# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| **Protocol Title:** | A Phase 1b Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors |
| **Protocol Identifier:** | BGB-900-103 |
| **Phase:** | 1b |
| **Investigational Products:** | Sitravatinib (MGCD516) and Tislelizumab (BGB-A317) |
| **Indication:** | Advanced Solid Tumors |
| **Sponsor:** | BeiGene, Ltd.<br>c/o BeiGene AUS Pty Ltd.<br>1C/528 Compton Road Stretton<br>Queensland 4116, Australia<br><br>BeiGene, Ltd.<br>c/o BeiGene USA, Inc.<br>2955 Campus Drive, Suite 200<br>San Mateo, CA 94403<br>USA<br><br>BeiGene (Beijing) Co., Ltd.<br>No. 30 Science Park Road<br>Zhong-Guan-Cun Life Science Park<br>Changping District<br>Beijing, China 102206<br>China |
| **Sponsor Medical Monitor:** | [redacted]<br>BeiGene, Ltd.<br>[redacted]<br>Email: [redacted] |
| **Original Protocol:** | 26 June 2018 |
| **Amendment 1.0** | 22 March 2019 |
| **Amendment 2.0** | 12 June 2019 |
| **Amendment 3.0** | 19 November 2019 |

# FINAL PROTOCOL APPROVAL SHEET

**BGB-900-103:** A Phase 1b Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors

**BeiGene, Ltd., Approval:**

[redacted] 20 Nov 2019

Date

BeiGene, Ltd.

# INVESTIGATOR SIGNATURE PAGE

**Protocol Title:** A Phase 1b Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors

**Protocol Identifier:** BGB-900-103

This protocol is a confidential communication of BeiGene, 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.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 3.0 (19 NOVEMBER 2019)

The main purpose of this amendment is to increase sample size to 60 subjects in Cohort E and update the background information of tislelizumab and sitravatinib.

| Applicable Section | Description of Revision |
|---|---|
| **Change:** | **Non-content related changes made throughout the document.** |
| **Reason:** | **Consistency with other sitravatinib/tislelizumab protocols and correction of errors.** |
| All Sections | • Administrative updates, editorial changes, and/or style and formatting revisions have been made to improve clarity and consistency throughout the document. |
| **Change:** | **Update the background information based on current sitravatinib Development Safety Update Report (DSUR).** |
| **Reason:** | **Consistency with current sitravatinib DSUR.** |
| Section 1.2.4.1: Study 516-001<br>Section 1.2.4.2: Study MRTX-500 | • Update safety data of Study 516-001.<br>• Update safety data of Study MRTX-500. |
| **Change:** | **Update the background information based on current tislelizumab IB.** |
| **Reason:** | **Consistency with current tislelizumab IB.** |
| Section 1.3.1: Pharmacology<br>Section 1.3.3: Clinical Pharmacology<br>Section 1.3.4: Clinical Experience With Tislelizumab | • Update section Pharmacology.<br>• Update section Clinical pharmacology.<br>• Update section Clinical experience with tislelizumab. |
| **Change:** | **Change the number of subjects and criteria in Cohort E as well as the study sample size.** |
| **Reason:** | **To increase the number of subjects with ovarian cancer.** |
| Synopsis: Study Design<br>Synopsis: Sample Size Consideration<br>Synopsis: Study Schema<br>Section 3.1: Summary of Study Design<br>Section 3.1: Figure 1<br>Section 9.7: Sample Size Consideration | • Approximately 220 to 240 patients (approximately 60 patients for Cohort E, and 20 patients for each of the rest of the cohorts) are expected to be enrolled to analyze safety and preliminary efficacy for sitravatinib plus tislelizumab. Of the approximately 60 patients enrolled into Cohort E, at least 20 patients who failed the prior bevacizumab treatment and at least 20 patients will be Caucasian.<br>• Delete Table 8 Estimates of 95% CI of ORR With 20 Patients. |

| Applicable Section | Description of Revision |
|---|---|
| **Change:** | **Clarify the enrollment plan of Cohort E.** |
| **Reason:** | **To update enrollment plan of Cohort E.** |
| Synopsis: Study Design<br>Section 3.1: Summary of Study Design | • Approximately 60 patients will be enrolled into Cohort E, including at least 20 patients who failed the prior bevacizumab treatment and at least 20 patients will be Caucasian. The additional 40 patients of Cohort E will not be enrolled in China after the amendment is effective. |
| **Change:** | **Revised the subject type of Cohort F.** |
| **Reason:** | **To refine the subject type of Cohort F.** |
| Synopsis: Study Design<br>Synopsis: Study Schema<br>Section 3.1: Summary of Study Design<br>Section 3.1: Figure 1<br>Section 4.1: Inclusion Criteria | • Revise the definition of Cohort F:<br>Cohort F: Anti-PD-1/PD-L1 antibody refractory/resistant metastatic, squamous NSCLC.<br>• Add the notes to clarify "anti-PD-1/PD-L1 antibody refractory/resistant metastatic, squamous NSCLC" in Cohort F:<br>**Note:** Radiographic progression per RECIST v1.1 on or after anti-PD-1/PD-L1-containing therapy as the most recent treatment for metastatic NSCLC with best response defined as follows:<br>○ Resistant (ie, RECIST v1.1-defined partial, complete response, or stable disease for at least 12 weeks after initiation of treatment followed by radiographic progression of disease).<br>○ Refractory (ie, radiographic progression of disease < 12 weeks after initiation of treatment). |
| **Change:** | **Combine the End-of-Treatment and Safety Follow-up visits.** |
| **Reason:** | **To simplify the study procedures.** |
| Section 3.4: End-of-Treatment and Safety Follow-up Phone calls<br>Section 3.5: Survival Follow-up<br>Section 3.7: End of Study<br>Section 7.3.4: Laboratory Safety Test<br>Section 7.7: Biomarkers<br>Appendix 1<br>Appendix 2<br>Appendix 3 | • Delete Section 3.3.2 and 3.4.1.<br>• Revise the text in Section 3.4, 3.5, 3.7, 7.3.4, 7.7; Appendix 1 EOT Visit and footnotes 5, 6, 12, 13 and 20; Appendix 2 EOT Visit and footnotes c, d, e; Appendix 3 footnotes. |

| Applicable Section | Description of Revision |
|---|---|
| **Change:** | **Revise the criteria of biomarker test and tumor sample collection for NSCLC cohorts.** |
| **Reason:** | **To specify the criteria of biomarker test and tumor sample collection for NSCLC cohorts.** |
| Section 4.1: Inclusion Criteria | • Specify the criteria of biomarker test and tumor sample collection in NSCLC cohorts (A, B, F, H, I).<br>o ALK/ROS1: No documented rearrangement.<br>o BRAF: No documented mutation. |
| **Change:** | **Revise the requirements to perform Pulmonary Function Tests (PFT) at Screening Visit.** |
| **Reason:** | **To specify the requirements to perform PFT at Screening Visit.** |
| Section 4.1: Inclusion Criteria<br>Section 7.1: Screening<br>Section 7.1.5: Pulmonary Function Tests<br>Appendix 1 | • Delete inclusion criterion 10.<br>• Revise the text in Section 7.1, 7.1.5, and Appendix 1 footnote 16 regarding PFT. |
| **Change:** | **Revise the dose resume criteria.** |
| **Reason:** | **To correct the dose resume criteria.** |
| Section 5.5.2: Dose Delay | • Revise text as shown below.<br>Patients should resume study drugs as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) within 4 weeks for sitravatinib or 12 weeks for tislelizumab after last dose of the respective study drug. |
| **Change:** | **Add safety monitoring for eye-related adverse events.** |
| **Reason:** | **To monitor eye-related adverse events.** |
| Section 7.3.2: Physical Examinations | • Add text as below.<br>In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance. |
| **Change:** | **Revise the management of Non-Hematological Toxicities of Sitravatinib.** |
| **Reason:** | **Consistency with the current management guideline of Non-Hematological Toxicities of Sitravatinib.** |

| Applicable Section | Description of Revision |
|---|---|
| Section 8.9.1: Management of Non-Hematological Toxicities of Sitravatinib<br><br>Section 8.9.1: Table 10 | • Update the management of Non-Hematological Toxicities of Sitravatinib. |
| **Change:** **Revise sampling volume and time of pharmacodynamic biomarker and ctDNA.**<br>**Reason:** **Avoid unnecessary blood sampling or testing.** | |
| Appendix 2 | • Revise sampling time of pharmacodynamic biomarker and footnote e. |

# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# SYNOPSIS

| | |
|---|---|
| **Name of Sponsor:** | BeiGene, Ltd. |
| **Investigational Products:** | Sitravatinib (MGCD516) and Tislelizumab (BGB-A317) |
| **Title of Study:** | A Phase 1b Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Sitravatinib in Combination With Tislelizumab in Patients With Advanced Solid Tumors |
| **Protocol Identifier:** | BGB-900-103 |
| **Phase of Development:** | 1b |
| **Study Centers:** | Approximately 20 to 30 centers in Asia Pacific including Australia and China |
| **Duration of Patient Participation:** | Patients will receive treatment of sitravatinib daily and tislelizumab once every 3 weeks during the study until occurrence of progressive disease (PD), unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor. |

**Study Objectives**

**Primary**:

- To characterize the safety and tolerability of sitravatinib in combination with tislelizumab

**Secondary**:

- To assess the preliminary antitumor activity of sitravatinib in combination with tislelizumab
- To characterize the pharmacokinetics (PK) profiles of sitravatinib after single dose and at steady state when given in combination with tislelizumab

**Exploratory:**

- To assess the PK and immunogenicity of tislelizumab when given in combination with sitravatinib
- To explore potential pharmacodynamic biomarkers for sitravatinib in combination with tislelizumab
- To explore potential biomarkers of efficacy, resistance, or PD in tumor tissue and in peripheral whole blood
- To assess overall survival (OS)
- To explore the effect of pharmacogenetic (PGx) polymorphisms on the PK of sitravatinib
- To assess the preliminary antitumor activity of sitravatinib in combination with tislelizumab for ovarian cancer patients based on the Gynecologic Cancer Intergroup (GCIG) working group criteria.

**Study Endpoints**

**Primary:**

- Safety and tolerability will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events (SAEs) per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0, relevant physical examinations, electrocardiograms (ECGs), and laboratory assessments as needed

**Secondary:**

- Efficacy evaluations: objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- Plasma concentrations and the derived PK parameters of sitravatinib:
    - Single dose: maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), area under the plasma concentration-time curve from time zero to the last measurable time point ($AUC_{(0-t)}$), clearance after oral administration (CL/F)
    - Repeated dose: $C_{max}$, trough concentration at steady state ($C_{\tau}$), $T_{max}$, area under the plasma concentration-time curve from time zero to 24 hours postdose at steady state ($AUC_{(0-\tau)}$), CL/F, accumulation ratio (Ro)

**Exploratory:**

- Serum concentrations of tislelizumab and anti-tislelizumab-antibodies
- Changes of potential pharmacodynamic biomarkers in response to sitravatinib in combination with tislelizumab, such as soluble vascular endothelial growth factor receptor 2 (sVEGFR-2), and immune cell subpopulations in peripheral blood
- Potential biomarkers including but not limited to programmed cell death protein ligand-1 (PD-L1) expression, immune-cell profiling, tumor mutation load and gene expression profiling, and the association with disease status and/or the response to sitravatinib in combination with tislelizumab
- OS
- The effect of genetic polymorphisms of hepatic metabolizing enzymes and transporters, including but not limited to CYP1A2, 2D6, and 2C8 on the PK of sitravatinib
- Efficacy evaluations for ovarian cancer patients: PFS per CA-125 (GCIG working group criteria)

**Study Population**

Patients with histologically or cytologically confirmed locally advanced or metastatic, non-squamous or squamous non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), ovarian cancer (OC), and melanoma.

**Key Eligibility Criteria**

Adult patients (≥ 18 years of age or acceptable age according to local regulations, whichever is older at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed advanced or metastatic solid tumors. All patients are also required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of ≤ 1 and adequate end-organ function.

**Test Product, Dose, and Mode of Administration**

**Sitravatinib:** 120 mg will be administered orally once daily.
**Tislelizumab:** 200 mg will be administered intravenously (IV) once every 3 weeks.

**Study Design**

This is an open-label, multicenter, non-randomized Phase 1b clinical trial for patients with histologically or cytologically confirmed locally advanced or metastatic tumors including non-squamous or squamous NSCLC, RCC, OC, or melanoma.

All patients will receive sitravatinib 120 mg orally once daily in combination with tislelizumab 200 mg IV once every 3 weeks until occurrence of PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.

There will be 9 cohorts in the study. Approximately 60 patients will be enrolled into Cohort E, including at least 20 patients who failed the prior bevacizumab treatment and at least 20 patients will be Caucasian. The additional 40 patients of Cohort E will not be enrolled in China after the amendment is effective. In addition, approximately 20 patients will be enrolled into each of the rest of the cohorts. The patients will be enrolled according to their tumor type and prior anti-programmed cell death protein-1 (PD-1)/PD-L1 antibody treatment.

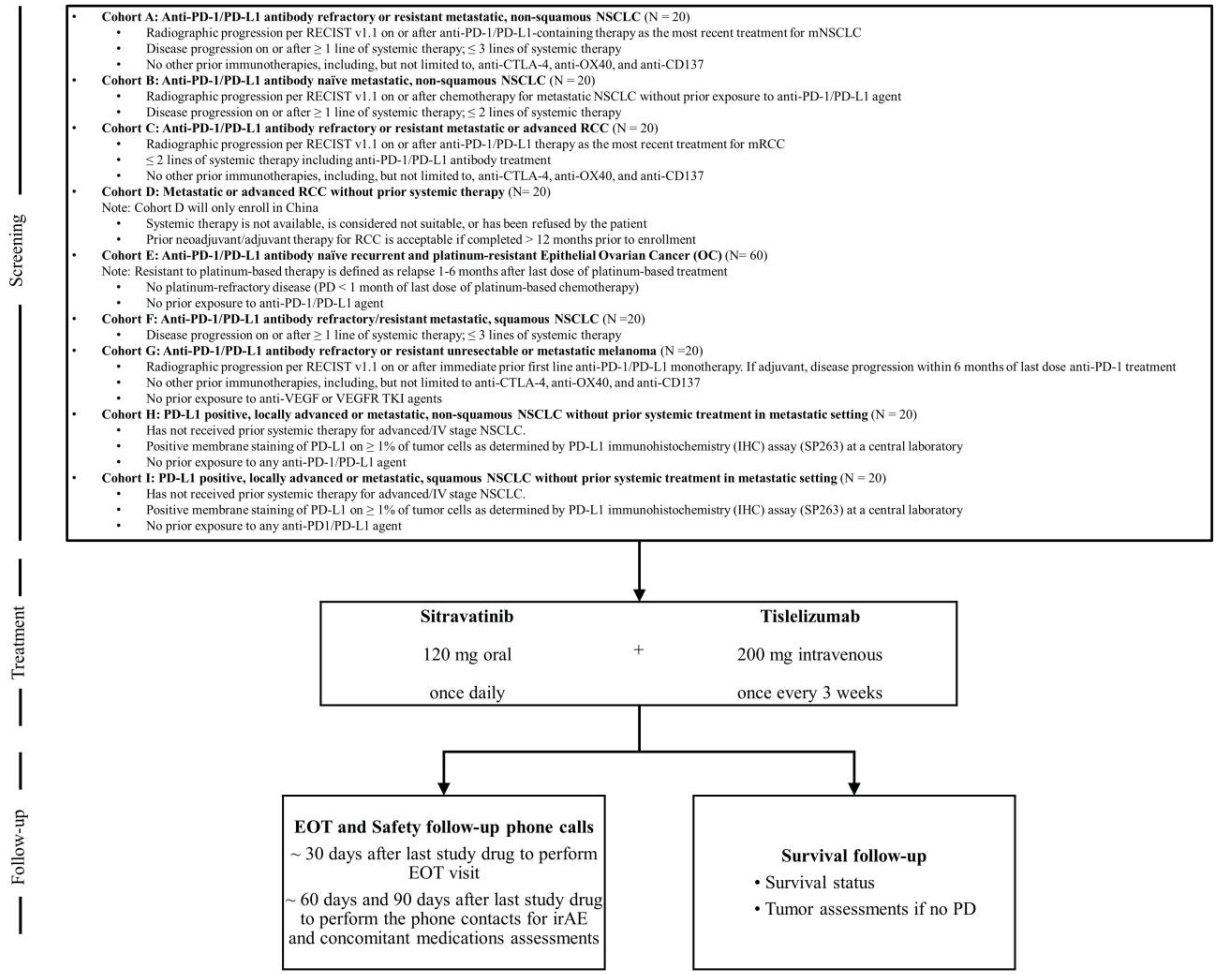
- Cohort A: Anti-PD-1/PD-L1 antibody refractory/resistant metastatic, non-squamous NSCLC
- Cohort B: Anti-PD-1/PD-L1 antibody naïve metastatic, non-squamous NSCLC
- Cohort C: Anti-PD-1/PD-L1 antibody refractory/resistant metastatic or advanced RCC
- Cohort D (China-only): Metastatic or advanced RCC without prior systemic therapy
- Cohort E: Anti-PD-1/PD-L1 antibody naïve recurrent and platinum resistant epithelial OC
- Cohort F: Anti-PD-1/PD-L1 antibody refractory/resistant metastatic, squamous NSCLC
- Cohort G: Anti-PD-1/PD-L1 antibody refractory/resistant unresectable or metastatic melanoma
- Cohort H: PD-L1 positive, locally advanced or metastatic, non-squamous NSCLC without prior systemic treatment in metastatic setting
- Cohort I: PD-L1 positive, locally advanced or metastatic, squamous NSCLC without prior systemic treatment in metastatic setting

Cohort F will only enroll prior anti-PD-1/PD-L1 antibody refractory/resistant squamous NSCLC until the total number of prior anti-PD-1/PD-L1 antibody treated squamous NSCLC reaches 20 patients. The prior anti-PD-1/PD-L1 naïve patients who enrolled before the amendment is effective can continue their treatment per the protocol. It is to further explore the safety and efficacy for patients with anti-PD-1/PD-L1 antibody treated squamous NSCLC. The anti-PD-1/PD-L1 antibody naïve patient will be no longer enrolled in this cohort after this amendment is effective.

A Safety Monitoring Committee (SMC) will review the safety, tolerability, and pharmacology data from the initial 6 patients (regardless of assigned cohort) that complete the first treatment cycle in Australia. Recruitment will be on hold in Australia until these data have been reviewed. For participating China sites only, the initial 6 patients enrolled in China regardless of assigned cohort will have their safety, tolerability, and pharmacology data reviewed by the SMC. Recruitment in China only will be on hold until the data have been reviewed.

The SMC may assess the combination regimen as safe, but may also decide to evaluate a dosing regimen that was not predefined or not previously studied, if evaluation of toxicity at such a dose is desired.

## Study Schema




Abbreviations: IHC, immunohistochemistry; mNSCLC, metastatic non-small cell lung cancer; mRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; RCC. renal cell carcinoma; SMC, Safety Monitoring Committee; VEGF, Vascular endothelial growth factor; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

**Note:** The SMC will review the safety, tolerability, and pharmacology data from the initial 6 patients regardless of assigned cohort that complete the first cycle of treatment in Australia. Recruitment will be on hold in Australia until the data have been reviewed. For participating China sites only, the SMC will also review the safety, tolerability, and pharmacology data of the initial 6 patients enrolled in China regardless of assigned cohort. Recruitment in China only will be on hold until the data have been reviewed.

### Study Assessments

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

### Tumor Assessments

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

Tumor response will be assessed by investigators using RECIST v1.1. For ovarian cancer patients, response will be assessed using RECIST v1.1 and the GCIG working group criteria.

