until resolution of toxicity to ≤ Grade 1 or to baseline value, unless otherwise noted (see table 16). Mild to moderate non-hematological and hematological toxicities (Grade 1 or 2)

generally do not require interruption of lenvatinib, unless Grade 2 toxicities which patients are still intolerant even after active treatment.

If the toxicity is adequately managed by routine supportive care (eg, antiemetics, antidiarrheals, or electrolyte supplementation), treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose as outlined in table 16. Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered. Detailed information on dosage modifications based on non-hematological and hematological toxicities see table 16. Detailed information on monitoring, dosage modifications and discontinuation see table 17.

**Table 16 Lenvatinib Dose Modifications Based on non-hematological and hematological Drug-Related Toxicities**

| Adverse Event | Toxicity Grade[a] | Management | Reduction dose and resumption of lenvatinib |
|---|---|---|---|
| Hypertension[b] | Grade 3 (Despite the best antihypertensive therapy)[c] | Interruption | Resume when hypertension is controlled at less than or equal to Grade 2. (refer to 8.8.2 Hypertension) |
| | Grade 4 | Discontinue | Permanently discontinue (refer to 8.8.2 Hypertension) |
| Proteinuria | 2 g or greater proteinuria in 24 hours | Interruption | Withhold until less than 2 grams of proteinuria per 24 hours |
| Nephrotic syndrome | ------- | Discontinue | Permanently discontinue |
| Renal Failure or Impairment | Grade 3 | Interruption | Withhold until improves to Grade 0 to 1 or baseline |
| | Grade 4[a] | Discontinue | Permanently discontinue |
| Cardiac Dysfunction | Grade 3 | Interruption | Withhold until improves to Grade 0 to 1 or baseline |
| | Grade 4 | Discontinue | Permanently discontinue |
| Reversible Posterior Leukoencephalopathy Syndrome (RPLS)/ Posterior Reversible Encephalopathy Syndrome (PRES) | Any Grade | Interruption | If improves to Grade 0 to 1, may consider resuming at a reduced dose |
| Hepatotoxicity[b] | Grade 3 | Interruption | Withhold until improves to Grade 0 to 1 or baseline |
| | Grade 4[a] | Discontinue | Permanently discontinue |
| Arterial Thromboembolic Event | Any Grade | Discontinue | Permanently discontinue |
| Hemorrhage | Grade 3 | Interruption | Withhold until improves to Grade 0 to 1 or baseline |
| | Grade 4 | Discontinue | Permanently discontinue |

| | | | |
|---|---|---|---|
| Gastrointestinal Perforation or Fistula Formation | Grade 3 | Interruption | Withhold until improves to Grade 0 to 1 or baseline |
| | Grade 4 | Discontinue | Permanently discontinue |
| Non-gastrointestinal Fistula Formation | Grade 4 | Discontinue | Permanently discontinue |
| QT Prolongation | Greater than 500 ms | Interruption | Withhold until improves to less than or equal to 480 ms or baseline |
| Diarrhea[b] | Grade 3 | Interruption | Withhold until improves to Grade 0 to 1 or baseline |
| | Grade 4（Despite best medical management） | Discontinue | Permanently discontinue |
| Other Adverse Reactions | ○ Persistent or intolerable<br>○ Grade 2 or 3 adverse reaction which have underwent active treatment<br>○ Grade 4 laboratory abnormality[a] | Interruption | Withhold until improves to Grade 0 to 1 or baseline |
| | Other Grade 4 adverse reaction | Discontinue | Permanently discontinue |

a. When the toxicities are grade 4 laboratory abnormalities, if judged to be non-life-threatening by investigator, these grade 4 toxicities can be treated as grade 3 toxicities. For asymptomatic laboratory abnormalities, such as grade 3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the medical monitor.
b. Not likely to be immune-mediated based on investigator's assessment.
c. Hypertension will be graded using NCI-CTCAE v 5.0, based on BP measurements only (and not on the number of antihypertensive medications).

## Table 17 Monitoring, Dose Modifications and Discontinuation for Lenvatinib-Specific AEs

| **Starting Dose** | | **Baseline Weight≥60 kg 12 mg QD. PO.** | **Baseline Weight<60 kg 8 mg QD. PO.** |
|---|---|---|---|
| Persistent or intolerable Grade 2 or 3[f] AE which have underwent active treatment [a] | | | |
| AE | Dose Modification | Reduced Dose [b] (Baseline Weight≥60 kg) | Reduced Dose [b] (Baseline Weight<60 kg) |

| | | | |
|---|---|---|---|
| First Occurrence [c] | Withhold until improves to Grade 0 to 1 or baseline [d] | 8 mg QD. PO. | 4 mg QD. PO. |
| Second Occurrence (Same event or new event) | Withhold until improves to Grade 0 to 1 or baseline [d] | 4 mg QD. PO. | 4 mg every other day, PO. |
| Third Occurrence (Same event or new event) | Withhold until improves to Grade 0 to 1 or baseline [d] | 4 mg every other day, PO. | Discontinue |
| Grade 4 AE: Discontinue [e] | | | |
| a. AEs such as nausea, vomiting and diarrhea should be actively treated before reduction dose or discontinue.<br>b. Based on the previous dose levels, the dose was gradually reduced in the order of 12 mg once a day, 8 mg once a day, 4 mg once a day or 4 mg every other day.<br>c. Hematological AEs or proteinuria occur for the first time - no dose modification is required.<br>d. Resume when hematological AEs is controlled at less than or equal to Grade 2 or proteinuria less than 2 grams per 24 hours.<br>e. When the toxicities are grade 4 laboratory abnormalities, if judged to be non-life-threatening by investigator, these grade 4 toxicities can be treated as grade 3 toxicities.<br>f. For asymptomatic laboratory abnormalities, such as grade 3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor. | | | |
| Depend on investigator's assessment, patients may resume at the same dose in the following cases:<br>• Grade 3 nausea, vomiting or diarrhea that is treated with supportive care and improves to Grand 0 to 1 or baseline within 72 hours<br>• Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours<br>• Grade 3 fatigue that improves to Grand 0 to 1 or baseline within 8 days<br>• Grade 3 or 4 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis<br>• Grade 3 or 4 alanine aminotransferase and aspartate aminotransferase elevation that is not associated with symptoms, other laboratory indication or clinical manifestations of hepatic failure or hepatic encephalopathy, that is treated with supportive care and improves to Grand 0 to 1 or baseline within ≤ 72 hours | | | |

Abbreviation: QD, once a day; PO, orally

### 8.8.2. Hypertension

Hypertension has been reported in several clinical studies of lenvatinib, which usually occurs in the early stages of treatment, for example, hypertension occurred in 45% of patients in REFLECT study receiving lenvatinib 8 mg or 12 mg orally once daily, and the median time to onset of new or worsening hypertension was 26 days in REFLECT study (Lenvatinib Pharmaceutical Instruction. 2018.). Blood pressure should be well controlled before lenvatinib administration. If the patient is known to have hypertension, a stable dose of antihypertensive therapy following local guidelines, should be administered for at least one week before lenvatinib administration. Severe complications (including aortic dissection) with poorly controlled hypertension have been reported. Early detection and active management of hypertension are important to reduce the interruption or dose modification of lenvatinib (Lenvatinib Pharmaceutical Instruction. 2018.).

Hypertension should be managed following below guideline:

**Management guideline of lenvatinib-specific hypertension**

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that patients enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before first dose of study drugs. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the schedule of assessment (refer to Appendix 1). Hypertension will be graded using NCI-CTCAE v 5.0, based on BP measurements only (and not on the number of antihypertensive medications).

Each assessment of BP and BP elevation confirmation (systolic and diastolic) should follow Section 7.3.1. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed. The choice of antihypertensive treatment should be individualized to the patient's clinical circumstances and follow standard medical practice. For previously normotensive patients, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first confirmed. For those patients already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a patient is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the patient has been on the stable antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Patients with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the patient must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. A diary will be provided to the patient to capture the blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat measurements after at least 30 minutes:

a. Continue study drug and institute antihypertensive therapy for patients not already receiving this.

b. For those patients already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added.

c. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists more than 48 hours, despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted, and restarted at 1 dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the patient has been on a stable dose of antihypertensive medication for at least 48 hours.

- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg, which lasts more than 48 hours, recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the patient has been on a stable dose of antihypertensive medication for at least 48 hours.
- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg, which lasts more than 48 hours, recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction dose only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the patient has been on a stable dose of antihypertensive medication for at least 48 hours.
- Additional dose reduction should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life threatening consequences):

a. Institute appropriate medical management

b. Discontinue lenvatinib

### 8.8.3. Proteinuria

Proteinuria has been reported in several clinical studies of lenvatinib, which usually occurs in the early stages of treatment, for example, 26% of lenvatinib-treated patients in REFLECT study occurred proteinuria, and the incidence of grade 3 was 5.9% in this study. The median time from first lenvatinib administration to onset of proteinuria was 6 weeks in REFLECT study.

If confirmation of lenvatinib-specific proteinuria, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. If nephrotic syndrome occurs, lenvatinib should be discontinued. (Lenvatinib Pharmaceutical Instruction. 2018.).

**Management guideline of lenvatinib-specific proteinuria**

Regular assessment of proteinuria should be conducted as detailed in the schedule of assessment (refer to Appendix 1). Guidelines for assessment and management of proteinuria are as follows:

Grading of proteinuria

Grading according to NCI-CTCAE v 5.0 will be based on the 24-hour urinary protein result if available.

Management of proteinuria

If nephrotic syndrome occurs, lenvatinib should be discontinued.

Detection and Confirmation:

1. Perform urinalysis per the schedule of assessment (refer to Appendix 1).
2. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) and a random

urine sample for total protein and creatinine to determine a protein to creatinine ratio is required in the following situations:

- Occurrence of ≥2+ (≥ 1+ in screening) proteinuria on urine dipstick while on study drugs
- A subsequent increase in severity of urine dipstick proteinuria

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.
4. To achieve the result prior to study drugs administration on the day of each scheduled assessment, the urine sample may be collected 24 hours ahead of schedule in 24-hour protein assessment.

Monitoring：

Urinalysis for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

### 8.8.4. Renal Failure or Impairment

Renal failure or impairment have been reported in several clinical studies of lenvatinib, for example renal impairment occurred in 7.1% of patients receiving lenvatinib in REFLECT study, and the incidence of grade 3 was 1.9%.

The main risk factors identified were dehydration and/or insufficient blood volume caused by gastrointestinal toxicity. It is necessary to initiate prompt management of diarrhea or dehydration/hypovolemia, to reduce the risk of renal failure or impairment. If confirmation renal failure or impairment, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.5. Cardiac Dysfunction

Serious and fatal cardiac dysfunction have been reported in several clinical studies of lenvatinib, for example cardiac dysfunction including congestive heart failure, cardiogenic shock and cardiopulmonary failure, occurred in 0.6% of patients receiving lenvatinib in REFLECT study , and the incidence of grade 3 or greater than grade 3 was 0.4%.

If confirmation of lenvatinib-specific cardiac dysfunction, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.6. Reversible Posterior Leukoencephalopathy Syndrome (RPLS)/ Posterior Reversible Encephalopathy Syndrome (PRES)

RPLS/ PRES have been reported in several clinical studies of lenvatinib, for example PRES (grade 2) occurred in 1 patient (＜1%) receiving lenvatinib in REFLECT study.

PRES is a neurological disease characterized by headache, seizures, lethargy, confusion, mental changes, blindness and other visual or neurological disorders. It may be accompanied by mild to severe hypertension. It is necessary to perform MRI to confirm the diagnosis of PRES. Appropriate treatment should be taken to control blood pressure (see Section 8.8.2 Hypertension). Patients with PRES signs or symptoms may need interruption, dose modification or discontinue of lenvatinib (see table 16 and table 17). (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.7. Hepatotoxicity

In REFLECT study, hepatic encephalopathy occurred in 8% of lenvatinib-treated patients. Grade 3 to 5 hepatic encephalopathy occurred in 5% of lenvatinib-treated patients. Grade 3 to 5 hepatic failure occurred in 3% of lenvatinib-treated patients (Lenvatinib Pharmaceutical Instruction. 2018.). Patients with more severe liver dysfunction and/or greater liver tumor load at baseline are at higher risk of developing hepatic encephalopathy and liver failure. Hepatic encephalopathy was more frequent in patients aged 75 and over. About half of the cases of liver failure and one third of the cases of hepatic encephalopathy were reported in patients with PD.

