Clinical Study Protocol

Protocol Title:	**A Phase 1A/1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors**
Protocol Number:	**BGB-A317_Study_001**
Date of Protocol:	**21 May 2018, Version 6.0 (Final)**
Study Phase:	**1**
Sponsor:	**BeiGene Aus Pty Ltd** **c/o Becis Pty Ltd, 1C/528 Compton Road, Stretton Queensland 4116, Australia**
Sponsor Medical Monitors:	[redacted]
Coordinating Investigator:	[redacted]

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Signatures

PROTOCOL TITLE: A Phase 1A/1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors

PROTOCOL NO: BGB-A317_Study_001

_____ _____

[redacted]

Date

Sponsor Medical Monitor

PROTOCOL AMENDMENT, VERSION 6.0 RATIONALE

The primary purpose of this amendment was to address the following requests from the FDA:

- To include additional hepatitis viral load testing in patients who had detectable hepatitis B (HBV) or hepatitis C (HCV) viral load at Screening,
- To add myocarditis and myositis/rhabodmyolysis as potential immune-related adverse events and provide guidelines for their treatment and study drug management,
- To add serum creatine kinase (CK) and creatine kinase cardiac muscle isoenzyme (CK-MB) monitoring due to 2 cases of myositis reported with tislelizumab, and
- To add additional ophthalmologic evaluation time points.

Additional changes made in the amendment are noted below. Minor editorial changes were also made throughout the protocol.

Applicable Sections	Description of Revision
Change: Changed BGB-A317 to the compound's INN name, tislelizumab, throughout the document (did not change the study number or protocol name). **Reason: INN name for BGB-A317 is available**	
Change: Included additional hepatitis viral load testing every 4 cycles throughout the study for patients who had detectable hepatitis B (HBV) or hepatitis C (HCV) viral load at Screening, and how to manage subjects with HCC who test positive for HBV or HCV. **Reason: Based on a request from the FDA, in order to reduce the risk of significant hepatic toxicity in patients with active or prior HBV infection, and for consistency across protocols.**	
Section 5.1: Table 5 + footnote 17, Table 7 + footnote 16, Table 8 + footnote 16, Table 9 + footnote 16, Table 11 + footnote 17 Section 8.2.2 Section 11.3.10	• In Section 8.2.2, revised heading to "Physical Examination, Ophthalmologic Examination ~~and~~**,** Vital Signs**, and Hepatitis B and C testing** • In Section 8.2.2, and in Section 5.1 footnotes for Tables 5, 7, 8, 9, 11 pertaining to hepatitis B and C assessment, added the following text: Subjects enrolled in the study who had detectable HBV DNA or HCV RNA at Screening should be tested for HBV or HCV viral load, respectively, every 4 cycles (± 7 days) throughout the study, eg Screening, Cycle 5, Cycle 9, and so on (and whenever clinically indicated). For subjects who already received 4 or more doses of study drug, the viral load test should be repeated at the subject's next visit and every 4 cycles according to the schedule from first dose (Cycle 1 Day 1), and whenever clinically indicated. HCC subjects who test positive for HCV will not be discontinued. HCC subjects who test positive for HBV should be treated as per local guidelines at the investigator's discretion.
Appendix 3	• In Section 5.1, study assessment tables for each phase/part of the study (Tables 5, 7, 8, 9, and 11), separated HIV assessment from hepatitis B and C assessment for clarity. For hepatitis B and C assessment, in addition to the "x" at Screening, added "x (Cycle 5 and every 4 cycles)" to each table.

Applicable Sections	Description of Revision
	• Added Section 11.3.10 Hepatitis B and C, to add the assessment as a safety analysis.
	• In Appendix 3, for each separate study phase, added collection of 3-5 mL blood for hepatitis B and C analysis on Cycle 5 Day 1 (and every 4 cycles thereafter).
Change: Clarified the timing of ophthalmologic examinations after Cycle 3 (for Q2W patients)/End of Week 9 (for Q3W patients) as shown below, including subjects who may not have previously had an assessment after Cycle 3/Week 9, respectively. Additionally, all references to "eyesight" as part of an ophthalmologic exam were changed to "eyesight/visual acuity". **Reason: Changes to ophthalmologic examination were made to ensure all subjects have an assessment every 15-16 weeks throughout the study. Reference to visual acuity was specifically requested by the FDA to ensure there is no confusion.**	
Section 5.1: Table 5 footnote 24, Table 7 footnote 23, Table 8 footnote 23, Table 9 footnote 23, Table 11 footnote 26 Section 8.2.2	• In Section 8.2.2 (first sentence of paragraph 3), and in footnotes for Tables 5, 7, 8, 9, 11 (Phases 1a and 1b) pertaining to ophthalmological examinations (first sentence), revised the text as follows: Ophthalmological examinations (such as eyesight/**visual acuity**, fundoscopy, slit lamp microscopy, and optical coherence tomography [or equivalent diagnostic test])… • In Section 8.2.2, revised last sentence of paragraph 3 as follows: **Subjects dosed on a Q2W schedule will then undergo ophthalmologic examinations by an appropriate specialist on Cycle 1 Day 15 (± 7 days) (Phase 1 A Part 1 only), Cycle 3 Day 1 (± 7 days), and thereafter every 4 cycles/16 weeks (± 7 days) during study treatment. Subjects dosed on a Q3W schedule will undergo an ophthalmologic examination by an appropriate specialist at the end of Week 9 (± 7 days), and thereafter every 5 cycles/15 weeks (± 7 days) during study treatment.** ~~Patients~~ **Subjects in all groups** will undergo ~~repeat assessments by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and~~ a final assessment <30 days after the last dose of study treatment. **For those subjects who have already received 2 or 3 more doses of study drug, respectively, the examination should be repeated at the subject's next visit and then approximately either every 4 cycles/16 weeks (± 7 days) for subjects dosed on a Q2W schedule or every 5 cycles/15 weeks (± 7 days) for subjects dosed on a Q3W schedule, according to the schedule from first dose (Cycle 1 Day 1).** • In Tables 5, 7, 8, 9, 11, footnotes pertaining to schedule of ophthalmological examinations (second sentence), revised sentences in accordance with the edits made to Section 8.2.2, above.
Change: Revised the window for the Safety Follow-up visit from 30 ± 7 days to 30 ± 3 days. **Reason: To increase clarity and consistency throughout the protocol.**	
Section 5.1 Tables 5, 7, 8, 9, 11 (including footnote 2 in each table)	• In each table, in the header column "Safety Follow-up", the "Days" box was changed as follows: "30 ± ~~7~~**3** Days after last dose". • Table 2 footnote in each table was similarly revised to state: "2. The mandatory Safety Follow-Up visit should be conducted 30 days (± ~~7~~**3** days)

Applicable Sections	Description of Revision
	after the last dose of study therapy or before the initiation of a new treatment, whichever comes first."
Section 10.5	• Changed the first sentence as follows: Subjects will be assessed for AEs and SAEs beginning immediately after signing the informed consent form and continuing through to follow up which is 30 ±~~7~~ **3** days of last dose of investigational drug.
Change: For subjects who have confirmed complete response, partial response, or stable disease after 2 years and want to take a break in treatment without discontinuing, the frequency of assessments and procedures was changed from once every cycle to once every 12 weeks. **Reason: To reduce the number of subject visits while on break, aligning the timing of assessments and procedures with the schedule for radiographic imaging.**	
Section 5.2.5.1	• Modified last bullet point as follows: If subjects have confirmed CR, PR, or SD after 2 years of tislelizumab, the treatment can be stopped if the subject agrees. . . ~~The study assessment and procedures schedule will remain the same.~~ **In such a case, the study assessments and procedures will be performed every 12 weeks (in conjunction with repeat radiographic imaging, as described in Section 8.5) rather than every cycle.** If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting tislelizumab therapy after discussion with the Sponsor, contingent on the continued availability of tislelizumab drug product.
Change: Clarified that during Survival Follow-up phase, in addition to survival data, immune-related AEs (irAEs) will be collected through 90 days post-treatment. Further clarified that the irAEs will be assessed by phone contact at 90 days rather than via office visit unless a suspected irAE is reported. **Reason: The AE follow-up period for irAEs is 90 days. Thus, information on irAEs needs to be collected during early Survival Follow-up, but does not require an office visit. These edits correct the discrepancies.**	
Section 5.1: Tables 5, 7, 8, 9, 11 (footnote 7 in each table), Section 8.4, Section 10.5	• Clarified the following sentence as follows: **Telephone contacts with patients should be conducted to assess** irAEs 90 days after the last dose of **tislelizumab**, regardless of whether or not the subject 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.**
Section 8.4	• Corrected the last paragraph as follows: Following completion of the treatment and safety follow-up periods, all subjects will be followed for survival status. Subjects will have their survival status assessed approximately every 3 months ± 2 weeks by either a telephone or in-person contact until subject death or termination by the Sponsor. ~~No~~ **With the exception of the collection of irAE data through 90 days post-treatment (as described above), no** other data (eg subsequent therapies, performance status etc.) beyond survival will be collected during these calls/visits.

Applicable Sections	Description of Revision
Change: Clarified that assessment of intensity and causality for each AE must be made at the time event is reported. **Reason: For clarification; and to reduce the number of AEs that are reported by the investigator without causality, as such events would automatically be considered Related.**	
Section 10.7.1	• Corrected the first sentence as follows: The Investigator will make an assessment of intensity for each AE and SAE reported during the study, **at the time the event is reported.**
Section 10.7.2	• Corrected the first sentence as follows: The Investigator is obligated to assess the relationship between the investigational product and the occurrence of each AE or SAE**, at the time the event is reported**.
Change: In Section 10.13.3, revised length of follow-up period post-birth for any child delivered to a female subject or female partner of a male subject who becomes pregnant while on study. In Appendix 12, contraception guidance was revised as shown. Additional edits were made to both sections for clarity. A cross-reference to Appendix 12 was added in Inclusion Criterion #10. **Reason: For patient safety, for clarification, and to bring guidance in line with other tislelizumab protocols.**	
Synopsis Key Inclusion Criteria, Section 5.2.1	• In Inclusion Criterion #10b, added a cross-reference to Appendix 12 for contraception guidelines and definition of "women of childbearing potential"/"not childbearing potential."
Section 10.13.3	• The last 2 sentences in paragraph 2 was edited as follows: • Generally, follow up will be no longer than ~~15 days~~ **8 weeks** following the ~~estimated~~ delivery date. Any premature termination **(spontaneous or elective abortion prior to 20 weeks or stillbirth after 20 weeks gestational age)** of the pregnancy will be reported.
Appendix 12	• Under "Contraception Guidelines", edited the following bullet points: ◦ Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (~~oral, intravaginal,~~ transdermal**, implants or subcutaneous or intramuscular injections**). ◦ **Combined oral contraceptives (birth control pills) may be used, but only if a concurrent barrier method is employed.** ◦ Vasectomized male partner **(with azoospermia demonstrated by a post-procedure medical examination of the semen)** • Under "Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential", edited the last bullet point and added text below: ◦ < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone (FSH) 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.**

Applicable Sections	Description of Revision
Change: Added myocarditis and myositis/rhabodmyolysis as potential immune-related adverse events and provided guidelines for their treatment and study drug management. Additionally, add CK and CK-MB evaluations to the list of serum chemistry laboratory evaluations in Appendix 2 and Schedule of Assessment tables. **Reason: Based on the request from the FDA, and due to 2 cases of myositis/myocarditis reported in the tislelizumab program.**	
Section 5.1.2	• In the list titled "Tislelizumab will be withheld for any of the following treatment related adverse events", added: **14. Grade 2-4 Myositis/Rhabdomyolysis** **15. Grade 1 Myocarditis** • In the list titled "Tislelizumab will be permanently discontinued for any of the following after consultation with the Sponsor", added: • **Grade 2-4 Myocarditis**
Appendix 10	• Edited table titled "Recommended Diagnostic Tests in the Management of Possible Immune-Related Adverse Events" to add joint and muscle inflammation and myocarditis, and their management. Removed rheumatology (covered in joint and muscle inflammation line). • In the section titled "Treatment of Immune Related Adverse Events", edited the table to include myositis/rhabdomyolysis Grade 1-4 and myocarditis Grade 1-4 as autoimmune toxicities, their respective treatment guidelines, and study drug management.
Section 5.1: Tables 5, 7, 8, 9, and 11 (footnote 8 in each table); Appendix 2	• Added CK and CK-MB to list of serum chemistry laboratory assessments in Appendix 2, and to footnote 8 in each Schedule of Assessment table in Section 5.1. Specified that in the event CK-MB fractionation is not available, troponin I and/or troponin T should be assessed instead.
Change: In Appendix 10, for the guideline for managing Grade 3 liver function adverse events associated with hepatitis, clarified prednisolone should be tapered for 4 weeks. Additional minor editorial changes were made. **Reason: To make consistent with other tislelizumab protocols, and for clarity.**	
Appendix 10	• In the section titled "Treatment of Immune-Related Adverse Events", in the subsection for Grade 3 hepatitis, edited Column 3 as follows: "ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least ~~2~~ 4 weeks." • Minor editorial changes were made.

SYNOPSIS

Name of Sponsor/Company:	BeiGene Aus Pty Ltd
Name of Finished Product:	Tislelizumab (BGB-A317)
Name of Active Ingredient:	tislelizumab
Title of Study:	A Phase 1A/1B, Open-Label, Multiple-Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors
Protocol No:	BGB-A317_Study_001
Investigators:	Approximately 30 Investigators
Study centers:	Approximately 30 study centers in Australia, New Zealand, the United States, Korea, and Taiwan
Study duration: Screening (up to 28 days), Treatment (up to 2 years of active therapy), and Safety Follow-up (30 days).	**Phase:** 1A/1B

Objectives:

Phase 1A

Primary:

- To assess the safety and tolerability of tislelizumab in subjects with advanced tumors

Secondary:

- To characterize the pharmacokinetics (PK) of tislelizumab
- To determine maximum tolerated dose (MTD), if any, and recommended Phase 2 dose (RP2D) for tislelizumab
- To assess the preliminary anti-tumor activity of tislelizumab
- To assess host immunogenicity to tislelizumab

Exploratory:

[redacted]

Phase 1B

Primary:

- To assess the anti-tumor activity of tislelizumab in select tumor types

Secondary:

- To further assess the safety and tolerability of tislelizumab in subjects with advanced tumors.
- To further characterize the PK of tislelizumab

Exploratory:

[redacted]

Methodology:
This is a two-stage study consisting of a Phase 1A dose escalation and dose-finding component to establish the MTD, if any, and RP2D(s), followed by a Phase 1B component to investigate efficacy in select tumor types and to further evaluate safety and tolerability of tislelizumab at RP2D(s).. Archival tumor tissue will be collected for purpose of biomarker analysis, although a fresh tumor biopsy at baseline is strongly recommended. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion is required at baseline; for these subjects, an optional biopsy for biomarker analysis after two cycles of treatment is strongly recommended. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

Mandatory biopsy at baseline and on treatment are required for some tumor types in the Phase 1B study.

Subjects will be monitored for safety, anti-tislelizumab antibodies and efficacy throughout the study. Radiological assessment of tumor response status should be performed approximately every 8 weeks or 9 weeks depending on dosing schedules in the first year, then every 12 weeks thereafter.

- *Phase 1A, Part 1*

The Phase 1A, Part 1 component is a multicenter, open-label, multiple-dose, dose escalation, first-in-human study. **Four dose levels are planned: 0.5, 2.0, 5.0 and 10 mg/kg, Q2W (once every two weeks)**. The study will follow a modified 3+3 dose escalation scheme. **At least three (3) subjects will be enrolled into each cohort. Additional subject(s), up to a maximum of six (6) subjects in total, will be enrolled if more than three (3) have been screened and are eligible for the cohort.** The dose-limiting toxicity (DLT) assessment will be conducted in the first cycle consisting of 28 days. Dose escalation will continue until identification of MTD or 10 mg/kg in the event that a MTD is not identified due to paucity of DLTs. Two (2) or more DLT in a cohort of three (3) to six (6) subjects is considered to have exceeded MTD.

Continuous safety evaluation will be performed by the Sponsor, the Coordinating Investigator, and Investigators. A Safety Monitoring Committee (SMC) will be established for the determination of dose levels to be administered and dose regimen during dose escalation based on the data available from the previous dose levels.

The SMC may decide to evaluate an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired. If this approach is taken, up to 6 new subjects should be enrolled at the new intermediate dose.

- *Phase 1A, Part 2*

The Phase 1A, Part 2 component will evaluate the safety and PK of two dosing schedules Q2W versus Q3W (once every three weeks) at selected doses that have cleared the DLT period without exceeding MTD (eg, 2 mg/kg or 5 mg/kg, up to 10 mg/kg). Ten to 20 subjects per dose schedule will be enrolled to evaluate the safety, the PK and preliminary efficacy. Tumor types to be enrolled include but are not limited to colorectal cancer (CRC), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), bladder cancer, melanoma and ovarian cancer. Other cancers that are deemed to be likely to benefit from programmed cell death-1 (PD-1) inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrollment subject to discussion with the medical monitor. Q2W and Q3W schedule cohorts for each dose may be evaluated sequentially or in parallel.

To adequately monitor safety of subjects enrolled in dosing schedule expansion, when at least 6 subjects have been treated at a specific dose and schedule and ≥33% of the subjects experienced a DLT during the first 28 days in both Q2W and Q3W schedules, study accrual will be held pending data review by the SMC. Tislelizumab will also be withheld in the event of other serious adverse reactions according to pre-specified criteria. In the event that a MTD is not identified, RP2D and dosing regimen used in the Phase 1B stage will be determined by the SMC and the Sponsor based on the PK, tolerability and preliminary antitumor activities

observed in the Phase 1A stage, as well as other available data. Based on the Phase 1A data, more than one dose or dosing regimen may be selected to be evaluated in Phase 1B for safety and preliminary efficacy in select tumor types.