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

**Statistical Methods**

This trial is designed to establish the safety and tolerability of sitravatinib in combination with tislelizumab and to assess the preliminary antitumor activity of the combination therapy in selected tumor types. No formal hypothesis testing is planned. Descriptive statistical analyses will be performed for all patients in the safety analysis set. The safety and efficacy (eg, ORR, PFS, DOR, DCR and OS) data will be presented by cohort.

**Analysis Sets**

- The Safety analysis set includes all patients who received ≥ 1 dose of any study drug (any component of the combination therapy).
- The Efficacy Evaluable analysis set includes all dosed patients who had measurable disease at baseline per RECIST v1.1 and who had at least 1 evaluable postbaseline tumor assessment unless treatment was discontinued due to disease progression or death before tumor assessment.
- The PK analysis set includes patients who contributed at least 1 quantifiable PK sample.
- The antidrug antibody (ADA) Analysis Set includes all patients who received at least 1 dose of tislelizumab and for whom both baseline ADA and at least 1 postbaseline ADA results are available.

**Safety Analysis**

Safety will be determined by the collection 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 NCI-CTCAE v5.0. The incidence of treatment-emergent AEs (TEAEs) will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term. Descriptive summary statistics (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. Safety analyses will be conducted in the Safety analysis set.

**Efficacy Analysis**

The efficacy endpoints (ie, ORR, DOR, PFS, and DCR) will be assessed by investigators using RECIST v1.1 and will be summarized to evaluate the antitumor activities of sitravatinib in combination with tislelizumab.

- ORR is defined as the proportion of patients who have confirmed or unconfirmed complete response (CR) or partial response (PR) as assessed by the investigator using RECIST v1.1. The ORR and its 95% confidence interval (CI) will be summarized.
- DOR is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier).
- DCR is defined as the proportion of patients with best overall response (BOR) of CR, PR, and stable disease (SD).

- PFS is defined as the time from the date of the first dose of study drugs to the date of the first documentation of PD as assessed by the investigator using RECIST v1.1 or death, whichever occurs first.
- OS is defined as the time from the date of the first dose of study drugs to the date of death due to any cause.
- PFS assessed per CA-125 criteria will be summarized descriptively.

Descriptive statistics will be used to summarize the efficacy analysis. Exact 95% CI will be calculated for the rate variables (ORR and DCR).

Time-to-event variables including PFS, DOR, and OS will be estimated using the Kaplan-Meier method and will be plotted over time. Median PFS, DOR and OS, if possible to estimate, will be presented for each cohort, with 2-sided 95% CIs.

Waterfall plots of maximum tumor shrinkage per patient will be presented.

Efficacy analyses will be provided based on both the Efficacy Evaluable analysis set and the Safety analysis set. The Efficacy Evaluable analysis set will be the primary analysis set for response analyses; and the Safety analysis set will be the primary analysis set for time-to-event analyses. Details of statistical analyses will be described in the Statistical Analysis Plan.

**Sample Size Considerations**

Approximately 220 to 240 patients (approximately 60 patients for Cohort E, and 20 patients for each of the rest of the cohorts) are expected to be enrolled to analyze safety and preliminary efficacy for sitravatinib plus tislelizumab. Of the approximately 60 patients enrolled into Cohort E, at least 20 patients who failed the prior bevacizumab treatment and at least 20 patients will be Caucasian. Enrollment into these cohorts will occur simultaneously, independently of each other. Each cohort will be evaluated separately.

# LIST OF ABBREVIATIONS AND TERMS

| Abbreviation | Definition |
|---|---|
| ADA | antidrug antibody |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AUC | area under the plasma or serum concentration-time curve |
| BOR | best overall response |
| CI | confidence interval |
| CL | clearance |
| CR | complete response |
| CT | computed tomography |
| DCR | disease control rate |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EOT | End-of-Treatment |
| FFPE | formalin-fixed paraffin-embedded |
| GCIG | Gynecologic Cancer Intergroup |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| ICF | informed consent form |
| ICH | International Council on Harmonisation |
| IEC | Independent Ethics Committee |
| irAE | immune-related adverse event |
| IRB | Institutional Review Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NSCLC | non-small cell lung carcinoma |
| OC | ovarian cancer |
| ORR | objective response rate |

| Abbreviation | Definition |
|---|---|
| OS | overall survival |
| PD | progressive disease |
| PD-1 | programmed cell death protein-1 |
| PD-L1 | programmed cell death protein ligand-1 |
| PFS | progression-free survival |
| PK | pharmacokinetic(s) |
| PR | partial response |
| RCC | renal cell carcinoma |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | recommended Phase 2 dose |
| RTK | receptor tyrosine kinase |
| SAE | serious adverse event |
| SMC | Safety Monitoring Committee |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| VEGF | vascular endothelial growth factor |
| VEGFR | vascular endothelial growth factor receptor |

# 1. INTRODUCTION AND RATIONALES

## 1.1. Background Information on Advanced Solid Tumors

### 1.1.1. Non-Small Cell Lung Cancer

Worldwide, lung cancer has been the most common malignancy in the past few decades and the leading cause of cancer death by far. In 2012, it was estimated that a total of 1.8 million new cases were diagnosed, accounting for 12.9% of all new cancer diagnoses (Wong et al 2017). Likewise, lung cancer is also the most common cancer and the leading cause of cancer death in China; about 782,000 new cases of lung cancer were diagnosed in 2014 (Chen et al 2015). According to statistics from the National Office on Tumor Cure and Prevention, about 626,000 people die of lung cancer each year in China (Chen et al 2018). Meanwhile, lung cancer was the fifth most commonly diagnosed cancer in Australia in 2013. In 2018, it is estimated that this will increase to 9,198 deaths from lung cancer in Australia (Australian Government 2018).

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers (PDQ Adult Treatment Editorial Board 2017). It includes 2 major pathological types: 1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other subtypes); 2) squamous cell (epidermoid) carcinoma (NCCN Guideline Version 4, 2019).

For decades, the conventional anticancer strategies have been surgery, chemotherapy, and radiotherapy. The success in immune checkpoint therapy in recent years has revolutionized traditional cancer treatment. PD-1 inhibitors and PD-L1 inhibitors are a group of checkpoint inhibitors being developed for the treatment of cancer. The FDA has approved six different monoclonal antibodies targeting the PD-1/PD-L1 pathway: pembrolizumab (PD-1 inhibitor) (KEYTRUDA® prescribing information), nivolumab (PD-1 inhibitor) (OPDIVO® prescribing information), atezolizumab (PD-L1 inhibitor) (TECENTRIQ® prescribing information), durvalumab (PD-L1 inhibitor) (IMFINZI™ prescribing information), avelumab (PD-L1 inhibitor) (BAVENCIO® prescribing information) and cemiplimab-rwlc (PD-1 inhibitor) (LIBTAYO® prescribing information).

In the first-line setting, KEYNOTE-042 (Lopes et al 2018) demonstrated that single-agent pembrolizumab significantly improved overall survival (OS) compared with platinum-based chemotherapy with advanced NSCLC, PD-L1 expression of 1% or more, but without EGFR mutation or ALK rearrangement. Treatment -related adverse events of Grade 3 or worse occurred in 113 (18%) of 636 treated patients in the pembrolizumab group and in 252 (41%) of 615 in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively (Mok et al, 2019).

Based on these results, the FDA approved pembrolizumab as a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 (tumor proportion score ≥ 1%) with no EGFR or ALK genomic tumor aberrations (KEYTRUDA® prescribing information).

Furthermore, pembrolizumab in combination with chemotherapy for patients with metastatic non-squamous or squamous NSCLC was also approved by FDA in 2018.

In the KEYNOTE-189 study, for patients with metastatic non-squamous NSCLC without sensitizing EGFR or ALK mutations, the addition of pembrolizumab to chemotherapy resulted in significantly longer OS (estimated rate of OS at 12 months was 69.2% versus 49.4%, hazard ration of 0.49) and PFS (median 8.8 months versus 4.9 months, hazard ration of 0.52) and a higher response rate (47.6% versus 18.9%) than chemotherapy alone (Gandhi et al 2018).

Equally in the KEYNOTE-407 study, the addition of pembrolizumab to standard chemotherapy in patients with previously untreated metastatic squamous NSCLC resulted in significantly longer OS (median 15.9 months versus 11.3 months, hazard ration of 0.64) and PFS (median 6.4 months versus 4.8 months, hazard ration of 0.56) and a higher response rate (57.9% versus 38.4%) than chemotherapy alone, regardless of the level of PD-L1 expression (Paz-Ares et al 2018).

The addition of pembrolizumab did not appear to increase the frequency of adverse events that are commonly associated with chemotherapy regimens involving pemetrexed and a platinum-based drugs. Adverse events of grade 3 or higher in the pembrolizumab-combination group versus placebo-combination group were 67.2% versus 65.8% in KEYNOTE-189 and 69.8% versus 68.2% in KEYNOTE-407.

Identically, three studies evaluated the efficacy and safety of atezolizumab plus chemotherapy (IMpower130 [Cappuzzo et al 2018], 131 [Jotte et al 2018] and 132 [Papadimitrakopoulou et al 2018]) as first line of treatment for advanced NSCLC. The use of the PD-L1 inhibitor atezolizumab in combination with chemotherapy demonstrated improved PFS in patients with stage IV non-squamous or squamous NSCLC.

In addition, adding atezolizumab to bevacizumab plus chemotherapy significantly improved PFS and OS among patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status (Socinski et al 2018) (Reck et al, 2019). Treatment-related adverse events of grade 3 or higher in atezolizumab/bevacizumab/chemotherapy group versus bevacizumab/chemotherapy group were 58.5% versus 50.0%.

While in second-line therapy, two immune checkpoint inhibitors targeting PD-1, nivolumab and pembrolizumab, were approved in 2015. Among these, nivolumab demonstrated a survival benefit versus docetaxel in advanced non-squamous NSCLC, reporting 27% lower risk of death at a minimum follow-up of 13.2 months (median OS: 12.2 versus 9.4 months; ORR: 19% versus 12%), and better safety profile than standard-of-care chemotherapy (Grade 3 and Grade 4 AEs: 10% versus 54%) (Borghaei et al 2015). In 2016, another checkpoint inhibitor targeting PD-L1, atezolizumab, was approved for the same indication.

Despite the recent advances with anti-PD-L1 therapy, most patients with advanced NSCLC have incurable disease; more effective treatment options with better tolerability profile are needed, as first-line treatment and as treatment after failure of a platinum-based chemotherapy regimen and resistance to anti- PD-L1 therapy. Alternative treatment approaches to eliminate the resistant tumor cells are warranted.

### 1.1.2. Renal Cell Carcinoma

Each year, an estimated 338,000 new cases of renal-cell carcinoma (RCC) are diagnosed worldwide, and approximately 30% of patients present with metastatic disease at the time of

diagnosis. According to the National Cancer Registry under the National Cancer Center of China, there were 68,000 new RCC cases in 2014. The incidence of RCC was 6.09/100,000 and 3.84/100,000 in males and females (Chen et al 2018). The mortality of RCC is 1.87/100,000 nationwide at about 26,000 cases in 2014. In 2018, it is estimated that 3,617 new cases of kidney cancer will be diagnosed in Australia and it is estimated that this will increase to 1,069 deaths. Between 1984-1988 and 2009-2013, 5-year relative survival from kidney cancer improved from 49% to 75% (Australia Institute of Health and Welfare 2017).

RCC is exquisitely resistant to chemotherapy. Targeted therapy utilizing tyrosine kinase inhibitors and anti-vascular endothelial growth factor (VEGF) antibodies is widely used in first- and second-line treatments. To date, 9 such agents have been approved by the FDA for the treatment of advanced RCC in the first or subsequent line of therapy. These agents have provided significant clinical benefit for many patients with metastatic RCC (mRCC), but infrequently lead to durable responses (Motzer et al 2013).

In 2015, the FDA approved the first checkpoint inhibitor, nivolumab, for patients with advanced RCC following treatment with antiangiogenic therapy based on improved OS compared with the standard of care. A strong biological rationale supports the strategy of combining immunotherapy with anti-VEGFR agents as the latter agents can promote T-cells infiltration into tumors and boost synergism with PD-1 or PD-L1 blockade. The treatment combination of pembrolizumab plus lenvatinib has shown promising antitumor activity with manageable AEs in patients with mRCC who had ≤ 2 prior systemic therapies (Lee et al 2018). The ORR per immune-related RECIST by investigator review was 70.0% (n = 21; 95% CI, 50.6% to 85.3%). Median duration of response for patients with complete response (CR) or partial response (PR) was 18.4 months (95% CI, 10.3 months to not evaluable). The combination of pembrolizumab and lenvatinib recently received a breakthrough therapy designation from the FDA for the treatment of patients with advanced and/or mRCC who had progressed after treatment with approved therapies or for which there are no standard effective therapies available (Merck 2018).

Several anti-PD-1/PD-L1 based combination regimens are being evaluated as first line RCC therapy. The treatment combination with pembrolizumab plus axitinib has demonstrated promising antitumor activity in 52 patients with treatment-naïve advanced RCC (Atkins et al 2018). The ORR was 73% (95% CI, 59.0% to 84.4%) with 4 patients achieving CR and 34 patients achieving PR. Median PFS was 22.1 months (95% CI, 15.2 months to not evaluable) and 20.7 months (95% CI, 8.2 months to not evaluable) for patients with PD-L1 negative and PD-L1-positive tumors, respectively. The most common ≥ Grade 3 treatment-emergent AEs (TEAEs) included hypertension (n = 12 [23%]), diarrhoea (n = 5 [10%]), fatigue (n = 5 [10%]), and increased alanine aminotransferase (ALT) concentration (n = 4 [8%]). Another study evaluating axitinib with avelumab as first-line therapy reported encouraging antitumor activity in patients with advanced RCC. The proportion of patients with confirmed objective responses was 58% in 55 patients treated (Choueiri et al 2018). Based on these promising data in early phase studies, two Phase 3 pivotal trials with anti-PD-L1 blocking agent plus axitinb as first-line treatment for patients with advanced RCC was initiated later (KeyNote-426 [Rini et al 2019] and JAVELIN Renal 101 [Motzer et al 2019]). With significant improvements in overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) versus sunitinib, FDA had approved pembrolizumab-axitinib combination [U.S. Food & Drug Administration 2019 a] and avelumab-axitinin combination

[U.S. Food & Drug Administration 2019 b] in the second quarter of 2019 for the frontline treatment of patients with advanced RCC. A Phase 3 study of lenvatinib plus everolimus or pembrolizumab versus sunitinib as first-line treatment for advanced RCC is also in progress (NCT02811861).

Despite the recent approval of new therapies for advanced RCC, many patients who do not respond to the existing treatments have a poor prognosis. The majority of patients who initially achieved regression inevitably develop recurrence with PD. For patients who have failed initial therapies, new treatment options are urgently needed. For treatment naïve patients, the new strategies of combining a more selective VEGF inhibitor with a PD-1 inhibitor to improve tolerability while offering synergistic antitumor activity may provide new treatment options.

### 1.1.3. Ovarian Cancer

Ovarian cancer (OC) is the eighth most common cancer among women, and it comprises about 4% of all women's cancers. According to global estimates 225,000 new cases were detected each year, and 140,000 people annually die from the disease (Ferlay et al 2010). According to the National Cancer Registry under the National Cancer Center of China, there were 51,000 new OC cases in 2014 (Chen et al 2018). The mortality of OC is 1.64/100,000 nationwide at about 23,000 cases in 2014. In 2018, it is estimated that 1,613 new cases of ovarian cancer will be diagnosed in Australia. In 2018, it is estimated that this will increase to 1,069 deaths. Between 1984-1988 and 2009-2013, 5-year relative survival from ovarian cancer improved from 34.1% to 44.4% (Australian Institute of Health and Welfare 2017).

Standard front-line systemic treatment for epithelial OC consists of platinum-based chemotherapy, with the option to add the antiangiogenic agent bevacizumab (anti-VEGF antibody) according to local approval and availability. Although response rates are high, disease recurrence is frequent and almost all patients eventually become refractory (PD < 1 month of last dose of platinum-based chemotherapy) or resistant (relapse 1 to 6 months after last dose of platinum-based treatment) to platinum-based therapy (Asano et al 2015). In either case, the prognosis for patients with platinum-resistant/refractory disease is poor.

The standard of care for patients with platinum-resistant/refractory disease includes single nonplatinum agents with or without bevacizumab. Pegylated liposomal doxorubicin monotherapy is a commonly used treatment option in this setting and has been associated with ORRs of 10% to 20%, a median PFS of 2.1 to 3.7 months, and median OS of 8.4 to 16.8 months in platinum-resistant ovarian cancer (Davis et al 2014).

In ovarian cancer, there are few published studies utilizing immunotherapies. Nevertheless, there is a strong rationale to investigate checkpoint inhibition in patients with ovarian cancer for whom high expression of PD-L1 in ovarian cancer is associated with lower 5-year survival rate. Furthermore, nonclinical experiments in syngeneic ovarian cancer murine models show tumor regression with PD-1/PD-L1 blockade. A Phase 2 study of nivolumab in 20 patients in Japan with platinum-resistant epithelial OC demonstrated a response rate of 15% (3/20) and a disease control rate of 45%. Two patients experienced a complete response, one with serous and one with clear cell histology (Hamanishi et al 2015). Although small, the presence of complete responses in a heavily pretreated group of patients with an overall poor prognosis is promising.

### 1.1.4. Melanoma

In 2018, it's estimated that 287,723 new cases of malignant melanoma were diagnosed worldwide. The age-standardized incidence rate and mortality rate worldwide were 3.1/100,000 and 0.63/100,000, respectively (Globocan 2018). Melanoma was the 4th most common cancer in Australia, with estimated 15,229 new cases and 1,725 deaths in 2019. From 1986 to 1990 and 2011 to 2015, 5-year relative survival from melanoma improved from 87.7% to 91.0% (Australia Institute of Health and Welfare 2017). According to the National Cancer Registry under the National Cancer Center of China, there were 7,000 new melanoma cases in 2014, with incidence rates of 0.36/100,000 in males and 0.33/100,000 in females (Chen et al 2018).

Melanoma is generally classified into 4 main subtypes based on the anatomical location and the degree of sun exposure: melanoma on skin without chronic sun-induced damage, melanoma on skin with chronic sun-induced damage, mucosal melanoma, and acral melanoma. Cutaneous subtype is the predominantly subtype among Caucasian melanoma patients. Acral and mucosal melanomas are biologically and clinically distinctive subtypes more frequently seen among Chinese melanoma patients, accounting for 41.8% and 22.6%, respectively (Chi et al 2011). Immune-checkpoint inhibitors are expected to be less effective against acral and mucosal melanomas because their somatic mutation burden is lower than those in non-acral cutaneous melanomas.

Since 2011, immune checkpoint inhibitors have revolutionized the treatment landscape of melanoma with remarkable PFS and OS improvement and a favorable safety profile. Consequently, they are now established standard of care options for patients with unresectable and metastatic melanoma.

Ipilimumab was the first immunotherapy to demonstrate a survival improvement in metastatic melanoma and was approved by FDA in 2011. In MDX010-20 study, 676 unresectable stage III or IV melanoma patients were randomly assigned in a 3:1:1 ratio to receive ipilimumab plus glycoprotein 100 (gp100) vaccine (n = 403), ipilimumab (n = 137), or gp100 (n = 136). The median OS was 10.0 months in ipilimumab arm, compared with 6.4 months in gp100 arm [HR 0.66 (95% CI: 0.55 to 0.85), p = 0.0004] (Hodi et al 2010). A pooled analysis demonstrated a median OS of 11.4 months (95% CI, 10.7 to 12.1 months) among 1,861 melanoma patients receiving ipilimumab monotherapy (Schadendorf et al 2015).