Due to the elimination of lenvatinib mainly through liver, it is expected that exposure in patients with moderate and severe hepatic insufficiency (Child - Pugh B and Child - Pugh C) will increase.

It's necessary to monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. If confirmation of lenvatinib-specific hepatotoxicity, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

For cases where transaminase increases are not likely to be immune-mediated, treatment management decisions should be made per investigator discretion in consideration of clinical factors.

### 8.8.8. Arterial Thromboembolic Event

There have been reports of arterial thromboembolism (cerebrovascular accident, transient ischemic attack and myocardial infarction) in patients treated with lenvatinib, for example arterial thromboembolism occurred in 2.3% of patients receiving lenvatinib in REFLECT study, and 0.45% of patients (10 patients) with arterial thromboembolism occurred including 5 cases of myocardial infarction and 5 cases of cerebrovascular events, fatal outcomes in REFLECT study.

The safety of resuming lenvatinib after an arterial thromboembolic event has not been established and lenvatinib has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

If confirmation of lenvatinib-specific arterial thromboembolic event, permanently discontinue lenvatinib should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.9. Hemorrhage

Severe tumor-related bleeding, including fatal bleeding, occurred in clinical trials, in REFLECT study 24.6% of the patients reported bleeding, of which 5.0% were grade 3 or above. The incidence of grade 3

was 3.4%, and grade 4 was 0.2%. Seven patients (1.5%) had grade 5 including cerebral hemorrhage, upper gastrointestinal hemorrhage, intestinal hemorrhage and tumor hemorrhage. The median time from first dose to the first occurrence of bleeding was 11.9 weeks.

Because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after treatment with lenvatinib, the invasion extent of large vessels (such as carotid artery) should be considered. Some hemorrhagic cases are secondary to tumor contraction and fistula formation, such as tracheoesophageal fistula. Fatal intracranial hemorrhage has been reported in some patients with or without brain metastasis. Hemorrhage (e.g. trachea, abdomen and lung) was also reported as well. A fatal case of hepatic tumor hemorrhage in a HCC patient was reported.

If confirmation of lenvatinib-specific hemorrhage, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.10. Gastrointestinal Perforation or Fistula Formation

Severe gastrointestinal perforation or fistula formation occurred in clinical trials, for example gastrointestinal perforation or fistula formation occurred in 1.9 % of patients receiving lenvatinib in REFLECT study.

In most cases, gastrointestinal perforation or fistula formation occurred in patients with risk factors, such as those who have previously undergone surgery or radiotherapy.

If confirmation of lenvatinib-specific gastrointestinal perforation or fistula formation, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.11. Non-gastrointestinal Fistula Formation

The risk of fistula formation may increase in patients treated with lenvatinib. In clinical trials and post-marketing experience, cases of gastrointestinal or non-gastrointestinal fistula formation or enlargement (e.g. tracheal fistula, tracheoesophageal fistula, esophageal fistula, skin fistula, female genital fistula) were observed. Previous surgery and radiotherapy may be high risk factors. In order to avoid deterioration, lenvatinib should not be started in patients with fistula. Patients with esophageal or tracheobronchial fistula formation and any grade 4 fistula formation should be permanently discontinued of lenvatinib, refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.). Due to limited data on the use of interruption or dose reduction to manage fistula formation, but deterioration is observed in some cases, caution should be exercised. And lenvatinib may have adverse effects on wound healing.

### 8.8.12. QT Prolongation

Incidence of reported prolonged QT/QTc intervals in patients treated with lenvatinib was higher compare with placebo. prolonged QT/QTc occurred in 6.9 % of patients receiving lenvatinib, and the incidence of prolongation of QTcF more than 500 ms was 2.4% in REFLECT study. ECG should be monitored in all patients and special attention should be paid to patients with congenital long QT syndrome, congestive

heart failure, bradyarrhythmia and those receiving drugs to prolong the QT interval, including Ia and III antiarrhythmic drugs. If the QT is greater than 500 ms, then lenvatinib should be interrupted. When the prolongation of the QTc is less than 480 ms or baseline, the lenvatinib should be resume at a reduced dose. Electrolyte disorders (such as hypokalemia, hypocalcemia or hypomagnesemia) can increase the risk of prolonged QT, so electrolyte abnormalities in all patients should be monitored and actively treated before lenvatinib administration.

If confirmation of lenvatinib-specific QT prolongation, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.13. Diarrhea

Frequent diarrhea was reported in patients treated with lenvatinib, which usually occurs in the early stages of treatment. For example, diarrhea occurred in 38.7% of patients receiving lenvatinib, of which 4.2% were grade 3 or above in REFLECT study.

Medical management of diarrhea should be carried out immediately to prevent dehydration. If confirmation of lenvatinib-specific diarrhea, withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib based on severity should refer to table 16 and table 17. (Lenvatinib Pharmaceutical Instruction. 2018.).

Patients should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea develops.

Investigators should also evaluate whether diarrhea may be attributable to the irAE of colitis. As with other small molecule RTK inhibitors, the presence of abdominal pain, mucus, or blood in the stool or peritoneal signs should raise the index of suspicion for immune-mediated colitis, as these features are generally not observed with lenvatinib treatment-associated diarrhea. The diarrhea observed with lenvatinib generally improves within several days of interrupting study medication, with close observation may help establish the most likely causality.

### 8.8.14. Thyrotropin Inhibition Impairment/Thyroid Dysfunction Other Than Immune-Mediated

The cases of hypothyroidism have reported in patients treated with lenvatinib, and lenvatinib can impairs exogenous thyroid suppression. For example, TSH levels were higher than the upper limit of normal values in 69.6% of patients treated with lenvatinib in REFLECT study.

Hypothyroidism should be treated according to standard treatment of local guideline in order to maintain normal thyroid function, for example hormone replacement therapy if applicable. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.15. Wound Healing Complications

No formal study has been carried out on the influence of lenvatinib on wound healing. Delayed wound healing has been reported in some patients treated with lenvatinib. Patients who underwent major surgery recently should not receive treatment of lenvatinib. (Lenvatinib Pharmaceutical Instruction. 2018.).

### 8.8.16. Palmar plantar erythrodysesthesia (PPE)

Palmar plantar erythrodysesthesia (PPE) has been reported in several studies of lenvatinib. Measures that can be taken to manage PPE include avoidance of exposure of hands and feet to hot water when washing dishes or bathing, or to other sources of heat, avoidance of activities that cause unnecessary force or friction (rubbing) on the hands or feet, avoiding contact with harsh chemicals such as cleaning products, use of tools or household items that result in pressure on the hands, such as garden tools, knives, and screwdrivers, and wearing of loose fitting, well-ventilated shoes and clothes. Treatment may include use of topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams. In more severe cases, dose interruption and reduction may be warranted.

## 9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

### 9.1. Statistical Analysis

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) per sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

The following descriptive statistics will be used to summarize the trial data on the basis of their nature unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum
- Categorical variables: frequencies and percentages
- Time-to-event variables: number of non-missing observations (N), median, minimum and maximum. Kaplan-Meier (KM) event rates may also be provided if applicable for specific time to event variables

### 9.1.1. Analysis Sets

- The safety analysis set (SAF) includes all patients who received at least 1 dose of any study drug (any component for the combination therapy).
- The efficacy evaluable analysis set (EFF) includes all dosed patients with measurable disease at baseline per RECIST v1.1 and who had at least one evaluable post-baseline tumor assessment unless treatment was discontinued due to clinical disease progression or death before the first post treatment tumor assessment.
- DLT evaluable analysis set for lenvatinib and tislelizumab combination includes patients who received at least 75% of the assigned total dose of lenvatinib and ≥ 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment window. Additionally, patients who had a DLT event will also be considered evaluable.

- The PK analysis set includes patients who received at least 1 dose of tislelizumab (lenvatinib) study drug and contributed at least 1 post-baseline quantifiable tislelizumab (lenvatinib) PK sample.

### 9.1.2. Patient Disposition

The number of patients treated, discontinued from study drug(s) and/or study, and those with major protocol deviations will be counted. The primary reason for study drug(s) discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, dead, withdrew consent, or lost to follow-up) at the data cut-off date will be summarized using the data from the eCRF.

Major protocol deviations will be summarized and listed by each category.

### 9.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the safety analysis set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include prior number of systemic treatment, gender, ECOG, country, race, and metastatic site.

### 9.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the day of first dose of study drugs. Concomitant medications will be defined as medications that 1) started before the first dose of study drugs and were continuing at the time of the first dose of study drugs, or 2) started on or after the date of the first dose of study drugs up to 30 days after the patient's last dose. A listing of prior and concomitant medications will be included in the clinical study report (CSR) for this trial. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, eg, associated with an irAE or is a new anticancer therapy) at 60 and 90 days (±14 days) after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy.

## 9.2. Efficacy Analyses

### 9.2.1. Primary Efficacy Analyses

No hypothesis testing will be done for Part 1 safety run-in.

Hypothesis testing of ORR in the EFF evaluated based on RECIST v1.1 by central site imaging facility for tumor assessment will be the primary efficacy analysis.

The ORR in studied BGB-A317 combination treatment is assumed as 40% in patients with previously treated unresectable HCC. The historical rate in a similar population is estimated as 18.8% for mono Lenvatinib. The null and alternative hypotheses are set as follows:

H0: ORR = 18.8%

Ha: ORR > 18.8%

A Simon's 2 stage design will be used to test the superiority of studied combination treatment vs. the historical control. When 30 patients dosed at RP2D level (including patients from both part 1 and part 2) are enrolled, the preliminary efficiency and safety of those 30 patients will be assessed as interim analysis.

- If within these 30 patients, ≤6 patients achieve response including complete response (CR) and partial response (PR) as their best overall response (BOR) assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will be terminated.
- If within these 30 patients, ＞6 patients achieve response including CR and PR as their BOR assessed by central site imaging facility for tumor assessment based on RECIST v1.1, the study will continue.

If patients don't meet any discontinuation criterion, such as investigator-assessed iCPD based on iRECIST, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor, lenvatinib and tislelizumab will be administered until patient completes his/her 12-month treatment duration of study drugs. After 12-month treatment duration completion, if the patients are still under the response (CR, PR) or stable disease (SD) assessed by investigator based on RECIST v1.1 or under the response (complete response [iCR], partial response [iPR]), stable disease (iSD) and unconfirmed progression (iUPD) assessed by investigator based on iRECIST, and may continue receiving benefit based on investigator's assessment, tislelizumab could be further provided by sponsor, this decision must be agreed with medical monitor and documented in the study records, patients are also required to be reconsented.

The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no more than 6 months after the last subject received the first dose of study drug.

### 9.2.2. Secondary Efficacy Analysis

For following proportion endpoints:

- ORR assessed by investigators based on RECIST v1.1
- ORR assessed by investigators and central site imaging facility for tumor assessment respectively based on mRECIST and iRECIST.
- DCR assessed by investigators and central site imaging facility based on RECIST v1.1, mRECIST, and iRECIST

Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR or DCR will be constructed to assess the precision of the point estimates.

The KM method will be used to estimate the key secondary endpoint DOR assessed by investigators and central site imaging facility based on RECIST v1.1, mRECIST, and iRECIST, and corresponding quantiles (including the medians), if estimable, in the responders. A two-sided 95% CIs of median, if

estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982).

The DOR censoring rule will follow the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2007).