- *Phase 1A, Part 3*

The Phase 1A, Part 3 component will evaluate the safety and PK of tislelizumab at flat doses (ie 200 mg, Q3W) that do not exceed the exposure of the MTD as determined in the Phase 1A, Part 1 study. Approximately 10 to 20 subjects will be enrolled. Tumors types to be enrolled include but not limited to NSCLC, RCC, head and neck squamous cell carcinoma (HNSCC), bladder cancer, melanoma, gastric, oesophageal, Merkel-cell carcinoma and HCC. Other cancers that are deemed to be likely to benefit from PD-1 inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrollment subject to discussion with the medical monitor in advance.

The doses selected for the flat dose exploration have been evaluated for DLT and demonstrated as safe in the Phase 1A Part 1 study. Nevertheless, to adequately monitor safety of subjects enrolled in flat dose exploration, study accrual at a specific dose level will be held pending data review by the SMC when at least 6 subjects have been treated and ≥33% of the subjects experienced a DLT during the first cycle consisting of 21 days. A planned formal SMC review of safety data will be performed after all subjects have completed the first cycle of treatment, or withdrew due to any reason (progressive disease [PD], adverse event [AE], or death).

This part of the Phase 1A study will be conducted in Australia and/or New Zealand sites only and may be conducted in parallel with a Phase 1B study that evaluates a RP2D selected based on the Phase IA, Part 1 and 2 data as described in Section 2.5.4.

- *Phase 1B*

The Phase 1B stage is a multicenter, open-label, multiple-dose, multiple-arm, indication expansion study. The various arms of the study will investigate RP2D(s) to examine the potential efficacy as well as safety and tolerability of tislelizumab in cancer patients who failed standard care therapies. The cancer indications may include:

Arm 1. Subjects with NSCLC (approximately 50 subjects)
Arm 2. Subjects with ovarian cancer (approximately 20 subjects)
Arm 3. Subjects with gastric cancer (approximately 50 subjects)
Arm 4. Subjects with HCC (approximately 50 subjects)
Arm 5. Subjects with HNSCC (approximately 20 subjects)
Arm 6. Subjects with esophageal carcinoma (approximately 50 subjects)
Arm 7. Subjects with triple negative breast cancer (TNBC) (approximately 20 subjects)
Arm 8. Subjects with cholangiocarcinoma (approximately 20 subjects)
Arm 9. Subjects with RCC, bladder cancer, melanoma, Merkel-cell carcinoma, sarcoma, gastrointestinal stromal tumor (GIST), or cutaneous squamous cell carcinoma (cuSCC). Or any other solid tumors with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), such as CRC or pancreatic cancer (approximately 50 subjects)

For Arms 1, 3, 4 and 6, at least 20 subjects each will be enrolled from Taiwan or Korea. Enrollment rates will be different for each expansion arm. Individual arms may be closed at the discretion of the Sponsor once the target number of enrolled subjects is reached. Individual arms may also be closed prematurely due to difficulty in recruitment at the discretion of the Sponsor. Subjects will receive tislelizumab at the RP2D as described in Section 2.5.4. Each treatment cycle will be 21 days in duration. Subjects will continue treatment until confirmed disease progression, intolerable toxicity, subject discontinuation/ withdrawal or at the discretion of the Investigator in consultation with Sponsor.

To adequately monitor safety of subjects enrolled in the Phase 1B indication expansion, when at least 6 subjects have been treated and ≥33% of the subjects experienced a DLT during the first 21 days, study accrual will be held pending data review by the SMC. Tumor response will be assessed by Investigators based on the Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1. For immune therapies such as tislelizumab, pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions (Wolchok et al, 2009). Thus for PD suspected by the Investigator as pseudo-progression, treatment may continue until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point, but not to exceed 12 weeks from the initial documentation of PD. But the patient must be re-consented and the following criteria must be met in order to continue the treatment after initial PD: a. Absence of clinical symptoms and signs of disease progression (including worsening laboratory values). b. Stable Eastern Cooperative Oncology Group (ECOG) performance status. c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg cord compression) that necessitates urgent alternative medical intervention.	
Planned number of subjects:	Phase 1A stage: Approximately **120 subjects** for the dose escalation, dosing schedule expansion and flat dose exploration. Phase 1B stage: Approximately **330 subjects** for indication expansion. One or more arms may be closed early in the event of difficulty with patient recruitment.
Study population	**Key inclusion criteria** 1. Subjects meet the following corresponding requirements for the stage of the study they will enroll into: a. In Phase 1A stage of the study, subjects must have a histologically or cytologically confirmed advanced or metastatic tumor for which no effective standard therapy is available. For Part 1, tumor types to be enrolled include but not limited to CRC, NSCLC, melanoma, squamous cell carcinoma (SCC), uveal melanoma, gastric cancer, pancreatic cancer, ovarian cancer, bladder cancer, HNSCC, RCC, TNBC and HCC. For Part 2 and Part 3, tumors types to be enrolled include but not limited to NSCLC (subjects with documented epidermal growth factor receptor [EGFR] mutation or anaplastic lymphoma kinase [ALK] rearrangement should be excluded), RCC, HNSCC, bladder cancer, melanoma, gastric, oesophageal, Merkel-cell carcinoma and HCC. Other cancers that are deemed to be likely to benefit from PD-1 inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrollment subject to discussion with the medical monitor in advance. b. In Phase 1B stage of the study, subjects recruited to one of the following expansion arms must have histologically or cytologically confirmed advanced or metastatic tumor (of the types described below) for which no effective standard therapy is available: i. Arm 1. Subjects with NSCLC (subjects with

	documented EGFR mutation or ALK rearrangement should be excluded) ii. Arm 2. Subjects with ovarian cancer iii. Arm 3. Subjects with gastric cancer iv. Arm 4. Subjects with HCC (Barcelona-Clinic Liver Cancer stage C, stage B not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach, and Child-Pugh A) v. Arm 5. Subjects with HNSCC vi. Arm 6. Subjects with esophageal carcinoma vii. Arm 7. Subjects with TNBC viii. Arm 8. Subjects with cholangiocarcinoma ix. Arm 9. Subjects with RCC, bladder cancer, melanoma, Merkel-cell carcinoma, sarcoma, GIST**,** or cuSCC**.** Or any other solid tumors with known MSI-H or dMMR status, such as CRC or pancreatic cancer 2. Subjects with previously treated brain metastasis(es) that is asymptomatic and radiographically stable and not requiring steroid medications for 4 weeks prior to enrollment are permitted. 3. Subjects must have archival tumor tissues or agree to a tumor biopsy for analysis of predictive biomarkers such as programmed death-ligand 1(PD-L1; fresh tumor biopsies are strongly recommended at baseline for biomarker analysis in subjects with readily accessible tumor lesions and who consent to the biopsies). **For Arm 2 (ovarian cancer), Arm 3 (gastric cancer), and Arm 4 (HCC) of Phase 1B study, a fresh baseline biopsy within 8 weeks before starting treatment is mandatory for biomarker analysis.** **For Arm 9 (melanoma) of Phase 1B study, a fresh baseline biopsy within 8 weeks before starting treatment and one approximately on Cycle 3 Day 1 are mandatory for biomarker analysis.** **All other subjects who have easily accessible lesions are strongly recommended for baseline or the paired biopsy.** Subjects may be permitted to enroll on a case-by-case basis after discussion with the medical monitor and in consultation with the Sponsor if tissue or biopsy is not available. 4. Subjects must have at least one measurable lesion as defined per RECIST v 1.1. Subjects with metastatic castration-resistant prostate cancer (mCRPC) and with only non-measurable bone lesions must have either progression with 2 or more new lesions or have prostate-specific antigen (PSA) progression within the 6-week period before study drug administration. 5. Male or female and ≥18 years of age on day of signing informed consent 6. ECOG performance status of ≤1 7. Life expectancy ≥12 weeks

	8. Subject must have adequate organ function as indicated by the following laboratory values a. Absolute neutrophil count (ANC) ≥1,500 /mcL b. Platelets ≥100,000 / mcL, OR ≥75,000 / mcL for subjects with HCC c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L d. Serum creatinine ≤1.5 X upper limit of normal (ULN) e. Serum total bilirubin ≤1.5 X ULN (total bilirubin must be <4 X ULN for subjects with Gilbert's syndrome) f. Aspartate aminotransferase (AST) (SGOT) and alanine aminotransferase (ALT) (SGPT) ≤2.5 X ULN, OR ≤5 X ULN for subjects with liver metastases or HCC g. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 X ULN h. Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN 9. Subjects have voluntarily agreed to participate by giving written informed consent 10. Female subjects are eligible to enter and participate in the study if they are of: a. Non-childbearing potential (ie, physiologically incapable of becoming pregnant), including any female who i. Has had a hysterectomy ii. Has had a bilateral oophorectomy (ovariectomy) iii. Has had a bilateral tubal ligation iv. Is post-menopausal (total cessation of menses for ≥1 year) b. Childbearing potential, has a negative serum pregnancy test at screening (within 7 days before the first investigational product administration), not be breast feeding, and uses adequate contraception (Appendix 12) before study entry and throughout the study until 120 days after the last investigational product administration. Adequate contraception, when used consistently and in accordance with both the product label and the instructions of the physician, are defined as follows: i. Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female ii. Any intrauterine device with a documented failure rate of less than 1% per year iii. Double barrier contraception defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with

	spermicide; OR male condom and diaphragm iv. Appropriate hormonal contraceptives that include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents) 11. Male subjects are eligible to participate in the study if they are vasectomized or agree to use of contraception during the study treatment period and for at least 120 days after the last dose of study drug **Key exclusion criteria:** 1. History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs) 2. Prior malignancy active within the previous 2 years except for tumor for which a subject is enrolled in the study, and locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast 3. Prior therapies targeting PD-1 or PD-L1 4. Subjects who failed to meet enrollment criteria for other PD-1 or PD-L1 trials solely due to low or negative predictive biomarkers, including but not limited to PD-L1, MSI, and deoxyribonucleic acid (DNA) mutation load 5. Subjects with active autoimmune diseases or history of autoimmune diseases should be excluded; these include but are not limited to subjects with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, systemic lupus erythematosus (SLE), connective tissue diseases, scleroderma, inflammatory bowel disease including Crohn's disease and ulcerative colitis, hepatitis, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or antiphospholipid syndrome. Note: Subjects are permitted to enroll if they have vitiligo, eczema, type I diabetes mellitus, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids. Subjects with rheumatoid arthritis and other arthropathies, Sjogren's syndrome, controlled celiac disease and psoriasis controlled with topical medication and subjects with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible. 6. Subjects should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration Note: Adrenal replacement doses ≤10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease; subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal

	systemic absorption); a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted 7. Has history of interstitial lung disease or non-infectious pneumonitis except for those induced by radiation therapies. 8. Known history of Human Immunodeficiency Virus 9. Except for HCC in Phase 1A or Arm 4 in Phase 1B, subjects who are Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) positive or Hepatitis C virus (HCV) antibody positive at screening must not be enrolled until further definite testing with Hepatitis B virus (HBV) DNA titers and HCV ribonucleic acid (RNA) tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C, respectively 10. HCC patients with active infection by HCV who are untreated are not allowed on study. However HCC patients with successful HCV treatment (defined as sustained virologic response [SVR] 12 or SVR 24) are allowed as long as 4 weeks have passed between completion of HCV therapy and start of study drug 11. HCC patients with evidence of prior HBV infection must fulfill the following criteria in order to be eligible for the study: HBV viral load (VL) <200 IU/mL (approximately 1000 cps/mL) before study enrollment, and subjects with active HBV infection need to be on anti-HBV suppression ≥3 months, throughout treatment and for 6 months after 12. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs 13. Prior chemotherapy, radiotherapy, immunotherapy or any investigational therapies used to control cancer, including local-regional treatment for HCC, must have been completed at least 4 weeks before study drug administration, and all AEs have either returned to baseline or Grade 0-1, and stabilized 14. Use of any live vaccines against infectious diseases (eg, influenza, varicella, etc.) within 4 weeks (28 days) of initiation of study therapy and any intended use until 60 days after the last administration of the study medication 15. Subjects who had prior liver transplant, allogeneic organ transplantation or bone marrow transplant (BMT) should be excluded
Test product, dose and mode of administration:	Tislelizumab, 10 ml/vial, 10 mg/ml. Phase 1A Part 1: four cohorts dosed at 0.5 mg/kg, 2 mg/kg, 5 mg/kg, and 10 mg/kg Q2W Phase 1A Part 2: selected doses based on Part 1 at Q2W and/or Q3W Phase 1A Part 3: flat doses not exceeding MTD, ie 200 mg Q3W Phase 1B: selected dose(s) administered Q2W and/or Q3W as determined by SMC. All cohorts are administered by intravenous (IV) infusion.

Reference therapy, dose, and mode of administration:	Not applicable

Criteria for evaluation:

Primary Endpoints:

The primary endpoint of the Phase 1A stage is the following:

- Tislelizumab safety and tolerability: The safety of tislelizumab will be assessed throughout the study by monitoring AEs per the National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) Version 4.03, physical examination, ophthalmologic examination, electrocardiograms, laboratory measurements and severity of AEs.

The primary endpoint of the Phase 1B stage is the following:

- ORR: (complete response [CR] + partial response [PR]) based on RECIST v 1.1 in subjects with select tumor types as evaluated by the Investigators.

Secondary Endpoints:

The secondary endpoints of the Phase 1A stage of the study are the following:

- Pharmacokinetic evaluations: include but not limited to area under the plasma concentration-time curve from Day 0 to Day 14 ($AUC_{0\text{-}14\ day)}$, maximum observed plasma concentration ($C_{max),}$ time to maximum observed plasma concentration ($T_{max)}$, minimum observed plasma concentration ($C_{trough)}$, half-life ($T_{½)}$, clearance (Cl), and volume of distribution ($V_{d)}$.
- The MTD, if any, and RP2D (s) for tislelizumab will be determined based on safety, tolerability, PK, preliminary efficacy, and other available data.
- Efficacy evaluations: ORR (CR+PR), CR rate, PR rate, stable disease (SD) rate, progression-free survival (PFS), overall survival (OS), and duration of response (DOR) will be determined based on RECIST v 1.1 and the results of Investigator evaluations.
- Anti-tislelizumab antibody: immunogenic responses to tislelizumab will be assessed to determine incidence of anti-drug antibody (ADA).

The secondary endpoints of the Phase 1B stage of the study are the following:

- PFS; disease control rate (DCR: CR + PR + SD); and clinical benefit rate (CBR: CR or PR or durable SD [SD ≥24 weeks]).
- Safety and tolerability assessment of AEs, serious adverse events (SAEs), physical examination, ophthalmologic examination, vital signs, electrocardiograms (ECGs), and laboratory measurements.
- Plasma concentrations of tislelizumab at selected time points.

Exploratory Endpoints for Phase 1A, and Phase 1B:

- [redacted]

Statistical methods

Data will be listed and summarized according to the Sponsor-agreed reporting standards, where applicable. Primary safety and efficacy analyses will be conducted approximately 6 months after the last subject being enrolled.

All subjects who are exposed to (or started receiving) tislelizumab will be included in the safety analysis set (SAF). All subjects for whom valid tislelizumab PK parameters can be estimated will be included in the PK Population on an as-treated basis.

Sample size

In Phase 1A, the number of dose levels and schedules examined and the emerging tislelizumab toxicities will determine the sample size. It is anticipated that approximately 24 subjects will be required to establish the RP2D(s) of tislelizumab when administered as a single agent. In addition, 10 to 20 subjects will be enrolled in each of the schedule expansion and flat dose cohort at one or more dose level (up to 10 mg/kg Q2W or Q3W in schedule expansion cohort; 200 mg Q3W in flat dose cohort) not exceeding MTD to further evaluate safety, tolerability, PK and preliminary efficacy of tislelizumab.

In Phase 1B, approximately 20 to 50 subjects for each arm (except Arm 9) will be evaluated to examine the potential efficacy as well as safety and tolerability of tislelizumab in select tumor types.