Anti-PD-1 antibodies have demonstrated a high response rate and durable responses in melanoma patients pretreated with ipilimumab in KEYNOTE 002 (Ribas et al 2015) and CheckMate 037 (Weber et al 2015) studies, which led to FDA accelerated approval of pembrolizumab and nivolumab in 2014. Soon after, both pembrolizumab and nivolumab showed superiority over ipilimumab, and both were approved in the first line setting (KEYTRUDA® prescribing information; OPDIVO® prescribing information).

KEYNOTE-006 was the first head-to-head comparison of pembrolizumab versus ipilimumab for advanced melanoma. In this open-label, randomized phase 3 study, ipilimumab-naïve melanoma patients were assigned by 1:1:1 to pembrolizumab in two dosing schedules (10 mg/kg every 2 or 3 weeks) versus ipilimumab 3 mg/kg (every 3 weeks for 4 doses) (Robert et al 2015). In treatment-naive population, ORR was 39.4% (95% CI, 34.4% to 44.6%) with pembrolizumab, almost triple of the ORR of 13.3% (95% CI, 8.7% to 19.1%) with ipilimumab, median PFS was 6.6 months (95% CI, 4.4 to 9.8 months) for pembrolizumab and 2.8 months (95% CI, 2.8 to 3.0

months) for ipilimumab (Carlino et al 2018). And the median OS was 38.7 months with pembrolizumab arm and 17.1 months with ipilimumab [HR=0.73(0.75-0.93)] (Long et al 2018).

CheckMate 067 was a phase 3 trial to evaluate safety and efficacy of nivolumab monotherapy or nivolumab and ipilimumab combination therapy, compared to ipilimumab monotherapy. In this study, 945 treatment-naïve melanoma patients with known BRAF mutation status were randomly assigned by 1:1:1 to receive nivolumab in combination with ipilimumab, or nivolumab plus placebo, or ipilimumab plus placebo. The confirmed ORR was 14% (95% CI, 10% to 18%) for ipilimumab, 40% (95% CI, 34% to 46%) for nivolumab, and 50% (95% CI, 44% to 55%) for nivolumab and ipilimumab combination, the median PFS was 2.9 months (95% CI, 2.8 to 3.4 months) , 6.9 months (95% CI, 4.3 to 9.5 months), and 11.5 months (95% CI, 8.9 to 16.7 months), respectively (Larkin et al 2015). After 4 years follow-up, the median OS was 19.9 months (95% CI, 16.9 to 24.6 months) for ipilimumab group, 36.9 months (95% CI, 28.3 months to not reached) for nivolumab group and was not reached (95% CI, 38.2 months to not reached) for the combination group. However, the downside to the nivolumab and ipilimumab combination therapy is significantly increased toxicity. The treatment-related grade 3-4 adverse events occurred in 28% of the patients treated with ipilimumab monotherapy, 22% of nivolumab monotherapy, and 59% of nivolumab plus ipilimumab combination (Hodi et al 2018).

Recently, FDA has approved nivolumab adjuvant treatment of melanoma patients with lymph node involvement on 20 December 2017 based on the recurrence-free survival improvement in CheckMate 238. Earlier this year, pembrolizumab adjuvant treatment has also been granted FDA approval based on KEYNOTE-054.

CheckMate 238 compared outcomes for nivolumab versus ipilimumab given for up to 1 year, in 906 surgically resected melanoma patients with stages IIIB, IIIC, and IV melanoma. In this phase 3, double-blind trial, patients were randomly allocated (1:1) to receive nivolumab (n = 453) or ipilimumab (n = 453). BRAF mutation was positive for 42% of the patients. Patients in nivolumab arm experienced fewer recurrences/deaths, 34% (n = 154), compared with 45.5% (n = 206) in ipilimumab arm (HR 0.65; 95% CI, 0.53 to 0.80; p<0.0001). Median recurrence-free survival was not reached on either arm (Weber et al 2017).

KEYNOTE-054 enrolled patients with completely resected stage IIIA, IIIB or IIIC melanoma to receive pembrolizumab (n = 514) or placebo (n = 505) for up to 1 year or until disease recurrence or unacceptable toxicity. BRAF mutation was positive for 50% of the patients. At a median follow-up of 15 months, pembrolizumab group achieved significantly longer recurrence-free survival than placebo group: 1-year rate of recurrence-free survival was 75.4% (95% CI, 71.3% to 78.9%) versus 61.0% (95% CI, 56.5% to 65.1%); (HR 0.57; 95% CI, 0.46 to 0.7) (Eggermont et al 2018).

In China, anti-PD-1 antibodies, including pembrolizumab and toripalimab (also known as JS001), have also been approved for patients with unresectable or metastatic melanoma in 2018.

KEYNOTE-151 was a phase 1b study investigating second line pembrolizumab for Chinese patients with advanced or metastatic melanoma that progressed after first-line therapy. In this study, 103 patients were enrolled, the ORR per RECIST v1.1 was 16.7% (95% CI, 10.0% to 25.3%), median PFS was 2.8 months (95% CI, 2.7 to 3.5 months) and median OS was 12.1 months (95% CI, 9.6 months to not reached). In this study, the ORR was 19.5% for nonacral subtype, 15.8% for acral subtype and 13.3% for mucosal subtype (Si et al 2018).

However, only approximately 20%-40% patients initially respond to anti-PD-1 checkpoint inhibitors, and increasing clinical evidence indicates that a substantial proportion of initial responders ultimately relapse with lethal, drug-resistant disease months or years later. Currently, the management for melanoma patients progressed on 1st line immune checkpoint inhibitor treatment remains challenging, representing a huge unmet medical need. Clinical trials investigating combination immunotherapy are ongoing in this field.

## 1.2. Sitravatinib as an RTK Inhibitor

Receptor tyrosine kinases (RTK) are essential components of signal transduction pathways that mediate cell-to-cell communication (Hubbard and Miller 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.

Sitravatinib is an orally bioavailable, RTK inhibitor with potential antineoplastic activity. It is a potent inhibitor of multiple RTKs including Axl, MER, MET, KIT, FLT3, RET, VEGFR1, VEGFR2, VEGFR3, PDGFRα, DDR2, TRKA, and TRKB. Sitravatinib targets are genetically altered in a variety of cancers and act as oncogenic drivers, promoting cancer development and progression. In addition to targeting genetically altered oncogenic drivers, sitravatinib 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. Simultaneously to the immunostimulatory effects, sitravatinib may further condition the TME in favor of antitumor activity by its immunomodulatory effects mediated through VEGFR and KIT inhibition. Preclinical data with sitravatinib indicate that it can increase expression of PD-L1 on tumor cells in vitro and in vivo. Pilot studies in syngeneic mouse tumor models also suggest that sitravatinib increases the proliferation and fraction of systemic/spleen CD4+ and CD8+ T lymphocytes and reduces the number of systemic myeloid-derived suppressor cells (MDSCs).

### 1.2.1. Pharmacology

Sitravatinib was demonstrated to be a potent inhibitor of the catalytic activity of a subset of closely related recombinant human RTKs with $IC_{50}$ values ranging from 0.5 to 76 nmol/L. Sitravatinib showed potent activity in RTK-target dependent cell-based assays with $IC_{50}$ values ranging from < 10 to 181 nmol/L. Consistent with this antitumor and anti-angiogenic mechanism of action, sitravatinib demonstrated antitumor efficacy over a broad spectrum of human tumor xenograft models. In addition, concurrent treatment with sitravatinib greatly enhanced the activity of anti-PD-1 therapy in the CT26 syngeneic mouse tumor model.

In vitro studies demonstrated that sitravatinib is classified as a highly permeable compound.

Sitravatinib was more extensively metabolized in dogs than in mice, rats, and humans in vitro.

In vitro results from the hERG assay demonstrate an $IC_{50}$ of 0.6 μM (0.38 μg/mL) on the potassium current. At the recommended Phase 2 dose (RP2D) of 150 mg, the mean steady state plasma concentrations (adjusted for free fraction) observed in patients are approximately

290-fold lower than the hERG $IC_{50}$ concentration. There were no adverse effects on the cardiovascular system, including no effect on the QTc interval, when sitravatinib was administered to dogs at doses up to 4 mg/kg (mean 6 hr concentration of 0.072 µg/mL). Minor increases in blood pressures were observed during the dog cardiovascular study.

Assessment of the neurological functional observation battery and respiratory evaluations in rats did not reveal any sitravatinib-related effects at doses up to 25 mg/kg.

Please refer to the sitravatinib Investigator's Brochure (IB) for additional details regarding nonclinical studies of sitravatinib.

### 1.2.2. Toxicology

In repeat dose toxicity studies in the dog, no target organs were identified, despite overt decreases in body weight and food consumption. Daily oral administration of sitravatinib to beagle dogs for up to 28 days at a dose level of 3 mg/kg/Day was not tolerated and resulted in marked body weight loss and anorexia, with one female requiring veterinary intervention and treatment discontinuation because of general debilitation. Based on the severity of test article-related toxicity at 3 mg/kg/day, the no-observed-adverse-effect level (NOAEL) of sitravatinib is 1 mg/kg/day.

In the rat, VEGF-related target organs were identified, including the adrenal gland, Brunner's glands in the duodenum, femur, and sternum (bone and bone marrow), spleen, lymph nodes, thymus, ovary, kidney (glomerulopathy, tubule necrosis, increased basophilic tubules), pancreas, and tongue. All effects, except those in the kidney and pancreas, either recovered or showed partial recovery. Daily oral administration of sitravatinib to Crl:CD (SD) rats at a dose level of 25 mg/kg/Day was not tolerated and resulted in adverse clinical observations, changes in body weight and food consumption, mortality, and early termination. Based on the severity of the sitravatinib-related toxicity at 25 mg/kg/Day and mortality (though reduced) in animals given ≥ 10 mg/kg/day, the NOAEL is 2.5 mg/kg/day.

Sitravatinib was evaluated in a standard battery of Good Laboratory Practice genotoxicity studies (Ames, chromosome aberrations and in vivo rat micronucleus assays) and was considered negative for mutagenicity and clastogenicity.

Refer to the sitravatinib IB for more detailed information on the toxicology of sitravatinib.

### 1.2.3. Clinical Pharmacology

The pharmacokinetics (PK) profile of single-agent sitravatinib has been evaluated in Study 516-001 after single and repeated dose administration. Plasma samples for PK analyses were collected over a 168-hour period following single dose administration and over a 24-hour period following repeated dose administration. Plasma drug concentrations were determined using a validated, sensitive, LC-MS/MS assay. The PK of sitravatinib was evaluated using non-compartmental analysis methods.

After single dose administration, sitravatinib reaches peak concentration in a median time of approximately 3 to 8 hours. Exposure parameters (maximum concentration [$C_{max}$] and area under the curve [AUC]) are approximately dose proportional with single doses up to 200 mg. Median elimination half-life varies between approximately 42 and 58 hours after oral administration. The

steady state PK is reached in a mean time of 11 to 15 days. Drug accumulation was observed after multiple dose administration and ranged from 1.8- to 3.5-fold for $C_{max}$ and 2.0- to 4.7-fold for $AUC_{0-24}$. The 150 mg was determined to be the maximum tolerated dose and RP2D; it results in a steady state geometric mean ($C_{avg}$), $C_{max}$ and $AUC_{0-24}$ of 91.0 ng/mL, 114 ng/mL and 2183 ng•h/mL, respectively. Plasma concentrations are overlapping for 120 mg and 150 mg dose levels.

Pharmacodynamic assessments of sitravatinib are ongoing; however, preliminary analysis shows a concentration dependent modulation of VEGF-A, soluble VEGF-R2 and soluble MET ectodomain (sMET) levels in patients' plasma samples. The mean prediction (95% CI) percent change from baseline in biomarker modulation with exposure, approached: VEGFA (300% increase), sVEGFR-2 (50% decrease) and sMET (35% increase), consistent with VEGFR and MET inhibition. Mean $C_{trough}$ at Cycle 1, Day 15 for the 120 mg QD dose level in study MRTX-500 is 68.0 ng/mL. At these sitravatinib plasma exposure levels, near optimal modulation of biomarker levels is expected.

Refer to the sitravatinib IB for more detailed information on clinical pharmacology of sitravatinib.

### 1.2.4. Clinical Experience With Sitravatinib

Sitravatinib monotherapy and sitravatinib in combination with nivolumab are being evaluated in ongoing studies. Please refer to the sitravatinib IB and sitravatinib Development Safety Update Report (DSUR) for more detailed information on sitravatinib and the currently ongoing studies

#### 1.2.4.1. Study 516-001

Study 516-001 is an ongoing multi-center Phase 1/1b study evaluating the safety, PK, metabolism, PD and clinical activity of sitravatinib in patients with advanced solid tumor malignancies. The study determined the 200-mg dose exceeded the maximum tolerated dose and continued to evaluate 150 mg once daily as the RP2D for monotherapy. The Phase 1b expansion included patients having tumors with selected histological diagnoses and/or molecular markers solid tumors. As of 26 June 2019, among the 186 patients with available safety data, 183 patients (98%) had experienced at least one treatment-emergent AE, and 167 patients (90%) had experienced treatment-related AEs. Treatment-related AEs reported in ≥ 10% of patients are provided in Table 1.

Treatment-related Grade 3-5 AEs reported in ≥ 5% of patients were hypertension (19%), diarrhea (10%), fatigue (7%), lipase increased (5%), and palmar-plantar erythrodysesthesia (5%). Treatment-related Grade 4 AEs were reported in 3 patients and included lipase increased in 2 patients (1%) and febrile neutropenia in 1 patient (1%). A treatment-related Grade 5 AE of cardiac arrest was reported in 1 patient (1%).

**Table 1. Summary of Treatment-Emergent, Treatment-Related Adverse Events (≥10%) by Preferred Term for Study 516-001**

| Adverse Event Term | Frequency (N=186) |
|---|---|
| Diarrhoea | 92 (50%) |
| Fatigue | 78 (42%) |
| Hypertension | 73 (39%) |
| Nausea | 53 (29%) |
| Decreased appetite | 50 (27%) |
| Vomiting | 44 (24%) |
| Palmar-plantar erythrodysaesthesia syndrome | 37 (20%) |
| Alanine aminotransferase increased | 34 (18%) |
| Aspartate aminotransferase increased | 34 (18%) |
| Hypothyroidism | 31 (17%) |
| Stomatitis | 27 (15%) |
| Dysphonia | 26 (14%) |
| Weight decreased | 26 (14%) |
| Abdominal pain | 22 (12%) |
| Rash | 21 (11%) |
| Constipation | 20 (11%) |
| Dry mouth | 20 (11%) |
| Lipase increased | 18 (10%) |
| Proteinuria | 18 (10%) |

**Serious Adverse Events:** Among the 186 patients with available safety data, 73 patients (39%) had experienced at least one treatment-emergent SAE. Treatment-related SAEs were reported in 28 patients (15%), and included diarrhea in 6 patients (3%), nausea and vomiting in 5 patients each (3%), fatigue in 4 patients (2%), hypertension in 3 patients (2%), and headache, pancreatitis and pulmonary embolism in 2 patients each (1%).

As of 26 June 2019, 90 deaths were reported in this study, with the primary causes of death being the disease under study (n=61), unknown (n=17), sepsis (n=5), respiratory failure (n=3), and aspiration pneumonia, cerebrovascular accident, cardiac arrest, and GI bleed (n=1 each).

### 1.2.4.2. Study MRTX-500

Study MRTX-500 is an open-label, parallel Phase 2 evaluation of sitravatinib in the combination with the PD-1 inhibitor nivolumab, in patients with locally advanced, unresectable or metastatic non-squamous NSCLC who have experienced PD either on or after prior treatment with a checkpoint inhibitor therapy or after treatment with a platinum-based doublet chemotherapy. The study began with a lead-in evaluation of sitravatinib 120 mg once daily in combination with

nivolumab administered by intravenous infusion, 240 mg every 2 weeks. No protocol defined dose-limiting toxicities (DLTs) were reported in the first 6 evaluable patients treated. Based on preliminary long-term tolerability assessments from Study 516-001 (Mirati 2018b) and data from MRTX-500, Mirati decided to evaluate only the 120-mg dose of sitravatinib as this dose level should be adequate to achieve plasma exposure required for inhibition of VEGF and TAM receptors necessary to achieve antitumor efficacy in the combination setting. The 120-mg dose level was selected as the RP2D.

As of 26 June 2019, patient data were entered in the clinical trial database for 135 patients (63 men/72 women; median age 66 years, range 37 to 89 years) with advanced or metastatic NSCLC. All cohorts have enrolled patients, with 107 patients in the CIT-experienced cohorts and 22 patients in the CIT-naïve cohorts. Six patients have enrolled into the PK drug formulation substudy. Enrollment is ongoing.

As of 26 June 2019, among the 135 patients with available safety data, 131 patients (97%) had experienced at least one treatment-emergent AE; 126 patients (93%) had experienced treatment-related AEs; 125 patients (93%) had experienced sitravatinib-related AEs; and 91 patients (67%) had experienced nivolumab-related AEs. Treatment-related AEs reported in ≥ 10% of patients provided in Table 2.

Treatment-related Grade ≥ 3 AEs reported in ≥ 5% of patients were hypertension (17%), diarrhea (11%), and fatigue (7%). Treatment-related Grade 4 AEs were reported in 4 patients and included gastric ulcer perforation, hypertensive crisis, lipase increased, and lymphocyte count decreased in 1 patient each (1%). A treatment-related Grade 5 AE of cardiac arrest was reported in 2 patients (2%).

**Table 2. Summary of Treatment-Emergent, Treatment-Related Adverse Events (≥10%) by Preferred Term for Study MRTX-500**

| Adverse Event Term | Frequency (N=135) |
|---|---|
| Diarrhoea | 66 (49%) |
| Fatigue | 58 (43%) |
| Nausea | 49 (36%) |
| Decreased appetite | 45 (33%) |
| Weight decreased | 40 (30%) |
| Hypertension | 38 (28%) |
| Vomiting | 33 (24%) |
| Hypothyroidism | 29 (22%) |
| Dysphonia | 24 (18%) |
| Aspartate aminotransferase increased | 22 (16%) |
| Palmar-plantar erythrodysaesthesia syndrome | 22 (16%) |
| Stomatitis | 22 (16%) |
| Alanine aminotransferase increased | 20 (15%) |
| Dehydration | 15 (11%) |
| Dry mouth | 13 (10%) |
| Dysgeusia | 13 (10%) |

**Serious Adverse Events:** Among the 135 patients with available safety data, 60 patients (44%) experienced at least one treatment-emergent SAE. Treatment-related SAEs were reported in 31 patients (23%), and included diarrhea in 5 patients (4%), cardiac arrest, deep vein thrombosis, hypertension, pancreatitis, pneumonitis in 2 patients (2%), and adrenalitis, anemia, cardiac failure, colitis, confusional state, dehydration, ejection fraction decreased, embolism, fatigue, gastric ulcer perforation, gastritis, hypertensive crisis, hyponatremia, hypothyroidism, hypoxia, myocarditis, nausea, palmar-plantar erythrodysesthesia syndrome, pericardial effusion, pneumonitis, posterior reversible encephalopathy syndrome, pulmonary embolism, syncope, and vomiting in 1 patient each (1%).

As of 26 June 2019, 57 deaths were reported in this study, with the primary causes of death being the disease under study (n=43), unknown (n=4), pneumonia (n=4), ischemic colitis (n=2), and aspiration, cardiac arrest, bronchopleural-cutaneous fistula hemorrhage, and pulmonary embolism (n=1 each).

### 1.2.5. Rationale for Selection of Sitravatinib Dose

Available nonclinical and safety and PK data from ongoing studies were analyzed to determine the recommended dose of sitravatinib. Nonclinical toxicology studies as well as clinical safety data from the Phase 1/1b and Phase 2 studies suggest that AEs associated with sitravatinib are similar to those observed with other small molecule inhibitors of the VEGFR pathway.