PFS, another time to event endpoint, assessed by investigators and central site imaging facility based on RECIST v1.1, mRECIST, and iRECIST, will be similarly analyzed in the efficacy evaluable population using the KM method as described above. The KM estimates of PFS will be plotted over time. The PFS time point estimates, defined as the percentages of patients in the analysis population who remain alive and progression-free at the specified time points (ie, 3 or 6 month), will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926).

### 9.3. Safety Analyses

All subjects who are exposed to (or started receiving) any study drug (any component for the combination therapy) will be evaluated for safety. Safety will be determined by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, and ECGs findings will also be used in determining the safety profile. The severity of AEs will be graded according to the CTCAE v5.0. The incidence of DLT events and TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables), and changes from baseline will be determined for laboratory parameters and vital signs.

#### 9.3.1. Dose-Limiting Toxicity Analysis

Dose-limiting toxicity (DLT) will be assessed among evaluable patients within 21 days after the first dose administration of lenvatinib plus tislelizumab at each dose level. For DLT assessment decision, only DLTs occurring within 21 days will be evaluated. The following patients will not be considered evaluable for DLT, and will be replaced if needed to meet the minimum patient number required for safety evaluation:

- Patients who withdraw or are withdrawn from the study before completing the DLT assessment window for reasons other than a DLT.
- Patients receiving combination therapy who do not receive ≥ 75% of scheduled lenvatinib and ≥ 67% (approximately two-thirds) of scheduled tislelizumab during the DLT assessment window, unless they experience a DLT.

The DLT events will be summarized descriptively for each combination dosing level in the DLT evaluable analysis set.

### 9.3.2. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity, and relative dose intensity.

The number (percentage) of patients requiring dose reduction, interruption, dose delay, and drug discontinuation due to AEs or other reasons will be summarized for each study drug.

Patient data listings will be provided for all dosing records and for calculated summary statistics.

### 9.3.3. Adverse Events

The AE verbatim descriptions (the investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be coded to MedDRA (v18.1 or higher) by lower-level term, preferred term, and primary SOC.

DLT will be summarized at each dose cohort in part 1.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days following study drug(s) discontinuation or initiation of new anticancer therapy, whichever occurs first. TEAE classification also applies to irAEs recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v.5.0 within an SOC and preferred term, even if the patient experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, irAE, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

### 9.3.4. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in NCI-CTCAE v5.0 or higher will be summarized by NCI-CTCAE grade. Parameters with NCI-CTCAE grading in both high and low directions (eg, glucose, potassium, sodium) will be summarized separately.

### 9.3.5. Vital Signs

Specific vital signs, eg, blood pressure and temperature, will be summarized and listed. The change from baseline will also be presented.

## 9.4. Pharmacokinetic Analysis

Blood samples for PK analysis of tislelizumab will be collected at specified time points (Appendix 2). The actual collection date and time of each blood sample will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points upon sponsor approval to ensure thorough PK monitoring.

The tislelizumab concentration data collected sparsely at predose and around $T_{max}$ will be tabulated and summarized by visit/cycle. Descriptive statistics will include means, standard deviations, medians, and ranges as appropriate.

Additional PK, including population PK analyses, may be conducted as appropriate, and the results of such analysis may be reported separately from the CSR.

## 9.5. Immunogenicity Analyses

Samples to assess anti-tislelizumab-antibodies will be collected. The immunogenicity results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADA. The incidence of positive ADA and neutralizing ADA will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

## 9.6. Other Exploratory Analyses

OS will be similarly analyzed in the efficacy evaluable population using the KM method as described above (Session 9.2.2). The KM estimates of OS will be plotted over time. The OS time point estimates will be calculated similarly as above.

## 9.7. Sample Size Consideration

The number of dose levels examined and the emerging toxicities of the combination therapy will determine the sample size. The study plans to enroll approximately 60-66 patients, including 6-12 patients in part 1 and 54 patients in part 2.

Sample size for Part 1 (lenvatinib in combination with tislelizumab safety run-in) will depend on the number of dose levels examined and the emerging toxicities of the combination therapy. It is expected approximately 6 to 12 patients with unresectable locally advanced will be enrolled.

With total of 60 patients at RP2D from both part 1 and part 2, based on Simon's 2 stage design, we have about 95% power to detect a statistical significant difference between ORR (assessed based on RECIST v1.1) in studied combination treatment (assumed to be around 40%) to a historical of 18.8% with 1-sided alpha as 0.025. Within first 30 pts (including the 6 patients from part 1 and 24 patients from part 2) in the efficacy analysis set, if we observe $\leqslant$ 6 responders, study will be terminated. Otherwise, study will continue. If within the final 60 patients in the efficacy analysis set, we observe $\geqslant$18 responders, we will claim we are statistically superior than a historical control of 18.8% under the settings. Participants

withdraw due to personal reason or AE before first assessment will be replaced, which might need 4-6 extra participants.

### 9.8. Interim Analysis

For Part 2, one futility interim analysis will be conducted based on the Simon 2-stage design (see Section 9.2.1for details).

## 10. STUDY COMMITTEES AND COMMUNICATION

### 10.1. Safety Monitoring Committee

An SMC will be established consisting of the sponsor's clinical, safety, and medical team representatives (eg, medical monitor, Clinical Pharmacology, Statistician, and Drug Safety) and investigators. All available safety data, including AEs, laboratory assessments, and PK analyses (as available), will be reviewed with input from other functional representatives as appropriate. Based on a review of these data and in consultation with the investigators, a determination will be made regarding dose and/or safety management.

### 10.2. Communication

Sponsor plans to have regular communications with all study sites (study investigators and coordinators) regarding:

- Study enrollment status
- Decisions on RP2D of lenvatinib in combination with tislelizumab
- Any significant safety findings
- Considerations for protocol amendments

## 11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include, but are not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

### 11.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the

eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

### 11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

## 12. QUALITY ASSURANCE AND QUALITY CONTROL

### 12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct study with the investigational drug from the appropriate regulatory agency in accordance with applicable country-specific regulatory requirements or file the protocol with the appropriate regulatory agency before the study is initiated at a study center in that country.

### 12.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

### 12.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the sponsor's or the contract research organization's (CRO's) qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

### 12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product.

Dispensation records will document quantities received from BeiGene's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug(s) disposal/destruction to ensure that it complies with BeiGene's requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study, the study site will dispose of and/or destroy all unused study drug(s) supplies following drug inventory reconciliation by the monitor. These including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug(s) supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study. A patient diary will be provided to each patient to record the lenvatinib dose taken each day. Any missed doses with explanation should be recorded in the diary. The diary should be returned to the site personnel for review and will be reviewed by the investigator/study personnel on a regular basis.

## 13. ETHICS/PROTECTION OF HUMAN PATIENTS

### 13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

### 13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written investigational new drug (IND) safety reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

### 13.2.1. Protocol Amendments

All protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming willingness to remain in the study.

## 13.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB-/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be reconsented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

## 13.4. Patient and Data Confidentiality

The sponsor will maintain confidentiality and privacy standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed only to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, the China FDA, and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the IB, this protocol, eCRFs, the IND, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

### 13.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient and accurate financial information, in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study, and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

## 14. DATA HANDLING AND RECORD KEEPING

### 14.1. Data Collection and Management Responsibilities

#### 14.1.1. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator must provide an e-signature in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

### 14.1.2. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored by BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out giving due consideration to data protection and medical confidentiality.

AEs will be coded using the MedDRA. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA.

## 14.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following categories: 1) investigator's study file, and/or 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations

or institutional policy, some or all these records can be maintained in a format other than hard copy (eg, 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 regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable backup 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 study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to the 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, or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

### 14.3. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the Sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

### 14.4. Publication and Data Sharing Policy

A clinical study report will be prepared. BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all

authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission or presentation in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

### 14.5. Study and Study Center 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
- Resolve and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend the enrollment or prematurely discontinue this study or suspend enrollment either at a single study center or at all study centers 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 institutions conducting the study if the study is suspended or terminated, 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 IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

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

### 14.6. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

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

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.4

If a written contract for the conduct of the study (which includes confidentiality provisions inconsistent with this section) is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

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# 16. APPENDICES

## APPENDIX 1. SCHEDULE OF ASSESSMENTS

| Assessment | Screening[1] | Treatment Period | | | | | | | EOT Visit[4] | Safety Follow-up Phone Call[5] | Survival Follow-up[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | Cycle 2 | | | Cycle 3 and Subsequent Cycles | | | |
| **Days (window)** | **-28 to -1** | **1** | **8 (±1)[2]** | **15 (±2)[2]** | **1 (±1)** | **8 (±1)[2]** | **15 (±2)[2]** | **1 (±3)[3]** | **Within 30 Days After Last Dose of Study Drug(s)** | **60 and 90 (± 14) days after last dose of tislelizumab** | **Approximately Every 3 Months (± 14 days)** |
| Informed consent[1] | x | | | | | | | | | | |
| Inclusion/exclusion criteria | x | | | | | | | | | | |
| Demographics/medical history/prior medications | x | | | | | | | | | | |
| Child-Pugh classification score[7] | x (-7 to -1) | | | | | | | | | | |
| Height | x | | | | | | | | | | |
| Vital signs /weight[8] | x | x | x | x | x | x | x | x | x | | |
| Complete physical examination[9] | x | | | | | | | | x | | |
| Limited physical examination[9] | | x | x | x | x | | | x | | | |
| ECOG Performance Status | x | x | | | x | | | x | x | | |
| 12-Lead ECG[10] | x | x | | | x | | | x | x | | |
| Hematology[11] | x (-7 to -1) | x (Part 1) | x (Part 1) | x (Part 1) | x (Part 1) | x (Part 1) | x (Part 1) | x (Part 1) | x | | |
| | | x (Part 2) | | | x (Part 2) | | | x (Part 2) | | | |
| Clinical chemistry[11] | x (-7 to -1) | x | x | x | x | x | x | x | x | | |
| Coagulation parameters[11] | x (-7 to -1) | x | | | x | | | x | x | | |

| **Assessment** | **Screening[1]** | **Treatment Period** | | | | | | | **EOT Visit[4]** | **Safety Follow-up Phone Call[5]** | **Survival Follow-up[6]** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Cycle 1** | | | **Cycle 2** | | | **Cycle 3 and Subsequent Cycles** | | | |
| **Days (window)** | **-28 to -1** | **1** | **8 (±1)[2]** | **15 (±2)[2]** | **1 (±1)** | **8 (±1)[2]** | **15 (±2)[2]** | **1 (±3)[3]** | **Within 30 Days After Last Dose of Study Drug(s)** | **60 and 90 (± 14) days after last dose of tislelizumab** | **Approximately Every 3 Months (± 14 days)** |
| Urinalysis[11] | x (-7 to -1) | x | x | x | x | x | x | x | x | | |
| AFP | x | x | | | x | | | x | x | | |
| Pregnancy test[12] | x (-7 to -1) | x | | | x | | | x | x | | |
| Thyroid function[13] | x | Cycles 4, 7, 10, and every 3 cycles thereafter | | | | | | | x | | |
| HBV/HCV tests[14] | x | Patients who have detectable HBV DNA at screening, the respective viral load test will be performed every 4 cycles starting at Cycle 5 (Day 1 of Cycles 5, 9, 13, etc), and EOT Visit. | | | | | | | | | |
| Tumor assessment[15] | x | In the first year, every 6 weeks (± 7 days) every 9 weeks (± 7 days) thereafter | | | | | | | | | |
| Pulmonary function test[16] | x | As clinically indicated | | | | | | | | | |
| MUGA (multigated acquisition)/echo-cardiogram[17] | x | Every 12 weeks (±7 days) | | | | | | | | | |
| PK sampling for tislelizumab [18] | | Patients enrolled in part 1 only, see Appendix 2 | | | | | | | | | |
| PK sampling for lenvatinib [18] | | | | | | | | | | | |
| ADA sampling for tislelizumab[18] | | | | | | | | | | | |
| Lenvatinib administration[19] | | Daily | | | | | | | | | |
| Tislelizumab administration [20] | | x | | | x | | | x | | | |
| AEs[21] | x | x | x | x | x | x | x | x | x | x | |

| Assessment | Screening[1] | Treatment Period | | | | | | | EOT Visit[4] | Safety Follow-up Phone Call[5] | Survival Follow-up[6] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1 | | | Cycle 2 | | | Cycle 3 and Subsequent Cycles | | | |
| **Days (window)** | **-28 to -1** | **1** | **8 (±1)[2]** | **15 (±2)[2]** | **1 (±1)** | **8 (±1)[2]** | **15 (±2)[2]** | **1 (±3)[3]** | **Within 30 Days After Last Dose of Study Drug(s)** | **60 and 90 (± 14) days after last dose of tislelizumab** | **Approximately Every 3 Months (± 14 days)** |
| Concomitant medications[22] | x | x | x | x | x | x | x | x | x | x | |
| Patient diary | | x | x | x | x | x | x | x | x | | |
| Survival status[6] | | | | | | | | | | | x |

Abbreviations: ADA, antidrug antibody, AE, adverse event; AFP, alpha fetoprotein; CR, complete response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HBV, hepatitis B virus; HCV, hepatitis C virus; MUGA, multigated acquisition; PD, progressive disease; PR, partial response; SAE, serious adverse event; x, to be performed.