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1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACD	Acid-citrate-dextrose
ADA	Anti-drug antibody
AE	Adverse event
AFP	Alpha fetoprotein
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}14\ day}$	Area under the plasma concentration-time curve from Day 0 to Day 14
BGB-A317	Code name for Monoclonal Antibody BGB-A317
BMI	Body mass index
BMT	Bone marrow transplant
CA 125	Cancer antigen 125
CBR	Clinical benefit rate
CD	Cluster of differentiation, such as CD274, CD279, CD3 and etc.
CI	Confidence interval
Cl	Clearance
C_{max}	Maximum observed plasma concentration
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
C_{trough}	Minimum observed plasma concentration
cuSCC	Cutaneous squamous cell carcinoma
DCR	Disease control rate
DLT	Dose-limiting toxicity
dMMR	Mismatch repair deficient
DNA	Deoxyribonucleic acid

Abbreviation	Definition
DOR	Duration of response
DP	Drug product
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ESMO	European Society for Medical Oncology
FACS	Fluorescence-activated cell sorting, or fluorescence-activated cell sorter
Fc	Fragment crystallizable region (typically, of immunoglobulin G)
FcγR	Fc gamma receptor, such as Fcγ-RI, Fcγ-RIII, etc.
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FIH	First-in-human
GBM	Glioblastoma multiforme
GCIG	The Gynecologic Cancer Intergroup
GCP	Good Clinical Practices
GIST	Gastrointestinal stromal tumor
GLP	Good Laboratory Practices
GMP	Good Manufacture Practice
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator's Brochure
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFN-α	Interferon-alpha
IFN-γ	Interferon-gamma

Abbreviation	Definition
IgG	Immunoglobulin G, such as IgG1, IgG2, IgG3 and IgG4; other types of immunoglobulins include IgM, IgD and etc.
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
KM	Kaplan-Meier
MABEL	Minimum anticipated biological effect level
MAD	Maximum administered dose
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NSAID	Nonsteroidal anti-inflammatory drugs
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1, programed death receptor ligand-1, programmed death-1 ligand-1
PD-L2	Programmed death-ligand 2

Abbreviation	Definition
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PSA	Prostate-specific antigen
PT	Prothrombin Time or preferred term
Q2W	Once every two weeks
Q3W	Once every three weeks
QTc	QT interval corrected for heart rate
RANO	Response Assessment in Neuro-Oncology
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SCC	Squamous cell carcinoma
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLE	Systemic lupus erythematosus
SMC	Safety Monitoring Committee
SOP	Standard operating procedure
$T_{1/2}$	Half-life
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TIL	Tumor-infiltrating lymphocyte
tislelizumab	BGB-A317
TK	Toxicokinetics
T_{max}	Time to maximum observed plasma concentration

Abbreviation	Definition
TNBC	Triple-negative breast cancer
ULN	Upper limit of normal
US	United States
V_d	Volume of distribution
VL	Viral load
WHO-DD	World Health Organization Drug Dictionary

2.0 INTRODUCTION

2.1 Background and Pharmacology

Immune check point-inhibitory receptor, programmed cell death-1 (PD-1) is mainly expressed in activated T-cells including cluster of differentiation (CD) 8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes (McDermott and Atkins, 2013). 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 (TCR) and attenuate T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes (TILs), while the expression of programmed death-ligand 1, (PD-L1) is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as interferon-gamma (IFN-γ) and interferon-alpha (IFN-α) in the tumor microenvironment (Riley, 2009). Furthermore, the increased PD-1 expression in TILs 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 (SCC), uveal melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), triple-negative breast cancer (TNBC), renal cell carcinoma (RCC), bladder cancer, and ovarian cancer (Ghebeh et al, 2006; Hamanishi et al, 2007; Konishi et al, 2004; Thompson et al, 2007; Thompson et al, 2004; Tsushima et al, 2006; Jie et al, 2013; Hino et al, 2010). This evidence provided the basis for cancer immunotherapeutic intervention via the approach of antagonizing PD-1.

Recent clinical trials have demonstrated significant efficacy for anti-PD-1 monoclonal antibodies such as nivolumab and pembrolizumab in advanced melanoma, NSCLC and RCC. These antibodies were well tolerated without demonstrating dose-limiting toxicities (DLT) when patients were dosed up to 10 mg/kg intravenously, once every two weeks (Q2W) or once every three weeks (Q3W). The first-in-human (FIH) phase 1 trial on nivolumab (a fully human anti–PD-1 immunoglobulin G [IgG] 4 antibody) evaluated its safety profile at increasing doses of 0.3, 1, 3 and 10 mg/kg given intravenously Q2W in 39 patients with advanced melanoma, colorectal cancer (CRC), castration-resistant prostate cancer (CRPC), NSCLC, or RCC (Brahmer et al, 2010; Topalian et al, 2012). The FIH Phase 1 study on pembrolizumab (a humanized anti–PD-1 IgG4 antibody) evaluated its safety at 1 to 10 mg/kg given intravenously at 4 week interval followed by bi-weekly doses in cohorts of three to six patients with various advanced solid tumors (Hamid et al, 2013). The most common adverse events (AEs) were Grade 1/2, including arthralgia, cough, diarrhea, fatigue, fever, nausea, pruritus, and rash. However, Grade 3/4 treatment-related AEs occurred in 15% of patients and there were three deaths in the nivolumab study, all attributed to pulmonary toxicity. Grade 3/4 AEs were also reported in the pembrolizumab studies and one patient

died of myocardial infarction while being treated for pneumonitis/pneumonia. Drug-related AEs of special interest (AEs with potentially immune-related etiology) included vitiligo, pneumonitis, hepatitis, colitis, thyroiditis, and hypophysitis.

Based on the overwhelming positive results that pembrolizumab and nivolumab demonstrated in their pivotal studies, the United States (US) Food and Drug Administration (FDA) approved these two drugs for the treatment of metastatic melanoma in 2nd or 3rd line. In the nivolumab pivotal study, the cohort of 120 patients treated at 3 mg/kg Q2W exhibited an objective response rate (ORR) of 32% with 4 complete responses (CRs) and 34 partial responses (PRs). Thirteen patients had objective responses lasting 6 months or longer (FDA News Release, Dec. 2, 2014). In the pivotal study of pembrolizumab, 173 patients were treated with pembrolizumab at either 2 or 10 mg/kg dose, approximately 24% patients demonstrated tumor shrinkage (2 mg/kg regimen; FDA News Release, Sept. 4, 2014).

Interestingly, melanoma patients who became resistant to ipilumumab treatment were still sensitive to pembrolizumab. The ORRs of ipilumumab-naïve and ipilumumab-resistant are 40% and 28%, respectively.

Anti-PD-1 antibody treatment not only generated higher response rate, but also prolonged overall survival (OS). In a cohort of 107 patients treated with nivolumab, 1 and 2 years OSs were 63% and 48%, respectively, with median OS at 17.3 months. Similarly in a cohort of 411 patients treated with pembrolizumab, 1 year OS was 69% and 18 month OS was 62%, respectively (Weber et al, 2014).

In addition to melanoma, anti-PD-1 antibodies were also reported to be efficacious in other cancer types including NSCLC, RCC and HNSCC. In the NSCLC study, 129 patients were treated with nivolumab in 2nd, 3rd or 4th line, one year or two year survival rate were 42% and 24%, respectively, with median OS of 9.9 months. Retrospective analysis indicated both patients with K-Ras and EGFR mutations responded to the immunotherapy (BMS Press Release, 2013).

Recent exploratory studies suggested that combinatory immunotherapies with anti-PD-1 antibody may provide more benefits to cancer patients. In one study in patients with metastatic melanoma, nivolumab in combination with ipilumumab generated remarkable ORR with two year OS rate at more than 80%. Patients with wild type or mutant BRAF, with or without PD-L1 expression, all responded well to the combination treatment (Sznol et al, 2014; Wolchok et al, 2013). Of note, the immune-related AEs (irAEs) also increased significantly in the combination treatment.

Tislelizumab (also known as BGB-A317) is a humanized IgG4 variant monoclonal antibody against PD-1. It is being developed for the treatment of human malignancies. Tislelizumab was manufactured under Good Manufacture Practice (GMP) quality control systems. The

clinical trial drug product is formulated in an aqueous buffer with pH 6.5 and isotonic osmolality. The suggested administration route is intravenous (IV) infusion after the appropriate dilution in 0.9% sodium chloride solution.

Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity (dissociation constant = 0.15 nM) as demonstrated by receptor binding assays based on surface plasmon resonance. It competitively blocks the binding of both PD-L1 and programmed death-ligand 2 (PD-L2), inhibiting PD-1 mediated negative signaling in T-cells. In *in vitro* cell-based assays, the humanized antibody consistently and dose-dependently enhanced the functional activity of human T-cells and pre-activated, primary peripheral blood mononuclear cells (PBMCs). In addition, tislelizumab demonstrated anti-tumor activity in several human cancer allogeneic xenograft models, including A431 human epidermoid carcinoma, BCCO-028 colon cancer, and BCLU-054 NSCLC models, where the PBMCs were co-injected with the human cancer cells (A431) or the tumor fragments (BCCO-028 and BCLU-054) into the immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to fragment crystallizable region gamma receptor (FcγR) IIIA and complement 1q by *in vitro* assays, suggesting a low or no antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effect in humans. Unlike natural IgG4 antibody, tislelizumab has no observable fragment antigen-binding-arm exchange activity by the *in vitro* assay, predicting the antibody would be stable *in vivo*, unlikely forming bispecific antibody.

Tislelizumab binds to the cynomolgus monkey and human PD-1 with similar affinity, but does not bind to mouse PD-1 due to the significant sequence divergence from human and monkey PD-1. Therefore, cynomolgus monkeys were considered to be the relevant species for nonclinical safety evaluation.

Refer to the Investigator's Brochure (IB) for more detailed information on the background of tislelizumab.

2.2 Nonclinical Pharmacokinetics

A pharmacokinetic (PK) study of tislelizumab was conducted in monkeys at single doses of 3, 10, or 30 mg/kg or at repeat dose of 10 mg/kg weekly for 5 doses via IV infusion. The systemic exposure appeared to increase dose-proportionally without gender difference or accumulation. After single dose administration of 3, 10, or 30 mg/kg, the half-life ($T_{1/2}$) ranged from 74 to 183 hours; maximum observed plasma concentration (C_{max}) ranged from 90 to 999 μg/mL, and the area under the plasma concentration time curve from 0 to 1008 hours ($AUC_{0\text{-}1008h}$) ranged from 12,322 to 163,755 h*μg/mL; volume of distribution (V_d) was low, ranged from 22 to 52 mL/kg.

A PK bridging study for tislelizumab manufactured by Boehringer Ingelheim and JHL Biotech Inc. was conducted in monkeys at a single dose of 10 mg/kg via IV infusion. No marked differences on $T_{1/2}$, C_{max}, AUC, V_d, clearance (Cl) and mean residence time were noted between the two batches.

The $T_{1/2}$ of tislelizumab in monkeys supported once biweekly dosing in the repeat-dose toxicology study with adequate systemic exposure to support toxicology evaluation of tislelizumab. Based on PK results in monkeys, the V_d of tislelizumab in humans is expected to be similar to that in monkeys. The $T_{1/2}$ of tislelizumab in humans is expected to be 10-20 days depending on the actual dose levels, which allows multiple-dose treatment of tislelizumab for humans with a dosing interval of 14 or 21 days to provide the target systemic exposure at the projected therapeutic dose of 0.5 to 10 mg/kg without excessive drug accumulation.

Refer to the IB for more detailed information on the PK properties of tislelizumab.

2.3 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 studies were conducted following Good Laboratory Practice (GLP) regulations. The single dosing regimens were spanning from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat dosing regimens spanning 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.

No apparent toxicity was noted in both mice and monkeys following a single dose up to 100 mg/kg and in monkeys following a repeat dose up to 30 mg/kg biweekly for 13 weeks. The toxicokinetics (TK) profile was characterized in monkey studies and the systemic exposure appeared to be dose proportional without gender difference or accumulation over the dosing period. No apparent immunotoxicity was observed as no apparent changes in clinical pathology or histopathology were noted in these studies. The immunogenicity with positive anti-drug antibody (ADA) against tislelizumab was noted in the single dose monkey study with one of two monkeys in each of three dose groups and in the repeat dose study with 8/12, 6/12, and 5/12 of animals at doses of 3, 10, and 30 mg/kg, respectively. The ADA against tislelizumab was demonstrated to have neutralization function in a cell based assay and it appeared to have some impact on the systemic exposure over the dosing period at 3 mg/kg, but little at 10 and 30 mg/kg.

The tissue cross reactivity of tislelizumab was evaluated in normal human and cynomolgus monkey frozen tissues using immunohistochemistry (IHC) method, with appropriate positive and negative controls. Under the study condition, no specific tissue cross reactivity with tislelizumab was noted in both human and cynomolgus monkey tissues. Neither hemolytic effects induced by tislelizumab in the rabbit blood cells nor increase of the cytokine release from human whole blood cells after treatment with tislelizumab was observed in *in vitro* evaluations.

Overall, no apparent toxicity was noted in mice and monkey toxicity studies. No tissue cross reactivity was found in both human and monkey tissues, nor effect on cytokine release was observed in human whole blood assay. The TK profile was well characterized with dose proportionally increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity and effect on the systemic exposure. The No Observed Adverse Effect Level (NOAEL) of tislelizumab in 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support FIH dose safely and ethically.

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

2.4 Benefit-Risk Assessment

As of March 29, 2016, 100 patients had received at least one dose of tislelizumab in the Phase 1A part of the study, ranging from 0.5 mg/kg to 10 mg/kg Q2W (n=62) and from 2 mg/kg to 5 mg/kg Q3W (n=38). During dose escalation, the following dose levels: 0.5 mg/kg Q2W (n=3), 2 mg/kg Q2W (n=6), 5 mg/kg Q2W (n=6), and 10 mg/kg Q2W (n=7) were evaluated for safety and tolerability. One DLT (1/6) of Grade 3 colitis was observed in the 5 mg/kg Q2W. Additional cohorts of 2 mg/kg Q2W (n=20), 5 mg/kg Q2W (n=20), 2 mg/kg Q3W (n=19) and 5 mg/kg Q3W (n=19) were further evaluated as tolerated in schedule expansion.

Preliminary safety analysis showed that the most common treatment-emergent adverse events (TEAEs) (≥10%) were fatigue (31%), diarrhoea (21%), nausea (20%), constipation (16%), abdominal pain (14%), pruritus (13%), rash (12%), decreased appetite (12%), back pain (12%) and vomiting (10%). Immune-mediated AEs were reported in 10 subjects including colitis (1 Grade 3, 2 Grade 2), diabetes mellitus (1 Grade 3, 1 Grade 2), alanine aminotransferase (ALT) increase (1 Grade 3), diarrhea (1 Grade 2), worsening liver functions (1 Grade 2), hypothyroidism (1 Grade 1) and onychoclasis (1 Grade 1). As of March 29, 2016, 9 drug-related serious adverse events (SAE) were reported including 1 Grade 2 colitis in the 2 mg/kg Q2W dose escalation cohort (n=6), 1 Grade 3 colitis in the 5 mg/kg Q2W dose escalation cohort (n=6), 1 Grade 2 colitis and 1 Grade 2 infusion reaction in the 5 mg/kg Q2W schedule expansion cohort (n=20), 1 Grade 3 diabetic ketoacidosis, 1 Grade 3 diabetes mellitus, 1 Grade 3 hypotension and 1 Grade 2 diarrhoea in the 2 mg/kg Q2W schedule

expansion cohort (n=20), and 1 Grade 3 hypotension in the 5 mg/kg Q3W schedule expansion cohort (n=19). Other Grade 3/4 AEs that were considered treatment-related by the investigators include 1 Grade 3 ALT increase in the 2 mg/kg Q2W dose escalation cohort (n=6), 1 Grade 3 hyperglycaemia in the 2 mg/kg Q2W schedule expansion cohort (n=20), 1 Grade 3 back pain and 1 Grade 3 fatigue in the 5 mg/kg Q2W schedule expansion cohort (n=20), and 1 Grade 3 fatigue and 1 Grade 3 hyperglycaemia in 5 mg/kg Q3W schedule expansion cohort (n=19).

In addition, as of May 5, 2016, 12 subjects have been treated with tislelizumab in combination with BGB-290 (a PARP1/2 inhibitor) in the BGB-A317/BGB-290_Study_001 combo study (NCT02660034). One subject, who was treated with tislelizumab at 2 mg/kg Q3W in combination of BGB-290 (a PARP1/2 inhibitor) at 20 mg BID, experienced an immune-mediated SAE of Grade 4 drug induced hepatopathy that was attributed to tislelizumab by the investigator.

Refer to the IB for more detailed information regarding the safety of tislelizumab.

Clinical experience with existing drugs of the same therapeutic class (anti-PD-1 monoclonal antibodies) suggests the most common AEs were Grade 1/2, including arthralgia, cough, diarrhea, fatigue, fever, nausea, pruritus, and rash. However, Grade 3/4 treatment-related AEs occurred in 15% of patients in the nivolumab study, and there were three deaths, all attributed to pulmonary toxicity (Brahmer et al, 2010, Topalian et al, 2012). Grade 3/4 AEs were also reported in the pembrolizumab studies with one subject died of myocardial infarction while being treated for pneumonitis/pneumonia (Hamid et al, 2013). Drug-related AEs of special interest (AEs with potentially immune-related etiology) included vitiligo, pneumonitis, hepatitis, colitis, thyroiditis, and hypophysitis may be observed during multiple dose escalation in subjects with cancer.

2.5 Study Rationale

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and any applicable regulatory requirements.

This study will evaluate the safety, tolerability, and PK profile of tislelizumab as well as preliminary evidence of the anti-tumor activity of tislelizumab. Through its dose escalation and safety, schedule and efficacy expansion components, it will determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for tislelizumab.

2.5.1 Rationale for Starting Dose Selection in Phase 1A Part 1

Selection of the Safe Starting Dose for First-In-Human Clinical Study

Tislelizumab has demonstrated a favorable toxicology and safety pharmacology profile in nonclinical experiments. Early clinical development of tislelizumab will be conducted in

patients with advanced cancer and failed standard-care treatment.

The relevant species for preclinical safety evaluation is monkey, because tislelizumab binds to human and monkey PD-1 almost equally well, but does not bind to mouse or rat PD-1. From conservative point of view, the NOAEL (100 mg/kg) observed in the single dose toxicity study in monkeys was not used for FIH dose estimation. Therefore, the NOAEL was considered to be 30 mg/kg based on the 3-month repeat dose toxicity study in cynomolgus monkeys. The FIH dose could be estimated based on NOAEL divided by a safety factor (10 or larger; FDA Guidance for Industry M3(R2), Zou et al, 2012). Based on this rule, the FIH dose for tislelizumab could be selected as 3 mg/kg.

Alternatively, the FIH dose for tislelizumab may be estimated based on the minimum anticipated biological effect level (MABEL). For tislelizumab, MABEL was determined to be around 0.5 mg/kg, through PK/pharmacodynamic modeling of allogeneic tumor models, the monkey PK, and predicted human exposure. Therefore, the FIH dose projected based on the MABEL should be 0.5 mg/kg.

Predicted efficacious doses in human

MABEL of tislelizumab as described above was predicted to be 0.5 mg/kg. Therefore, the selected FIH dose at 0.5 mg/kg may have efficacy on human tumor growth inhibition.