Study MRTX-500, an ongoing Phase 2 combination therapy study in patients with NSCLC, began with a lead-in evaluation of 120 mg once daily of sitravatinib in combination with nivolumab. No protocol defined DLTs were reported in the first 6 evaluable patients treated at 120 mg which was selected as the RP2D for combination therapy. As recently reported (Mirati 2018a), 45 patients have been enrolled in this ongoing study as of March 2018 and most AEs reported by investigators were Grade 1 or 2. The 120-mg dose of sitravatinib is expected to achieve plasma exposure required for inhibition of VEGF and TAM receptors necessary to achieve antitumor efficacy in the combination setting.

Sitravatinib 120 mg once daily is the recommended initial dose for combination with tislelizumab.

## 1.3. Tislelizumab as a PD-1 Blocker

Immune checkpoint-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, RCC, bladder cancer, and ovarian cancer (Jin and Yoon 2016, ONO 2017, Patel and Kurzrock 2015, Van Der Kraak et al 2016, McDaniel 2016, Gong et al 2011). Several anti-PD-1 agents have been approved for the treatment of several cancers. Thus, PD-1 is an established target for cancer immunotherapy.

### 1.3.1. Pharmacology

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

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [$K_D$]=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 pre-activated, primary peripheral blood mononuclear cells (PBMCs). In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which PBMCs were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

In addition, tislelizumab is an IgG4-variant antibody to gamma fragment crystallizable (Fc) region receptors (FcγR) such as FcγRI and FcγRIIIA, and it has very low binding affinity to complement 1q (C1q), a subunit of complement 1. In vitro assays with tislelizumab suggest

either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009; Zhang et al 2018). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

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

### 1.3.2. 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 monkeys. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human whole blood cells. The pivotal toxicology studies were conducted following Good Laboratory Practice 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. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

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 considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study of BGB-900-103.

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

### 1.3.3. Clinical Pharmacology

Population PK analysis was conducted on data from 798 patients who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks, and 200 mg once every 3 weeks. The PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume ($V_c$), and peripheral volumes ($V_2$, $V_3$), were 0.164 L/day, 2.92 L, 0.928 L, and 1.39 L, respectively, with moderate inter-individual variability in CL (32.2%), $V_c$ (16.7%), $V_2$ (56.6%), and $V_3$ (94.2%). The volume of distribution at steady state (Vss) was 5.238 L, which is typical of monoclonal antibodies with limited distribution, which is consistent with a standard immunoglobulin G (IgG) monoclonal antibody (Deng et al 2012; Dirksand Meibohm 2010; Keizer et al 2010; Ryman and Meibohm 2017). Based on the population PK analysis, tislelizumab PK was characterized by a terminal half-life of approximately 25.5 days, which is consistent with other therapeutic IgG monoclonal antibodies.

Population PK analysis demonstrated that baseline age, race, alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, ECOG Performance Status, immunogenicity, and sum of products of perpendicular diameters in classical Hodgkin lymphoma patients did not show statistically significant impact on the PK of tislelizumab. Although tumor size, albumin, and tumor type were significant covariates on CL, while body weight, sex, and tumor type were significant covariates on $V_c$, these covariates are not expected to have a clinically relevant impact on tislelizumab exposure. Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. Population PK analysis supports fixed-dosing across different ethnic groups.

### 1.3.4. Clinical Experience With Tislelizumab

As of 20 May 2019, there are 22 ongoing studies with tislelizumab with over 1705 patients treated. Of these, 13 studies have preliminary data available in the Investigator's Brochure (IB): 7 monotherapy studies, 2 chemotherapy combination therapy studies; and 4 investigational agent combination therapy studies.

Please refer to the tislelizumab IB for more detailed information on tislelizumab safety and efficacy data when given as monotherapy or in combination with chemotherapy.

#### 1.3.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy. Overall, there were 1273 patients in the Pooled Monotherapy studies: 1137 patients treated in 5 solid tumor studies and 136 patients treated in 2 hematologic malignancies studies. Of the 1273 enrolled, 544 patients (42.7%) remained on study as of 20 May 2019; and 272 patients (21.4%) were still receiving tislelizumab treatment.

##### 1.3.4.1.1. Pooled Demographics and Baseline Characteristics

Table 3 shows the demographics and baseline characteristics for the patients treated in the Pooled Monotherapy studies.

**Table 3. Demographics, Baseline Characteristics, Treatment Exposure Duration, and Study Follow-up Duration in Pooled Monotherapy Studies**

| Measure | Overall N = 1273 |
|---|---|
| **Age (years)** | |
| Median | 59.0 |
| Min, Max | 18, 90 |
| **Sex, n (%)** | |
| Male | 852 (66.9) |
| Female | 421 (33.1) |
| **Race, n (%)** | |
| Asian | 807 (63.4) |
| Black | 11 (0.9) |
| White | 405 (31.8) |
| Missing | 2 (0.2) |
| Other | 48 (3.8) |
| **Prior systemic anticancer therapy regimens**[a] | |
| Median | 1.0 |
| Min, Max | 0, 12 |
| **Prior systemic anticancer therapy regimens (grouped)**[a]**, n (%)** | |
| 0 | 271 (21.3) |
| 1 | 413 (32.4) |
| 2 | 265 (20.8) |
| ≥3 | 324 (25.5) |
| **Study treatment exposure duration (months)** | |
| Median | 3.58 |
| Min, Max | 0.1, 43.6 |
| **Study follow-up duration (months)** | |
| Median | 8.34 |
| Min, Max | 0.1, 47.5 |

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N, total number of patients treated; n, number of patients within each category.
Data cutoff 20 May 2019.
[a] Only systemic therapies were selected.

Overall, the 1273 patients in the pooled monotherapy analysis had a median treatment exposure duration of 3.58 months (range: 0.1 to 43.6) and median study follow-up duration of 8.34 months (range: 0.1 to 47.5). Overall, the total pooled monotherapy population had a median age of 59 years and was 66.9% male.

#### 1.3.4.1.2. Treatment-Emergent Adverse Events Assessed as Related to Treatment

Of the 1273 total patients treated in the Pooled Monotherapy studies, 846 (66.5%) experienced at least one treatment-related TEAE. The most commonly occurring TEAEs assessed as related to tislelizumab were aspartate aminotransferase increased (128 patients, 10.1%), alanine aminotransferase increased (123 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (96 patients, 7.5%), and pyrexia (94 patients, 7.4%).

Of the 1273 total patients treated in the Pooled Monotherapy studies, 162 (12.7%) experienced at least one ≥ Grade 3 TEAE assessed as related to tislelizumab. The only ≥ Grade 3 TEAEs that occurred in ≥ 1% (≥ 12 patients) in the total study population were aspartate aminotransferase increased (19 patients, 1.5%) and alanine aminotransferase increased (15 patients, 1.2%).

#### 1.3.4.1.3. Treatment-Emergent Serious Adverse Events

Of the 1273 total patients treated in the Pooled Monotherapy studies, 424 (33.3%) experienced at least one treatment-emergent SAE. The most commonly occurring treatment-emergent SAEs were pneumonia (35 patients, 2.7%), pyrexia (22 patients, 1.7%), and ascites (17 patients, 1.3%).

#### 1.3.4.1.4. Special Categories of Immune-Related Adverse Events

Immune-related adverse events (irAEs) are of special interest in tislelizumab studies because treatment with anti-PD-1 therapy can cause autoimmune disorders. As AEs of special interest, irAEs are monitored and captured consistently and rapidly.

Immune-related AEs are consistent with an immune-related mechanism or immune-related component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. Immune-related AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an irAE that spans a window of days to several months.

All irAEs presented here are assessed as related to study drug by the investigator and categorized by the BeiGene Safety/Pharmacovigilance team. Certain irAEs have multiple Medical Dictionary for Regulatory Activities (MedDRA) terms associated with the same category. Special categories have been created to group patients experiencing these events.

All irAEs that occur in ≥ 1% in the total Pooled Monotherapy studies are shown in Table 4.

**Table 4. Immune-Related Adverse Events of Any Grade Occurring in ≥ 1% in Pooled Monotherapy Studies**

| Categories<br>Preferred Term | Total (N = 1273) | |
|---|---|---|
| | **Any Grade n (%)[a]** | **Grade ≥ 3 n (%)[a]** |
| Patients with at least one potential immune-related AE[a] | 602 (47.3) | 121 (9.5) |
| **Immune-related skin adverse reaction** | 242 (19.0) | 11 (0.9) |
| Rash | 97 (7.6) | 4 (0.3) |
| Pruritus | 78 (6.1) | 0 |
| Pruritus generalised | 29 (2.3) | 0 |
| Rash maculo-papular | 24 (1.9) | 1 (0.1) |
| **Immune-related hepatitis** | 233 (18.3) | 51 (4.0) |
| Aspartate aminotransferase increased | 129 (10.1) | 21 (1.6) |
| Alanine aminotransferase increased | 124 (9.7) | 16 (1.3) |
| Blood bilirubin increased | 74 (5.8) | 4 (0.3) |
| Gamma-glutamyltransferase increased | 45 (3.5) | 17 (1.3) |
| Bilirubin conjugated increased | 40 (3.1) | 3 (0.2) |
| **Immune-related endocrinopathies** | 187 (14.7) | 7 (0.5) |
| Hypothyroidism | 113 (8.9) | 0 |
| Hyperthyroidism | 47 (3.7) | 1 (0.1) |
| Hyperglycaemia | 17 (1.3) | 4 (0.3) |
| **Immune-related colitis** | 75 (5.9) | 10 (0.8) |
| Diarrhoea | 66 (5.2) | 5 (0.4) |
| **Immune-related pneumonitis** | 50 (3.9) | 30 (2.4) |
| Pneumonitis | 22 (1.7) | 9 (0.7) |
| Lung infection | 13 (1.0) | 8 (0.6) |
| **Immune-related myositis/rhabdomyolysis/cardiomyopathy** | 39 (3.1) | 7 (0.5) |
| Blood creatine phosphokinase increased | 30 (2.4) | 4 (0.3) |
| **Immune-related nephritis and renal dysfunction** | 33 (2.6) | 6 (0.5) |
| Blood creatinine increased | 25 (2.0) | 2 (0.2) |

Source: Tislelizumab Investigator's Brochure.
Abbreviations: AE, adverse event; N, total number of patients treated; n, number of patients within each category; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PT, preferred term; SOC, system organ class.
Note: All AEs are coded using MedDRA and graded according to NCI-CTCAE v4.03. Maximum CTCAE grade was selected per patient under each PT. Potential immune-related AE is identified based on a predefined list of AEs and assessed as treatment-related by investigators.
Sorted in descending order of the number of patients in SOC and PT in Any Grade under Total column.
Data cutoff 20 May 2019.
[a] Percentages are based on the total population.

Of the 1273 total patients for the Pooled Monotherapy studies, 602 (47.3%) experienced at least one irAE of any grade. The most commonly occurring irAEs of any grade were aspartate aminotransferase increased (129 patients, 10.1%), alanine aminotransferase increased (124 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (97 patients, 7.6%), and pruritus (78 patients, 6.1%). Analysis of the total patients with at least one irAE that also was ≥ Grade 3 in severity showed that 121 patients (9.5%) experienced such events. The most commonly occurring irAEs ≥ Grade 3 in severity were aspartate aminotransferase increased (21 patients, 1.6%), gamma-glutamyltransferase increased (17 patients, 1.3%), alanine aminotransferase increased (16 patients, 1.3%), pneumonitis and pneumonia (9 patients each, 0.7%), and lung infection (8 patients, 0.6%).

#### 1.3.4.1.5. Infusion-Related Reactions

Infusion reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are uncommon. Of the 1273 total patients in the Pooled Monotherapy studies, 97 (7.6%) experienced at least one infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade that occurred in the total pooled analysis were pyrexia (50 patients, 3.9%), infusion-related reactions (28 patients, 2.2%), and pruritus (11 patients, 0.9%). There were 6 patients who reported a total of 7 ≥ Grade 3 infusion-related reactions in the Pooled Monotherapy studies (events of back pain, hypotension, infusion-related reaction, musculoskeletal chest pain, pyrexia, and rash).

#### 1.3.4.1.6. Fatal Adverse Events

Treatment-emergent fatal AEs that occurred in the Pooled Monotherapy studies are shown in Table 5.

**Table 5. Treatment-Emergent Fatal Adverse Events Regardless of Causality in Pooled Monotherapy Studies**

| Category | Overall (N = 1273) n (%) |
|---|---|
| **All deaths at data cutoff** | 641 (50.4) |
| **Death ≤ 30 days after last dose** | 105 (8.2) |
| **Primary cause of death** | |
| Adverse event | 21 (1.6) |
| Concurrent illness | 0 |
| Disease under study | 22 (1.7) |
| Indeterminate | 0 |
| Progressive disease | 52 (4.1) |
| Other | 10 (0.8) |
| **Death > 30 days after last dose** | 536 (42.1) |
| **Primary cause of death** | |
| Adverse event | 14 (1.1) |
| Concurrent illness | 0 |
| Disease under study | 95 (7.5) |
| Indeterminate | 3 (0.2) |
| Progressive disease | 399 (31.3) |
| Other | 24 (1.9) |
| Missing | 1 (0.1) |

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N, total number of patients treated; n, number of patients within each category.
Data cutoff 20 May 2019.

Table 5 shows a total of 105 patients (8.2% of the total population) died ≤ 30 days after the last study drug dose in the Pooled Monotherapy studies as of 20 May 2019. Of these 105 patients, there were 21 patients (1.6% of the total population) who had an AE with a fatal outcome ≤ 30 days after the last study drug dose. Of the 536 patients (42.1% of the total population) who died > 30 days after the last study drug dose, 14 patients (1.1% of the total population) died as a result of an AE.

### 1.3.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 2 of the ongoing monotherapy studies in solid tumors, BGB-A317_Study_001 and BGB-A317-102, which are summarized below (data cutoff 20 May 2019).

#### 1.3.4.2.1. Study BGB-A317_Study_001

BGB-A317_Study_001 is a 2-stage study. Phase 1a consists of a dose escalation and dose-finding component, and Phase 1b investigates efficacy and safety in select tumor types.

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

There were 451 patients treated in the study and 441 patients were included in the efficacy evaluable 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 postbaseline tumor assessment.

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 SD. A total of 199 patients (45.1%) had a best response of PD in this study.

#### 1.3.4.2.2. 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 postbaseline tumor assessment.

The tumor responses in the Efficacy Evaluable Analysis Set of Study BGB-A317-102 across all disease cohorts and study phases was 1 patient (0.4%) with a CR and 44 patients (17.7%) with 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.

### 1.3.5. 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 maximum tolerated dose 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).

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 partial response (PR), 4 patients (31%) had a BOR of 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.

Tislelizumab 200 mg once every 3 weeks is the recommended initial dose for combination with sitravatinib.

## 1.4. Rationale for Combination of Sitravatinib 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. This phenomenon of acquired resistance helps cancer cells adapt to the environment and survive immune attacks and is a reminder of therapeutic challenges that need to be overcome (Syn et al 2017).

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 tyrosine kinase inhibitors to treat cancer is well established based on robust clinical efficacy achieved with well tolerated inhibitors directed toward oncogenic tyrosine kinases. In addition, selected tyrosine kinase inhibitors have been shown to modulate the immunogenic status of tumors, improve tumor perfusion by reducing intratumoral pressure and modulate subsets of immune cells, thereby increasing the frequency and function of effector immune elements while decreasing the number and function of immune suppressor cells.

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 non-responders to single-agent checkpoint inhibitors escape through innate mechanisms that allow the cancer cells to grow and survive. As a result, disease progresses at a rate consistent with the natural history. 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.

Together, sitravatinib and tislelizumab may elicit greater antitumor activity, as sitravatinib is predicted to enhance several steps in the cancer immunity Cycle that may augment the efficacy of tislelizumab. First, the antitumor activity of sitravatinib may promote the release of tumor antigens. Second, inhibition of the split kinase receptors VEGFR-2 and KIT may decrease the number of Tregs and MDSCs, thus promoting the expansion and migration of antitumor cytotoxic T cells, and their infiltration into tumor tissue. Third, sitravatinib may reverse the immunosuppressive effects within the tumor microenvironment that are mediated by the TAM receptors through inhibition of MERTK, resulting in an increased number of M1- versus M2-polarized macrophages and release of IL-12, IL-6, and TNF. These downstream effects

enhance CD8+ T-cell activation, and through the inhibition of AXL, promote increased antigen presentation through termination of the Toll-like receptor dependent inflammatory response in dendritic cells.

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 receptor tyrosine kinases 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.

## 1.5. Benefit-Risk Assessment

Immunotherapy with checkpoint inhibitors has demonstrated responses in patients with NSCLC or RCC. 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 1.1.2 and Section 1.2.4.2). For patients with OC, combination therapy may improve the clinical efficacy of single-agent immunotherapies. Access to new treatment options and/or treatment options after prior immunotherapy remain a significant unmet medical need. Based on available tislelizumab and sitravatinib data and the publication from other PD-1 or PD-L1 inhibitors and other small molecule inhibitors of the VEGFR pathway, the combination of sitravatinib 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.

More than 100 patients have been treated with sitravatinib monotherapy and in combination. Nonclinical toxicology studies as well as clinical safety data from the Phase 1/1b and Phase 2 studies suggest that AEs associated with sitravatinib are similar to those observed with other small molecule inhibitors of the VEGFR pathway. For further discussion on the safety profile of sitravatinib, please refer to the sitravatinib IB.

More than 1000 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. 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.

A Safety Monitoring Committee (SMC) will be established and will monitor the preliminary safety and activity data for sitravatinib in combination with tislelizumab. The SMC will be tasked with reviewing all available safety, tolerability, PK, and exploratory data and make recommendations on safety management.

# 2. STUDY OBJECTIVES AND ENDPOINTS

## 2.1. Study Objectives

### 2.1.1. Primary Objective

- To characterize safety and tolerability of sitravatinib in combination with tislelizumab

### 2.1.2. Secondary Objectives

- To assess the preliminary antitumor activity of sitravatinib in combination with tislelizumab
- To characterize the PK profiles of sitravatinib after single dose and at steady state when given in combination with tislelizumab

### 2.1.3. Exploratory Objectives

- To assess PK and immunogenicity of tislelizumab when given in combination with sitravatinib
- To explore potential pharmacodynamic biomarkers for sitravatinib in combination with tislelizumab
- To explore potential biomarkers of efficacy, resistance, or progressive disease (PD) in tumor tissue and in peripheral whole blood
- To assess overall survival (OS)
- To explore effect of pharmacogenetic (PGx) polymorphisms on PK of sitravatinib
- To assess the preliminary antitumor activity of sitravatinib in combination with tislelizumab for ovarian cancer patients based on the Gynecologic Cancer Intergroup (GCIG) working group criteria

## 2.2. Study Endpoints

### 2.2.1. Primary Endpoints

- Safety and tolerability will be assessed throughout the study by monitoring AEs and SAEs per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0, relevant physical examination, electrocardiograms, and laboratory assessments as needed

### 2.2.2. Secondary Endpoints

- Efficacy evaluations: ORR, duration of response (DOR), disease control rate (DCR), and PFS based on RECIST version 1.1
- Plasma concentrations and the derived PK parameters of sitravatinib:
  - Single dose: $C_{max}$, time to maximum plasma concentration ($T_{max}$), $AUC_{(0\text{-}t)}$, clearance after oral administration (CL/F)

- Repeat dose: $C_{max}$, $C_{\tau}$, $T_{max}$, $AUC_{(0-\tau)}$, CL/F, accumulation ratio (Ro)

### 2.2.3. Exploratory Endpoints

- Serum concentrations of tislelizumab and anti-tislelizumab antibodies
- Changes of potential pharmacodynamic biomarkers in response to sitravatinib in combination with tislelizumab, such as, but not limited to, soluble vascular endothelial growth factor receptor-2 (sVEGFR-2) and immune cell subpopulations in peripheral blood
- Potential biomarkers, including but not limited to PD-L1 expression, immune cell profiling, tumor mutation load and gene expression profiling; and the association with disease status and or the response to sitravatinib in combination with tislelizumab
- OS
- Effect of genetic polymorphisms of hepatic metabolizing enzymes and transporters, including but not limited to CYP1A2, 2D6, 2C8 on the PK of sitravatinib
- Efficacy evaluations for ovarian cancer patients: PFS per CA-125 (GCIG working group criteria, Appendix 12)

# 3. STUDY DESIGN

## 3.1. Summary of Study Design

This is an open-label, multicenter, non-randomized Phase 1b clinical trial for patients with histologically or cytologically confirmed locally advanced or metastatic tumors including non-squamous or squamous non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), epithelial ovarian cancer (OC), or melanoma.