**Note:** On days when lenvatinib and tislelizumab dosing are both scheduled, the daily dose of lenvatinib should precede tislelizumab infusion.

1. **During Screening,** written informed consent must be signed before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed before obtaining informed consent and within 28 days before the first dose of study drug(s) may be used for screening assessments rather than repeating such tests.
2. **In Cycle 1 and cycle 2**, besides Days 1 of both cycles, patients enrolled in Part 1 and part 2 will return to study sites for assessments on Days 8 and 15 of both cycles. On Days 1, 8 and 15 of Cycle 1 and Cycle 2, lenvatinib will be given in the clinic.
3. A window of ± 3 days is allowed.
4. **The EOT Visit** is conducted within 30 days after last dose of the study drugs or before initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, clinical chemistry) have been performed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. A tumor assessment is not required at the EOT Visit if ≤ 6 weeks have passed since the last assessment. If the study drugs were initially interrupted due to AEs and then permanently discontinued, the EOT Visit may occur later, but no later than the permitted time of dose delay plus 7 days.
5. **The Safety Follow-up Phone calls.** Telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a subsequent anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy.
6. **Survival follow-up** information will be collected via telephone calls for all patients, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the EOT Visit until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.
7. **Child-Pugh classification** for liver function is required to be assessed for HCC patients only within 7 days before the first dose of study drugs.
8. **Vital signs** collected on study include temperature, pulse, and the assessment of blood pressure (systolic and diastolic) should follow Section 7.3.1. The patient's vital signs are required to be recorded within 60 minutes before; during; and 30 minutes after the first infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinically indicated, during and 30 minutes after the infusion. Vital signs

should also be recorded prior to administration of lenvatinib; recorded values may be used for pre-tislelizumab assessment if vital signs are collected within 60 minutes before tislelizumab infusion.

**Vital** should be collected at screening, weekly of first two cycles, on Day 1 of each subsequent cycle and at the EOT Visit for all patients.

9. **Complete physical examination** including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems is required to be performed at screening and EOT Visit. **Limited physical examination:** At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed.
10. **12-Lead ECG:** The ECG recordings will be obtained during screening, C1D1, at the beginning of every subsequent cycle, EOT visit and as clinically indicated at other time points. Patients should be resting for at least 10 minutes before each ECG collection.
11. **Hematology, urinalysis and clinical chemistry (**Appendix 3 **clinical laboratory assessment)** will be performed by the local laboratory at screening and within 7 days prior to the administration of study drugs on C1D1 in both Parts.

    **Hematology**, patients enrolled in part 1 will be assessed weekly during the first 2 cycles and then on Day 1 of each subsequent cycle. Patients enrolled in part 2 will be assessed on Day 1 of each cycle. In both Part 1 and Part 2, patients will be assessed at the EOT Visit.

    **Coagulation tests** includes international normalized ratio, prothrombin time, and activated partial thrombin time. **Coagulation tests** will be performed at screening, the beginning of every cycle, EOT visit.

    **Clinical chemistry (**Appendix 3 **clinical laboratory assessment)** will be performed by the local laboratory at screening and within 7 days prior to the administration of study drugs on C1D1 in both Parts. Patients enrolled in both part 1 and part 2 will be assessed weekly during the first 2 cycles, then on Day 1 of each subsequent cycle. In both Part 1 and Part 2, patients will be assessed at the EOT Visit.

    **Urinalysis** on routine urinalysis, if urine protein is ≥ 2+ (≥ 1+ in screening) by dipstick, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio. In 24-hour protein assessment, to achieve the result prior to study drugs administration on the day of each scheduled assessment, the urine sample may be collected 24 hours ahead of schedule in 24-hour protein assessment. **Urinalysis** will be performed by the local laboratory at screening and within 7 days prior to the administration of study drugs on C1D1 in both Parts. Patients enrolled in both part 1 and part 2 will be assessed weekly during the first 2 cycles, then on Day 1 of each subsequent cycle. In both Part 1 and Part 2, patients will be assessed at the EOT Visit. For CK and CK-MB tests and coagulation tests, refer to Appendix 3.
12. **Serum pregnancy test** (for women of childbearing potential, including women who have had a tubal ligation) must be performed by the local laboratory and documented as negative within 7 days before administration of study drugs. **Urine or serum pregnancy tests** will be performed during treatment before study drugs administration at each cycle, EOT visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drugs at each cycle.
13. **TFTs** (thyroid function test) by analysis of FT3, FT4, and TSH will be performed by the local laboratory at screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and EOT Visit. The test does not need to be repeated at the EOT Visit within 63 days after last test.
14. **HBV/HCV tests**: Testing will be performed by the local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). Testing at screening is mandatory for patients. Additionally, for patients who have detectable HBV DNA at screening, the respective viral load test will be performed every 4 cycles starting at Cycle 5 (ie, Day 1 of Cycles 5, 9, 13, etc), and EOT Visit.
15. **Tumor imaging** for tumor assessment should be performed based on Tumor and Response Evaluations (see Section 7.4.). Radiological images captured as standard of care before obtaining written informed consent and within 28 days before the first dose of study drugs may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented. An MRI (or CT scan if MRI is contraindicated or not readily available) of

the head may be required at screening based on clinical judgement; bone scan or PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient.

The investigator must review radiograph results before dosing at the next cycle. During the study, tumor imaging will be performed within 28 days prior to C1D1 and while on study approximately every 6 weeks ± 7 days in the first 12 months and approximately every 9 weeks ± 7 days thereafter. The investigator may perform additional scans or more frequent assessments if clinically indicated. Patients who discontinue study treatment early for reasons other than iCPD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient withdraws consent, dies, or until the study terminates, whichever occurs first. Patients who continue tislelizumab treatment beyond radiographic investigator-assessed PD based on RECIST v1.1 will be monitored with a follow-up scan no more than 8 weeks beyond the initial diagnosis of radiographic PD (repeated imaging on next scheduled tumor assessment visit date, around 6 weeks from the date of initial documentation of PD is recommended).

16. **Pulmonary function test** only for patients treated with tislelizumab**:** Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will have pulmonary function testing which may in clude, but is not limited to, spirometry and assessment of diffusion capacity done during the screening period to assist the determination of suitability on the study.
17. **MUGA/Echocardiogram**: Evaluations of cardiac function will be performed at screening and every 12 weeks (±7 days). Investigator will decide the method (MUGA or echocardiograms) for evaluation of cardiac function. The method used for individual patients should be consistent throughout study participation.
18. The PK sampling for tislelizumab, PK sampling for lenvatinib PK and ADA sampling for tislelizumab will be collected only in patients enrolled in part 1. See Appendix2 Appendix2for PK sampling for tislelizumab, PK sampling for lenvatinib and ADA sampling for tislelizumab while study treatment. Unless the events of DLT occurred frequently (defined as which leads to Part 1 discontinued. See Section 3.1.1 for details), the test of lenvatinib PK won't be performed.
19. **Lenvatinib administration** orally once daily with or without food in the morning.
20. **Tislelizumab administration** on Day 1 of every cycle after lenvatinib administration.
21. **AEs** will be graded and recorded throughout the study according to NCI-CTCAE, v5.0. During screening section just SAEs will be collected. After first dose AEs will be collected.
22. **All concomitant medications** received within 30 days before the first dose of study drugs and 30 days after the last dose of study treatment should be recorded.

## APPENDIX 2. SCHEDULE OF PK ASSESSMENTS

| Collection Time and Allowable Window | Patients Enrolled in Part 1 | | | |
|---|---|---|---|---|
| | C1D1, C5D1 | | C2D1, C9D1, C17D1 | EOT visit |
| **PK-Tisle**[a] | x<br>Pre-Tisle dose<br>-60 min | X<br>Post-Tisle infusion<br>+30 min | x<br>Pre-Tisle-dose<br>-60 min | x |
| **PK-Lenva**[b] | x<br>Pre-Lenva dose<br>-30 min | X<br>Post-Lenva dose<br>2h ± 10min | | |
| **ADA-Tisle**[c] | x<br>pre-Tisle dose<br>-60 min | | x<br>Pre-Tisle dose<br>-60 min | x |

Abbreviations: PK, pharmacokinetic; Tisle, tislelizumab; Lenva, lenvatinib; x, to be performed

a. PK sampling for tislelizumab: predose (within 60 min before the start of tislelizumab infusion) samples should be collected on Day 1 of Cycles 1, 2, 5, 9, and 17 (if achieved); two postdose (within 30 min after the end of tislelizumab infusion) samples should be collected at C1D1 and C5D1; and an additional PK sample should be collected at the EOT Visit. Should a patient present with DLT event or ≥ Grade 3 or above irAE, additional PK samples may be taken to determine the serum concentration of tislelizumab.

b. PK sampling for lenvaitnib: predose (within 30 min before administration of lenvatinib) samples should be collected on Day 1 of Cycles 1, 5; two postdose samples at **2h (± 10min)** should be collected at C1D1 and C5D1.Unless the events of DLT occurred frequently (defined as which leads to Part 1 discontinued. See Section 3.3.1 for details), the test of lenvatinib PK won't be performed. It's highly recommended that perdose samples of lenvatinib and tislelizumab are drawn through once blood sampling on scheduled days if both in allowed windows, and postdose samples of lenvatinib and tislelizumab are drawn through once blood sampling on scheduled days as well if both in allowed windows.

c. ADA sampling for tislelizumab: samples should be collected before start of Day 1 tislelizumab infusion of Cycles 1, 2, 5, 9 and 17 (if achieved) and at the EOT Visit (See Appendix 1). All samples should be drawn at the same time as blood collection for predose PK samples.