Furthermore, the best efficacious dose rang is predicted to be in the range of 1 to 5 mg/kg based on the PK/pharmacodynamic modeling.

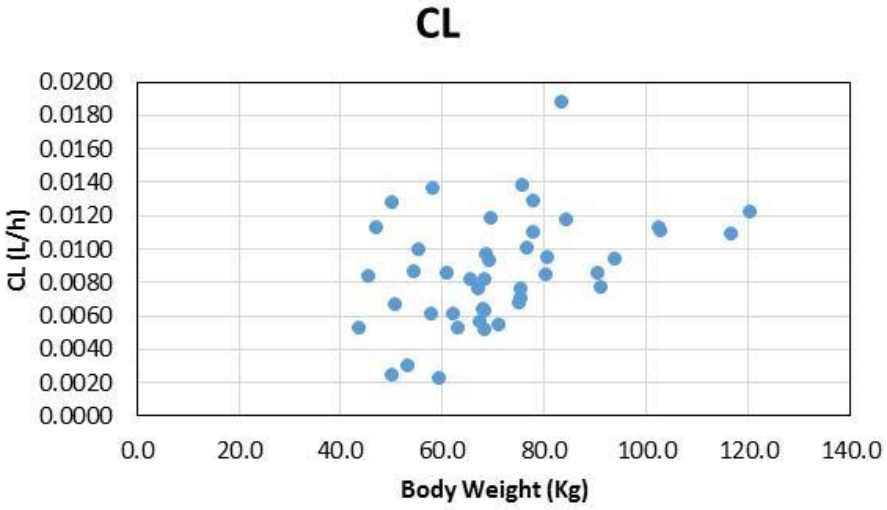
2.5.2 Rationale for Evaluating Different Dosing Schedules in Phase 1A Part 2

Preliminary PK data of subjects in Phase 1A study indicate that the half-life of tislelizumab is approximately 17 days and there is moderate drug accumulation in the blood when dosed at a Q2W schedule. Thus a decision is made to investigate a less frequent dosing schedule at Q3W. The objective is to identify one or two safe, effective and convenient dose regimen for the Phase 1B study.

2.5.3 Rationale for Evaluating Flat Dosing in Phase 1A Part 3

Population PK analysis was conducted using 411 observed tislelizumab serum concentrations from 31 patients who received doses of 0.5, 2.0, 5.0 and 10 mg/kg Q2W and 13 patients who received doses of 2.0 and 5.0 mg/kg Q3W (Phase 1A Part 1 and Part 2). As described in Section 2.5.4, PK from tislelizumab is linear and was characterized with a 2-compartment model with 1st order elimination. In the covariate analysis, patient body weight was not found to be a significant covariate on the clearance of tislelizumab (Figure 2-1), which supports the exploration of flat-dosing.

Figure 2-1 Lack of Correlation between Clearance (Cl) and Patient Body Weight



Thus a decision is made to explore flat dosing as part of the Phase 1A study, conducted in parallel with a Phase 1B study that evaluates the RP2D as described in Section 2.5.4. The proposed flat dose of 200 mg Q3W has the dose intensity between 2 mg/kg Q3W and 10 mg/kg Q2W. Tislelizumab is generally well tolerated between these doses.

2.5.4 Rationale for Dose Selection in Phase 1B

After reviewing safety and PK data from Phase 1A Part 1 (dose escalation) and Phase 1A Part 2 (schedule expansion), the Safety Monitoring Committee (SMC) has recommended 5 mg/kg Q3W as the dose regimen to be taken into Phase 1B of the study, based on the following rationales:

Safety

As of March 29, 2016, 100 patients received at least one dose of tislelizumab in the Phase 1A part of the study, ranging from 0.5 mg/kg to 10 mg/kg Q2W (n=62) and from 2 mg/kg to 5 mg/kg Q3W (n=38). Safety and tolerability including dose limiting toxicities, PK, and preliminary efficacy were evaluated.

As described in Section 2.4, all dose levels in the dose escalation part were well tolerated with only one reported DLT. MTD was not reached and 10 mg/kg Q2W was considered the maximum administered dose (MAD). No apparent relationship between dose level and AEs was established.

Drug-related AE from 2 mg/kg Q2W to 10 mg/kg Q2W were similar (Table 1 and Table 2). AE profiles from Q3W regimen between 2 mg/kg and 5 mg/kg based on data reported from the first 2 cycles slightly favor 2 mg/kg, although with short treatment duration.

Tislelizumab is generally well tolerated between these doses with slightly fewer AEs from the Q3W regimen.

Efficacy

Clinical response (PR or better) was observed in patients who received 0.5 mg/kg, 2 mg/kg, 5 mg/kg Q2W, and 2 mg/kg Q3W cohorts (Table 3). The majority of responses came from 5 mg/kg cohorts. The proposed Phase 1B dose of 5 mg/kg Q3W has a dose intensity between 2 mg/kg Q3W and 5 mg/kg Q2W. Further investigation of 5 mg/kg Q3W is warranted.

Table 1 Summary of All Adverse Events Reported in Phase 1A from Study Initiation through March 29, 2016

Number of Patients with at least one of the following	Dose Escalation				Schedule Expansion			
	0.5mg/kg Q2W n=3	2mg/kg Q2W n=6	5mg/kg Q2W n=6	10mg/kg Q2W n=7	2mg/kg Q2W n=20	5mg/kg Q2W n=20	2mg/kg Q3W n=19	5mg/kg Q3W n=19
Median Treatment Duration (days)	126 (99-153)	138 (41-251)	87 (16-210)	79 (23-161)	86 (15-191)	93 (29-160)	45 (9-127)	46 (13-107)
Any AE	3	6	6	7	20	20	10	11
Any Drug-related AE	0	5	4	4	15	14	2	9
Grade 3/4 Drug-related AE	0	1	1	0	2	2	0	3
Serious Drug-related AE	0	1	1	0	3	2	0	1
AE leading to discontinuation from Study	0	0	0	0	0	1	0	0

Table 2 Most Common Drug-related Adverse Events (all Grade ≥5% or Grade 3/4 ≥1%) Reported in Phase 1A from Study Initiation through March 29, 2016

SOC/PT	All Grade		Grade 3-4		Number of patients with AE in each cohort							
	n*	%	n*	%	0.5 mg/kg Q2W Dose escalation	2 mg/kg Q2W Dose escalation	5 mg/kg Q2W Dose escalation	10 mg/kg Q2W Dose escalation	2 mg/kg Q2W Schedule expansion	5 mg/kg Q2W Schedule expansion	2 mg/kg Q3W Schedule expansion	5 mg/kg Q3W Schedule expansion
	(pts)	(N=100)	(pts)	(N=100)	n=3	n=6	n=6	n=7	n=20	n=20	n=19	n=19
General disorders and administration site conditions												
Fatigue	14	14%	2	2%	0	2	2	0	4	4	0	2
Gastrointestinal disorders												
Diarrhoea	11	11%	0	0%	0	3	1	0	5	2	0	0
Nausea	5	5%	0	0%	0	0	1	1	1	2	0	0
Colitis	2	2%	1	1%	0	0	1	0	0	1	0	0
Skin and subcutaneous tissue disorders												
Pruritus	8	8%	0	0%	0	1	0	1	3	0	0	3
Rash	7	7%	0	0%	0	0	1	1	1	3	0	1
Investigations												
Alanine aminotransferase increased	3	3%	1	1%	0	1	1	0	1	0	0	0
Metabolism and nutrition disorders												
Hyperglycaemia	2	2%	2	2%	0	0	0	0	1	0	0	1
Diabetes mellitus	2	2%	1	1%	0	0	0	0	1	0	0	1
Diabetic ketoacidosis	1	1%	1	1%	0	0	0	0	1	0	0	0
Vascular disorders												
Hypotension	2	2%	2	2%	0	0	0	0	1	0	0	1
Musculoskeletal and connective tissue disorders												
Back pain	1	1%	1	1%	0	0	0	0	0	1	0	0

Abbreviations: SOC, System Organ Class; PT, Preferred Term.
*If a patient experiences more than one occurrence of the same event, only the highest grade event is counted.

Table 3 Summary of Enrollment and Response by Cohort in Phase 1A as of March 29, 2016

Cohort	Number of patients	Number Evaluable	Number of confirmed PR	Number of unconfirmed PR
0.5 mg/kg Q2W Dose escalation	3	3	0	1
2 mg/kg Q2W Dose escalation	6	6	1	1
5 mg/kg Q2W Dose escalation	6	6	0	0
10 mg/kg Q2W Dose escalation	7	7	0	0
2 mg/kg Q2W Schedule expansion	20	20	1	0
5 mg/kg Q2W Schedule expansion	20	19	1	3
2 mg/kg Q3W Schedule expansion	19	4	1	0
5 mg/kg Q3W Schedule expansion	19	3	0	0

Abbreviations: Q2W, every two weeks; Q3W, every three weeks.

Population Pharmacokinetics

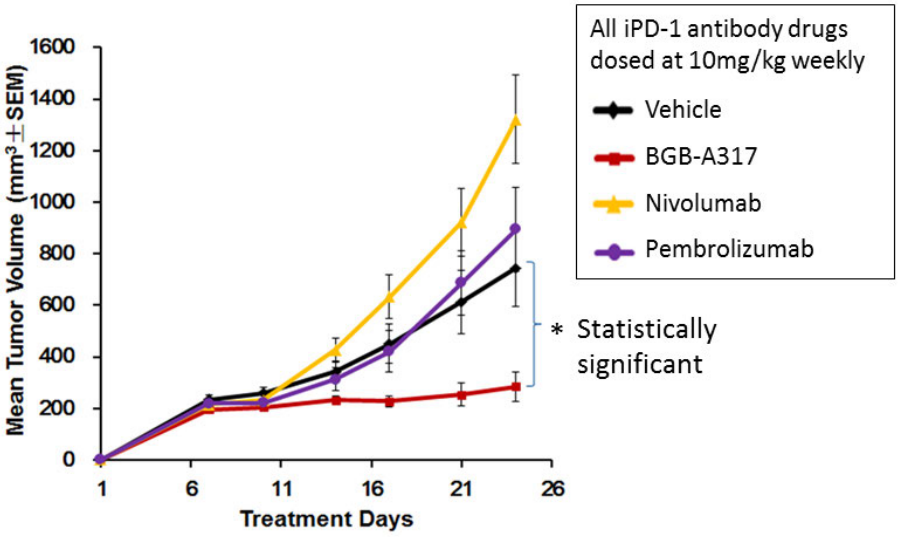
Population PK analysis was conducted using 411 observed tislelizumab serum concentrations from 31 patients who received doses of 0.5, 2.0, 5.0 and 10 mg/kg Q2W and 13 patients who received doses of 2.0 and 5.0 mg/kg Q3W (Phase 1A Part 1 and Part 2). PK from tislelizumab is linear and was characterized with a 2-compartment model with 1st order elimination. Systemic clearance of A317 was 0.00789 L/h, volume of distribution in the central and peripheral compartment are 2.79 and 1.44 L, respectively, and terminal elimination half-life is 16 days.

In conclusion, tislelizumab regimen of 5 mg/kg Q3W was well-tolerated with promising clinical activity from a limited number of patients in the Phase 1A trial. Further testing of this regimen is warranted in Phase 1B.

2.5.5 Rationale for Selection of Different Expansion Arms in Phase 1B

Rationale for the selection of cancer indications included in the 9 expansion arms is based on *in vivo* tumor growth inhibition studies, which demonstrated that tislelizumab have significantly higher antitumor activities than nivolumab and pembrolizumab in mouse models carrying allogenic human cancer cells and PBMCs (see Figure 2-2). Therefore, we hypothesized that tislelizumab may be more efficacious than nivolumab and pembrolizumab in certain insensitive cancer types.

Figure 2-2 Comparison of Tumor Growth Inhibition by the Treatment with Tislelizumab versus Nivolumab and Pembrolizumab in the Mouse Cancer Model



We also selected tumor types where nivolumab and pembrolizumab have shown various clinical efficacies, including melanoma, lung cancer, RCC, HNSCC, hepatocellular carcinoma (HCC), bladder, gastric, ovarian and breast cancer. The ORRs for nivolumab and pembrolizumab in these tumors range from 15 to 35% with durable response shown in most cases. Tislelizumab is expected to be equal or more efficacious in some indications such as HCC, ovarian, gastric, TNBC, bladder cancer and NSCLC. It is also hypothesized that tislelizumab may show better therapeutic potential when used in combination with certain cancer therapeutic agents. The hypothesis that tislelizumab may pose differential activities from nivolumab and pembrolizumab is based on our studies on tumor microenvironment and other factors driving tumorigenesis and progression in different cancer types.

Based on the discussion above, the 9 expansion arms may be classified into the following categories:

1. Indications where nivolumab and pembrolizumab have shown variable efficacy with ORR ranging from 10+ to 20+%, but tislelizumab is expected to be more active, such as NSCLC, HCC, ovarian cancer, gastric cancer, esophageal cancer and TNBC, which are covered in the expansion arms 1-8.

2. Indications in which nivolumab and pembrolizumab have shown very good efficacy and tislelizumab is anticipated to be equally or more active, such as melanoma, RCC and bladder cancer, which are covered in the expansion Arm 9. A recent study indicated that a small portion (15%) of CRC patients with mismatch repair deficiency (dMMR) responded well to pembrolizumab (Le et al, 2015). Tislelizumab is

expected to be equally or more active based on promising Phase 1A data. Cancers with microsatellite instability-high (MSI-H) or dMMR will be explored in this arm.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective of the Phase 1A stage of the study is the following:

- To assess the safety and tolerability of tislelizumab in subjects with advanced or refractory malignancies

The primary objective of the Phase 1B stage of the study is the following:

- To assess the anti-tumor activity of tislelizumab in select tumor types

3.2 Secondary Objectives

The secondary objectives of the Phase 1A stage of the study are the following:

- To characterize the PK of tislelizumab
- To determine MTD, if any, and RP2D for tislelizumab
- To assess the preliminary anti-tumor activity of tislelizumab
- To assess host immunogenicity to tislelizumab

The secondary objectives of the Phase 1B stage of the study are the following:

- To further assess the safety and tolerability of tislelizumab in subjects with advanced tumors
    - To further characterize the PK of tislelizumab

3.3 Exploratory Objectives

- [redacted]

4.0 STUDY ENDPOINTS

4.1 Primary Endpoints

The primary endpoint of the Phase 1A stage is the following:

- Tislelizumab safety and tolerability: The safety of tislelizumab will be assessed throughout the study by monitoring AEs per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version [v] 4.03 2010), physical examination, ophthalmologic examination, electrocardiograms, laboratory measurements and severity of AEs

Given the mechanism of action by tislelizumab involves immune regulatory function, particular attention should be given to irAEs, which include pruritus, vitiligo, pruritic rash, macular rash, hypopigmentation, and other skin disorders; hypo- and hyperthyroidism, hypophysitis, pneumonitis, hepatitis, nephritis, allergic rhinitis, diarrhea, abdominal pain, fatigue, hypersensitivity and any other irAEs (see Section 7.3.4). Appropriate investigations should be undertaken to exclude toxic, metabolic, infectious, neoplastic or other non-drug-related etiologic causes of such events.

The primary endpoint of the Phase 1B stage is the following:

- ORR (CR + PR) based on Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 in subjects with select tumor types as evaluated by the Investigators

Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (Scher et al, 2008) may also be used to evaluate responses in patients with prostate cancer enrolled on the study as described in Appendix 9.

The Gynecologic Cancer Intergroup (GCIG) criteria (Rustin et al, 2011) in addition to RECIST v 1.1 may also be used to evaluate response in patients with ovarian cancer enrolled on the study.

Response Assessment in Neuro-Oncology (RANO) criteria (Wen et al, 2010) may also be used to evaluate response in patients with glioblastoma multiforme (GBM) enrolled on the study.

4.2 Secondary Endpoints

The secondary endpoints of the Phase 1A stage of the study are the following:

- Pharmacokinetic evaluations: include but not limited to AUC from Day 0 to Day 14 ($AUC_{0\text{-}14\ day}$), C_{max}, time to maximum concentration (T_{max}), minimum observed

plasma concentration (C_{trough}), $T_{½}$, clearance (Cl), and V_d. The MTD, if any, and RP2D (s) for tislelizumab will be determined based on safety, tolerability, PK, preliminary efficacy, and other available data.

- Efficacy evaluations: ORR (CR+PR), CR rate, PR rate, stable disease (SD) rate, progression-free survival (PFS), OS and duration of response (DOR) will be determined based on RECIST v 1.1 and the results of Investigator evaluations
- Anti-tislelizumab antibody: Immunogenic responses to tislelizumab will be assessed to determine incidence of ADA

The secondary endpoints of the Phase 1B stage of the study are the following:

- PFS as described above; disease control rate (DCR: CR + PR + SD); and clinical benefit rate (CBR: CR or PR or durable SD [SD ≥24 weeks])
- Safety and tolerability assessment of AEs, SAEs, physical examination, ophthalmologic examination, vital signs, ECG, and laboratory measurements
- Plasma concentrations of tislelizumab at selected time points

4.3 Exploratory Endpoints

- [redacted]

5.0 INVESTIGATIONAL PLAN

5.1 Summary of Study Design

This is a two-stage study consisting of a Phase 1A dose escalation and dose-finding component to establish the MTD, if any, and RP2D(s), followed by a Phase 1B component to

investigate efficacy in select tumor types and to further evaluate safety and tolerability of tislelizumab at RP2D(s).

Archival tumor tissue will be collected for purpose of biomarker analysis, although a fresh tumor biopsy at baseline is strongly recommended. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion is required at baseline; for these subjects, an optional biopsy for biomarker analysis after two cycles of treatment is strongly recommended. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

Mandatory biopsies at baseline and on treatment are required for some tumor types in the Phase 1B study.