All patients will receive sitravatinib 120 mg orally, once daily in combination with tislelizumab 200 mg intravenously once every 3 weeks until occurrence of PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.

There will be a total of 9 cohorts in the study. Approximately 60 patients will be enrolled into Cohort E, including at least 20 patients who failed the prior bevacizumab treatment and at least 20 patients will be Caucasian. The additional 40 patients of Cohort E will not be enrolled in China after the amendment is effective. In addition, approximately 20 patients will be enrolled into each of the rest of the cohorts. The patients will be enrolled according to their tumor type and prior anti-PD-1/PD-L1 antibody treatment.

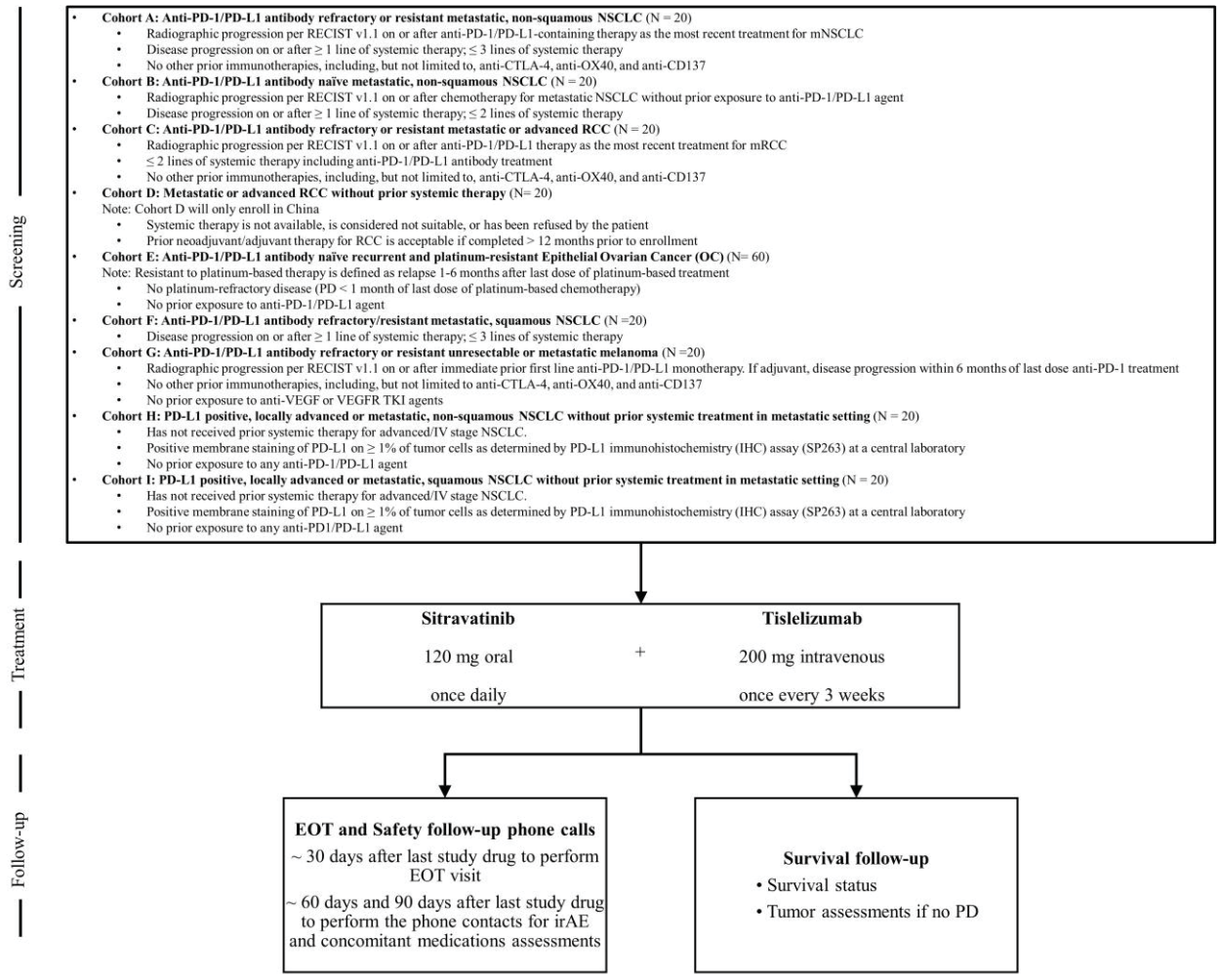
- Cohort A: Anti-PD-1/PD-L1 antibody refractory/resistant metastatic, non-squamous NSCLC
- Cohort B: Anti-PD-1/PD-L1 antibody naïve metastatic, non-squamous NSCLC
- Cohort C: Anti-PD-1/PD-L1 antibody refractory/resistant metastatic or advanced RCC
- Cohort D (China-only): Metastatic or advanced RCC without prior systemic therapy
- Cohort E: Anti-PD-1/PD-L1 antibody naïve recurrent and platinum-resistant epithelial OC
- Cohort F: Anti-PD-1/PD-L1 antibody refractory/resistant metastatic, squamous NSCLC
- Cohort G: Anti-PD-1/PD-L1 antibody refractory/resistant unresectable or metastatic melanoma
- Cohort H: PD-L1 positive, locally advanced or metastatic, non-squamous NSCLC without prior systemic treatment in metastatic setting
- Cohort I: PD-L1 positive, locally advanced or metastatic, squamous NSCLC without prior systemic treatment in metastatic setting

Cohort F will only enroll prior anti-PD-1/PD-L1 antibody refractory/resistant squamous NSCLC until the total number of prior anti-PD-1/PD-L1 antibody treated squamous NSCLC reaches 20 patients. The prior anti-PD-1/PD-L1 naïve patients who enrolled before the amendment is effective can continue their treatment per the protocol. It is to further investigate the safety and efficacy for patients with anti-PD-1/PD-L1 antibody treated squamous NSCLC. The anti-PD-1/PD-L1 antibody naïve patient will be no longer enrolled in this cohort after this amendment is effective.

The SMC will review the safety, tolerability, and pharmacology data from the initial 6 patients regardless of assigned cohort that complete the first cycle of treatment (21 days per cycle) in Australia. Recruitment will be on hold in Australia until these data have been reviewed by the SMC. For participating China sites only, the initial 6 patients enrolled in China regardless of assigned cohort will have their safety, tolerability, and pharmacology data reviewed by the SMC after the first cycle of treatment. Recruitment in China only will be on hold until the data have been reviewed.

The SMC may assess the combination regimen as safe, but may also decide to evaluate a dosing regimen that was not predefined or not previously studied, if evaluation of toxicity at such a dose is desired.

**Figure 1. Study Schema**




Abbreviations: IHC, immunohistochemistry; mNSCLC, metastatic non-small cell lung cancer; mRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; RCC. renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SMC, Safety Monitoring Committee; VEGF, Vascular endothelial growth factor; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitors.

**Note:** The SMC will review the safety, tolerability, and pharmacology data from the initial 6 patients and, additionally, 6 patients from China sites regardless of assigned cohort that complete the first cycle of treatment. Refer to Section 3.1 for additional details.

## 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. Repeating screening assessments within the original screening window is allowed if the patient did not previously meet certain eligibility criteria (eg, when a patient narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or PD) after consultation with the medical monitor; the investigator is to assess patient eligibility according to the latest screening assessment results. 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 will be treated with sitravatinib in combination with tislelizumab. All patients will receive study drug until occurrence of PD, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor.

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

On days with PK assessments, study drug should be administered in the clinic in accordance with the schedule for the PK samples. Assessments should be obtained before study drug 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 by the investigator or subinvestigator and doses should be adjusted, if necessary, before study drug administration.

### 3.3.1. Unscheduled Visit

Unscheduled visits may be performed at any time at the patient's or investigator's request for reasons such as assessment or follow-up of AEs. Study activities of an unscheduled visit should be performed based on the reason for the unscheduled visit and are outlined in Appendix 1. The date and reason for the unscheduled visit must be recorded in the unscheduled visit electronic case report form (eCRF).

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

Patients who discontinue treatment for any reason will be asked to return to the clinic for the End-of-Treatment (EOT) Visit within 30 days after the last dose of study drug, or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, clinical chemistry) were completed ≤ 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 drug(s) 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.

In addition, telephone contacts with patients should be conducted to assess immune-related AEs and concomitant medications (if appropriate, ie, associated with an immune-related AE or is a new anticancer therapy) at 60 days (± 14 days) and 90 days (± 14 days) after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune-related AE 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 PD will have their tumors assessed as outlined in Section 7.4.

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

## 3.5. Survival Follow-up

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 PD, 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 eCRF. Patients may discontinue study treatment for reasons that 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 the patient were to continue the study treatment
- Use of any concurrent antineoplastic therapy (ie, 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
- PD

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

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

- Patient withdrawal of consent
- Death
- Lost to follow-up
- Patients have completed all study assessments
- Sponsor termination of study

## 3.7. End of Study

The end of study is defined as the time point when the final data for a clinical study were collected after the last study patient has made the final visit to the study location.

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:

- 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 completed and all obligations have been fulfilled)

# 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 of 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 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place)
3. At least 1 measurable lesion as defined by RECIST v1.1

   **Note:** Selected target lesion(s) must meet one of these criteria: 1) not previously treated with local therapy or 2) within the field of prior local therapy but with subsequent progression as per RECIST v1.1.
4. Biomarker tests and tumor sample collections meet the following criteria for respective cohorts:

<table>
<tr><th colspan="3"></th><th>PD-L1</th><th>EGFR</th><th>ALK/ROS1</th><th>BRAF</th></tr>
<tr><td rowspan="4">NSCLC</td><td rowspan="2">nsq</td><td>Cohort A/B</td><td>N/A</td><td rowspan="2">Documented wild-type</td><td rowspan="4">No documented rearrangement</td><td rowspan="4">No documented mutation</td></tr>
<tr><td>Cohort H</td><td>Central testing required</td></tr>
<tr><td rowspan="2">sq</td><td>Cohort F</td><td>N/A</td><td rowspan="2">No documented mutation</td></tr>
<tr><td>Cohort I</td><td>Central testing required</td></tr>
<tr><td colspan="2">RCC</td><td>Cohort C/D</td><td>N/A</td><td colspan="3">N/A</td></tr>
<tr><td colspan="2">Melanoma</td><td>Cohort G</td><td>N/A</td><td>N/A</td><td>N/A</td><td>Documented status</td></tr>
</table>

Abbreviations: NSCLC, non-small cell lung carcinoma; nsq, non-squamous; RCC, renal cell carcinoma; sq, squamous
Documented tests results: identified by local or central tissue-based testing.
For Cohorts A and B patients with unknown EGFR mutation status, Cohort G patients with unknown BRAF mutation status as well as Cohorts H and I patients, archival/fresh biopsy tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks with tumor tissues or unstained FFPE slides) will be required during screening period. If no archival tumor tissue(s) can be provided, a fresh biopsy is mandatory.
Notes: Written informed consent is required prior to obtaining fresh tumor biopsies. Biopsy tumor tissue needs to originate from core or punch biopsy. Tumor tissue from fine-needle aspiration is not acceptable.

5. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 1 (Appendix 4)

6. Adequate hematologic and end-organ function, as defined by the following laboratory values (obtained ≤ 7 days before first dose):
   a. Patients must not have required a blood or platelet transfusion or growth factor support ≤ 14 days before sample collection
      i. Absolute neutrophil count ≥ 1.5 x 109/L
      ii. Platelets ≥ 75 x 109/L
      iii. Hemoglobin ≥ 90 g/L
   b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN), or estimated glomerular filtration rate ≥ 60 mL/min/1.73 $m^2$ by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 8)
   c. AST and ALT ≤ 3.0 x ULN, or AST and ALT ≤ 5.0 x ULN for patients with documented liver metastases
   d. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)
   e. International normalized ratio (INR) ≤ 1.5 or prothrombin time ≤ 1.5 x ULN
   f. Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
7. Patients with inactive/asymptomatic carrier, chronic, or active hepatitis B virus (HBV) must have 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 enrollment.
8. 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
9. Non-sterile males 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
10. Criteria removed.

**Cohort-Specific Inclusion Criteria**

**Cohort A:** Anti-PD-1/PD-L1 antibody refractory or resistant metastatic, non-squamous NSCLC

11. Histologically or cytologically confirmed, Stage IV NSCLC
12. Disease progression on or after ≥ 1 line of systemic therapy; and ≤ 3 lines of systemic therapy

    **Note**: Patients who have progressed or have disease recurrence during or after neo-adjuvant or adjuvant therapy with platinum-containing regimen (counted as one line of therapy) within 6 months after last dose are eligible provided the target lesion(s) have not been previously treated with local therapy (radiation) or the target lesion(s) within the field of local therapy have subsequently progressed as defined per RECIST v1.1

13. Radiographic progression per RECIST v1.1 on or after anti-PD-1/PD-L1-containing therapy as the most recent treatment for metastatic NSCLC with best response defined as follows:
    a. Resistant (ie, RECIST v1.1-defined partial, complete response, or stable disease for at least 12 weeks after initiation of treatment followed by radiographic progression of disease)
    b. Refractory (ie, radiographic progression of disease < 12 weeks after initiation of treatment)
14. Wild-type EGFR status is required and patients with documented ALK rearrangement, ROS1 rearrangement, or BRAF mutations are not eligible for the study.
15. No other prior immunotherapies, including, but not limited to, anti-CTLA-4, anti-OX40 and anti-CD137

**Cohort B:** Anti-PD-1/PD-L1 antibody naïve metastatic, non-squamous NSCLC

16. Histologically or cytologically confirmed, Stage IV NSCLC
17. Disease progression on or after ≥ 1 line of systemic therapy; and ≤ 2 lines of systemic therapy
18. Wild-type EGFR status is required and patients with documented ALK rearrangement, ROS1 rearrangement, or BRAF mutations are not eligible for the study.

    **Note**: Patients who have progressed or have disease recurrence during or after neo-adjuvant or adjuvant therapy with platinum-containing regimen (counted as one line of therapy) within 6 months after last dose are eligible provided the target lesion(s) have not been previously treated with local therapy (radiation) or the target lesion(s) within the field of local therapy have subsequently progressed as defined per RECIST v1.1
19. Radiographic progression per RECIST v1.1 on or after systemic treatment for metastatic NSCLC without prior exposure to anti-PD-1/PD-L1 agent

**Cohort C, Cohort D:** Metastatic or advanced Renal Cell Carcinoma (RCC)

20. Histologically or cytologically confirmed metastatic or advanced clear cell RCC, or RCC with a primary clear cell component

**Cohort C:** Anti-PD-1/PD-L1 antibody refractory or resistant metastatic or advanced RCC

21. Radiographic progression per RECIST v1.1 on or after anti-PD-1/PD-L1 therapy as the most recent treatment for mRCC with best response defined as follows:
    a. Resistant (ie, RECIST-defined partial, complete response, or stable disease for at least 12 weeks followed by radiographic progression of disease)
    b. Refractory (ie, radiographic progression of disease < 12 weeks after initiation of treatment)
22. ≤ 2 lines of systemic therapy including anti-PD-1/PD-L1 antibody treatment
23. No other prior immunotherapies, including, but not limited to, anti-CTLA-4, anti-OX40 and anti-CD137

**Cohort D:** Metastatic or advanced RCC without prior systemic therapy

**Note:** Cohort D will only enroll in China.

24. Systemic therapy is not available, is considered not suitable, or has been refused by the patient
25. Prior neoadjuvant/adjuvant therapy for RCC is acceptable if completed > 12 months prior to enrollment.

**Cohort E:** Anti-PD-1/PD-L1 antibody naïve recurrent and platinum-resistant Epithelial Ovarian Cancer (OC)

**Note:** Resistant to platinum-based therapy is defined as relapse about 1 to 6 months after last dose of platinum-based treatment.

26. Histologically confirmed advanced ovarian cancer
27. No platinum-refractory disease (PD < 1 month of last dose of platinum-based chemotherapy)
28. No prior exposure to anti-PD-1/PD-L1 agent

**Cohort F:** Anti-PD-1/PD-L1 antibody refractory/resistant metastatic, squamous NSCLC

**Note:** Radiographic progression per RECIST v1.1 on or after anti-PD-1/PD-L1-containing therapy as the most recent treatment for metastatic NSCLC with best response defined as follows:

a. Resistant (ie, RECIST v1.1-defined partial, complete response, or stable disease for at least 12 weeks after initiation of treatment followed by radiographic progression of disease).
b. Refractory (ie, radiographic progression of disease < 12 weeks after initiation of treatment).

29. Histologically or cytologically confirmed, Stage IV NSCLC
30. Disease progression on or after ≥ 1 line of systemic therapy; and ≤ 3 lines of systemic therapy

**Note**: Patients who have progressed or have disease recurrence during or after neo-adjuvant or adjuvant therapy with platinum-containing regimen (counted as one line of therapy) within 6 months after last dose are eligible provided the target lesion(s) have not been previously treated with local therapy (radiation) or the target lesion(s) within the field of local therapy have subsequently progressed as defined per RECIST v1.1

31. Patients with documented EGFR mutation, BRAF mutation, ALK rearrangement, or ROS1 rearrangement are not eligible for the study.

**Cohort G**: Anti-PD-1/PD-L1 antibody refractory or resistant unresectable or metastatic melanoma

**Note:** Patients with ocular melanoma are not allowed.

32. Radiographic disease progression per RECIST v1.1 on or after the immediate prior first line anti-PD-1/PD-L1 monotherapy. If adjuvant, disease progression within 6 months of last dose of anti-PD-1 therapy
    a. Resistant (ie, RECIST v1.1 defined partial, complete response or stable disease for at least 12 weeks after initiation of treatment followed by radiographic progression of disease. If treated with anti-PD-1/PD-L1 adjuvant therapy, patient relapses while on treatment or within 6 months after last dose of anti-PD-1/PD-L1 therapy is also considered resistant
    b. Refractory (ie, radiographic progression of disease < 12 weeks after initiation of treatment
33. No other prior immunotherapies, including, but not limited to, anti-CTLA-4, anti-OX40 and anti-CD137
34. No prior exposure to anti-VEGF or VEGFR TKI agents
35. Patients with BRAF wild-type, or BRAF mutation but are not suitable for or refuse BRAF inhibitor and/or MEK inhibitor targeted therapy.

    **Note:** Patients with a BRAF mutation and received prior BRAF inhibitor and/or MEK inhibitor targeted therapy in metastatic setting will be excluded.
36. Documentation of BRAF status is required.