## APPENDIX 3. CLINICAL LABORATORY ASSESSMENTS

| Clinical Chemistry | Hematology | Coagulation[a] | Urinalysis |
|---|---|---|---|
| Alkaline phosphatase | Hematocrit | Prothrombin time or INR | Glucose |
| Alanine aminotransferase | Hemoglobin | aPTT | Protein |
| Aspartate aminotransferase | Platelet counts | | Blood |
| Albumin | WBC count | | Ketones |
| Total protein | Lymphocyte count | | 24-hour protein[b] |
| Lactate dehydrogenase | Neutrophil count | | |
| Total bilirubin | | | |
| Direct bilirubin | | | |
| Blood urea nitrogen or urea | | | |
| Potassium | | | |
| Sodium | | | |
| Corrected calcium[c] | | | |
| Creatinine | | | |
| Glucose | | | |
| CK[d] | | | |
| CK-MB[d, e] | | | |
| Lipase | | | |
| Serum amylase | | | |

Abbreviations: aPTT, activated partial thromboplastin time; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; INR, International Normalized Ratio; WBC, white blood cell.

a. Coagulation tests are required at screening, the beginning of every cycle and EOT visit Visit.
b. On routine urinalysis, if urine protein is ≥ 2+ (≥ 1+ in screening) by dipstick, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio. To achieve the result prior to study drugs administration on the day of each scheduled assessment, the urine sample may be collected 24 hours ahead of schedule in 24-hour protein assessment (see Section 7.3.5).
c. If testing for corrected calcium is not feasible at the local laboratory, total calcium may be performed instead
d. Patients receiving tislelizumab will receive CK and CK-MB testing. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required. Patients with a history of cardiological disease or after discontinuation of tislelizumab, may receive CK and CK-MB testing if clinically indicated.
e. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

In addition, the following tests will be conducted in this study:

- **Serum pregnancy test** (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to administration of study drug(s). **Urine or serum pregnancy tests** will be performed once every 3 weeks or monthly during treatment and at the EOT Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug(s) at each cycle
- **Thyroid function tests** (thyroid-stimulating hormone [TSH], free T3, free T4) will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and EOT Visit (see Section 7.3.4 for details).

## APPENDIX 4. ECOG PERFORMANCE STATUS

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

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

## APPENDIX 5. CHILD-PUGH CLASSIFICATION SCORING SYSTEM

The information presented here has been obtained from the Washington University Medical Center, with sources as follows:

- Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-37.
- Pugh RNH, Murray-Lyon IN, Dawson DL, et al. Transection of the esophagus for bleeding esophageal varices. Brit J Surgery. 1973;60:646-64.
- Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med. 1966;274(9):473-81.

Child-Pugh classification is either Grade A (mild: score 5 to 6 points), B (moderate: from 7 to 9 points), or C (severe: from 10 to 15 points) and is determined by both clinical and biochemical parameters (as shown below).

| Clinical/Biochemical Parameter | Score (Anomaly Severity) | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Hepatic encephalopathy (NCI-CTCAE grade)[a] | 0[b] | 1[c] or 2[d] | 3[e] or 4[f] |
| Ascites (presence and severity) | None | Mild | Moderate |
| Total bilirubin (mg/dL) | < 2.0 | 2.0 to 3.0 | > 3.0 |
| Serum albumin (g/dL) | > 3.5 | 2.8 to 3.5 | < 2.8 |
| Prolonged prothrombin time (seconds)<br>or<br>Activated partial thromboplastin time<br>(INR[g]) | < 4<br>or<br>< 1.7 | 4 to 6<br>or<br>1.7 to 2.3 | > 6<br>or<br>> 2.3 |

Abbreviations: INR, international normalized ratio; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

a. Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.
b. Grade 0: Consciousness, personality, neurological examination, and electrocardiogram are all normal.
c. Grade 1: Restlessness, sleep disorders, irritability/anxiety, hand tremor, writing disorders, 5CPS waves.
d. Grade 2: Lethargy, time barrier, discomfort, asterixis, ataxia, three-phase slow wave.
e. Grade 3: Drowsiness, coma, orientation disorder, over-reflection, stiff/slow wave.
f. Grade 4: Cannot wake up from coma, no independent personality/behavior, irrational, slow 2-3CPS Delta activity.
g. Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-637.

## APPENDIX 6. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Please contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

| | |
|---|---|
| Acute disseminated encephalomyelitis | Addison's disease |
| Ankylosing spondylitis | Antiphospholipid antibody syndrome |
| Aplastic anemia | Autoimmune hemolytic anemia |
| Autoimmune hepatitis | Autoimmune hypoparathyroidism |
| Autoimmune hypophysitis | Autoimmune myocarditis |
| Autoimmune oophoritis | Autoimmune orchitis |
| Autoimmune thrombocytopenic purpura | Behcet's disease |
| Bullous pemphigoid | Chronic inflammatory demyelinating polyneuropathy |
| Chung-Strauss syndrome | Crohn's disease |
| Dermatomyositis | Dysautonomia |
| Epidermolysis bullosa acquisita | Gestational pemphigoid |
| Giant cell arteritis | Goodpasture's syndrome |
| Granulomatosis with polyangiitis | Graves' disease |
| Guillain-Barré syndrome | Hashimoto's disease |
| Immunoglobulin A (IgA) neuropathy | Inflammatory bowel disease |
| Interstitial cystitis | Kawasaki's disease |
| Lambert-Eaton myasthenia syndrome | Lupus erythematosus |
| Lyme disease (chronic) | Mooren's ulcer |
| Morphea | Multiple sclerosis |
| Myasthenia gravis | Neuromyotonia |
| Opsoclonus myoclonus syndrome | Optic neuritis |
| Ord's thyroiditis | Pemphigus |
| Pernicious anemia | Polyarteritis nodusa |
| Polyarthritis | Polyglandular autoimmune syndrome |
| Primary biliary cirrhosis | Psoriasis |
| Reiter's syndrome | Rheumatoid arthritis |
| Sarcoidosis | Sjögren's syndrome |
| Stiff person syndrome | Takayasu's arteritis |
| Ulcerative colitis | Vogt-Kovangai-Harada disease |

## APPENDIX 7. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment)
    - **Note:** Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and if used, this method must be combined with a highly effective form of birth control, listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
    - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
    - < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all

alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group (CTFG).

## APPENDIX 8. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

| Class | Symptoms |
|---|---|
| I | Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, et cetera). |
| II | Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity. |
| III | Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 meters). Comfortable only at rest. |
| IV | Severe limitations. Experiences symptoms even while at rest. Mostly bedbound. |

Adapted from Dolgin M, ed. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed.

Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

## APPENDIX 9. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) Study equation. NKDEP's calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

The CKD-EPI equation calculator should be used when serum creatinine ($S_{cr}$) reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 $m^2$ are desired.

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\,[\text{if female}] \times 1.159\,[\text{if black}]$$

where:

$S_{cr}$ is serum creatinine in mg/dL,

$\kappa$ is 0.7 for females and 0.9 for males,

$\alpha$ is -0.329 for females and -0.411 for males,

min indicates the minimum of $S_{cr}/\kappa$ or 1, and

max indicates the maximum of $S_{cr}/\kappa$ or 1.

The equation does not require weight because the results are reported normalized to 1.73 $m^2$ body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found on the National Institute of Diabetes and Digestive and Kidney Diseases webpage (https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators)

### Classification of Renal Impairment Using FDA Guidance for Industry

The renal impairment classification scale provided in the guidance document considers eGFR and Estimated Creatinine Clearance (CLcr). It allows for the fact that equations to calculate eGFR are evolving. In this study, eGFR will be calculated using the CKD-EPI equation.

| Classification of Renal Function Based on Estimated GFR or Estimated Creatinine Clearance | | | |
|---|---|---|---|
| **Stage** | **Description** | **eGFR (mL/min/1.73 $m^2$)** | **CLcr (mL/min)** |
| 1 | Control (Normal) GFR | ≥ 90 | ≥ 90 |
| 2 | Mild Decrease in GFR | 60-89 | 60-89 |
| 3 | Moderate Decrease in GFR | 30-59 | 30-59 |
| 4 | Severe Decrease in GFR | 15-29 | 15-29 |
| 5 | End Stage Renal Disease | <15 not on dialysis or requiring dialysis | <15 not on dialysis or requiring dialysis |

## APPENDIX 10. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose irAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, PD, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is PD or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the irAE field associated with the AE in the eCRF should be checked.

### Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events

| Immune-Related Toxicity | Diagnostic Evaluation Guideline |
|---|---|
| Thyroid Disorders | Scheduled and repeat thyroid function tests (TSH and T4). |
| Hypophysitis | Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss and unexplained constitutional symptoms.<br>Consider consultation with an endocrinologist if an abnormality is detected. |
| Pneumonitis | All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO.<br>Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause. |

## Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events

| Immune-Related Toxicity | Diagnostic Evaluation Guideline |
|---|---|
| Neurological Toxicity | Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings. |
| Colitis | Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism).<br>In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate. |
| Eye Disorders | If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management. |
| Hepatitis | Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist. A liver biopsy is encouraged. |
| Renal toxicity | Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance. |
| Dermatology | Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy. |
| Joint or muscle inflammation | Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance.<br>For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy. |
| Myocarditis | Perform ECG, echocardiogram, CK, CK-MB, troponin I and T analysis, and refer to a cardiologist. |

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; *D*LCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function testing; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Treatment of Immune-Related AEs