Subjects will be monitored for safety, anti-tislelizumab antibodies and efficacy throughout the study. Radiological assessment of tumor response status should be performed approximately every 8 weeks or 9 weeks depending on dosing schedules in the first year, then every 12 weeks thereafter.

A flow chart of the study design is presented in Appendix 7.

5.1.1 Dose-Limiting Toxicity

All toxicities or AEs will be graded according to the NCI-CTCAE Version 4.0. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

Non-hematologic:

1. Grade 5 adverse events
2. Grade 4 toxicity
3. Grade 3 toxicities irrespective of duration, with the exception of laboratory abnormalities, diarrhea, nausea and vomiting, and asymptomatic biochemical abnormalities that improve to Grade 2 or lesser severity within 3 days of institution of supportive care
4. Grade 3 tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) of > 7 day duration
5. Immune-related adverse events (irAE) of Grade 3 or greater severity

6. Grade 4 laboratory abnormalities irrespective of duration

7. Grade 2 ophthalmologic toxicities

Hematologic:

1. Grade 4 neutropenia lasting >7 days

2. Febrile neutropenia (defined as absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of 38.3ºC or a sustained temperature of 38ºC for >1 hour)

3. Grade 3 neutropenic infection

4. Grade 3 thrombocytopenia with bleeding

5. Grade 4 thrombocytopenia

6. Grade 4 (life threatening) anemia

Any grade toxicity which in the judgment of the Investigator or Sponsor requires removal of the subject from the study.

Subjects who received <90% of the tislelizumab infusion in Cycle 1 (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will need to be replaced.

Resumption of tislelizumab administration for subjects experiencing DLTs may be permitted according to the criteria described in Section 5.1.2, if clinically appropriate, contingent on the return of the DLT to ≤ Grade 0-1 severity and interruption or delay of treatment for no more than 6 weeks (12 weeks for Phase 1A Part 3 and Phase 1B).

5.1.2 Dose Modifications, Dose Delay and Missing Dose

Dose adjustments will be allowed for tislelizumab for weight changes at the beginning of each cycle. Dose must be adjusted if body weight changes reach 10% or greater (increase or decrease).

In the case that an infusion cannot be administered at a scheduled visit, the instruction below should be followed. If the delay is between 1 and 7 days for Q2W schedule and 1 to 10 days for Q3W schedule, the subject should be dosed as soon as possible and procedures at the original scheduled visit should be performed. If the delay is more than 7 (for Q2W) or 10 (for Q3W) days, the delayed dose should be skipped and considered a missed dose, the

subject will be dosed at Day 1 of the next scheduled cycle. In both cases, subsequent visits will follow every 2 weeks (Q2W schedule) or Q3W schedule according to the original schedules. Subjects with infusion delays > 6 weeks from planned dosing date for reason(s) other than treatment-related toxicity should normally discontinue treatment and enter the Follow-up Period with the exception of delays related to prophylactic vaccinations or after specific consultation and agreement between the Investigator and Sponsor medical monitor in settings where benefit/risk may justify continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT irAEs).

Tislelizumab will be withheld for any of the following treatment-related adverse reactions:

1. Grade 2 pneumonitis
2. Grade 2 or 3 colitis/diarrhea
3. Grade 3-4 hypophysitis
4. Grade 2-3 nephritis
5. Grade 3-4 thyroid disorders
6. Grade 2-3 ALT or aspartate aminotransferase (AST) elevations
7. Grade 2 neurological toxicity
8. Grade 3 skin reactions
9. Grade 3-4 diabetes/hyperglycemia
10. Grade 3 ocular toxicity
11. Grade 3 pancreatitis
12. Grade 3 arthritis
13. Grade 3 mucositis/stomatitis
14. Grade 2-4 Myositis/Rhabdomyolysis
15. Grade 1 Myocarditis
16. Any other severe or Grade 3 treatment-related adverse reaction except for asymptomatic laboratory abnormalities

Refer to Section 7.3 and Appendix 10 for more detailed information regarding dose modification and management of irAEs.

In Phase 1A Part 1 and 2, tislelizumab dosing can be resumed for subjects whose adverse reactions recover to Grade 0-1 within 6 weeks. The dosing interval in subsequent cycles may be increased by 1 week (eg, to 3 weeks in subjects who were on Q2W schedule, and to 4 weeks in subjects who were on Q3W schedule). The visit and assessment schedule for subjects on 3 week interval will follow those designed for Q3W, and the visit and assessment schedule for subjects on 4 week interval will follow those designed for Q2W, but maybe with reduced frequency for some of the assessments at the Investigator's discretion. The dosing interval can only be prolonged once.

In Phase 1A Part 3, tislelizumab dosing can be resumed for subjects whose adverse reactions recover to Grade 0-1 within 12 weeks after last dose of tislelizumab. The tislelizumab dose may be resumed to original dose level and schedule if deemed necessary by the Investigator after consultation with the Sponsor.

In Phase 1B, tislelizumab dosing can be resumed for subjects whose adverse reactions recover to Grade 0-1 within 12 weeks after last dose of tislelizumab. The tislelizumab dose may be resumed to original dose level and schedule if deemed necessary by the investigator after consultation with the Sponsor.

Two dosing delays due to toxicity will be permitted. In the event of a third occurrence of a toxicity which would require dosing delay, study therapy will be discontinued permanently after consultation with the Sponsor.

Tislelizumab will be permanently discontinued for any of the following after consultation with the Sponsor:

1. Severe or life-threatening adverse reactions, including any of the following:
    - Grade 4 non-hematologic toxicity
    - Grade 4 hematologic toxicity, including Grade 4 neutropenia that last >7 days
    - Grade 4 colitis/diarrhea, diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
    - Grade 4 AST or ALT

- Grade 4 skin reactions, Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations
- Severe (ie, CTCAE Grade 3 or 4) motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
- Severe (ie, CTCAE Grade 3 or 4) immune-mediated reactions involving any organs (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy, Grade 4 ocular toxicity
- Grade 4 mucositis/stomatitis
- Grade 2-4 Myocarditis
- Grade 3 or above infusion reaction (except for a transient Grade 3 infusion reaction that resolves within 6 hours of onset) (Section 7.3.2)

2. Inability to reduce corticosteroid dose for immune-related adverse reactions to <10 mg prednisone or equivalent per day

In case a subject is benefiting from the study treatment while meeting the discontinuation criteria described above, discussion between Sponsor and Investigator will be conducted to make a decision that will be in the best interest of the subject.

Refer to Section 7.3.4 and Appendix 10 for more details about irAEs and management of such events.

5.1.3 Phase 1A Part 1: Dose Escalation

The Phase 1A, Part 1 component is a multicenter, open label, multiple dose, dose escalation, first in human study. Four dose levels are planned: 0.5, 2.0, 5.0 and 10 mg/kg, Q2W as presented in Table 4. The highest dose to be tested during dose escalation is 10 mg/kg Q2W. If 0/3 subjects or ≥ 1/6 subjects develop a DLT at that dose, then MTD is not reached and 10 mg/kg is considered the MAD.

Table 4 Suggested Dose Escalation Scheme

Step	Dose[1]
1	0.5 mg/kg Q2W
2	2 mg/kg Q2W
3	5 mg/kg Q2W
4	10 mg/kg Q2W

Abbreviations: Q2W, every two weeks.

[1] The actual dose levels and dose regimens administered in each step will depend on the data available from the previous step, as determined by the SMC.

After the first subject in the first dose level receives the Cycle 1, Day 1 dose, subsequent subjects in the first cohort will not be dosed until the first subject has been observed for at least 24 hours to exclude unexpected acute toxicity.

Continuous safety evaluation will be performed by the Sponsor, the Coordinating Investigator, and Investigators. An SMC will be established for the determination of dose levels to be administered and dose regimen during dose escalation, and will utilize the data available from the previous dose levels (see Section 8.3.1 for committee composition).

5.1.3.1 Dose Escalation and Dose Finding

Evaluation of a cohort of at least three (3) subjects completing one cycle of treatment at that dose level and dose regimen without a DLT is required prior to determining the next dose level and dose regimen for the next cohort.

The study will follow a modified 3+3 dose escalation scheme. At least three (3) subjects will be enrolled into each cohort. Additional subject(s), up to a maximum of six (6) subjects in total, will be enrolled if more than three (3) have been screened and are eligible for the cohort. Dose-escalation scheme will follow the rules stipulated in the standard 3 + 3 dose escalation scheme. For example, three (3) additional subjects will be enrolled if a DLT is observed in one (1) of three (3) subjects; additional two (2) subjects will be enrolled if a DLT is observed in one (1) of four (4) subjects; and additional one (1) subject will be enrolled if a DLT is observed in one (1) of five (5) subjects. No additional subjects are required if a DLT is observed in one (1) of six (6) subjects.

If none (0) of the subjects in the cohort experience a DLT by the end of Cycle 1, escalation to the next dose will occur, as determined by the SMC.

If one (1) out of six (6) subjects experience a DLT by the end of Cycle 1, escalation to the next dose will occur, as determined by the SMC.

No additional subjects will be treated at a given dose level if two (2) or more of the subjects in a cohort develop a DLT in Cycle 1. In this instance the MTD is considered to have been

exceeded and as noted above, the MTD will be considered to be the dose level below this level or an intermediate dose level that has been evaluated and has not exceeded the MTD.

The SMC may decide to evaluate an intermediate, not pre-defined and not previously-studied dose or less frequent dosing schedule (eg, Q3W), if evaluation of toxicity at such a dose or schedule is desired. If this approach is taken, up to 6 new subjects should be enrolled at the new intermediate dose or schedule.

Subjects who received <90% of the tislelizumab infusion in Cycle 1 (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and need to be replaced.

5.1.3.2 Schedule of Assessment

The schedule of events for Phase 1A Part 1 is presented in Table 5 and the PK sampling schedule in Table 6.

Table 5 Phase 1A Part 1 Study Assessments and Procedures Schedule

Phase 1A Part 1	Screening [1]	Treatment Period													Safety Follow-up [2]	Survival Follow-up [23]
		Cycle 1 (28 Days, DLT period)						Cycle 2 and Additional Cycles (except Cycle 4) (28 Days)		Cycle 4 (28 Days)						
Days	-28 to -1	1	2	4 (or 5)	8	15 ± 1	22 ± 1	1 ± 2	15 ± 2	1 ±2	2	4 (or 5)	8	15 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Informed consent [3]	x															
Inclusion/exclusion criteria	x															
Demographic/Medical History/ Prior Medications [4]	x															
Vital signs/Weight [5]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Physical examination	x	x				x		x	x	x				x	x	
Ophthalmologic examination[24]	x					x		x[24]							x	
ECOG performance status	x	x						x		x					x	
12-lead ECG [6]	x	x				x		x		x					x	
Review Adverse Events [7]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Review Concomitant Medications	x	x			x	x	x	x	x	x				x	x	
Hematology [8]	x	x			x	x		x	x	x				x	x	
Comprehensive Serum Chemistry Panel [8]	x	x			x	x		x	x	x				x	x	
Coagulation Parameters [9]	x														x	
Urinalysis [8]	x	x			x	x		x	x	x				x	x	
Pregnancy Test [10]	x															
Immune Cell Subtyping (FACS) and Cytokine/Chemokine Panel [11]		x				x		x		x					x	
Thyroid Function [12]		x						x		x					x	
Immunoglubulins [13]		x						x		x					x	
Anti-tislelizumab Antibodies [14]		x						x		x					x	
Protein biomarkers in Blood [15]		x						x		x					x	
Genomics biomarkers in Blood [15]		x						x		x					x	
Pharmacokinetics [16]		x	x	x	x	x		x		x	x	x	x	x	x	
HIV [17]	x															

Phase 1A Part 1 (cont.)	Screening [1]	Treatment Period													Safety Follow-up [2]	Survival Follow-up [24]
		Cycle 1 (28 Days, DLT period)						Cycle 2 and Additional Cycles (except Cycle 4) (28 Days)		Cycle 4 (28 Days)						
Days	-28 to -1	1	2	4 (or 5)	8	15 ± 1	22 ± 1	1 ± 2	15 ± 2	1 ±2	2	4 (or 5)	8	15 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Hepatitis B and C [17]	x									x (Cycle 5 and every 4 cycles)[17]						
Serum Tumor Markers (if appropriate) [18]	x							x[18]							x	
Tumor Imaging [19]	x							x[19]								
Bone Scan [20]	x							x[20]								
Study Drug administration (30-120 minutes infusion)		x				x		x	x	x				x		
Archival Tumor Tissues [21] (additional consent required)	x															
Fresh Tumor Tissues [22] (additional consent required)	x							x[22]							x	
Survival Status																x

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; X, to be performed.

1. It is preferred that routine laboratory tests (eg, hematology, chemistry, and urinalysis) for screening are conducted within 10 days prior to the first dosing, although tests done within 28 days are acceptable.
2. The mandatory Safety Follow-Up visit should be conducted 30 days (± 3 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
3. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg within 28 days prior to Cycle 1 Day 1). Assign Baseline number when the study informed consent is signed.
4. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the Investigator. Complete medication history for 30 days before the first dose (C1D1) of study mediation needs to be reported.
5. Vital signs to include temperature, pulse, respiratory rate and blood pressure.

6. Electrocardiogram assessments are to be performed with the subject in semi recumbent supine position and rested for 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening as baseline, at the time of PK blood collection for PK (C_{max}) within 30 minutes after the end of the first infusion of tislelizumab, after infusion of tislelizumab in Day 15 of Cycle 1 and Day 1 of every subsequent cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up visit. Additional ECGs may be obtained if clinically indicated (refer to Section 8.2.3).
7. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE v 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. Telephone contacts with patients should be conducted to assess immune-related AEs 90 days after the last dose of tislelizumab 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 drug-related SAEs will be recorded by the Investigator after treatment discontinuation until subject death or loss to follow-up, whichever occurs first.
8. Routine laboratory tests (eg, hematology, chemistry, and urinalysis) will be performed by the local study site laboratory or their contract laboratory. Hematology, chemistry, and urinalysis may be collected up to 72 hours prior to any Cycle Day 1 and Day 15 dosing. Of note, creatine kinase (CK) and creatine kinase – cardiac muscle isoenzyme (CK-MB) will be assessed as part of the serum chemistry panel (as per Appendix 2). In the event CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.
9. Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT) should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
10. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 7 days before the first investigational product administration).
11. Only for the dose-escalation subjects treated in Melbourne sites due to sample and assay logistics. Cycle 1: predose Day 1 and Day 15; Cycle 2 and every cycle in first 6 months: predose Day 1; at the mandatory Safety Follow-Up Visit. Collect 40 mL blood in acid-citrate-dextrose (ACD) on the date indicated, transport within 8 hours to the central laboratory. Fluorescence-activated cell sorting (FACS) analysis of lymphocyte subpopulations and other immune cells, and analysis of cytokines/chemokines will be performed.
12. T3, T4, TSH; at every cycle, and at the mandatory Safety Follow-Up Visit. Analysis of T3, T4 and TSH will be performed by the local study site laboratory.

13. Analysis of IgG and IgM at predose of Day 1 of every cycle in the first 12 months, approximately every 8 weeks thereafter, and at the Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.
14. Blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every cycle in the first 6 months, every 2 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. Analysis will be performed by a central laboratory.
15. Blood collected at predose on Day 1 of every cycle until 6 months of study, and at the safety follow up visit for the subjects who have confirmed disease progression during the study to explore resistance mechanism. Samples will be processed according to the Lab Manual.
16. For timing refer to Table 6Phase 1A Part 1 Pharmacokinetic Sampling for details on timing of pharmacokinetics sample collection. Procedures for collection of samples are described in the Lab Manual.
17. Testing will be performed by the local laboratory at Screening. Include Hepatitis C virus (HCV) antibody (HCVAb), Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb) and human immunodeficiency virus (HIV) 1/2 antibodies. Subjects who are HBsAg and HBcAb positive or HCV antibody positive at screening must not be enrolled until further definite testing with Hepatitis B virus (HBV) deoxyribonucleic acid (DNA) titers and HCV ribonucleic acid (RNA) tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C, respectively. Subjects enrolled in the study who had detectable HBV DNA or HCV RNA at Screening should be tested for HBV or HCV viral load, respectively, every 4 cycles (± 7 days) throughout the study, eg Screening, Cycle 5, Cycle 9, and so on (and whenever clinically indicated). For subjects who already received 4 or more doses of study drug, the viral load test should be repeated at the subject's next visit and every 4 cycles according to the schedule from first dose (Cycle 1 Day 1), and whenever clinically indicated. HCC subjects who test positive for HCV will not be discontinued. HCC subjects who test positive for HBV should be treated as per local guidelines at the investigator's discretion.
18. Standard tumor markers (eg, alpha fetoprotein [AFP] for HCC and cancer antigen 125 [CA 125] for ovarian cancer, as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter, and at the mandatory Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.
19. Tumor imaging (either computed tomography [CT] or magnetic resonance imaging [MRI], with preference for CT) will be performed within 28 days prior to enrollment, and while on study approximately every 8 weeks in the first 12 months and approximately every 12 weeks thereafter. The same imaging technique should be used in a subject throughout the study. After first documentation of response (CR or PR), imaging performed at the next

regularly scheduled time point will be used for response confirmation. **After patient's re-consenting, Progressive disease (PD) suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next regularly scheduled time point but not to exceed 12 weeks, before discontinuation of study treatment**. **Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging (Section 5.2.5.2).**

20. **Bone scans must be done for subjects with metastatic castration-resistant prostate cancer (mCRPC) as described in Section 8.2.4. For other subjects, bone scans at baseline or subsequent visits will be performed only if clinically indicated.**
21. Collection of archival tumor tissue for purpose of biomarker analysis. Written patient consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the Lab Manual.
22. Archival tumor tissue will be collected for purpose of biomarker analysis, although a fresh baseline tumor biopsy (within 8 weeks before starting treatment) is strongly recommended. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is mandatory; for these subjects, an optional biopsy for biomarker analysis after 2 cycles of treatment (approximately Cycle 3 Day 1) is strongly recommended. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a core or excisional biopsy of the tumor (cytologic or fine-needle aspiration samples are not acceptable) should be obtained that has proper size for histological examination and biomarker analysis (eg, IHC of PD-1, PD-L1, PD-L2; genomic profiling).
23. Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow up all subjects for their survival status until subject death or termination by the Sponsor.
24. Ophthalmologic exam (such as eyesight/visual acuity, fundoscopic, slit lamp microscopy, and optical coherence tomography [or equivalent diagnostic test]) within 28 days prior to first dose, Cycle 1 Day 15 (±1 day), and Cycle 3 Day 1 (±7 days). Subjects will subsequently undergo repeat assessments

by an appropriate specialist approximately every 4 cycles/16 weeks (± 7 days) during study treatment and a final assessment <30 days after the last dose of study treatment. For those subjects who have already received 2 or more doses of study drug, the exam should be repeated at the subject's next visit and then approximately every 4 cycles/16 weeks according to the schedule from first dose (Cycle 1 Day1). Investigators should solicit subjects regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see **Appendix 10**).