**Cohorts H, Cohort I: Locally advanced or metastatic (Stage IIIB-IV) NSCLC**

37. Histologically or cytologically confirmed, locally advanced (Stage IIIB-IIIC) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) non-squamous or squamous NSCLC
38. Has not received prior systemic therapy in metastatic setting

    **Note**: Patients who have received prior neoadjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for nonmetastatic disease must have experienced a disease-free interval of ≥ 6 months from the last dose of chemotherapy and/or chemoradiotherapy prior to the first dose of study drugs.
39. Positive membrane staining of PD-L1 on ≥ 1% of tumor cells as determined by PD-L1 immunohistochemistry assay (SP263) at a central laboratory during screening
40. No prior exposure to any anti-PD-1/PD-L1 agent or other immunotherapies, including, but not limited to, anti-CTLA-4, anti-OX40 and anti-CD137

**Cohort H:** PD-L1 positive, locally advanced or metastatic, non-squamous NSCLC without prior systemic treatment in metastatic setting

41. Wild-type EGFR status required and patients with documented ALK rearrangement, ROS1 rearrangement, or BRAF mutations are not eligible for the study.

**Cohort I:** PD-L1 positive, locally advanced or metastatic, squamous NSCLC without prior systemic treatment in metastatic setting

42. Patients with documented EGFR mutation, BRAF mutation, ALK rearrangement, or ROS1 rearrangement are not eligible for the study

## 4.2. Exclusion Criteria

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

1. Unacceptable toxicity on prior anti-PD-1/PD-L1 treatment, defined as follows:
   a. ≥ Grade 3 AE related to anti-PD-1/PD-L1 treatment that did not respond to standard therapy and warranted treatment discontinuation.
   b. ≥ Grade 2 irAE associated with anti-PD-1/PD-L1 unless the AE resolved or was well controlled by withholding the anti-PD-1/PD-L1 and/or treatment with steroids, with the exception of prior colitis, encephalitis, myocarditis, hepatitis, uveitis and pneumonitis, which are exclusionary.
   c. Central nervous system or ocular AE of any grade related to anti-PD-1/PD-L1

   **Note:** Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

2. Active leptomeningeal disease or uncontrolled, untreated brain metastasis

   - Patients with a history of treated and, at the time of screening, asymptomatic CNS metastases are eligible, provided they meet all the following:

   a. Brain imaging at screening shows no evidence of interim progression
   b. All brain metastases with supratentorial location
   c. No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
   d. No stereotactic radiation or whole-brain radiation within 14 days prior to first dose of study drug(s)

   - Patients with new asymptomatic central nervous system metastases detected at the screening scan must receive radiation therapy and/or surgery for central nervous system metastases.

   e. Following treatment, these patients may then be eligible, provided all other criteria, including those for patients with a history of brain metastases, are met.

3. Active autoimmune diseases or history of autoimmune diseases that may relapse (Appendix 5)

   **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

4. Any active malignancy ≤ 2 years before first dose of study drugs except for the 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)
5. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before 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 non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
6. 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 first dose of study drugs
7. History of interstitial lung disease, noninfectious pneumonitis or uncontrolled diseases, including pulmonary fibrosis, acute lung diseases, etc.
8. 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
9. Known history of HIV infection
10. Active hepatitis C infection (defined by a detectable HCV RNA).
11. Any major surgical procedure requiring general anesthesia ≤ 28 days before first dose of study drugs
12. Prior allogeneic stem cell transplantation or organ transplantation
13. Any of the following cardiovascular risk criteria:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before first dose of study drugs
    b. Symptomatic pulmonary embolism ≤ 28 days before first dose of study drugs
    c. Any history of acute myocardial infarction ≤ 6 months before first dose of study drugs
    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 7) ≤ 6 months before first dose of study drugs
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before first dose of study drugs
    f. Any history of cerebrovascular accident ≤ 6 months before first dose of study drugs

g. QTc interval (corrected by Fridericia's method) > 450 msec
**Note:** If QTc interval is > 450 msec on initial electrocardiogram (ECG), a follow up ECG will be performed to confirm result
h. Cardiac left ventricular ejection fraction ≤ 40% or lower limit of normal as assessed by echocardiography. The same modality used at baseline must be applied for subsequent evaluations.
i. Any episode of syncope or seizure ≤ 28 days before first dose of study drugs

14. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
15. Hypersensitivity to tislelizumab or sitravatinib, to any ingredient in the formulation, or to any component of the container
16. Bleeding or thrombotic disorders or use of anticoagulants such as warfarin or similar agents requiring therapeutic INR monitoring within 6 months before first dose of study drugs
17. Any systemic chemotherapy within 28 days of the first dose of study drugs or immunotherapy (eg, interleukin, interferon, thymoxin, 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
18. Any herbal medicine used to control cancer within 14 days of first dose of study drugs
19. Toxicities (as a result of prior anticancer therapy) that have not improved to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
20. Administration of live vaccine ≤ 4 weeks prior to 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.
21. Underlying medical conditions 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 expected insufficient compliance during the study according to investigator's judgement
22. Participation in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
23. Inability to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
24. Spinal cord compression in one or more of the following criteria
    a. Not definitively treated with surgery and/or radiation
    b. Treated but without evidence that disease has been clinically stable for > 2 weeks prior to first dose of study drugs
25. Pregnant or breastfeeding woman

26. Regardless of the severity, patients with any signs or medical history of bleeding; within 4 weeks prior to allocation, patients with any bleeding events ≥ CTCAE level 3, unhealed wounds, ulcers or fractures
27. Patients with artery/venous thrombotic occurred within 6 months before allocation, such as cerebrovascular accident (including temporary ischemic attack), deep vein thrombosis and pulmonary embolism
28. For NSCLC, patients with hemoptysis of > 50 mL/day
29. For squamous NSCLC, patients with central cavitation or tumor(s) shown to be invading or abutting major blood vessels by imaging or the investigator determines the tumor(s) is likely to invade major blood vessels and cause fatal bleeding

# 5. STUDY TREATMENT

## 5.1. Formulation, Packaging, and Handling

### 5.1.1. Sitravatinib

Sitravatinib will be provided as 10-mg and 40-mg unit dose strength capsules.

Sitravatinib drug product is packaged in 30-count, high-density polyethylene (HDPE), opaque white, round 60 cc bottles. A tamper proof heat induction seal and a child resistant closure are used. The provided bottles may be labeled for specific patient use and given to the patient if the capsule count is the needed number.

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

The bottles of study drug must be stored in a labeled carton at refrigerated conditions (2-8°C) in the study site Pharmacy. Once dispensed to patients, the bottles will be removed from the carton and should be stored at room temperature as specified on the bottle label.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal. Please also refer to the sitravatinib IB for other details regarding sitravatinib.

### 5.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, USP type I), containing a total of 100 mg 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 tislelizumab IB for other details regarding tislelizumab.

## 5.2. Dosage and Administration

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

### 5.2.1. Sitravatinib

Sitravatinib capsules will be administered orally, once daily continuously for a total daily dose of 120 mg. The following guidelines should be followed for sitravatinib administration:

- Dosing in the morning is preferred.
- Capsules should be taken on an empty stomach (at least 2-hour fast before each dose and no food for a minimum of 1 hour after each dose).
- Capsules should be taken with at least 200 mL (1 cup) of water.
- Patients should swallow the capsules whole and not chew them.

- If vomiting occurs after dosing, sitravatinib doses should not be replaced.
- If a patient forgets to take sitravatinib for more than 12 hours, he/she should skip the dose and resume taking the drug the next day.

### 5.2.2. Tislelizumab

Tislelizumab (200 mg) will be administered on Day 1 of each 21-day cycle (every 3 weeks). Tislelizumab will be administered by IV infusion through an IV line containing a sterile, non-pyrogenic, 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 for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 8.8 and Appendix 9.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

## 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 sitravatinib 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 required for completion of this study (sitravatinib and tislelizumab) will be provided by the sponsor, as required by local or country-specific guidance. 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 drug management.

## 5.4. Overdose

### 5.4.1. Sitravatinib

Any overdose or incorrect administration of sitravatinib 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. 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.

## 5.5. Dose Modification and Delay

Every effort should be made to administer the study drug(s) 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 below. 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.

Based on the known toxicity profiles of sitravatinib and tislelizumab, it is known that certain AEs are likely to be associated with one drug versus the other. For example, treatment-emergent hypertension or proteinuria are likely to be associated with sitravatinib rather than tislelizumab; similarly, immune-related AEs are likely to be associated with tislelizumab rather than sitravatinib. However, some drug-related AEs such as diarrhea and elevation in the liver function tests are overlapping. Therefore, it is crucial to fully evaluate each AE to confirm etiology or exclude other causes in order to determine proper management of the adverse reaction and action regarding study treatment. The management guidelines for AEs of special interest of tislelizumab and sitravatinib-specific adverse events are provided in detail in Section 8.8 and Section 8.9, respectively.

Adverse events (both non-serious and serious) associated with tislelizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Therefore, early recognition and initiation of treatment is critical to reduce complications. Tislelizumab must be withheld for drug related toxicities and severe or life-threatening AEs. See Appendix 9 for supportive care guidelines, including use of corticosteroids.

### 5.5.1. Dose Modification

There will be no dose reductions for tislelizumab in this study. Dose reductions for sitravatinib are presented in in Table 6. 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 sitravatinib 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 sitravatinib are presented in Section 8.9.

**Table 6. Sitravatinib Dose Reductions**

| Dose Level | Dose |
|---|---|
| Starting Dose | 120 mg once daily |
| Dose Level -1 | 80 mg once daily |
| Dose Level -2 | 60 mg once daily |

**Note:** Dose reduction below 60 mg once daily may be undertaken after discussion with the sponsor.

### 5.5.2. Dose Delay

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 more severe) within 4 weeks for sitravatinib or 12 weeks for tislelizumab after last dose of the respective study drug.

The following dose delays or interruptions will be permitted:

- Sitravatinib can be interrupted for up to approximately 28 days consecutively. If treatment with sitravatinib 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.
- Tislelizumab can be delayed or interrupted for up to 12 weeks. If a dose is delayed for tislelizumab for ≤ 10 days for a planned dosing cycle (eg, Cycle 3, Day 1), tislelizumab should be administered (on the same day with sitravatinib, if applicable) and all assessments should be conducted according to the original cycle (ie, Cycle 3). If the delay is more than 10 days, the subject should skip the tislelizumab, and tislelizumab will be administered on Day 1 of the next planned cycle (ie, Cycle 4, Day 1).

The tumor assessment schedule will not be altered even if the administration of study drug(s) is delayed.

If the patient is unable to resume sitravatinib or tislelizumab within the permitted timeframe after the last dose of study drug(s), then the patient should be discontinued from the study drug(s). If a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the medical monitor.

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

# 6. PRIOR AND CONCOMITANT THERAPY

## 6.1. Concomitant Therapy

### 6.1.1. Permitted Concomitant Medications and Therapy

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, anti-emetics, antidiarrheals) and in a patient's interest are allowed.

Proton pump inhibitors and $H_2$ antagonists should be avoided during treatment 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 9) and be at nonimmunosuppressive doses (≤ 10 mg/Day of prednisone or equivalent) before the next administration of study drug(s). The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

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 drug(s). 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.

Palliative (limited-field) radiation therapy for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline is permitted. 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 and the medical monitor agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation or other focally ablative therapy for other non-target sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out PD.

### 6.1.2. Prohibited Concomitant Medications and Therapy

The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese or other country herbal medicine] for the treatment of cancer)

- Live vaccines within 28 days prior to the first dose of study drug(s) and 60 days following the last dose of study drug(s)
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin). Patients must notify the investigator of all herbal remedies used during the study.

### 6.1.3. Restricted Concomitant Medications and Therapy

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
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.1.1
- 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.

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

Sitravatinib was not considered as a high-risk compound as a victim drug-drug interaction (DDI) because multiple enzymes, including CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4 are involved in its metabolism.

Based on the in vitro CYP inhibition/induction assay results, high plasma protein binding and less than 0.1 μM potency, Sitravatinib perpetrator risk at projected clinical dose and exposure levels is considered to be low.

Per the International Council on Harmonisation (ICH) E14 guidance, it is recommended to avoid medications with potential to prolong QT/QTc or cause Torsades. Please refer to Appendix 11 for a list of medications or substances to be avoided or used with caution during treatment with sitravatinib.

**Potential Interaction With Tislelizumab**

Sitravatinib 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 (mAb) and is administered intravenously, whereas sitravatinib is a small molecule therapeutic administered orally. No absorption interactions are expected. No studies on the metabolism of tislelizumab have been reported in vitro or in humans.

Like most therapeutic proteins, tislelizumab is not expected to be metabolized by liver cytochrome P-450 (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. 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 drug(s) 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. Patients who are suspected or known to have concurrent serious respiratory illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details) based upon the treatment physician's judgement. 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) and Biomarkers (Section 7.7) sections. 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

Demographic data will include gender, date of birth (or age), and race/ethnicity.

### 7.1.2. Medical History

Clinically significant medical history findings (eg, previous diagnoses, diseases, or surgeries) that were present before signing the ICF and considered relevant for the patient's study eligibility will be collected and captured, including baseline severity if the finding is ongoing, in the eCRF. Clinically significant is defined as any events, diagnoses, or laboratory values that require

treatment or follow-up, or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

Cancer history will include an assessment of prior surgery, prior radiotherapy, 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.

### 7.1.3. Other Baseline Characteristics

Information will also be collected regarding alcohol and smoking history, prior medications/significant nondrug therapies, childbearing potential (refer to Appendix 6), and any other assessments that are performed for the purpose of eligibility for inclusion in the study (Section 4), such as physical examination, vital signs, hematology, chemistry, pregnancy test, and ECG.

### 7.1.4. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. Informed consent forms 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 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.

### 7.1.5. Pulmonary Function Tests

Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients in Cohort A, B, F, H, and I during the Screening Period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor.

For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, forced expiratory volume (FEV1) < 60% or carbon monoxide diffusing capacity (DLCO) (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility.

Tests may be repeated as clinically indicated while on study.

Patients in Cohort C, D, E, and G who are suspected or known to have serious/severe respiratory conditions, or exhibit significant respiratory symptoms unrelated to the underlying cancer, or with a history of thoracic radiotherapy 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 will confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. Eligible patients must meet all inclusion criteria and patients who meet any of the exclusion criteria are not eligible to enroll. 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 email it to the medical monitor or designee to approve the enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Authorization Packet has been received before proceeding with study procedures.

## 7.3. Safety Assessments

### 7.3.1. Vital Signs

Vital signs will include measurements of temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated or supine position after resting for 10 minutes.

### 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 v5.0 and recorded on the eCRF with appropriate disease/condition terms.

In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

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 AE eCRF. Refer to Section 8.3 Adverse Events regarding AE definitions and reporting and follow-up requirements.

### 7.3.3. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (refer to Appendix 4) will be assessed during the study.

### 7.3.4. Laboratory Safety Test

Local laboratory assessments on hematology, serum chemistry, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 3.

If laboratory tests at screening are performed within 7 days prior to the administration of study drug(s) on Cycle 1 Day 1, these tests (hematology, clinical chemistry, urinalysis, and pregnancy test) do not have to be repeated and must be reviewed before study drug(s) administration. For

the first 6 patients enrolled in both Australia and in China, hematology and serum chemistry (including liver function tests [LFTs]) as specified in Appendix 3 should be performed weekly for the first 2 cycles and at the beginning of subsequent cycles. For all other patients, hematology and serum chemistry should be performed at the beginning of all cycles. After Cycle 1, laboratory safety results should be reviewed within 48 hours before study drug administration.

Details about sample collection and shipment will be provided in a separate instruction manual. 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 drug(s). Urine or serum pregnancy tests will be performed once every 3 weeks during treatment before administration of study drug(s) at each cycle, at the EOT Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
- Thyroid function testing (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.
- Creatine kinase (CK) and creatine kinase cardiac isoenzyme (CK-MB) testing will be performed at screening, scheduled assessments during the first 2 treatment cycles, all predose assessments from Cycle 3 onward, and at the EOT Visit. Troponin I and/or T may be performed if the local lab does not provide CK and CK-MB analysis. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required.

### 7.3.5. Hepatitis B and Hepatitis 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). Viral load assessment (HBV DNA and HCV RNA) will be performed if the HBsAg and/or HCV antibody test is positive.

Patients who have detectable HBV DNA or HCV RNA at Screening will perform the respective viral load test every 4 cycles.

### 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 semi-recumbent 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. For study purposes, evaluation by MUGA scan is preferred. Evaluation by echocardiogram is an acceptable alternative if necessary. The method used for individual patients should be consistent throughout study participation.

### 7.3.8. Adverse Events

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE v5.0. 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 drug(s) 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).

Tumor assessments must include computed tomography (CT) scans (with oral/intravenous contrast, unless contraindicated) or magnetic resonance imaging (MRI), with preference for CT, of the chest, abdomen, and pelvis. 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 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) should be performed at Screening if clinically indicated.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast 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/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or positron emission tomography 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 positron emission tomography 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 (refer to Appendix 10). For ovarian cancer patients, response will be assessed using RECIST v1.1 and the GCIG working group criteria (refer to Appendix 12). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with study drug(s) until PD is confirmed by repeated imaging ≥ 4 weeks later but not exceeding 8 weeks from the date of initial documentation of PD. The following criteria must be met in order to continue study drugs in patients with suspected pseudoprogression:

- 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 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 re-consented.

Patients who discontinue study treatment early for reasons other than PD (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences PD, 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.

## 7.5. Pharmacokinetic Assessment

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

In the event of a significant toxicity, it is recommended that an unscheduled PK blood 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. Full details on sample collection, processing, storage, and shipment will be provided in the Study Laboratory Manual.

## 7.6. Antidrug Antibody Testing

The anti-tislelizumab-antibody concentrations will be determined using serum samples collected at specified time points within a reasonable variation window (refer to Appendix 1 and Appendix 2). Shipping, storage, and processing of samples will be managed through a central laboratory.

## 7.7. Biomarkers

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Please refer to the laboratory manual for details of sample handling.

If archival tissues are available, archival tumor tissues (FFPE blocks with tumor tissues or approximately 15 freshly cut unstained FFPE slides from each block) must be sent to central laboratory for biomarker analysis, including but not limited to PD-L1 expression, EGFR or BRAF mutation status (for selected cohorts), tumor infiltrating lymphocytes, gene expression profiling, and tumor mutation burden. Submission of < 15 unstained slides is not a protocol deviation.

For patients with non-squamous NSCLC (Cohorts A, B and H) and melanoma (Cohort G), documentation of wild type EGFR status (Cohorts A, B and H only) or BRAF status (Cohort G only) by tissue-based test is required to enter the study. For undocumented cases in these cohorts, an archival or fresh biopsy tumor tissue(s) (a FFPE block(s) or approximately 15 freshly cut unstained FFPE slides from each block) will be required for central assessment of EGFR or BRAF mutation prior to enrollment and retrospective analysis of other biomarkers. For treatment naive non-squamous NSCLC (Cohort H) and squamous NSCLC (Cohort I), only patients with PD-L1 membrane staining on ≥ 1% of tumor cells as determined by PD-L1 (SP263) immunohistochemistry assay at a central laboratory during screening will be eligible for the study. An archival or fresh biopsy tumor tissue(s) (a [FFPE] block(s) or approximately 15 freshly cut unstained FFPE slides) will be required for central assessment of PD-L1 expression prior to enrollment and retrospective analysis of other biomarkers. If no archival sample(s) can be provided, a fresh tumor biopsy(ies) at baseline is required. Written informed consent is required for fresh tumor biopsies. Submission of < 15 unstained slides is not a protocol deviation.

For patients in all cohorts, in addition to archival tumor tissue, a fresh biopsy(ies) from an accessible tumor site(s) at baseline and/or after 2 cycles of treatment (Cycle 3 Day 1) and/or at EOT Visit for the patients who have confirmed PD during the study is recommended to evaluate pharmacodynamic effects and to explore of potential response or resistance mechanism(s). If feasible, any post-treatment biopsy(ies) should be ideally taken from the same tumor lesion(s) as

the baseline biopsy. Written patient informed consent is required before obtaining fresh tumor biopsies.