- An irAEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- An irAEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| **Thyroid Disorders** | **1-2**<br>Asymptomatic TFT abnormality or mild symptoms | Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range.<br>Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement. | Continue study treatment or withhold treatment in cases with systemic symptoms. |
| | **3-4**<br>Severe symptoms, hospitalization required | Refer patient to an endocrinologist.<br>If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves. | Hold study treatment; resume when resolved/improved to Grade 0-1. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| **Hypophysitis** | **1-2**<br>Mild symptoms | Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month. | Continue study treatment. |
| | **3-4**<br>Moderate-severe symptoms | Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. | Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary. |
| **Pneumonitis** | **1**<br>Radiographic changes only | Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2. | Consider holding study treatment until appearance improves and cause is determined. |
| | **2**<br>Symptomatic: exertional breathlessness | Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks.<br>Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement. | Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone $\leq$ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment. |
| | **3-4**<br>Severe or life-threatening symptoms<br>Breathless at rest | Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. | Discontinue study treatment. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| **Neurological Toxicity** | **1**<br>Mild symptoms | – | Continue study treatment. |
| | **2**<br>Moderate symptoms | Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation. | Hold study treatment; resume when resolved/improved to Grade 0-1. |
| | **3-4**<br>Severe/life-threatening | Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours. | Discontinue study treatment. |
| **Colitis/Diarrhea** | **1**<br>Mild symptoms:<br>< 3 liquid stools per day over baseline and feeling well | Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet.<br>If Grade 1 persists for > 14 days manage as a Grade 2 event. | Continue study treatment. |
| | **2**<br>Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes | Oral prednisolone 0.5 mg/kg/day (non-enteric coated).<br>Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring. | Hold study treatment; resume when resolved/improved to baseline grade. |
| | **3**<br>Severe symptoms:<br>> 6 liquid stools per day over baseline, or if episodic within 1 hour of eating | Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.<br>If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus.<br>Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy. | Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the medical monitor. |
| | **4**<br>Life-threatening symptoms | | Discontinue study treatment. |
| **Skin reactions** | **1**<br>Skin rash, with or without symptoms,<br>< 10% BSA | Avoid skin irritants and sun exposure; topical emollients recommended. | Continue study treatment. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **2**<br>Rash covers 10%-30% of BSA | Avoid skin irritants and sun exposure; topical emollients recommended.<br>Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids. | Continue study treatment. |
| | **3**<br>Rash covers > 30% BSA or Grade 2 with substantial symptoms | Avoid skin irritants and sun exposure; topical emollients recommended.<br>Initiate steroids as follows based on clinical judgement:<br>For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks.<br>For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks. | Hold study treatment.<br>Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the medical monitor. |
| | **4**<br>Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment) | Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.<br>Admit to a hospital and seek urgent dermatology consultation. | Discontinue study treatment. |
| **Hepatitis** | **1**<br>ALT or AST > ULN to 3X ULN | Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening.<br>If LFTs are worsening, recheck every 48-72 hours until improvement is seen. | Continue study treatment if LFTs are unchanged or improving.<br>Hold study treatment if LFTs are worsening until improvement is seen. |
| | **2**<br>ALT or AST 3-5X ULN | Recheck LFTs every 48-72 hours:<br>For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks.<br>For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement. | Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤ 10 mg. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **3**<br>ALT or AST 5-20X ULN | ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks.<br>ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks. | Hold study treatment until improved to baseline Grade; reintroduce only after discussion with the medical monitor. |
| | **4**<br>ALT or AST > 20X ULN | Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks. | Discontinue study treatment. |
| | **Worsening LFTs despite steroids:**<br>• If on oral prednisolone, change to pulsed intravenous methylprednisolone<br>• If on intravenous, add mycophenolate mofetil (MMF) 500-1000 mg twice a day<br>• If worsens on MMF, consider addition of tacrolimus<br>Duration and dose of steroid required will depend on severity of event | | |
| **Nephritis** | **1**<br>Creatinine 1.5X baseline or > ULN to 1.5X ULN | Repeat creatinine weekly.<br>If symptoms worsen, manage as per criteria below. | Continue study treatment. |
| | **2**<br>Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN | Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy.<br>If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks.<br>Repeat creatinine/U&E every 48-72 hours. | Hold study treatment.<br>If not attributed to drug toxicity, restart treatment.<br>If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone. |
| | **3**<br>Creatinine > 3X baseline or > 3X-6X ULN | Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks. | Hold study treatment until the cause is investigated.<br>If study drug suspected: Discontinue study treatment. |
| | **4**<br>Creatinine > 6X ULN | As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available. | Discontinue study treatment. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| **Diabetes/ Hyperglycemia** | **1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L | Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended | Continue study treatment. |
| | **2** Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L | Obtain a repeat blood glucose level at least every week. Manage according to local guideline. | Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1. |
| | **3** Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L | Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided. | Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1. |
| | **4** Fasting glucose value > 500 mg/dL; > 27.8 mmol/L | Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring. | |
| Ocular Toxicity | **1** Asymptomatic eye exam/test abnormality | Consider alternative causes and prescribe topical treatment as required. | Continue study treatment. |
| | **2** Anterior uveitis or mild symptoms | Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids. | Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance. |
| | **3** Posterior uveitis/ panuveitis or significant symptoms | Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks. | Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the medical monitor. |
| | **4** Blindness (at least 20/200) in the affected eyes | Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. | Discontinue study treatment. |
| Pancreatitis | **2** Asymptomatic, blood test abnormalities | Monitor pancreatic enzymes. | Continue study treatment. |
| | **3** Abdominal pain, nausea, and vomiting | Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. | Hold study treatment; reintroduce only after discussion with the |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | | Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks. | medical monitor. |
| | **4** Acute abdominal pain, surgical emergency | Admit to hospital for emergency management and appropriate referral. | Discontinue study treatment. |
| Arthritis | **1** Mild pain with inflammation, swelling | Management per local guideline. | Continue study treatment. |
| | **2** Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities | Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event. | Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1. |
| | **3** Severe pain with inflammation or permanent joint damage, daily living activity limited | Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks. | Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the medical monitor. |
| Mucositis/ stomatitis | **1** Test findings only or minimal symptoms | Consider topical treatment or analgesia as per local guideline. | Continue study treatment. |
| | **2** Moderate pain, reduced oral intake, limited instrumental activities | As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event. | Continue study treatment. |
| | **3** Severe pain, limited food and fluid intake, daily living activity limited | Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks. | Hold study treatment until improved to Grade 0-1. |
| | **4** Life-threatening complications or dehydration | Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection. | Discontinue study treatment. |
| **Myositis/ Rhabdomyolysis** | **1** Mild weakness with/without pain | Prescribe analgesics.<br>If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2 | Continue study treatment. |
| | **2** Moderate weakness | If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and | Hold study treatment until improved to Grade |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | with/without pain | taper over at least 4 weeks | 0-1 |
| | **3-4**<br>Severe weakness, limiting self-care | Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks | Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement |
| **Myocarditis** | **1**<br>Asymptomatic but abnormal CK-MB, cardiac troponin, or intraventricular conduction delay | Admit to hospital and refer to a cardiologist.<br>Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit.<br>Initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines.<br>If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or antithymocyte globulin | Hold study treatment until completely resolved or myocarditis has been ruled out. |
| | **2**<br>Symptoms on mild-moderate exertion | | Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved |
| | **3**<br>Severe symptoms with mild exertion | | |
| | **4**<br>Life-threatening | | |

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; INR, international normalized ratio; LFT, liver function testing; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

## APPENDIX 11. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following Eisenhauer et al 2009.

### DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥10 to <15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, 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.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression” (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ

as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

**GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for

both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and PD.

## RESPONSE CRITERIA

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- 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 (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".

- When this occurs, it is important that a value be recorded on the eCRF. 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 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, 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 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- 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. Similarly, 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".

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- 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 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept

applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. 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: ie, 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. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, 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 trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on trial 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.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drugs until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR 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 trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "BOR".

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

| **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 |

| Target Lesions | Non-target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

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 eCRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

**CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE**

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

## APPENDIX 12. MODFIED RECIST (mRECIST) ASSESSMENT FOR HEPATOCELLULAR CARCINOMA

The text below was obtained from the following Lencioni R et al 2010.

### DEFINITIONS

The AASLD-JNCI (Journal of the National Cancer Institute) guidelines included for the first time a formal modification of the assessment of response based on the RECIST criteria, and aimed to translate the concept of viable tumor posed by the previous guidelines in a more updated framework. These amendments are referred to as modified RECIST assessment (mRECIST) for HCC.

### AASLD-JNCI GUIDELINES FOR Assessment of Standardizing Response

Image acquisition

Optimization of image acquisition protocols and consistency in the use of the same protocol throughout follow-up examinations are key for proper application of mRECIST. Patients can be followed with either contrast-enhanced spiral computed tomography (CT) preferably with use of multislice scanners or contrastenhanced dynamic magnetic resonance imaging (MRI). The administration of intravenous contrast is recommended for all CT or MRI studies if not medically contraindicated. In contrast-enhanced studies, it is mandatory to obtain a dual-phase imaging of the liver. Every effort should be made to time the contrast administration so that high-quality arterial-phase imaging is obtained throughout the liver on the first run, and high-quality portal venous-phase imaging is obtained throughout the liver on the second run. Delayed imaging obtained in the equilibrium phase may be useful, but it is not mandatory and should be done only if it is part of clinical practice. For multidetector CT scanners that are capable of acquiring very thin slices, it is necessary to keep in mind that it is mandatory to use contiguous slices for image read and interpretation, to avoid missing small lesions. For example, the analysis of contiguous slices with traditional 5 mm thickness and 5 mm reconstruction interval is acceptable; however, the analysis of 2.5 mm thickness slices at 5 mm intervals is not acceptable.

Image interpretation

To properly use the proposed mRECIST for HCC to assess response rates and time to progression in HCC clinical trials and to ensure comparability across studies, uniform image acquisition parameters, rigorous quality control, and independent blinded multireader assessments are mandatory. Therefore, the expert panel recommended adopting a centralized radiologic review for image interpretation rather than base the assessment on the image evaluation performed by local investigators. Independent radiologists will be responsible for performing qualitative and quantitative assessments of imaging data. They will assess baseline imaging to determine the overall tumor burden and use this as a comparator for subsequent measurements. Tumor response will then be determined for each follow-up imaging time point. Overall response assessment includes, according to RECIST, evaluation of target lesions response, nontarget lesions response, and new lesions.

Assessment of tumor lesions at baseline

According to RECIST, tumor lesions are categorized at baseline as follows: measurable (lesions that can be accurately measured in at least one dimension as ≥1 cm with a spiral CT scan) or nonmeasurable [all other lesions, including small lesions (longest diameter <1 cm with spiral CT scan) and truly

nonmeasurable lesions]. The original RECIST publication states that all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. The recent 1.1 release of RECIST has reduced the number of lesions to select as target lesions to a maximum of two lesions per organ and five lesions in total. In fact, analyses on a large prospective database has shown that assessment of five versus 10 lesions per patient did not affect the overall response rate, and that progression-free survival was only minimally affected. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements. All other lesions (or sites of disease) should be identified as nontarget 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.

It is our understanding that the measurement of the longest viable tumor diameter for the assessment of response according to mRECIST can be only applied in case of typical lesions. Conversely, for non-enhancing atypical lesions, as well as for any extrahepatic neoplastic niches, the measurements of the longest overall tumor diameter as per conventional RECIST should prevail.

To be selected as a target lesion using mRECIST, an HCC lesion should meet all the following criteria:

- The lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

It is important to point out that only well-delineated, arterially enhancing lesions can be selected as target lesions for mRECIST. This may not be the case of infiltrative-type HCC. Infiltrative-type HCC should be considered as a nontarget lesion when the mass shows ill-defined borders and therefore does not appear to be suitable for accurate and repeat measurements. HCC lesions previously treated with locoregional or systemic treatments may or may not be considered as suitable to be selected as target lesions for mRECIST: if the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is at least 1 cm in longest diameter, then it can be selected as a target lesion. In contrast, if the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion for mRECIST.

**RESPONSE CRITERIA**

Evaluation of Target Lesions Response

The mRECIST for HCC has introduced the following amendments to RECIST in the determination of tumor response for target lesions:

- Complete response: the disappearance of any intratumoral arterial enhancement in all target lesions.
- Partial response: at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.

- Progressive disease: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started.
- Stable disease: any cases that do not qualify for either partial response or progressive disease.

The measurement of the longest diameter of the viable tumor may be challenging in lesions showing partial internal necrosis. The following points should be taken into account in such cases:

- The measurement of the viable tumor should be performed on CT or MRI obtained in the arterial phase, when the contrast between viable vascularized tumor tissue and nonenhancing necrotic tissue is the highest.
- The longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured: a thorough careful evaluation of the CT or MRI scans is required.
- The measurement of the viable tumor diameter should not include any major intervening areas of necrosis.

It is important to point out that a reduction of at least 30% in the diameter of the viable tumor (the threshold required to declare partial response according to mRECIST) corresponds to a decrease of 65% in viable tumor volume. In contrast, an increase of at least 20% in the diameter of the viable tumor (the threshold required to declare progressive disease according to mRECIST) corresponds to an increase of at least 73% in viable tumor volume. The panel acknowledged that direct volumetric measurement to identify partial response and progression should be a priority in future clinical trial research.

Evaluation of Nontarget lesions response

The RECIST guideline provides the following definitions of the criteria used to determine the objective tumor response for nontarget lesions: complete response is the disappearance of all nontarget lesions; incomplete response/stable disease is the persistence of one or more nontarget lesions; and progressive disease is the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

According to mRECIST for HCC, tumor necrosis should be taken into account when assessing the response of nontarget lesions. The disappearance of intratumoral arterial enhancement in nontarget lesions should be considered equivalent to the disappearance of nontarget lesions, and therefore, should declare complete response of nontarget lesions. The persistence of intratumoral arterial enhancement in one or more nontarget lesions should be considered equivalent to persistence of one or more nontarget lesions, and therefore, should declare incomplete response / stable disease. The appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions should declare progressive disease.

Special recommendations for the assessment of tumor response in nontarget lesions in patients with HCC and cirrhosis can be made regarding the following point:

- Portal vein thrombosis. Malignant portal vein thrombosis should be considered a nonmeasurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during

the course of the treatment. Measurements of the extent of the malignant thrombus may be impaired by the possible presence of a bland component of the thrombosis.

- Porta hepatis lymph node. Lymph nodes detected at the portal hepatis can be considered as malignant if the lymph node short axis is at least 20 mm. Evidence of reactive lymph nodes at the porta hepatis, in fact, is a common finding in patients with cirrhosis regardless of the presence of an HCC. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor.
- Pleural effusion and ascites. The original RECIST publication specifies that cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). The mRECIST for HCC panel of experts considered this issue to be of high importance in the setting of HCC in cirrhosis. The emergence or the increase in ascites is a common event during the course of treatment in a cirrhotic patient, which may be due to worsening of the underlying chronic liver disease and be unrelated to cancer progression. Other effusions, such as pleural effusion, may also be unrelated to cancer progression and be caused by the liver insufficiency. Thus, the mRECIST for HCC emphasizes that cytopathologic confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. It has to be underlined that peritoneal carcinomatosis is a very rare event in HCC.