Table 6 Phase 1A Part 1 Pharmacokinetic Sampling

Phase 1A Part 1		Days		Time Points	For subjects in the dose escalation cohorts
Treatment Period	Cycle 1 (28 Days, DLT period)	1	Predose	-60 min to 0 h	x
			Postdose	End infusion to 30 min[1]	x
				90 min[2]	x
				360 min[3]	x
		2		24 h[3]	x
		4 (or 5)		72 h[3]	x
		8			x
		15 ± 1	Predose	-60 min to 0 h	x
			Postdose	End infusion to 30 min[1]	x
	Cycle 2 and Additional Cycles (except for Cycle 4) (28 Days) [4]	1 ± 2	Predose	-60 min to 0 h	x
			Postdose	End infusion to 30 min[1]	x
	Cycle 4 (28 days)	1 ± 2	Predose	-60 min to 0 h	x
			Postdose	End infusion to 30 min[1]	x
				90 min	x
				360 min[3]	x
		2		24 h[3]	x
		4 (or 5)		72 h[3]	x
		8			x
		15 ± 2	Predose		x
Safety Follow-up	(30 Days ± 7 Days after last dose)				x[5]

Abbreviations: DLT, dose-limiting toxicity; min, minute.
Please note: Actual drug dosing and PK sampling times have to be documented by the sites and will be captured in the database.

1. Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

2. Window: ±20 minutes.

3. Window: ±2 hours.

4. Cycle 2 and subsequently every cycle except for Cycle 4 during the first 12 months of study therapy, approximately every 6 months thereafter.

5. PK assays should be performed at the mandatory Safety Follow-Up Visit.

Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

5.1.4 Phase 1A Part 2: Schedule Expansion

The Phase 1A, Part 2 component will evaluate the safety and PK of two dosing schedules Q2W versus Q3W at selected doses that have cleared the DLT period without exceeding MTD (eg, 2 mg/kg or 5 mg/kg, up to 10 mg/kg). Ten to 20 subjects per dose schedule will be enrolled to evaluate the safety, the PK and preliminary efficacy. Tumors types to be enrolled include but not limited to CRC, NSCLC, RCC, bladder cancer, ovarian cancer and melanoma. Other cancers that are deemed to be likely to benefit from PD-1 inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrollment subject to discussion with the medical monitor.

5.1.4.1 Criteria for Stopping Phase 1A Part 2

The doses selected for the Q2W schedule expansion will have been evaluated for DLT and demonstrated as safe in the Phase 1A Part 1 study. These doses administrated at a less frequent schedule of Q3W should be safe as well. Nevertheless, to adequately monitor safety of subjects enrolled in dosing schedule expansion, when at least 6 subjects have been treated at a specific dose and schedule and ≥33% of the subjects experienced a DLT during the first cycle in both Q2W and Q3W schedules (as defined in Section 5.1.1 of the protocol), study accrual will be held pending data review by the SMC. Tislelizumab will also be withheld in the event of other serious adverse reactions according to pre-specified criteria (as defined in Section 5.1.2 of the protocol). Q2W and Q3W schedule expansion may be conducted sequentially or in parallel.

In the event that a MTD is not identified, RP2D and dosing regimen used in the Phase 1B stage will be determined by the SMC and the Sponsor based on the PK, tolerability and preliminary antitumor activities observed in the Phase 1A stage, as well as other available data. Based on the Phase 1A data, more than one dose or dosing regimen may be selected to be further evaluated in Phase 1B for safety and preliminary efficacy in select tumor types.

5.1.4.2 Schedule of Assessment

The schedule of events for Phase 1A Part 2 is presented in Table 7 (Q2W schedule) and Table 8 (Q3W schedule).

Table 7 Phase 1A Part 2 Study Assessments and Procedures Schedule (For Q2W schedule)

Phase 1A Part 2: Q2W schedule	Screening [1]	Treatment Period						Safety Follow-up [2]	Survival Follow-up [22]
		Cycle 1 (28 Days)				Cycle 2 and Additional Cycles (Every 28 Days)			
Days	-28 to -1	1	4 (or 5)	8	15 ± 1	1 ± 2	15 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Informed consent [3]	x								
Inclusion/exclusion criteria	x								
Demographic/Medical History/ Prior Medications [4]	x								
Vital signs/Weight [5]	x	x	x	x	x	x	x	x	
Physical examination	x	x			x	x	x	x	
Ophthalmologic examination [23]	x					x[23]		x	
ECOG performance status	x	x				x		x	
12-lead ECG [6]	x	x			x	x		x	
Review Adverse Events [7]		x	x	x	x	x	x	x	
Review Concomitant Medications	x	x			x	x	x	x	
Hematology [8]	x	x		x	x	x	x	x	
Comprehensive Serum Chemistry Panel [8]	x	x		x	x	x	x	x	
Coagulation Parameters [9]	x							x	
Urinalysis [8]	x	x		x	x	x	x	x	
Pregnancy Test [10]	x								
Thyroid Function [11]		x				x		x	
Immunoglubulins [12]		x				x		x	
Anti-tislelizumab Antibodies [13]		x				x		x	
Protein biomarkers in Blood [14]		x				x		x	

Phase 1A Part 2: Q2W schedule (cont.)	Screening [1]	Treatment Period						Safety Follow-up [2]	Survival Follow-up [23]
		Cycle 1 (28 Days)				Cycle 2 and Additional Cycles (Every 28 Days)			
Days	-28 to -1	1	4 (or 5)	8	15 ± 1	1 ± 2	15 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Genomics biomarkers in Blood [14]		x				x		x	
Pharmacokinetics [15]		x	x	x	x	x		x	
HIV [16]	x								
Hepatitis B and C [16]	x					x (Cycle 5 and every 4 cycles)[16]			
Serum Tumor Markers (if appropriate) [17]	x					x[17]		x	
Tumor Imaging [18]	x					x[18]			
Bone Scan [19]	x					x[19]			
Study Drug Administration (30-120 minutes infusion)		x			x	x	x		
Archival Tumor Tissues [20] (additional consent required)	x								
Fresh Tumor Tissues [21] (additional consent required)	x					x[21]		x	
Survival Status									x

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; x, to be performed.

1. It is preferred that routine laboratory tests (eg, hematology, chemistry, and urinalysis) for screening are conducted within 10 days prior to the first dosing, although tests done within 28 days are acceptable.
2. The mandatory Safety Follow-Up visit should be conducted 30 days (± 3 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
3. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical

management are acceptable in lieu of a screening test if performed within the specified time frame (eg, within 28 days prior to Cycle 1 Day 1). Assign Baseline number when the study informed consent is signed.

4. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the Investigator. Complete medication history for 30 days before the first dose (C1D1) of study mediation needs to be reported.
5. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
6. Electrocardiogram assessments are to be performed with the subject in semi recumbent supine position and rested for 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening as baseline, at the time of PK blood collection for PK (C_{max}) within 30 minutes after the end of the first infusion of tislelizumab, after infusion of tislelizumab in Day 15 of Cycle 1 and Day 1 of every subsequent cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up visit. Additional ECGs may be obtained if clinically indicated (refer to Section 8.2.3).
7. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE v 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. Telephone contacts with patients should be conducted to assess immune-related AEs 90 days after the last dose of tislelizumab 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 drug-related SAEs will be recorded by the Investigator after treatment discontinuation until subject death or loss to follow-up, whichever occurs first.
8. Routine laboratory tests (eg, hematology, chemistry, and urinalysis) will be performed by the local study site laboratory or their contract laboratory. Hematology, chemistry, and urinalysis may be collected up to 72 hours prior to any Cycle Day 1 dosing. Of note, creatine kinase (CK) and creatine kinase – cardiac muscle isoenzyme (CK-MB) will be assessed as part of the serum chemistry panel (as per Appendix 2). In the event CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.
9. PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
10. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 7 days before the first investigational product administration).

11. T3, T4, TSH; at every cycle, and at the mandatory Safety Follow-Up Visit. Analysis of T3, T4 and TSH will be performed by the local study site laboratory.
12. Analysis of IgG and IgM at predose of Day 1 of every cycle in the first 12 months, approximately every 8 weeks thereafter, and at the Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.
13. Blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every cycle in the first 6 months, every 2 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. Analysis will be performed by a central laboratory.
14. Blood collected at predose on Day 1 of every cycle until 6 months of study, and at the safety follow up visit for the subjects who have confirmed disease progression during the study to explore resistance mechanism. Samples will be processed according to the Lab Manual.
15. Procedures for collection of PK samples are described in the Lab Manual. Predose (within 60 min before start infusion) and postdose (within 30 min after the end of infusion) samples should be collected at Cycle 1 Day 1, Day 15, Day 1 of Cycle 2 and subsequently every cycle in the first 12 months, then approximately every 6 months thereafter; two PK samples should be collected at Cycle 1 Day 4 (or 5) and Day 8; additional PK samples should be collected at the mandatory Safety Follow-Up Visit. Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.
16. Testing will be performed by the local laboratory at Screening. Include HCV antibody, HBsAg, HBcAb and HIV 1/2 antibodies. Subjects who are HBsAg and HBcAb positive or HCV antibody positive at screening must not be enrolled until further definite testing with HBV DNA titers and HCV RNA tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C respectively. Subjects enrolled in the study who had detectable HBV DNA or HCV RNA at Screening should be tested for HBV or HCV viral load, respectively, every 4 cycles (± 7 days) throughout the study, eg Screening, Cycle 5, Cycle 9, and so on (and whenever clinically indicated). For subjects who already received 4 or more doses of study drug, the viral load test should be repeated at the subject's next visit and every 4 cycles according to the schedule from first dose (Cycle 1 Day 1), and whenever clinically indicated. HCC subjects who test positive for HCV will not be discontinued. HCC subjects who test positive for HBV should be treated as per local guidelines at the investigator's discretion.
17. Standard tumor markers (eg, AFP or HCC and CA 125 for ovarian cancer, as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter, and at the mandatory Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be

performed by a central laboratory.

18. Tumor imaging (either CT or MRI, with preference for CT) will be performed within 28 days prior to enrollment, and while on study approximately every 8 weeks in the first 12 months and approximately every 12 weeks thereafter. The same imaging technique should be used in a subject throughout the study. After first documentation of response (CR or PR), imaging performed at the next regularly scheduled time point will be used for response confirmation. **After patient's re-consenting, PD suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next regularly scheduled time point but not to exceed 12 weeks, before discontinuation of study treatment**. **Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging (Section 5.2.5.2).**
19. Bone scans must be done for subjects with mCRPC as described in Section 8.2.4. For other subjects, bone scans at baseline or subsequent visits will be performed only if clinically indicated.
20. Collection of archival tumor tissue for purpose of biomarker analysis. Written patient consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the Lab Manual.
21. Archival tumor tissue will be collected for purpose of biomarker analysis, although a fresh baseline tumor biopsy (within 8 weeks before starting treatment) is strongly recommended. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is mandatory; for these subjects, an optional biopsy for biomarker analysis after 2 cycles of treatment (approximately Cycle 3 Day 1) is strongly recommended. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a core or excisional biopsy of the tumor (cytologic or fine-needle aspiration samples are not acceptable) should be obtained that has proper size for histological examination and biomarker analysis (eg, IHC of PD-1, PD-L1, PD-L2; genomic profiling).
22. Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow up all subjects for their

survival status until subject death or termination by the Sponsor.

23. Ophthalmologic exam (such as eyesight/visual acuity, fundoscopic, slit lamp microscopy, and optical coherence tomography [or equivalent diagnostic test]) within 28 days prior to first dose and Cycle 3 Day 1 (±7 days). Subjects will subsequently undergo repeat assessments by an appropriate specialist approximately every 4 cycles/16 weeks (± 7 days) during study treatment and a final assessment <30 days after the last dose of study treatment. For those subjects who have already received 2 or more doses of study drug, the exam should be repeated at the subject's next visit and then approximately every 4 cycles/16 weeks (± 7 days) according to the schedule from first dose (Cycle 1 Day1). Investigators should solicit subjects regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 10).

Table 8 Phase 1A Part 2 Study Assessments and Procedures Schedule (For Q3W schedule)

Phase 1A Part 2: Q3W schedule	Screening [1]	Treatment Period					Safety Follow-up [2]	Survival Follow-up [23]
		Cycle 1 (21 Days)				Cycle 2 and Additional Cycles (Every 21 Days)		
Days	-28 to -1	1	4 (or 5)	8	15 ± 1	1 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Informed consent [3]	x							
Inclusion/exclusion criteria	x							
Demographic/Medical History/ Prior Medications [4]	x							
Vital signs/Weight [5]	x	x	x	x	x	x	x	
Physical examination	x	x				x	x	
Ophthalmologic examination [23]	x					x[23]	x	
ECOG performance status	x	x				x	x	
12-lead ECG [6]	x	x			x	x	x	
Review Adverse Events [7]		x	x	x	x	x	x	
Review Concomitant Medications	x	x				x	x	
Hematology [8]	x	x		x	x	x	x	
Comprehensive Serum Chemistry Panel [8]	x	x		x	x	x	x	
Coagulation Parameters [9]	x						x	
Urinalysis [8]	x	x		x	x	x	x	
Pregnancy Test [10]	x							
Thyroid Function [11]		x				x	x	
Immunoglubulins [12]		x				x	x	
Anti-tislelizumab Antibodies [13]		x				x	x	
Protein biomarkers in Blood [14]		x				x	x	

Phase 1A Part 2: Q3W schedule (cont.)	Screening [1]	Treatment Period					Safety Follow-up [2]	Survival Follow-up [22]
		Cycle 1 (21 Days)				Cycle 2 and Additional Cycles (Every 21 Days)		
Days	-28 to -1	1	4 (or 5)	8	15 ± 1	1 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Genomics biomarkers in Blood [14]		x				x	x	
Pharmacokinetics [15]		x	x	x	x	x	x	
HIV [16]	x							
Hepatitis B and C [16]	x					x (Cycle 5 and every 4 cycles)[16]		
Serum Tumor Markers (if appropriate) [17]	x					x[17]	x	
Tumor Imaging [18]	x					x[18]		
Bone Scan [19]	x					x[19]		
Study Drug Administration (30-120 minutes infusion)		x				x		
Archival Tumor Tissues [20] (additional consent required)	x							
Fresh Tumor Tissues [21] (additional consent required)	x					x[21]	x	
Survival Status								x

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; x, to be performed.

1. It is preferred that routine laboratory tests (eg, hematology, chemistry, and urinalysis) for screening are conducted within 10 days prior to the first dosing, although tests done within 28 days are acceptable.
2. The mandatory Safety Follow-Up visit should be conducted 30 days (± 3 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
3. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg within 28 days prior to Cycle 1 Day 1). Assign Baseline

number when the study informed consent is signed.

4. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the Investigator. Complete medication history for 30 days before the first dose (C1D1) of study mediation needs to be reported.
5. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
6. Electrocardiogram assessments are to be performed with the subject in semi recumbent supine position and rested for 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening as baseline, at the time of PK blood collection for PK (C_{max}) within 30 minutes after the end of the first infusion of tislelizumab, at Cycle 1 Day 15, after infusion of tislelizumab in every subsequent cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up visit. Additional ECGs may be obtained if clinically indicated (refer to Section 8.2.3).
7. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE v 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. Telephone contacts with patients should be conducted to assess immune-related AEs 90 days after the last dose of tislelizumab 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 drug-related SAEs will be recorded by the Investigator after treatment discontinuation until subject death or loss to follow-up, whichever occurs first.
8. Routine laboratory tests (eg, hematology, chemistry, and urinalysis) will be performed by the local study site laboratory or their contract laboratory. Hematology, chemistry, and urinalysis may be collected up to 72 hours prior to any Cycle Day 1 dosing. Of note, creatine kinase (CK) and creatine kinase – cardiac muscle isoenzyme (CK-MB) will be assessed as part of the serum chemistry panel (as per Appendix 2). In the event CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.
9. PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
10. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 7 days before the first investigational product administration).
11. T3, T4, TSH; at every cycle, and at the mandatory Safety Follow-Up Visit. Analysis of T3, T4 and TSH will be performed by the local study site laboratory.