For fresh biopsy, acceptable samples include core needle biopsies for non-superficial tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

Blood samples will be collected at specified time points as described in the Schedule of Assessments for the evaluation of pharmacodynamic and exploratory biomarkers, including but not limited to cytokines, plasma proteins, immune cell populations, and circulating tumor DNA (ctDNA).

# 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 Sitravatinib and Tislelizumab

Sitravatinib and tislelizumab are investigational agents that are currently in clinical development. Limited safety data for sitravatinib and 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 sitravatinib 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 8.8.

The guidelines for management of potential AEs more specific to treatment with sitravatinib or agents in the same class of cancer treatment are presented in Section 8.9.

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 9.

## 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 sitravatinib and tislelizumab, clinical data with sitravatinib 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 of 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.

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 antibodies (ADAs) to tislelizumab in patients. 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 drug(s) 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 end of treatment, 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 drug 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 drug 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 drug(s) 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: 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.

### 8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug 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 drug should be considered and investigated. The investigator should refer to the Investigator’s Brochures of sitravatinib and tislelizumab 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). A number of 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, 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 LFT testing should be performed according to the schedule in Appendix 9.

## 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 is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information [RSI]) 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 the last dose of study drugs or initiation of new anticancer therapy, whichever occurs first. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy.

### 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 7.

**Table 7. 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 form | As expeditiously as possible | Updated SAE form | 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 suspected unexpected serious adverse reactions (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for sitravatinib and tislelizumab studies.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) 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

PD (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 multi-organ failure due to PD, the term “multi-organ 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 sitravatinib, 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 drug 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 drug 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:

- Sitravatinib IB and tislelizumab IB

### 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 8.8.3) should be classified as irAEs and identified as such in the eCRF AE page until Day 90 after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of irAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 9.

An extensive list of potential irAEs appears in Table 9. 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 9 .

## 8.7. Management of Adverse Events Potentially Associated with Either or Both of Sitravatinib and Tislelizumab

Based on the known toxicity profiles of sitravatinib and tislelizumab, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial

thrombotic events, proteinuria, and hemorrhagic events are known risks for sitravatinib treatment, while immune-related AEs are risks for tislelizumab treatment. However, certain AEs may be initially considered attributed to either study drugs, such as diarrhea, hypothyroidism, and liver enzyme elevation. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

### 8.7.1. Timing of Adverse Event Onset

Since sitravatinib is dosed QD continuously due to a short half-life, and tislelizumab is dosed Q3W due to a long half-life, sitravatinib can be interrupted to assess whether an AE improves/resolves with de-challenge (ie, interruption of treatment) based on the following two scenarios.

1. If an AE occurs during a treatment cycle (ie, between 2 tislelizumab doses), only sitravatinib dose interruption is needed.
2. If an AE occurs at the beginning of a treatment cycle, sitravatinib can be interrupted and dosing of tislelizumab should be held.

If a patient recovers from an AE in response to sitravatinib interruption (ie, positive de-challenge), the event is more likely to be attributed to sitravatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

### 8.7.2. Severity of Adverse Event

If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting or holding both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

## 8.8. Management of AEs 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.

### 8.8.1. 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 study drug(s) is provided in Table 8.

**Table 8. 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 has 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 drug(s) 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 drug(s) 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.

### 8.8.2. 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 drugs(s) infusion. Alternative treatments for fever (ie, paracetamol) may be given to patients at the discretion of the investigator.

### 8.8.3. Immune-Related Adverse Events

While sitravatinib may have immunostimulatory effects, autoimmune AEs have not been reported in clinical trials, including to date in combination with nivolumab, nor are they recognized as class effects for this agent. However, the potential for sitravatinib 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 (biopsy) 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 non-specific, most often mild to moderate AE (eg, rash and colitis) observed with sitravatinib. The time to onset may be helpful in distinguishing an AE that may be attributed to autoimmune effects versus non-specific toxicity.

A list of potential irAEs is shown below in Table 9. 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 9. For any AEs not included in Appendix 9 please refer to ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-related toxicities.

**Table 9. 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.

In the event of an immune-related AE during study treatment, administration of sitravatinib and tislelizumab should be interrupted until the event stabilizes to ≤ Grade 1. If a toxicity does not resolve to ≤ Grade 1 within 4 weeks for sitravatinib or 12 weeks for tislelizumab, study drug(s) 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.

## 8.9. Management of Sitravatinib-Specific Adverse Events

### 8.9.1. Management of Non-Hematological Toxicities of Sitravatinib

Patients experiencing symptomatic Grade 2 non-hematological sitravatinib-related adverse events are recommended to have a dose reduction to the next lower dose level at the discretion of the investigator, per the reduction schedule (Table 10). Dose reductions are expected to improve treatment tolerability.

Non-hematological toxicities ≥ Grade 3 and considered to be related to sitravatinib treatment should be managed with sitravatinib interruption, until resolution of toxicity to ≤ Grade 1 or to baseline value. In the case of Grade 3 or 4 electrolyte abnormalities that are not clinically complicated and resolve spontaneously or with conventional medical treatment within 72 hours, or Grade 3 asymptomatic amylase or lipase elevation treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose as outlined in Table 10. Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

**Table 10. Sitravatinib Dose Modifications – Non-Hematological Drug-Related Toxicities**

| Toxicity | Treatment Delay | Dose Modification |
|---|---|---|
| Grade 1 | May be implemented based on investigator and patient discretion | |
| Grade 2 - Asymptomatic | May be implemented based on investigator and patient discretion | |
| Grade 2 - Symptomatic | May be implemented based on investigator and patient discretion | Recommend dose reduction to next lower dose level |
| Grade 3 or 4 | Hold until ≤ Grade 1 or return to baseline | Resume at dose one or more levels below that inducing the toxicity. Exceptions presented in footnotes |

Notes:
a. Management of specific adverse events (e.g., hypertension) for sitravatinib are presented in sections below.
b. Patients may resume at the same dose in the following cases:
- Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours
- Grade 3 amylase or lipase elevation that is not associated with the symptoms or the clinical manifestations of pancreatitis

### 8.9.2. Management of Hematological Toxicities of Sitravatinib

Hematological toxicities are not a frequent cause of treatment interruption or discontinuation of sitravatinib treatment. Observed ≥ Grade 3 hematological events that are considered to be causally related to sitravatinib should initially be managed using treatment interruption. In addition, dose reduction at the discretion of sitravatinib should be implemented in the following cases:

- Grade 3 or 4 febrile neutropenia
- Grade 4 neutropenia persisting for ≥ 8 days
- Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding

### 8.9.3. Dose Modification Guidelines for Sitravatinib-Specific AEs

Dose modification guidelines for increased blood pressure and increased hepatic transaminase not likely to be immune-mediated are presented in Table 11 and Table 12 below. Guidance for

management of Hy's Law cases is also provided below. Additional management guidelines for sitravatinib-specific AEs are also described below.

**Table 11. Sitravatinib Dose Modification for Increased Blood Pressure**

| Toxicity | Drug Interruption | Dose Modification |
|---|---|---|
| Grade 1 or 2 hypertension | May be implemented based on investigator and patient discretion | |
| Grade 3 hypertension without clinically significant increases in BP as defined below | Investigator discretion.<br>Consider antihypertensives per Section 8.9.4 | |
| Grade 3 hypertension with clinically significant increases in BP *defined as* either an increase of ≥ 30 mm Hg in systolic BP to ≥ 180 mm Hg *or* increase of ≥ 20 mm Hg in diastolic BP to ≥ 110 mm Hg, confirmed with repeated testing after at least 5 minutes | Hold until ≤ Grade 2 or return to baseline | Investigator discretion |
| Grade 4 hypertension | Discontinue sitravatinib | Discontinue sitravatinib |

Abbreviation: BP, blood pressure.

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. Recommended treatment modifications for sitravatinib are provided in Table 12.

**Table 12. Sitravatinib Dose Modification for Increased Hepatic Transaminase**

| Toxicity | Drug Interruption | Dose Modification |
|---|---|---|
| Grade 1 (>ULN to 3.0 x ULN) | May be implemented based on investigator and patient discretion | |
| Grade 2 (>3.0 to 5.0 x ULN) | Not required | Decrease by 1 dose level |
| Grade 3 or 4 (>5.0 x ULN) | Hold until ≤ Grade 1 or return to baseline | If resolution occurs within 22 days, decrease by 1 dose level.<br>If no resolution within 22 days, discontinue sitravatinib. |

Abbreviation: ULN, upper limit of normal.

#### 8.9.3.1. Management of Hy's Law Cases

In the event a patient develops concurrent increase in AST and/or ALT ≥ 3 x ULN, bilirubin ≥ 2 x ULN but without concurrent increases in alkaline phosphatase (ie, alkaline phosphatase < 2 x ULN), that is not attributable to liver metastases or biliary obstruction, sitravatinib and tislelizumab should be permanently discontinued and steroids administered.

### 8.9.4. Hypertension

Hypertension, including Grade 3 events, has been reported with sitravatinib. Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine may be considered if antihypertensive therapy is required and should be considered for patients with Grade 3 hypertension without clinically significant increases in blood pressure (BP) (see Table 11). In

cases of Grade 3 hypertension with clinically significant increases in blood pressure, temporary suspension of sitravatinib dosing is recommended until blood pressure is controlled. Treatment with sitravatinib may resume at the same or a lower dose at the discretion of the investigator. If significant hypertension recurs, options include change in medical management of the patient, reduction of sitravatinib dose, or discontinuation of study treatment, at the discretion of the investigator. In the event of Grade 4 hypertension, sitravatinib should be permanently discontinued (see Table 11).

### 8.9.5. Palmar-Plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia syndrome has been reported as a DLT in the Phase 1 study of sitravatinib. Measures that can be taken to manage 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.

### 8.9.6. Diarrhea

Diarrhea has been reported with sitravatinib treatment, though the mechanism remains unclear, as with other small molecule RTK inhibitors. 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. Any patients developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhea is controlled. investigators should also evaluate whether diarrhea may be attributable to the irAE of colitis.

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 sitravatinib treatment associated diarrhea. The diarrhea observed with sitravatinib generally improves within several days of interrupting study medication, with close observation may help establish the most likely causality.

### 8.9.7. Hemorrhagic Events

The risk of hemorrhagic events with sitravatinib is unknown; however, such events have been reported with inhibitors of VEGFR. Patients with active hemoptysis or gastrointestinal bleeding should not take sitravatinib, and suspension of treatment is recommended for patients developing clinically significant bleeding.

### 8.9.8. Thrombotic Events

Though thrombotic events (eg, pulmonary embolism) have been reported with sitravatinib and with inhibitors of VEGFR, the risk of such events with sitravatinib is unknown. Precautions should be taken in patients with recent, clinically significant thrombotic events, and treatment should be discontinued in patients who develop clinically significant thromboembolic complications such as acute myocardial infarction or severe pulmonary embolism.

### 8.9.9. Thyroid Dysfunction Other Than Immune-Mediated

Hypothyroidism and increases in TSH have been reported in patients taking sitravatinib. Patients diagnosed with hypothyroidism should be treated with thyroid replacement and may continue treatment with sitravatinib at the investigator's discretion.

### 8.9.10. Decreased Left Ventricular Ejection Fraction

Decreased left ventricular ejection fraction has been reported with sitravatinib. In addition, decreases of left ventricular ejection fraction to < 50% on-study were observed in patients undergoing scheduled multigated acquisition (MUGA) scans or echocardiograms. The dose of sitravatinib should be interrupted and/or reduced in patients with an ejection fraction < 50% and > 20% below baseline. Discontinuation should be considered for patients requiring acute hospitalization for treatment of congestive heart failure (CHF).

### 8.9.11. Proteinuria

Although the risk with sitravatinib is unknown, proteinuria has been described with other inhibitors of the VEGFR pathway. Patients who develop ≥ 2+ proteinuria should undergo 24-hour urine collection for assessment of urine protein; treatment with sitravatinib should be discontinued in the presence of ≥ 2 grams of proteinuria/24 hours and may restart when protein levels decrease to less than 2 grams/24 hours. Patients who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

# 9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

## 9.1. Statistical Analysis

### 9.1.1. Analysis Sets

The Safety analysis set includes all patients who received at least 1 dose of any study drug (any component of the combination therapy).

The Efficacy Evaluable analysis set includes all dosed patients who had measurable disease at baseline per RECIST v1.1 and who had at least 1 evaluable postbaseline tumor assessment unless treatment was discontinued due to disease progression or death before tumor assessment.

The PK analysis set includes all patients who contributed at least 1 quantifiable PK sample.

The ADA Analysis Set includes all patients who received at least 1 dose of tislelizumab and for whom both baseline ADA and at least 1 postbaseline ADA results are available.

### 9.1.2. Patient Disposition

The number of patients treated, discontinued from study drug and/or study and those with major protocol deviations will be counted. The primary reason for study drug 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 cutoff 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. 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

The efficacy endpoints (ie, ORR, DOR, PFS, and DCR) assessed by investigators using RECIST v1.1 will be summarized to evaluate the antitumor activities of sitravatinib in combination with tislelizumab.

Efficacy analyses will be provided based on both the Efficacy Evaluable analysis set and the Safety analysis set. The Efficacy Evaluable analysis set will be the primary analysis set for response analyses; and the Safety analysis set will be the primary analysis set for time-to-event analyses.

Details of statistical analyses will be described in detail in the Statistical Analysis Plan.

Objective Response Rate (ORR)

The number and proportion of patients who achieve confirmed or unconfirmed objective tumor response (CR or PR) according to RECIST v1.1 will be summarized. Patients without postbaseline tumor assessment will be considered as non-responders for the summary based on the Safety analysis set. The ORR will be estimated along with Clopper-Pearson 2-sided 95% confidence interval.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients with BOR of CR, PR, and SD in accordance with RECIST v1.1 criteria. Patients without postbaseline tumor assessment will be considered as non-responders for the summary based on the Safety analysis set. DCR will be reported with the 95% confidence interval.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first dose of study drugs to the date of the first documentation of PD as assessed by the investigator using RECIST v1.1 or death, whichever occurs first. Kaplan-Meier methodology will be used to estimate median PFS and 95% confidence interval. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

Duration of Response (DOR)

Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier). Duration of response analysis will only include responders. Censoring rule for DOR will follow PFS censoring rule.

Kaplan-Meier curve will be used to estimate median time and 95% confidence interval for duration of response. The censoring rule for PFS and DOR will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2007).

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion. The maximum tumor shrinkage based on target lesion used in the plots will be listed. The postbaseline nadir will be summarized using descriptive statistics. These analyses will be performed based on RECIST v1.1.

OS is defined as the time from the date of first dose of study drugs to the date of death due to any cause. Patients who remained alive before data cutoff or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the time of data cutoff or the last date the patient was known to be alive. Kaplan-Meier curve will be used to estimate OS at different time points.

PFS assessed per CA-125 criteria will be summarized descriptively.

## 9.3. Safety Analyses

Safety will be determined by the spontaneous reporting of adverse events 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 adverse events will be graded according to the NCI-CTCAE v5.0. The incidence of 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. Safety analyses will be conducted in the Safety analysis set.

### 9.3.1. 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 will be summarized for each study drug. Frequency of the above dose adjustments and discontinuation will be summarized by category.

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

### 9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA (Version 18.1 or higher) lower-level term, preferred term, and primary SOC.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug and up to 30 days following study drug 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 v5.0 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.

### 9.3.3. 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.

### 9.3.4. 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

For the PK analysis set that contributed serial plasma samples for sitravatinib on Cycle 1 Day 1 and Day 21, plasma concentration-time data of each patient will be tabulated and graphically presented on linear and semi-logarithmic scales. Plots of sitravatinib concentration-time data will be presented for Cycle 1 Day 1 (after single dose) and Day 21 (at steady state). Pharmacokinetic parameters will be determined using standard non-compartmental method. A listing of patients excluded from the analysis set and individual data points excluded from the analysis will be provided. The final analysis of PK parameters will be calculated based on actual sample collection time, rather than scheduled times. The parameters will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) % associated to the geometric mean).

PK parameters will include, but are not limited to, the following as allowed by data:

| | |
|---|---|
| $C_{max}$ (μg/mL) | Observed maximum plasma concentration during a sample interval. |
| $C_{\tau}$ (μg/mL) | Observed trough concentration at steady state |
| $T_{max}$ (hr) | Observed time to maximum plasma concentration during a sampling interval. |
| λz ($hr^{-1}$) | Elimination rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. A minimum of three data points will be used for determination ($C_{max}$ excluded). |
| $t_{½}$ (h) | Terminal elimination half-life, determined from the quotient 0.693/λz. |
| $AUC_{(0-t)}$ (μg.h/mL) | Area under the plasma concentration-time curve from time zero to the last measurable time point calculated by log-linear trapezoidal summation. |
| $AUC_{(0-\tau)}$ (μg.h/mL) | Area under the plasma concentration-time curve from time zero to 24 hour postdose at steady state; calculated by log-linear trapezoidal summation. |
| CL/F (L/hr) | Apparent clearance after oral administration |
| Ro | Observed accumulation ratio determined by $AUC_{(0-\tau),ss}$ /$AUC_{(0-24),\ Day\ 1}$ |

The sitravatinib and 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 clinical study report (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

Summary statistics will be provided for PD biomarkers, including, but not limited to, plasma protein, cytokine, and immune cell subtypes in blood. An exploratory analysis on a potential correlation of these pharmacodynamic markers with PK parameters, safety, and antitumor activity will be performed as appropriate.

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, such as efficacy and treatment resistance.

For potential PGx analysis of genes that may affect the PK of sitravatinib, a blood sample for DNA isolation will be collected from patients predose on Cycle 1 Day 1. If needed, these samples will be analyzed together with PGx samples from other studies to assess the impact of genetic polymorphisms on the PK of sitravatinib, and these results may be reported separately.

## 9.7. Sample Size Consideration

Approximately 220 to 240 patients (approximately 60 patients for Cohort E, and 20 patients for each of the rest of the cohorts) are expected to be enrolled to analyze safety and preliminary efficacy for sitravatinib plus tislelizumab. Of the approximately 60 patients enrolled into Cohort E, at least 20 patients who failed the prior bevacizumab treatment and at least 20 patients will be Caucasian. Enrollment into these cohorts will occur simultaneously, independently of each other. Each cohort will be evaluated separately.

# 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, 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. On the basis of 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
- 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 Good Clinical Practice 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 the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

## 12.2. Quality Assurance

To ensure compliance with Good Clinical Practice 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 lot or batch number, date dispensed, patient identifier number, patient initials, if allowed 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 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 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 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 sitravatinib dose taken each day. Any missed doses with explanations 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 Good Clinical Practice 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 re-consented 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 United States FDA, the China National Medical Products Administration, 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 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 or designee must provide an e-signature in the electronic data capture 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 v18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA v18.1 or higher.