New lesions

The AASLD practice guideline for the clinical management of HCC has recommended strict criteria for the imaging diagnosis of HCC in cirrhosis. Noninvasive diagnostic criteria of HCC can be made without histology in lesions of at least 1 cm in diameter showing characteristic vascular features of HCC arterial hypervascularization with washout in the portal venous or the late phase at dynamic imaging studies. For diagnostic purposes, two imaging techniques CT and MRI are required for such a confirmation in tumors of 1 to 2 cm in diameter, and one imaging technique in tumors beyond 2 cm in cirrhotic patients.

In the assessment of tumor progression, these concepts have been adopted by the mRECIST assessment proposal, considering some specificities for the frame of progression mode:

- A newly detected hepatic nodule will be classified as HCC and therefore will be declared as evidence of progression when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with washout in the portal venous or late venous phase.
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans.
- An individual radiologic event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

Overall Response Assessment

In mRECIST for HCC, identical to conventional RECIST, overall patient response is a result of the combined assessment of target lesions, nontarget lesions, and new lesions. It is important to point out that appearance of one or more new lesions declares progression whatever the response of target and nontarget lesions. Overcalling of equivocal lesions as new HCC, therefore, has a major impact on the outcome of studies with a radiologic endpoint, such as tumor response or time to progression. Hence, any newly detected focal liver lesion that does not meet the criteria reported above should be considered equivocal and not conclusive for disease progression.

| Target Lesions | Non-target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | IR/SD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

Abbreviations: CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.

**VALIDATION**

The proposed mRECIST assessment is expected to provide a reliable method for assessing tumor response in HCC clinical trials. These new criteria need now to pass the same examination as other methods used before.

- At one time point pathologic correlation with tumor measurements will be required.
- The effect of specific antiangiogenic agents changing the tumor inflow of blood might also have impact in the response assessment.
- Regulatory agencies have to be persuaded that the mRECIST based on the AASLD-JNCI guidelines is the needed step forward to align the response rates induced by molecular drugs and hard endpoints such as survival.

## APPENDIX 13. iRECIST: GUIDELINES FOR RESPONSE CRITERIA FOR USE IN TRIALS TESTING IMMUNOTHERAPEUTICS

The text below was obtained from the following Lesley Seymour et al 2017.

### DEFINITIONS

iRECIST is a consensus guideline developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data, and ultimate validation of the guideline.

Note: iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of "I" (ie, immune) eg, "immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD). New lesions are assessed and subcategorised into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target).

Tumor lesions

The continued use of RECIST 1.1 is recommended to define whether tumour lesions, including lymph nodes, are measurable or non-measurable, as well as for the management of bone lesions, cystic lesions, and lesions with previous local treatment (eg, radiotherapy). Similarly, no changes have been made to the recommendations regarding the method of measurement, although clinical examination and chest radiograph are rarely used, with the availability of more modern imaging techniques (eg, CT scans and MRI). The principles used to establish objective tumour response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumour shrinkage.

Measurable Disease (RECIST 1.1)

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease (RECIST 1.1)

All other lesions (or sites of disease), including small lesions (longest diameter ≥10 to <15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease,

lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, 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.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

<u>iUPD</u>

iRECIST defines iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterised.

**GUIDELINES FOR CONTINUED TREATMENT AFTER iUPD**

We recommend that clinical trials in which treatment beyond initial RECIST 1.1-defined progression (ie, iUPD) is permitted should only allow patients who are clinically stable to continue on treatment until the next assessment (≥4 weeks later); this next imaging assessment should be no longer than 8 weeks later, to

ensure that patients remain fit for salvage therapies. A longer timeframe before the next assessment might be reasonable if pseudoprogression is well described in the tumour type (eg, melanoma treated with a CTLA4 inhibitor), especially if no effective salvage therapies are available (eg, BRAF wild-type melanoma) but should be justified in the trial protocol. All decisions regarding continuation or discontinuation of therapy should be made by the patient and their health-care provider; iRECIST describes what data are to be collected, submitted, and analysed in clinical trials of immune-based therapies.

An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnoea occur that are thought to be associated with disease progression (these symptoms are generally understood to mean a requirement for increased palliative intervention), and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the patient before a decision is made about whether or not to continue therapy. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form. This designation will allow the best overall response to be calculated and the date of iUPD to be used in estimates of progression-free survival.

If the confirmatory scan confirms iCPD, but the investigator or patient believes that continued treatment is appropriate, imaging should continue and data should be collected to allow further elucidation of tumour growth dynamics with immune modulators. For the same reason, and if feasible, even patients who discontinue therapy for iCPD are recommended to continue to have disease assessments until they start other systemic or local therapies.

**RESPONSE CRITERIA**

Assessment of Target Lesions

For target lesions, iCR, iPR, and iSD can all be assigned after iUPD has been documented, as long as iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria for progressive disease; iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4-8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. However, the criteria for iCPD (after iUPD) are not considered to have been met if complete response, partial response, or stable disease criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST 1.1, in which any progression precludes later complete response, partial response, or stable disease). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

Assessment of Non-target Lesions

The assessment of non-target lesions at each timepoint follows similar principles. iUPD (but not iCPD) can have been documented before iCR or when the criteria for neither CR nor PD have been met (referred to as non-iCPD/non-iUPD) and can be assigned several times, as long as iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria; however, iUPD can be assigned multiple times as long as iCPD is not

confirmed at the next assessment. Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4–8 weeks after iUPD, shows a further increase from iUPD. The criteria for iCPD are not judged to have been met if RECIST 1.1 criteria for complete response or non-iCR/non-iUPD are met after a previous iUPD. The status is reset (unlike RECIST 1.1) and iCR, or non-iCR/non-iUPD is assigned; if no change is detected, the timepoint response is iUPD.

New Lesions

Many aspects of new lesion assessment are unique to iRECIST. If a new lesion is identified (thus meeting the criteria for iUPD) and the patient is clinically stable, treatment should be continued. New lesions should be assessed and categorised as measurable or non-measurable using RECIST 1.1 principles. Five lesions (no more than two per organ) should be measured and recorded as a new lesion target, but should not be included in the sum of measures of the original target lesions identified at baseline (appendix p 17). Other measurable and non-measurable lesions are recorded as new lesion non-target. Trialists might choose to measure and record more than five new lesions for research purposes, but this method is not believed to be practical for general use. New lesions do not need to meet the criteria for new lesion target to result in iUPD (or iCPD); new lesion non-target can also drive iUPD or iCPD. Progressive disease is confirmed (iCPD) in the new lesion category if the next imaging assessment, done at 4–8 weeks after iUPD, confirms additional new lesions or a further increase in new lesion size from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target).

Notably, if iUPD criteria were met on the basis of progression in the target or non-target disease, or the appearance of new lesions, then RECIST 1.1-assigned progression in another lesion category in the confirmatory scan also confirms iCPD.

Assessment of Timepoint and Best Overall Response

Although the principles of the assignment of the timepoint response and best overall response closely follow RECIST 1.1, and reflect assessment of target and non-target lesions as well as the presence of new lesions, the possibility of pseudoprogression adds complexity. The timepoint response is calculated using the response assigned for each category of lesion (as for RECIST 1.1), but takes into account the last timepoint response.

If the criteria for iUPD have never been met, principles follow RECIST 1.1.However, if the criteria for iUPD have been met, the next timepoint response could be:

- iUPD: no change noted in any category of lesion.
- iSD, iPR, or iCR. Here, iUPD (followed by iCPD) should occur again.
- iCPD, if the category in which iUPD was met at the last timepoint response shows a further increase in tumour burden as evidenced (as applicable) by a ≥5 mm increase in sum of measures of target or new target lesions, further increase in non-target or new non-target lesions, or an increase in the number of new lesions.

Note: iCPD of a category which did not meet criteria for iUPD now meets the criteria for RECIST 1.1 progression Prefix “i” indicates immune responses assigned using iRECIST. RECIST=Response

Evaluation Criteria in Solid Tumours. iCR=complete response. iCPD=complete progression. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression.

The algorithm for patients with no previous iUPD is identical to RECIST 1.1. For patients with iUPD at the last timepoint response, the next timepoint response is dependent on the status of all lesions, including target, non-target, new lesion target, and new lesion non-target; on whether any increase in size has occurred (either a further increase in size or a sufficient increase to assign a new iUPD if the criteria were not previously met); or the appearance of additional new lesions.

For iRECIST, the best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. iUPD will not override a subsequent best overall response of iSD, iPR, or iCR, meaning that iPR or iSD can be assigned (timepoint response or iBOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for iCPD are not met.

Confirmation of response is not required when using RECIST 1.1, except in non-randomised trials, and this approach is also recommended for iRECIST. The duration of iCR and iPR is from the timepoint when the criteria for iCR or iPR are first met, whereas the duration of iSD is still calculated from baseline.

Assessments that are not done or are not evaluable should be disregarded. For example, an iUPD followed by an assessment that was not done or not evaluable, and then another unconfirmed progressive disease, would be indicative of iCPD. Protocols should clearly specify whether assessments done after protocol therapy is discontinued can be considered in identification of iBOR; it might be reasonable to include assessments done several weeks or months after protocol treatment has been discontinued if late responses are anticipated (such as with a CTLA4 inhibitor) and patients have not received other systemic or local therapies. Protocols should also specify how any new therapy introduced before progression (eg, radiotherapy or surgery) will affect iBOR designation. Other RECIST 1.1 recommendations, including the management of missing assessments, remain unchanged, including requiring that the statistical analysis plan should indicate how missing data or assessments will be addressed in the determination of response and progression.

**TUMOR REASSESSMENT/DISEASE PROGRESSION**

Tumor Reassessment

In general, follow-up response assessment every 6-12 weeks is recommended for iRECIST, depending on the frequency of treatment visits, as recommended for RECIST 1.1. The protocol should specify which anatomical locations are assessed at baseline and follow-up, and whether bone scans should be repeated at each response assessment, only to confirm iPR or iCR, or when clinically indicated. For all trials, especially comparative ones, response assessments should be done on a calendar schedule and not be affected by delays in therapy or the requirement for earlier confirmatory scans, which might be done to confirm iUPD or in some trials, to confirm complete or partial response.

Tumour reassessment can be done earlier than originally planned (but only between 4 and 8 weeks after iUPD) to confirm iUPD (or, in non-randomised trials, to confirm iCR or iPR 4 weeks after the scan showing complete or partial response). If progression is not confirmed, reassessment should continue as

originally planned (ie, if scans were to be done at 8, 16, and 24 weeks, and a scan was done at 12 weeks to confirm response, then the next scans should be done at 16 weeks and 24 weeks, as planned). If patients continue on treatment per protocol after iCPD, assessments should continue to be done, at the same planned schedule, until protocol treatment is discontinued.

Ideally, all imaging done after protocol treatment has been discontinued should continue to be recorded on the case report form until subsequent therapies are initiated, as the protocol and informed consent document permit. These data will allow further refinement of iRECIST.

Primary Criteria of Disease Progression

The event date to be used for calculation of progression-free survival (iPFS) should be the first date at which progression criteria are met (ie, the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios: if the patient stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol noncompliance, or patient death); the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from their cancer. The case report form collects the reason why confirmatory response assessment was not done at any timepoint, such as not clinically stable, centre error, patient refusal, or patient death.

For protocols that permit crossover, or if intermittent schedules are being tested, the protocol should clearly specify whether iUPD or iCPD would be used for a treatment decision leading to crossover and how data subsequent to crossover will be managed and analysed. In general, we suggest that iCPD be used especially for scenarios with immunotherapy in both treatment groups and when pseudoprogression is anticipated.

Adjuvant trials of immune modulators given after curative surgery for melanoma or lung cancer are ongoing (NCT 02437279, 02388906, 02595944, 02504372, and 02273375) but have yet to report their results. Suspected new lesions in the curative setting should always be investigated thoroughly and preferably have a biopsy taken before the designation of relapse is assigned. If taking a biopsy sample is not technically feasible, then it would seem to be reasonable to follow the principles of iRECIST, with a follow-up scan to confirm relapse in patients who are clinically stable.