12. Analysis of IgG and IgM at predose of Day 1 of every cycle in the first 12 months, approximately every 9 weeks thereafter, and at the Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.
13. Blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every cycle in the first 6 months, every 3 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. Analysis will be performed by a central laboratory.
14. Blood collected at predose on Day 1 of every cycle until 6 months of study, and at the safety follow up visit for the subjects who have confirmed disease progression during the study to explore resistance mechanism. Samples will be processed according to the Lab Manual.
15. Procedures for collection of PK samples are described in the Lab Manual. Predose (within 60 min before start infusion) and postdose (within 30 min after the end of infusion) samples should be collected at Day 1 of Cycle 1, Cycle 2 and subsequently every cycle in the first 12 months, then approximately every 6 months thereafter; three PK samples should be collected at Cycle 1 Day 4 (or 5), Day 8 and Day 15; additional PK samples should be collected at the mandatory Safety Follow-Up Visit. Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.
16. Testing will be performed by the local laboratory at Screening. Include HCV antibody, HBsAg, HBcAb and HIV 1/2 antibodies. Subjects who are HBsAg and HBcAb positive or HCV antibody positive at Screening must not be enrolled until further definite testing with HBV DNA titers and HCV RNA tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C respectively. Subjects enrolled in the study who had detectable HBV DNA or HCV RNA at Screening should be tested for HBV or HCV viral load, respectively, every 4 cycles (± 7 days) throughout the study, eg Screening, Cycle 5, Cycle 9, and so on (and whenever clinically indicated). For subjects who already received 4 or more doses of study drug, the viral load test should be repeated at the subject's next visit and every 4 cycles according to the schedule from first dose (Cycle 1 Day 1), and whenever clinically indicated. HCC subjects who test positive for HCV will not be discontinued. HCC subjects who test positive for HBV should be treated as per local guidelines at the investigator's discretion.
17. Standard tumor markers (eg, AFP for HCC and CA 125 for ovarian cancer, as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter, and at the mandatory Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.
18. Tumor imaging (either CT or MRI, with preference for CT) will be performed within 28 days prior to enrollment, and while on study approximately

every 9 weeks in the first 12 months and approximately every 12 weeks thereafter. The same imaging technique should be used in a subject throughout the study. After first documentation of response (CR or PR), imaging performed at the next regularly scheduled time point will be used for response confirmation. **After patient's re-consenting, PD suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next regularly scheduled time point before discontinuation of study treatment**. **Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging (Section 5.2.5.2).**

19. **Bone scans must be done for subjects with mCRPC as described in Section 8.2.4. For other subjects, bone scans at baseline or subsequent visits will be performed only if clinically indicated.**
20. Collection of archival tumor tissue for purpose of biomarker analysis. Written patient consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the Lab Manual.
21. Archival tumor tissue will be collected for purpose of biomarker analysis, although a fresh baseline tumor biopsy (within 8 weeks before starting treatment) is strongly recommended. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is mandatory; for these subjects, an optional biopsy for biomarker analysis after 2 cycles of treatment (approximately Cycle 3 Day 1) is strongly recommended. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a core or excisional biopsy of the tumor (cytologic or fine-needle aspiration samples are not acceptable) should be obtained that has proper size for histological examination and biomarker analysis (eg, IHC of PD-1, PD-L1, PD-L2; genomic profiling).
22. Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow up all subjects for their survival status until subject death or termination by the Sponsor.
23. Ophthalmologic exam (such as eyesight/visual acuity, fundoscopic, slit lamp microscopy, and optical coherence tomography [or equivalent diagnostic

test]) will be performed within 28 days prior to first dose and at the end of week 9 (±7 days). Subjects will subsequently undergo repeat assessments by an appropriate specialist approximately every 5 cycles/15 weeks (± 7 days) during study treatment and a final assessment <30 days after the last dose of study treatment. For those subjects who have already received 3 or more doses of study drug, the tests should be repeated at the patient's next visit and then every approximately every 5 cycles/15 weeks (± 7 days) according to the schedule from first dose (Cycle 1 Day1). Investigators should solicit subjects regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 10).

5.1.5 Phase 1A Part 3: Flat Dose Exploration

The Phase 1A, Part 3 component will evaluate the safety and PK of tislelizumab at flat doses (ie 200 mg, Q3W) that do not exceed the exposure of the MTD as determined in the Phase 1A Part 1 study. Approximately 10 to 20 subjects will be enrolled. Tumor types to be enrolled include but not limited to NSCLC, RCC, HNSCC, bladder cancer, melanoma, gastric, oesophageal, Merkel-cell carcinoma and HCC. Other cancers that are deemed to be likely to benefit from PD-1 inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrolment subject to discussion with the Medical Monitor in advance.

This part of the Phase 1A study will be conducted in Australia and/or New Zealand sites only and may be conducted in parallel with a Phase 1B study that evaluates a RP2D selected based on the Phase IA, Part 1 and 2 data as described in Section 2.5.4.

5.1.5.1 Criteria for Stopping Phase 1A Part 3

The doses selected for the flat dose exploration will have been evaluated for DLT and demonstrated as safe in the Phase 1A Part 1 study. Nevertheless, to adequately monitor safety of subjects enrolled in flat dose exploration, study accrual will be held pending data review by the SMC when at least 6 subjects have been treated and ≥33% of the subjects experienced a DLT during the first cycles consisting of 21 days (as defined in Section 5.1.1 of the protocol). A planned formal SMC review of safety data will be performed after all subjects have completed first cycle (21 days) of treatment, or withdrew due to any reason (PD, AE, or death).

5.1.5.2 Schedule of Assessment

The schedule of events for Phase 1A Part 3 is presented in Table 9 and the pharmacokinetic sampling schedule is presented in Table 10.

Table 9 Phase 1A Part 3 Study Assessments and Procedures Schedule

Phase 1A Part 3: Q3W schedule	Screening [1]	Treatment Period												Safety Follow-up [2]	Survival Follow-up [23]
		Cycle 1 (21 Days)					Cycle 2 and Additional Cycles (except for Cycle 5) (Every 21 Days)	Cycle 5 (21 days)							
Days	-28 to -1	1	2	4 (or 5)	8	15 ± 1	1 ± 2	1	2	4 (or 5)	8	15 ± 1	22 ± 2 [24]	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Informed consent [3]	x														
Inclusion/exclusion criteria	x														
Demographic/Medical History/ Prior Medications [4]	x														
Vital signs/Weight [5]	x	x		x	x	x	x	x					x	x	
Physical examination	x	x					x	x					x	x	
Ophthalmologic examination [23]	x						x[23]							x	
ECOG performance status	x	x					x	x					x	x	
12-lead ECG [6]	x	x				x	x	x					x	x	
Review Adverse Events [7]		x	x	x	x	x	x	x	x	x	x	x	x	x	
Review Concomitant Medications	x	x					x	x					x	x	
Hematology [8]	x	x			x	x	x	x					x	x	
Comprehensive Serum Chemistry Panel [8]	x	x			x	x	x	x					x	x	
Coagulation Parameters [9]	x													x	
Urinalysis [8]	x	x			x	x	x	x					x	x	
Pregnancy Test [10]	x														
Thyroid Function [11]		x					x	x					x	x	

Phase 1A Part 3: Q3W schedule	Screening [1]	Treatment Period												Safety Follow-up [2]	Survival Follow-up [23]
		Cycle 1 (21 Days)					Cycle 2 and Additional Cycles (except for Cycle 5) (Every 21 Days)	Cycle 5 (21 days)							
Days	-28 to -1	1	2	4 (or 5)	8	15 ± 1	1 ± 2	1	2	4 (or 5)	8	15 ± 1	22 ± 2 [24]	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Immunoglubulins [12]		x					x[12]	x					x	x	
Anti-tislelizumab Antibodies [13]		x					x[13]	x						x	
Protein biomarkers in Blood [14]		x					x[14]	x					x	x	
Genomics biomarkers in Blood [14]		x					x[14]	x					x	x	
Pharmacokinetics [15]		x	x	x	x	x	x[15]	x	x	x	x	x	x	x	
HIV [16]	x														
Hepatitis B and C [16]	x						x (Cycle 5 and every 4 cycles)[16]								
Serum Tumor Markers (if appropriate) [17]	x						x[17]							x	
Tumor Imaging [18]	x						x[18]								
Bone Scan [19]	x						x[19]								
Study Drug Administration (30-120 minutes infusion)		x					x	x					x		
Archival Tumor Tissues [20] (additional consent required)	x														
Fresh Tumor Tissues [21] (additional consent required)	x						x[21]							x	
Survival Status															x

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; x, to be performed.

1. It is preferred that routine laboratory tests (eg, hematology, chemistry; and urinalysis) for screening are conducted within 10 days prior to the first dosing, although tests done within 28 days are acceptable.
2. The mandatory Safety Follow-Up visit should be conducted 30 days (± 3 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
3. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg within 28 days prior to Cycle 1 Day 1). Assign Baseline number when the study informed consent is signed.
4. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the Investigator. Complete medication history for 30 days before the first dose (C1D1) of study mediation needs to be reported.
5. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
6. Electrocardiogram assessments are to be performed with the subject in semi recumbent supine position and rested for 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening as baseline, at the time of PK blood collection for PK (C_{max}) within 30 minutes after the end of the first infusion of tislelizumab, at Cycle 1 Day 15, after infusion of tislelizumab in every subsequent cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up visit. Additional ECGs may be obtained if clinically indicated (refer to Section 8.2.3).
7. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE v 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. Telephone contacts with patients should be conducted to assess immune-related AEs 90 days after the last dose of tislelizumab 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 drug-related SAEs will be recorded by the Investigator after treatment discontinuation until subject death or loss to follow-up, whichever occurs first.
8. Routine laboratory tests (eg, hematology, chemistry, and urinalysis) will be performed by the local study site laboratory or their contract laboratory. Hematology, chemistry, and urinalysis may be collected up to 72 hours prior to any Cycle Day 1 dosing. Of note, creatine kinase (CK) and creatine kinase – cardiac muscle isoenzyme (CK-MB) will be assessed as part of the serum chemistry panel (as per Appendix 2). In the event CK-MB

fractionation is not available, please assess troponin I and/or troponin T instead.

9. PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
10. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 7 days before the first investigational product administration).
11. T3, T4, TSH; at every cycle, and at the mandatory Safety Follow-Up Visit. Analysis of T3, T4 and TSH will be performed by the local study site laboratory.
12. Analysis of IgG and IgM at predose of Day 1 of every cycle in the first 12 months, approximately every 9 weeks thereafter, and at the Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.
13. Blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every 2 cycles in the first 6 months, every 4 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. All samples should be drawn at the same time as blood collection for C_{trough}. Analysis will be performed by a central laboratory.
14. Blood collected at predose on Day 1 of every cycle until 6 months of study, and at the safety follow up visit for the subjects who have confirmed disease progression during the study to explore resistance mechanism. Samples will be processed according to the Lab Manual.
15. For timing refer to Table 10 for details on timing of pharmacokinetics sample collection. Procedures for collection of PK samples are described in the Lab Manual. All trough samples should be drawn at the same time as blood collection for anti-tislelizumab antibodies.
16. Testing will be performed by the local laboratory at Screening. Include HCV antibody, HBsAg, HBcAb and HIV 1/2 antibodies. Subjects who are HBsAg and HBcAb positive or HCV antibody positive at screening must not be enrolled until further definite testing with HBV DNA titers and HCV RNA tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C respectively. Subjects enrolled in the study who had detectable HBV DNA or HCV RNA at Screening should be tested for HBV or HCV viral load, respectively, every 4 cycles (± 7 days) throughout the study, eg Screening, Cycle 5, Cycle 9, and so on (and whenever clinically indicated). For subjects who already received 4 or more doses of study drug, the viral load test should be repeated at the subject's next visit and every 4 cycles according to the schedule from first dose (Cycle 1 Day 1), and whenever clinically indicated. HCC subjects who test positive for HCV will not be discontinued. HCC subjects who test positive for HBV should be treated as per local guidelines at the investigator's discretion.
17. Standard tumor markers (eg, AFP for HCC and CA 125 for ovarian cancer, as appropriate for a given tumor type) will be collected within 14 days prior

to Cycle 1 Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter, and at the mandatory Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.

18. Tumor imaging (either CT or MRI, with preference for CT) will be performed within 28 days prior to enrollment, and while on study approximately every 9 weeks in the first 12 months and approximately every 12 weeks thereafter. The same imaging technique should be used in a subject throughout the study. After first documentation of response (CR or PR), imaging performed at the next regularly scheduled time point will be used for response confirmation. **After patient's re-consenting, PD suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next regularly scheduled time point before discontinuation of study treatment. Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging (Section 5.2.5.2).**
19. **Bone scans must be done for subjects with mCRPC as described in Section 8.2.4. For other subjects, bone scans at baseline or subsequent visits will be performed only if clinically indicated.**
20. Collection of archival tumor tissue for purpose of biomarker analysis. Written patient consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the Lab Manual.
21. Archival tumor tissue will be collected for purpose of biomarker analysis, although a fresh baseline tumor biopsy (within 8 weeks before starting treatment) is strongly recommended. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is mandatory; for these subjects, an optional biopsy for biomarker analysis after 2 cycles of treatment (approximately Cycle 3 Day 1) is strongly recommended. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a core or excisional biopsy of the tumor (cytologic or fine-needle aspiration samples are not acceptable) should be obtained that has proper size for histological examination and

biomarker analysis (eg, IHC of PD-1, PD-L1, PD-L2; genomic profiling).

22. Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow up all subjects for their survival status until subject death or termination by the Sponsor.
23. Ophthalmological examinations (such as eyesight/visual acuity, fundoscopy, slit lamp microscopy, and optical coherence tomography [or equivalent diagnostic test]) will be performed within 28 days prior to first dose and at the end of week 9 (±7 days). Subjects will subsequently undergo repeat assessments by an appropriate specialist approximately every 5 cycles/15 weeks (± 7 days) during study treatment and a final assessment <30 days after the last dose of study treatment. For those subjects who have already received 3 or more doses of study drug, the tests should be repeated at the patient's next visit and then every approximately every 5 cycles/15 weeks (± 7 days) according to the schedule from first dose (Cycle 1 Day1). Investigators should solicit subjects regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 10).
24. Visit on Cycle 5 Day 22 is same as Cycle 6 Day 1.

Table 10 Phase 1A Part 3 Pharmacokinetic Sampling

Phase 1A Part 3		Days		Time Points	For subjects in the flat dose exploration cohorts
Treatment Period	Cycle 1 (21 Days)	1	Predose	-60 min to 0 h	x
			Postdose	End infusion to 30 min[1]	x
		2		24 h[2]	x
		4		72 h[2]	x
		8			x
		15			x
	Cycle 2 and Additional Cycles (except for Cycle 5) (21 Days) [3]	1 ± 2	Predose	-60 min to 0 h	x
			Postdose	End infusion to 30 min[1]	x
	Cycle 5 (21 days)	1 ± 2	Predose	-60 min to 0 h	x
			Postdose	End infusion to 30 min[1]	x
		2		24 h[2]	x
		4		72 h[2]	x
		8			x
		15			x
		22 ± 2[4]	Predose		x
Safety Follow-up	(30 Days ± 7 Days after last dose)				x[5]

Abbreviations: h, hour; min, minutes.

Please note: Actual drug dosing and PK sampling times have to be documented by the sites and will be captured in the database.

1. Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

2. Window: ±2 hours.

3. Cycle 2, Cycle 3 and subsequently every 2 cycles except for Cycle 5 during the first 6 months of study therapy, every 4 cycles in the next 6 months, approximately every 6 months thereafter.

4. Visit on Cycle 5 Day 22 is same as Cycle 6 Day 1.

5. PK assays should be performed at the mandatory Safety Follow-Up Visit.

Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

5.1.6 Phase 1B: Indication Expansion

The Phase 1B stage is a multicenter, open label, multiple dose, multiple arm, indication expansion study. The various arms of the study will investigate RP2D(s) to examine the potential efficacy as well as safety and tolerability of tislelizumab in cancer patients who failed standard care therapies. The cancer indications may include:

- Arm 1. Subjects with NSCLC (approximately 50 subjects)
- Arm 2. Subjects with ovarian cancer (approximately 20 subjects)
- Arm 3. Subjects with gastric cancer (approximately 50 subjects)
- Arm 4. Subjects with HCC (approximately 50 subjects)
- Arm 5. Subjects with HNSCC (approximately 20 subjects)
- Arm 6. Subjects with esophageal carcinoma (approximately 50 subjects)
- Arm 7. Subjects with TNBC (approximately 20 subjects)
- Arm 8. Subjects with cholangiocarcinoma (approximately 20 subjects)
- Arm 9. Subjects with RCC, bladder cancer, melanoma, Merkel-cell carcinoma, sarcoma, gastrointestinal stromal tumor (GIST), or cutaneous squamous cell carcinoma (cuSCC). Or any other solid tumors with MSI-H or dMMR, such as CRC or pancreatic cancer (approximately 50 subjects)

For Arms 1, 3, 4 and 6, at least 20 subjects each will be enrolled from Taiwan or Korea. Enrollment rates will be different for each expansion arm. Individual arms may be closed at the discretion of the Sponsor once the target number of enrolled subjects is reached. Individual arms may also be closed prematurely due to difficulty in recruitment at the discretion of the Sponsor. Subjects will receive tislelizumab at the RP2D as described in Section 2.5.4. Each treatment cycle will be 21 days in duration depending on selected dosing regimen. Subjects will continue treatment until confirmed disease progression, intolerable toxicity, subject discontinuation/ withdrawal or at the discretion of the Investigator in consultation with Sponsor.

5.1.6.1 Criteria for Stopping Phase 1B

To adequately monitor safety of subjects enrolled in the Phase 1B indication expansion, when at least 6 subjects have been treated and ≥33% of the subjects experienced a DLT during the first cycle consisting of 21 days (as defined in Section 5.1.1 of the protocol), study accrual will be held pending data review by the SMC.