## 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 and query forms, 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 of 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 re-generating 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 and provided to the regulatory agency(ies). 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. As this is a multicenter study, 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. 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
- Resolution 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 | | | | | End-of-Treatment (EOT) Visit[5] | Safety Follow-up Phone Calls[6] | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1-2 | | | Cycle 3 and Subsequent Cycles | Unscheduled Visit[4] | | | |
| Days (window) | -28 to -1 | 1[2] | 8 (± 1)[3] | 15 (± 2)[3] | 1 (± 3) | | Within 30 days after last dose of study drug | 60 (± 14 days) and 90 (± 14) days after last dose of tislelizumab | Every 3 months |
| Informed consent[1] | X | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | |
| Demographics/Medical history/Prior medications | X | | | | | | | | |
| Height | X | | | | | | | | |
| Vital signs/weight[7] | X | X | X | X | X | X | X | | |
| Complete physical examination | X | | | | | | X | | |
| Limited physical examination | | X | | | X | | | | |
| ECOG performance status | X | X | | | X | X | X | | |
| 12-lead ECG[8] | X | X | | | X | X | X | | |
| Adverse events[9] | X | X | X | X | X | X | X | X | |
| Concomitant medications[10] | X | X | X | X | X | X | X | X | |
| Hematology[11] | X | X[1] | X | X | X | X | X | | |
| Clinical chemistry[11] | X | X[1] | X | X | X | X | X | | |
| Coagulation parameters[11] | X | As clinically indicated | | | | | X | | |
| Urinalysis[11] | X | X[1] | As clinically indicated | | | | X | | |

| Assessment | Screening[1] | Treatment Period | | | | | End-of-Treatment (EOT) Visit[5] | Safety Follow-up Phone Calls[6] | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1-2 | | | Cycle 3 and Subsequent Cycles | Unscheduled Visit[4] | | | |
| **Days (window)** | **-28 to -1** | **1[2]** | **8 (± 1)[3]** | **15 (± 2)[3]** | **1 (± 3)** | | **Within 30 days after last dose of study drug** | **60 (± 14 days) and 90 (± 14) days after last dose of tislelizumab** | **Every 3 months** |
| Pregnancy test[12] | X | X[1] | | | X | X | X | | |
| Thyroid function[13] | X | Cycles 4, 7, 10, and every 3 cycles thereafter | | | | | X | | |
| CA-125 test (ovarian cancer patients only)[14] | -14 to -1 | Every 6 weeks (± 7 days) in the first 12 months; every 9 weeks (± 7 days) thereafter | | | | | | | |
| HBV/HCV tests[15] | X | As clinically indicated | | | | | | | |
| Pulmonary function tests[16] | X | As clinically indicated | | | | | | | |
| Tumor assessment[17] | X | Every 6 weeks (± 7 days) in the first 12 months; every 9 weeks (± 7 days) thereafter | | | | | | | |
| Archival tumor tissue[18] | X | | | | | | | | |
| Fresh tumor tissue[19] | X | | | | Cycle 3 only | | X | | |
| Sitravatinib administration | | Daily | | | | | | | |
| Tislelizumab administration | | X | | | X | | | | |
| Patient diary | | X | X | X | X | | X | | |
| Survival status[20] | | | | | | | | | X |
| MUGA /Echocardiogram[21] | X | Every 12 weeks (± 7 days) | | | | | | | |
| PK sampling for sitravatinib[22] | See Appendix 2 | | | | | | | | |
| PK sampling for tislelizumab[22] | | | | | | | | | |
| ADA sampling for tislelizumab[22] | | | | | | | | | |
| Blood sampling for biomarker analysis[22] | | | | | | | | | |
| ctDNA[22] | | | | | | | | | |
| PGx[22] | | | | | | | | | |

Abbreviations: ADA, antidrug antibody; AE, adverse event; CA-125, cancer antigen 125; CR, completed response; ctDNA, circulating tumor DNA; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EGFR, epidermal growth factor receptor; EOT, end-of-treatment; FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAb , hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; irAE, immune-related adverse event; MUGA, multigated acquisition; NSCLC, non-small cell lung cancer; PD, disease progression; PGx, pharmacogenetic; PK, pharmacokinetic; PR, partial response; X, to be performed

**Note:** On days when sitravatinib and tislelizumab dosing are both scheduled, the daily dose of sitravatinib 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 prior to obtaining informed consent and within 28 days prior to first dose of study drugs may be used for screening assessments rather than repeating such tests. If laboratory tests at screening are performed within 7 days prior to first dose of study drugs, these tests (hematology, clinical chemistry, urinalysis, and pregnancy test) do not have to be repeated and must be reviewed before first dose of study drugs.
2. All assessments on Cycle 2 Day 1 may be performed within a time window of ± 3 days.
3. In Cycle 1 and Cycle 2, the first 6 patients in both Australia and in China regardless of assigned cohort will return for assessments on Day 8 and Day 15. Sitravatinib will be given in the clinic.
4. Unscheduled visits may occur any time as necessary as per investigator decision or patient's request for reasons such as assessment or follow-up of AEs. Study activities, as indicated by 'X,' should be performed based on the reason for the unscheduled visit. If PD is suspected, imaging studies should be performed. The date and reason for an unscheduled visit should be recorded in the eCRF.
5. Patients who discontinue treatment for any reason will be asked to return to the clinic for the EOT Visit within 30 days after the last dose of study drug, or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, clinical chemistry) were completed ≤ 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 drug(s) 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.
6. Telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, eg, associated with an AE or is a new anticancer therapy) at 60 days (±14 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 patients report a suspected irAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
7. Vital signs collected on study include temperature, pulse, and blood pressure (systolic and diastolic) while the patient is in a seated or supine position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before; during; and within 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 within 30 minutes after the infusion. Vital signs should also be recorded prior to administration of sitravatinib; recorded values may be used for pre-tislelizumab assessment if vital signs are collected within 60 minutes before tislelizumab infusion.
8. Patients should rest in semi-recumbent supine position for at least 10 minutes prior to each ECG collection. ECG collection may be done at other time points as clinically indicated.
9. Adverse events will be graded and recorded throughout the study according to NCI-CTCAE v5.0.
10. All concomitant medications received within 30 days before the first dose of study treatment should be recorded.
11. Hematology and clinical chemistry will be performed weekly in Cycle 1 and Cycle 2 for the first 6 patients enrolled in both Australia and in China and then at the beginning of subsequent cycles. For all other patients, assessments will be performed on Day 1 of each cycle. After Cycle 1, laboratory tests can be performed up to 2 days prior to Day 1 of subsequent cycles and results are to be reviewed within 48 hours before study drug administration. Coagulation tests as specified in Appendix 3 are required at Screening and subsequently as clinically indicated. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities. Urinalysis will be performed on Cycle 1 Day 1 and subsequently as clinically indicated.

12. 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 Day 1. Urine or serum pregnancy tests will be performed during treatment and the EOT Visit. A negative pregnancy test must be completed and recorded before administration of study drug(s) at each cycle. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
13. Thyroid function tests will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the EOT Visit.
14. CA-125 test will be performed within 14 days prior to Cycle 1 Day 1 and while on study approximately every 6 weeks ± 7 days in the first 12 months and approximately every 9 weeks ± 7 days thereafter. The CA-125 responses must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a screening sample that is at least twice the upper limit of reference range.
15. Testing will be performed by the local laboratory at Screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody). Viral load assessment (HBV DNA and HCV RNA) will be performed if the HBsAg and/or HCV antibody test is positive.
16. Cohort C, D, E, and G: Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer or with a history of thoracic radiotherapy will have 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.
    Cohort A, B, F, H, and I: Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum, pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the Screening Period to assist the determination of suitability on the study. Respective test results need to be submitted to the sponsor. For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry < 90% on room air and further desaturation upon exercise, FEV1 < 60% or Dlco (if performed) < 60% of age and sex adjusted predicted performance levels (Pellegrino et al 2005), the medical monitor needs to be consulted to confirm eligibility. Tests may be repeated as clinically indicated while on study.
17. Tumor imaging will be performed within 28 days prior to Cycle 1 Day 1 and while on study approximately every 6 weeks ± 7 days in the first 12 months and approximately every 9 weeks ± 7 days thereafter. All measurable and evaluable lesions should be assessed and documented; MRI scan of brain should be performed if clinically indicated. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. The same imaging technique should be used throughout the study for each patient. After the first documentation of response (CR or PR), confirmation of tumor response should occur ≥ 4 weeks after the first response or at the next scheduled assessment time point. Progressive disease suspected as pseudo-progression needs to be confirmed by repeated imaging ≥ 4 weeks later but not exceeding 8 weeks from the date of initial documentation of PD. Patients who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments (see Section 7.4 for details).
18. Archival tumor tissues (a FFPE blocks or approximately 15 freshly cut unstained FFPE slides from each block) must be collected, if archival tissues are available. Submission of < 15 unstained slides is not a protocol deviation. For Cohorts A (Anti-PD-1/PD-L1 antibody refractory or resistant metastatic, non-squamous NSCLC), B (Anti-PD-1/PD-L1 antibody naïve metastatic, non-squamous NSCLC), and G (PD-1/PD-L1 treatment refractory or resistant melanoma), an archival or fresh biopsy tumor tissue(s) (a FFPE block(s) or approximately 15 freshly cut unstained FFPE slides from each block) will be required for central assessment of EGFR mutation status (Cohorts A, and B only) and BRAF mutation status (Cohort G only) during the screening period in undocumented cases. For Cohorts H (treatment naive non-squamous NSCLC) and I (treatment naïve squamous NSCLC), an archival or fresh biopsy tumor tissue(s) (a [FFPE] block(s) or approximately 15 freshly cut unstained FFPE slides from each block) will be required for central assessment of PD-L1 expression and EGFR mutation status (Cohort H patients with undocumented EGFR status only) during screening.
19. In addition to archival tumor tissue(s), a fresh biopsy(ies) from an accessible tumor site(s) at baseline (within 28 days before Cycle 1 Day 1) and/or after 2 cycles of treatment (approximately Cycle 3 Day 1) and/or at End of Study Visit for patients who have confirmed PD during the study is recommended to evaluate pharmacodynamic biomarkers and/or to explore response or resistance mechanism(s). If feasible, post treatment biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. For Cohorts A and B patients with unknown EGFR mutation status, Cohort

G patients with unknown BRAF mutation status as well as Cohorts H and I patients, if no archival tumor tissue(s) can be provided, a fresh biopsy(ies) is mandatory during screening. Written informed consent is required prior to obtaining fresh tumor biopsies.

20. Information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months 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.
21. Evaluations of cardiac function will be performed at screening and every 12 weeks (±7 days). Evaluation by MUGA scan is preferred. Evaluation by echocardiogram is an acceptable alternative if necessary. The method used for individual patients should be consistent throughout study participation.
22. See Appendix 2 for schedule of PK sampling for sitravatinib, PK sampling for tislelizumab, ADA sampling for tislelizumab, and blood sampling for pharmacogenetic and biomarker analysis.

# APPENDIX 2. SCHEDULE OF PK, ADA, PGX, AND BIOMARKER ASSESSMENTS

| | **Collection Time** (Allowable Window) | **PK** sitravatinib[b] | | **PK** Tislelizumab[c] | **ADA** Tislelizumab[d] | **Pharmaco-dynamic Biomarker**[e] | **ctDNA**[e] | **PGx** |
|---|---|---|---|---|---|---|---|---|
| | | The first 5 patients/cohort | Other patients | | | | | |
| **Screening** (D -28 to D -1) | | | | | | | | |
| **Cycle 1 D1 & D21** | **Predose** (-30 min) | Pre-sitra–dose | Pre-sitra–dose | *Day 1 only* Pre-tisle–dose (-30 min) | *Day 1 only* Pre-tisle–dose (-30 min) | *Day 1 only* Pre-sitra-dose (-30 min) | *Day 1 only* Pre-sitra-dose (-30 min) | *Day 1 only* Pre-sitra–dose |
| | **0.5 hr** (+10 min) | X | | *Day 1 only* Post-tisle–dose (+30 min) | | | Confirmed PR or CR (± 14 days) | |
| | **1 hr** (± 10 min) | X | | | | | | |
| | **2 hr** (± 15 min) | X | | | | | | |
| | **4 hr** (± 20 min) | X | | | | | | |
| | **6 hr** (± 20 min) | X | X | | | | | |
| | **8 hr** (± 30 min) | X | | | | | | |
| | **10 hr** (± 1 hr) | X | | | | | | |
| | **12 hr** [a] (± 2 hr) | X | | | | | | |
| **Cycle 1 D2 & D22** | **24 hr** [a] (± 2 hr) Pre-C2D1 dose | X | | | | | | |
| **Cycle 2 D1** | **Predose** (-30 min) | X | X | Pre-tisle–dose (-30 min) | X | Pre-sitra-dose (-30 min) | | |
| | **6 hr** (± 1 hr) | X | X | | | | | |
| **Cycle 3 D1** | **Predose** (-30 min) | | | | | Pre-sitra-dose (-30 min) | | |
| **Cycle 5 D1** | **Predose** (-30 min) | X | X | Pre-tisle–dose (-30 min) | X | | | |
| | **6 hr** (± 1 hr) | X | X | Post-tisle–dose (+30 min) | | | | |
| **Cycle 9, 17 D1** | **Predose** (-30 min) | | | Pre-tisle–dose (-30 min) | X | | | |
| **End-of-Treatment Visit** | Within 30 days after last dose of study drug(s) | | | X | X | | X | |

Abbreviations: ADA, anti-drug antibody; ctDNA, circulating tumor DNA; CR, completed response; D, Day; EC, ethics committee; ECG, electrocardiogram; EOT, end-of-treatment; h, hour; IRB, institutional review board; min,

minutes; PGx, pharmacogenetics; PK, pharmacokinetic; PR, partial response; SAE, serious adverse event; sitra, sitravatinib; SMC, Safety Monitoring Committee; tisle, tislelizumab

**Note:** Scheduled vital signs and ECGs precede PK sample collection in all cases. Sitravatinib dosing and sampling should precede tislelizumab infusion.

a. Postdose samples for sitravatinib at 12 h and 24 h are optional and depend on site feasibility.
b. PK for sitravatinib: the first five (5) patients per cohort and the twelve (12) patients (6 patients from Australian sites and 6 patients from China sites, regardless of cohort) for SMC safety review will contribute serial PK samples on Cycle 1 Days 1 and 21 and sparse PK samples on Cycle 2 Day 1 and Cycle 5 Day 1. All other patients will contribute sparse PK samples on Cycle 1 Days 1 and 21, Cycle 2 Day 1, and Cycle 5 Day 1. An additional PK blood sample should be drawn before a daily sitravatinib dose (trough sample) in any of the following events: 1) as soon as possible after an SAE, 2) at a clinic visit at least one week following a dose modification of sitravatinib, or 3) as soon as possible after renal function declines by one stage as defined in Appendix 8 if the patient continues study treatment. These tests are required when it is allowed by local regulations/IRBs/ECs.
c. PK sampling for tislelizumab: samples should be collected predose of tislelizumab (-30 min) on Day 1 of Cycles 1, 2, 5, 9 and 17; postdose (within 30 min after the end of tislelizumab infusion) on Day 1 of Cycle 1 and Cycle 5; and at the EOT Visit. Should a patient present with any ≥ Grade 3 irAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.
d. ADA sampling for tislelizumab should be collected Day 1 (Predose of tislelizumab, -30 min) of Cycles 1, 2, 5, 9 and 17, and at the EOT Visit. All samples should be drawn at the same time as the PK blood collection for predose of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.
e. Biomarker sampling: approximately 20 mL and 10 mL of peripheral blood samples will be collected on Cycle 1 Day 1 (predose sitravatinib and tislelizumab, -30 min before dosing) and Day 1 (predose sitravatinib and tislelizumab, -30 min before dosing) of Cycle 2, and 3, respectively. For the patients who have confirmed CR, PR or PD (at EOT Visit) as assessed by the investigator, an additional blood samples (approximately 10 mL) will be collected one time.

# 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 bilirubin | Lymphocyte count | | 24-hour protein[b] |
| Direct bilirubin | Neutrophil count | | |
| Blood urea nitrogen or urea | | | |
| Potassium | | | |
| Sodium | | | |
| Corrected calcium[c] | | | |
| Creatinine | | | |
| Glucose | | | |
| Lactate dehydrogenase | | | |
| Total protein | | | |
| Creatine Kinase (CK)[d] | | | |
| CK-MB[d] | | | |

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

a. Coagulation tests are required at baseline and subsequently as clinically indicated
b. On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein
c. if not feasible at the local laboratory, total calcium may be performed instead of corrected calcium.
d. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead. If tislelizumab has been permanently discontinued, CK and CK-MB testing is no longer required.

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, at End of Study Visit, 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 testing (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 (see Section 7.3.4 for details).

# APPENDIX 4. ECOG PERFORMANCE STATUS

| Grade | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light 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. 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) nephropathy | 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 6. 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 7. 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).<br>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 8. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate 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.

$GFR = 141 \times \min (S_{cr} /\kappa, 1)^{\alpha} \times \max(S_{cr} /\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [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 Scr /$\kappa$ 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/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx)

**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/1.73m$^2$)** | **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 9. 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. |
| 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. |

**Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events**

| Immune-Related Toxicity | Diagnostic Evaluation Guideline |
|---|---|
| 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 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 Adverse Events

- 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. |
| **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. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **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. 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.<br>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 ≤ 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. |
| **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. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **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.<br>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.<br>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, < 10% BSA | Avoid skin irritants and sun exposure; topical emollients recommended. | Continue study treatment. |
| | **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. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **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. |
| | **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. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **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. |
| **Diabetes/ Hyperglycemia** | **1**<br>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. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **2**<br>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**<br>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**<br>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**<br>Asymptomatic eye exam/test abnormality | Consider alternative causes and prescribe topical treatment as required. | Continue study treatment. |
| | **2**<br>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**<br>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**<br>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**<br>Asymptomatic, blood test abnormalities | Monitor pancreatic enzymes. | Continue study treatment. |
| | **3**<br>Abdominal pain, nausea, and vomiting | Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks. | Hold study treatment; reintroduce only after discussion with the medical monitor. |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **4**<br>Acute abdominal pain, surgical emergency | Admit to hospital for emergency management and appropriate referral. | Discontinue study treatment. |
| **Arthritis** | **1**<br>Mild pain with inflammation, swelling | Management per local guideline. | Continue study treatment. |
| | **2**<br>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**<br>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**<br>Test findings only or minimal symptoms | Consider topical treatment or analgesia as per local guideline. | Continue study treatment. |
| | **2**<br>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**<br>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**<br>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**<br>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**<br>Moderate weakness with/without pain | If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks | Hold study treatment until improved to Grade 0-1 |

| Autoimmune Toxicity | Grade | Treatment Guidelines (Subject to Clinical Judgement) | Study Drug Management |
|---|---|---|---|
| | **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. | Hold study treatment until completely resolved or myocarditis has been ruled out. |
| | **2**<br>Symptoms on mild-moderate exertion | 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 | 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 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 10. 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 (uni-dimensional 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 progressive disease.

**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 |
| 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 PFS 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 11. MEDICATIONS OR SUBSTANCES TO BE AVOIDED OR USED WITH CAUTION DURING TREATMENT WITH SITRAVATINIB

The text below was obtained from 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 sitravatinib for management of a concurrent illness.

## MEDICATIONS THAT SHOULD BE AVOIDED

### Drugs with a Known Risk of 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 12. CA-125 RESPONSE CRITERIA

The text below was obtained from Rustin et al 2011.

**Definition of Response:**

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained by using the next scheduled CA-125 data (at least 28 days). Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-Day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the reference range of CA-125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.
- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human antimouse antibody4, 5) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (eg, paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (eg, surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate response, an intent-to-treat analysis should be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responder (see following table).

| CA-125 Level | CA-125 Measurement |
|---|---|
| Baseline CA-125 more than twice upper limit of normal, later reduced by 50% to normal and maintaining for at least 28 days | CR |
| Baseline CA-125 more than twice upper limit of normal, later reduced by 50% but not to normal | PR |
| CA-125 change out of range of PR and PD | Non-PR, non-PD |
| CA-125 increased at baseline returning to normal after treatment, later twice or higher upper limit of normal (2 consecutive measurements at interval of at least 1 week) | PD (date of first evaluation of progression) |
| CA-125 increased at baseline not returning to normal after treatment, later twice or higher the lowest value (2 consecutive measurements at interval of at least 1 week) | PD (date of first evaluation of progression) |
| CA-125 within reference range at baseline, later twice or higher upper limit of normal (2 consecutive measurements at interval of at least 1 week) | PD (date of first evaluation of progression) |

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response.