The collection of anonymised imaging (even if centralised blinded review of imaging studies is not planned) is recommended for all studies using an imaging-based endpoint (ie, response or progression-free survival) if feasible. Although the iRECIST guideline requires the recording of the measurements of up to five new lesions, it might eventually be necessary to record additional lesions to obtain a more precise estimate of progression. Central collection of images will allow further assessment by an independent radiologist if necessary. If real-time central review is planned, the protocol should clearly explain how treatment decisions will be made.

We recommend that phase 3 clinical trials continue to incorporate both RECIST 1.1 and iRECIST and that RECIST 1.1 should continue to be used to define the primary efficacy outcomes (progression-free

survival, disease progression, and best overall response). Exploratory analyses using the iPD date (ie, the first date of iUPD that is subsequently confirmed) can be defined in the statistical analysis plan. Early-phase trials can consider using iRECIST as the primary criteria. The protocol should carefully explain which will be the primary criteria used to assess response, and which would be exploratory. This information is especially important for trials that compare an immune modulator treatment with a non-immune modulator treatment.

**VALIDATION**

iRECIST requires the confirmation of progression to rule out or confirm pseudoprogression. Although this recommendation is in keeping with that of RECIST 1.1 to continue treatment and repeat imaging in the case of a mixed response or equivocal findings, if pseudoprogression is common, patients might be exposed to a higher risk (of continuing ineffective therapy or increasing exposure to radiotherapy) or cost (for the potentially ineffective therapy or the costs of imaging). We recommend that these criteria are used for clinical trial protocols rather than to guide clinical practice. Treatment beyond RECIST 1.1-based progression should be considered only in carefully selected scenarios in which the patient is stable (or improving) symptomatically and if there is just a short period remaining before reassessment.

RECIST 1.1 and iRECIST should yield almost identical results for non-immunotherapy treatments, based on the RECIST warehouses; whereas an immune modulator warehouse and associated sensitivity analysis of endpoints will enable the quantification of potential added benefit for the immunotherapy component. Although comparison of iRECIST in such situations incorporates an element of bias by construction, confirmation and validation of the guideline by overall survival results might gain additional importance.

Our recommendation for the design of randomised studies planned for licensing applications is to continue to use RECIST 1.1 as the primary criteria for response-based endpoints. iRECIST should be regarded as exploratory in such trials, although earlier phase trials might consider using primarily iRECIST.

**Comparison of RECIST 1.1 and iRECIST**

| | RECIST 1.1 | iRECIST |
|---|---|---|
| Definitions of measurable and non-measurable disease; numbers and site of target disease | Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease) | No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline) |
| Complete response, partial response, or stable disease | Cannot have met criteria for progression before complete response, partial response, or stable disease | Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD |

| | | |
|---|---|---|
| Confirmation of complete response or partial response | Only required for non-randomised trials | As per RECIST 1.1 |
| Confirmation of stable disease | Not required | As per RECIST 1.1 |
| New lesions | Result in progression; recorded but not measured | Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD |
| Independent blinded review and central collection of scans | Recommended in some circumstances-eg, in some trials with progression-based endpoints planned for marketing approval | Collection of scans (but not independent review) recommended for all trials |
| Confirmation of progression | Not required (unless equivocal) | Required |
| Consideration of clinical status | Not included in assessment | Clinical stability is considered when deciding whether treatment is continued after iUPD |

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

**Assignment of timepoint response using iRECIST**

| | Timepoint response with no previous iUPD in any category | Timepoint response with previous iUPD in any category* |
|---|---|---|
| Target lesions: iCR; non-target lesions: iCR; new lesions: no | iCR | iCR |

| | | |
|---|---|---|
| Target lesions: iCR; non-target lesions: noniCR/non-iUPD; new lesions: no | iPR | iPR |
| Target lesions: iPR; non-target lesions: noniCR/non-iUPD; new lesions: no | iPR | iPR |
| Target lesions: iSD; non-target lesions: noniCR/non-iUPD; new lesions: no | iSD | iSD |
| Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes | Not applicable | New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD |
| Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no | iUPD | Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression) |
| | | |
| Target lesions: iUPD; non-target lesions: noniCR/non-iUPD, or iCR; new lesions: no | iUPD | Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD |
| Target lesions: iUPD; non-target lesions: iUPD; new lesions: no | iUPD | Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures >5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression) |

| | | |
|---|---|---|
| Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes | iUPD | Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified |
| Target lesions: non-iUPD or progression; nontarget lesions: non-iUPD or progression; new lesions: yes | iUPD | Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified |

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

* Previously identified in assessment immediately before this timepoint.

Abbreviation: "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumors.

**Scenarios of assignments of best overall response using iRECIST**

| | Timepoint response 1 | Timepoint response 2 | Timepoint response 3 | Timepoint response 4 | Timepoint response 5 | iBOR |
|---|---|---|---|---|---|---|
| Example 1 | iCR | iCR, iPR, iUPD, or NE | iCR, iPR, iUPD, or NE | iUPD | iCPD | iCR |
| Example 2 | iUPD | iPR, iSD, or NE | iCR | iCR, iUPD, or NE | iCR, iPR, iSD, iUPD, iCPD, or NE | iCR |
| Example 3 | iUPD | iPR | iPR, iSD, iUPD, or NE | iPR, iSD, iUPD, NE, or iCPD | iPR, iSD, iUPD, NE, or iCPD | iPR |
| Example 4 | iUPD | iSD or NE | iPR | iPR, iSD, iUPD, or NE | iPR, iSD, iUPD, iCPD, or NE | iPR |

| | | | | | | |
|---|---|---|---|---|---|---|
| Example 5 | iUPD | iSD | iSD, iUPD, or NE | iSD, iUPD, iCPD, or NE | iSD, iUPD, iCPD, or NE | iSD |
| Example 6 | iUPD | iCPD | Any | Any | Any | iCPD |
| Example 7 | iUPD | iUPD (no iCPD) | iCPD | Any | Any | iCPD |
| Example 8 | iUPD | NE | NE | NE | NE | iCPD |

Eight examples are presented for patients with target disease at baseline, but many more scenarios exist following the same principles. Table assumes a randomised study in which confirmation of complete response or partial response is not required. For patients with non-target disease only at baseline, only iCR or non-complete response or non-progression of disease can be assigned at each timepoint (not shown in the table for ease of presentation).

Abbreviation: "i" indicates immune responses assigned using iRECIST. iBOR=best overall response. iCR=complete response. iPR=partial response. NE=not evaluable. iUPD=unconfirmed progression. iCPD=confirmed progression. iSD=stable disease. RECIST=Response Evaluation Criteria in Solid Tumours.

## APPENDIX 14. MEDICATIONS OR SUBSTANCES TO BE AVOIDED OR USED WITH CAUTION DURING TREATMENT WITH LENVATINIB

The text below was obtained from the followings https://crediblemeds.org/ and http://medicine.iupui.edu/clinpharm/ddis/main-table/.

**Bold font** indicates medications or substances that might be relatively commonly used.

*Italic font* indicates medications for indications that are exclusionary for the current study or would likely result in discontinuation from study treatment with lenvatinib for management of a concurrent illness.

### MEDICATIONS THAT SHOULD BE AVOIDED

**Drugs with a Known Risk of QT Prolongation/Torsades de Pointes**

| |
|---|
| Amiodarone, anagrelide, *arsenic trioxide*, astemizole (off US market), **azithromycin**, bepridil (off US market), chloroquine, **chlorpromazine**, cilostazol, **ciprofloxacin**, cisapride (off US market), **citalopram**, **clarithromycin**, cocaine, disopyramide, dofetilide, domperidone (not on US market), donepezil, dronedarone, **droperidol**, **erythromycin**, **escitalopram**, flecainide, fluconazole, gatifloxacin (off US market), grepafloxacin (not on US market), halofantrine (not on US market), haloperidol, ibogaine (not on US market), ibutilide, levofloxacin, levomepromazine / methotrimeprazine (not on US market), levomethadyl (off US market), levosulpiride (not on US market), mesoridazine (off US market), **methadone**, moxifloxacin, **ondansetron**, *oxaliplatin*, *pentamidine*, pimozide, probucol (off US market), procainamide, propofol, quinidine, roxithromycin (not on US market), sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), sultopride (non on US market), terfenadine (off US market), terlipressin (not on US market), terodiline (not on US market), thioridazine, *vandetanib*. |

### CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS

**Sensitive Substrates and Substrates with Narrow Therapeutic Index for P-gp and BCRP Transporters**

| **Enzyme** | |
|---|---|
| P-gp | Aliskiren, ambrisentan, colchicine, dabigatran etexilate, **digoxin**, *everolimus*, **fexofenadine**, *imatinib*, *lapatinib*, *maraviroc*, *nilotinib*, posaconazole, ranolazine, saxagliptin, sirolimus, **sitagliptin**, talinolol, tolvaptan, *topotecan.* |
| BCRP | Methotrexate, *mitoxantrone*, *imatinib*, *irinotecan*, *lapatinib*, **rosuvastatin**, sulfasalazine, *topotecan.* |

### CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS (CONTINUED)

**Sensitive Substrates and Substrates With Narrow Therapeutic Index for the Indicated CYP Enzymes**

| **Enzyme** | |
|---|---|
| CYP2B6 | Bupropion. |
| CYP2C8 | Repaglinide. |
| CYP2D6 | Atomoxetine, desipramine, **dextromethorphan**, *eliglustat,* nebivolol, **nortriptyline**, perphenazine, tolterodine, venlafaxine. |
| CYP3A | Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, *darunavir*, *dasatinib*, dronedarone, ebastine, eletriptan, eplerenone, *everolimus*, **felodipine**, ibrutinib, *indinavir*, lomitapide, **lovastatin**, lurasidone, *maraviroc*, **midazolam**, |

| | |
|---|---|
| | naloxegol, nisoldipine, quetiapine, *saquinavir*, sildenafil, **simvastatin**, sirolimus, tacrolimus, ticagrelor, *tipranavir*, tolvaptan, triazolam, vardenafil. |

**Drugs with Conditional Risk of Torsades de Pointes**

| |
|---|
| **Amantadine**, amisulpride (not on US market), amitriptyline, amphotericin B, *atazanavir*, bendroflumethiazide / bendrofluazide (not on US market), chloral hydrate, **diphenhydramine**, doxepin, **esomeprazole**, **famotidine**, **fluoxetine**, fluvoxamine**, furosemide / frusemide**, galantamine, garenoxacin (not on US market), **hydrochlorothiazide**, hydroxychloroquine, hydroxyzine, indapamide, itraconazole, ivabradine, ketoconazole, **lansoprazole**, **loperamide**, **metoclopramide**, metolazone, metronidazole, *nelfinavir*, olanzapine, **omeprazole**, **pantoprazole**, **paroxetine**, piperacillin/tazobactam, posaconazole, propafenone, quetiapine, quinine sulfate, ranolazine, **sertraline**, solifenacin, *telaprevir*, torsemide / torasemide, trazodone, voriconazole, ziprasidone. |

## APPENDIX 15. BARCELONA CLINIC LIVER CANCER (BCLC) STAGING CLASSIFICATION

The Barcelona Clinic Liver Cancer (BCLC) system has been widely validated and is the most commonly used staging system for HCC. It determines cancer stage and patient prognosis based on tumor burden, severity of liver disease, and the patient's ECOG Performance Status.

The staging according to the BCLC classification assigns prognoses based on clinical and tumor parameters and is summarized as follows:

| BCLC Stage[a, b] | | | | |
|---|---|---|---|---|
| Very early stage (0) | Early stage (A) | Intermediate stage (B) | Advanced stage (C) | Terminal stage (D) |
| Single nodule <2 cm Carcinoma in situ Child–Pugh A, ECOG PS 0 | Single or 3 nodules <3 cm Child–Pugh A-B, ECOG PS 0 | Multinodular, Child–Pugh A-B, ECOG PS 0 | Portal invasion, Extrahepatic spread, Child–Pugh A-B, ECOG PS 1-2 | Child–Pugh C ECOG PS 3-4 |

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

a. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology. 2016;150:835-53.
b. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–38.