5.1.6.2 Schedule of Assessment

The schedule of events for Phase 1B is presented in Table 11.

Table 11 Phase 1B Study Assessments and Procedures Schedule

Phase 1B: Q3W schedule	Screening [1]	Treatment Period			Safety Follow-up [2]	Survival Follow-up [24]
		Cycle 1 (21 Days)		Cycle 2 and Additional Cycles (Every 21 Days)		
Days	-28 to -1	1	2 [24]	1 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Informed consent [3]	x					
Inclusion/exclusion criteria	x					
Demographic/Medical History/ Prior Medications [4]	x					
Vital signs/Weight [5]	x	x	x	x	x	
Physical examination	x	x		x	x	
Ophthalmologic examination [26]	x			x	x	
ECOG performance status	x	x		x	x	
12-lead ECG [6]	x	x		x	x	
Review Adverse Events [7]		x	x	x	x	
Review Concomitant Medications	x	x		x	x	
Hematology [8]	x	x		x	x	
Comprehensive Serum Chemistry Panel [8]	x	x		x	x	
Coagulation Parameters [9]	x				x	
Urinalysis [8]	x	x		x	x	
Pregnancy Test [10]	x					
Thyroid Function [11]		x		x[11]	x	
Immunoglubulins [12]		x		x[12]	x	
Anti-tislelizumab Antibodies [13]		x		x[13]	x	
Protein biomarkers in Blood [14]		x		x[14]	x	

Phase 1B: Q3W schedule (cont.)	Screening [1]	Treatment Period			Safety Follow-up [2]	Survival Follow-up [23]
		Cycle 1 (21 Days)		Cycle 2 and Additional Cycles (Every 21 Days)		
Days	-28 to -1	1	2 [24]	1 ± 2	30 ± 3 Days after last dose	Every 3 months ± 2 weeks
Genomics biomarkers in Blood [14]		x		x[14]	x	
Pharmacokinetics [15]		x		x[15]	x	
PD-1 Receptor Occupancy Assay [16]		x	x	x[16]		
HIV [17]	x					
Hepatitis B and C [17]	x			x (Cycle 5 and every 4 cycles) [17]		
Serum Tumor Markers (if appropriate) [18]	x			x[18]	x	
Tumor Imaging [19]	x			x[19]		
Bone Scan [20]	x			x[20]		
Pulmonary Function Tests[21]	x					
Study Drug Administration (30-120 minutes infusion)		x		x		
Archival Tumor Tissues [22] (additional consent required)	x					
Fresh Tumor Tissues [23] (additional consent required)	x			x[23]	x	
Survival Status						x

Abbreviations: ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus;x, to be performed.

1. It is preferred that routine laboratory tests (eg, hematology, chemistry, and urinalysis) for screening are conducted within 10 days prior to the first dosing, although tests done within 28 days are acceptable.
2. The mandatory Safety Follow-Up visit should be conducted 30 days (± 3 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

3. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg within 28 days prior to Cycle 1 Day 1). Assign Baseline number when the study informed consent is signed.
4. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the Investigator. Complete medication history for 30 days before the first dose (C1D1) of study mediation needs to be reported.
5. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
6. Electrocardiogram assessments are to be performed with the subject in semi recumbent supine position and rested for 5 minutes. Electrocardiogram (12-lead ECG) should be performed at Screening as baseline, at the time of PK blood collection for PK (C_{max}) within 30 minutes after the end of the first infusion of tislelizumab, after infusion of tislelizumab in every cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up visit. Additional ECGs may be obtained if clinically indicated (refer to Section 8.2.3).
7. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE v 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of study treatment or the initiation of new anticancer therapy, whichever occurs first. Telephone contacts with patients should be conducted to assess immune-related AEs 90 days after the last dose of tislelizumab 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 drug-related SAEs will be recorded by the Investigator after treatment discontinuation until subject death or loss to follow-up, whichever occurs first.
8. Routine laboratory tests (eg, hematology, chemistry, and urinalysis) will be performed by the local study site laboratory or their contract laboratory. Hematology, chemistry, and urinalysis may be collected up to 72 hours prior to any Cycle Day 1 dosing. Of note, creatine kinase (CK) and creatine kinase – cardiac muscle isoenzyme (CK-MB) will be assessed as part of the serum chemistry panel (as per Appendix 2). In the event CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.
9. PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
10. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 7 days before the first investigational product administration).

11. Analysis of T3, T4 and TSH will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every 2 cycles, and at the mandatory Safety Follow-Up Visit.
12. Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed approximately every 9 weeks thereafter, and at the mandatory Safety Follow-Up Visit.
13. Blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion of Cycle 1 and subsequent every 2 cycles in the first 6 months, every 4 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for C_{trough}. Analysis will be performed by a central laboratory.
14. Blood collected at predose on Day 1 of every 4 cycles until 6 months of study, and at the safety follow up visit for the subjects who have confirmed disease progression during the study to explore resistance mechanism. Samples will be processed according to the Lab Manual.
15. Procedures for collection of PK samples are described in the Lab Manual. Predose (trough, within 24 hours before start infusion) and postdose (within 30 min after the end of infusion) samples should be collected at Day 1 of Cycle 1, and subsequent every 2 cycles in the first 6 months, every 4 cycles in next 6 months, then approximately every 6 months thereafter; additional PK samples should be collected at the mandatory Safety Follow-Up Visit. All trough samples should be drawn at the same time as blood collection for anti-tislelizumab antibodies. Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.
16. **Only for subjects in Arm 2 that are enrolled at Melbourne sites.** Cycle 1 Day 1: predose; Day 2 (approximately 24 hours after the first dose); Cycle 2 Day 1 and Cycle 3 Day 1 at predose. Procedures for collection of samples are described in the Procedures Manual. PD-1 receptor occupancy assay will be performed in a central laboratory.
17. Testing will be performed by the local laboratory at Screening. Include HCV antibody, HBsAg, HBcAb and HIV 1/2 antibodies. Except for Arm 4, subjects who are HBsAg and HBcAb positive or HCV antibody positive at screening must not be enrolled until further definite testing with HBV DNA titers and HCV RNA tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C respectively. Subjects enrolled in the study who had detectable HBV DNA or HCV RNA at Screening should be tested for HBV or HCV viral load, respectively, every 4 cycles (± 7 days) throughout the study, eg Screening, Cycle 5, Cycle 9, and so on (and whenever clinically indicated). For subjects who already received 4 or more doses of study drug, the viral load test should be repeated at the subject's next visit and every 4 cycles according to the schedule from first dose (Cycle 1 Day 1), and whenever clinically indicated. HCC subjects who test positive for HCV will not be discontinued. HCC subjects who test positive for HBV should be treated as per local guidelines at the investigator's discretion.

18. Standard tumor markers (eg, AFP for HCC and CA 125 for ovarian cancer, as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter, and at the mandatory Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.
19. Tumor imaging (either CT or MRI, with preference for CT) will be performed within 28 days prior to enrollment, and while on study approximately every 9 weeks in the first 12 months and approximately every 12 weeks thereafter. The same imaging technique should be used in a subject throughout the study. After first documentation of response (CR or PR), imaging performed at the next regularly scheduled time point will be used for response confirmation. After patient's re-consenting, PD suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next regularly scheduled time point before discontinuation of study treatment. Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging (Section 5.2.5.2).
20. Bone scans must be done for subjects with mCRPC as described in Section 8.2.4. For other subjects, bone scans at baseline or subsequent visits will be performed only if clinically indicated.
21. Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer should 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.
22. Collection of archival tumor tissue for purpose of biomarker analysis. Written patient consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the Lab Manual.
23. Archival tumor tissue will be collected for purpose of biomarker analysis, although a fresh baseline tumor biopsy (within 8 weeks before starting treatment) is strongly recommended. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is mandatory; for these subjects, an optional biopsy for biomarker analysis after 2 cycles of treatment (approximately Cycle 3 Day 1) is strongly recommended. **Please refer to Section 8.9 for mandatory biopsy requirement**. Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy

should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a core or excisional biopsy of the tumor (cytologic or fine-needle aspiration samples are not acceptable) should be obtained that has proper size for histological examination and biomarker analysis (eg, IHC of PD-1, PD-L1, PD-L2; genomic profiling).

24. Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow up all subjects for their survival status until subject death or termination by the Sponsor.
25. Visit on Cycle 1 Day 2 only apply to subjects in Arm 2 that are enrolled at Melbourne sites.
26. Ophthalmologic exam (such as eyesight/visual acuity, fundoscopic, slit lamp microscopy, and optical coherence tomography [or equivalent diagnostic test]) within 28 days prior to first dose and at the end of week 9 (±7 days). Subjects will subsequently undergo repeat assessments by an appropriate specialist approximately every 5 cycles/15 weeks (± 7 days) during study treatment and a final assessment <30 days after the last dose of study treatment. For those subjects who have already received 3 or more doses of study drug, the tests should be repeated at the patient's next visit and then every approximately every 5 cycles/15 weeks (± 7 days) according to the schedule from first dose (Cycle 1 Day1). Investigators should solicit subjects regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 10).

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1. Subjects meet the following corresponding requirements for the stage of the study they will enroll into:

    a) In Phase 1A stage of the study, subjects must have a histologically or cytologically confirmed advanced or metastatic tumor for which no effective standard therapy is available. For Part 1, tumor types to be enrolled include but not limited to CRC, NSCLC, melanoma, SCC, uveal melanoma, gastric cancer, pancreatic cancer, ovarian cancer, bladder cancer, HNSCC, RCC, TNBC and HCC. For Part 2 and Part 3, tumors types to be enrolled include but not limited to NSCLC, (subjects with documented EGFR mutation or ALK rearrangement should be excluded), RCC, HNSCC, bladder cancer, melanoma, gastric, oesophageal, Merkel-cell carcinoma and HCC. Other cancers that are deemed to be likely to benefit from PD-1 inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrollment subject to discussion with the medical monitor in advance.

    b) In Phase 1B stage of the study, subjects recruited to 1 of the following expansion arms must have histologically or cytologically confirmed advanced or metastatic tumor (of the types described below) for which no effective standard therapy is available:

        - Arm 1. Subjects with NSCLC (subjects with documented EGFR mutation or ALK rearrangement should be excluded)
        - Arm 2. Subjects with ovarian cancer
        - Arm 3. Subjects with gastric cancer
        - Arm 4. Subjects with HCC, Barcelona-Clinic Liver Cancer stage C, stage B not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach, and Child-Pugh A, without encephalopathy of any grade
        - Arm 5. Subjects with HNSCC
        - Arm 6. Subjects with esophageal carcinoma
        - Arm 7. Subjects with TNBC
        - Arm 8. Subjects with cholangiocarcinoma

- Arm 9. Subjects with RCC, bladder cancer, melanoma, Merkel-cell carcinoma, sarcoma, GIST, or cuSCC. Or any other solid tumors with known MSI-H or dMMR status, such as CRC or pancreatic cancer

2. Subjects with previously treated brain metastasis(es) that is asymptomatic and radiographically stable and not requiring steroids medications for 4 weeks prior to enrollment are permitted

3. Subjects must have archival tumor tissues or agree to a tumor biopsy for analysis of predictive biomarkers such as PD-L1 (fresh tumor biopsies are strongly recommended at baseline for biomarker analysis in subjects with readily accessible tumor lesions and who consent to the biopsies)

   For Arm 2 (ovarian cancer), Arm 3 (gastric cancer), and Arm 4 (HCC) of Phase 1B study, a fresh baseline biopsy within 8 weeks before starting treatment is mandatory for biomarker analysis.

   For Arm 9 (melanoma) of Phase 1B study, a fresh baseline biopsy within 8 weeks before starting treatment and one approximately on Cycle 3 Day 1 are mandatory for biomarker analysis. All other subjects who have easily accessible lesions are strongly recommended for baseline or the paired biopsy.

   Subjects may be permitted to enroll on a case-by-case basis after discussion with the medical monitor in consultation with the Sponsor if tissue or biopsy is not available.

4. Subjects must have at least one measurable lesion as defined per RECIST v 1.1. Subjects with mCRPC and with only non-measurable bone lesions must have either progression with 2 or more new lesions or have prostate-specific antigen (PSA) progression within the 6-week period before study drug administration

5. Male or female and ≥18 years of age on day of signing informed consent

6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1

7. Life expectancy ≥12 weeks

8. Subject must have adequate organ function as indicated by the following laboratory values

   a) Absolute neutrophil count (ANC) ≥1,500 /mcL

   b) Platelets ≥100,000 / mcL, OR ≥75,000 / mcL for subjects with HCC

   c) Hemoglobin ≥9 g/dL or ≥5.6 mmol/L

d) Serum creatinine ≤1.5 X upper limit of normal (ULN)

e) Serum total bilirubin ≤1.5 X ULN (total bilirubin must be <4 X ULN for subjects with Gilbert's syndrome)

f) AST (SGOT) and ALT (SGPT) ≤2.5 X ULN, OR ≤5 X ULN for subjects with liver metastases or HCC

g) International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 X ULN

h) Activated Partial Thromboplastin Time (aPTT) ≤1.5 X ULN

9. Subjects have voluntarily agreed to participate by giving written informed consent.

10. Female subjects are eligible to enter and participate in the study if they are of:

a) Non-childbearing potential (ie, physiologically incapable of becoming pregnant), including any female who:

- Has had a hysterectomy
- Has had a bilateral oophorectomy (ovariectomy)
- Has had a bilateral tubal ligation
- Is post-menopausal (total cessation of menses for ≥1 year)

b) Childbearing potential, has a negative serum pregnancy test at screening (within 7 days before the first investigational product administration), not be breast feeding, and uses adequate contraception (Appendix 12) before study entry and throughout the study until 120 days after the last investigational product administration. Adequate contraception, when used consistently and in accordance with both the product label and the instructions of the physician, are defined as follows:

- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female
- Any intrauterine device with a documented failure rate of less than 1% per year
- Double barrier contraception defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with spermicide; OR male condom and diaphragm

- Appropriate hormonal contraceptives that include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents)

11. Male subjects are eligible to participate in the study if they are vasectomized or agree to use of contraception during the study treatment period and for at least 120 days after the last dose of study drug.

5.2.2 Exclusion Criteria

Subjects will not be entered in the study for any of the following reasons:

1. History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs)
2. Prior malignancy active within the previous 2 years except for tumor for which a subject is enrolled in the study, and locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast
3. Prior therapies targeting PD-1 or PD-L1
4. Subjects who failed to meet enrollment criteria for other PD-1 or PD-L1 trials solely due to low or negative predictive biomarkers, including but not limited to PD-L1, MSI, and DNA mutation load
5. Subjects with active autoimmune diseases or history of autoimmune diseases should be excluded; these include but are not limited to subjects with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, systemic lupus erythematosus (SLE), connective tissue diseases, scleroderma, inflammatory bowel disease including Crohn's disease and ulcerative colitis, hepatitis, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or antiphospholipid syndrome

   Note: Subject are permitted to enroll if they have vitiligo, eczema, type I diabetes mellitus, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids. Subjects with rheumatoid arthritis and other arthropathies, Sjogren's syndrome, controlled celiac disease and psoriasis controlled with topical medication and subjects with positive serology, such as antinuclear antibodies (ANAs), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

6. Subjects should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration

   Note: Adrenal replacement doses ≤10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease; subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption); a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

7. Has history of interstitial lung disease or non-infectious pneumonitis except for those induced by radiation therapies

8. Known history of HIV

9. Except for HCC in Phase 1A or Arm 4 in Phase 1B, subjects who are HBsAg and HBcAb positive or HCV antibody positive at screening must not be enrolled until further definite testing with HBV DNA titers and HCV RNA tests can conclusively rule out presence of active infection requiring therapy with Hepatitis B and C respectively

10. HCC patients with active infection by HCV who are untreated are not allowed on study. However HCC patients with successful HCV treatment (defined as sustained virologic response [SVR] 12 or SVR 24) are allowed as long as 4 weeks have passed between completion of HCV therapy and start of study drug

11. HCC patients with evidence of prior HBV infection must fulfill the following criteria in order to be eligible for the study: HBV viral load (VL) <200 IU/mL (approximately 1000 cps/mL) before study enrollment and subjects with active HBV infection need to be on anti-HBV suppression ≥3 months, throughout treatment and for 6 months after

12. Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs

13. Prior chemotherapy, radiotherapy, immunotherapy or any investigational therapies used to control cancer, including local-regional treatment for HCC, must have been completed at least 4 weeks before study drug administration, and all AEs have either returned to baseline or Grade 0~1, and stabilized

14. Use of any live vaccines against infectious diseases (eg, influenza, varicella, etc.) within 4 weeks (28 days) of initiation of study therapy and any intended use until 60 days after the last administration of the study medication

15. Subjects who had prior liver transplant, allogeneic organ transplantation or bone marrow transplant (BMT) should be excluded

5.2.3 Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regards to safety, the Investigator must refer to the IB for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study.

Re-screening under limited conditions should be allowed after consultation with the Sponsor, eg when a subject narrowly misses a lab criterion and it's correctable and not due to rapidly deteriorating condition or PD. Re-screening is allowed only once.

5.2.4 Subject Restrictions

The following restrictions may affect subject participation in this study:

- The Investigator must be informed as soon as possible about any medications taken from the time of screening until the subject is discharged from the study

5.2.5 Subject Completion and Withdrawal

5.2.5.1 Subject Completion

For Phase 1A, Part 1, a subject will be considered complete if he/she has a valid PK profile (including data from Cycle 2 Day 1, predose or Day 29 predose for subjects who discontinue after Cycle 1) and has not withdrawn from the study prior to completing DLT period (28 days from first dose of tislelizumab). A subject will be considered complete is he/she discontinued study treatment due to a DLT with or without a valid PK profile.

For Phase 1A Part 2 and Phase 1B, a subject will be considered complete if he/she has had at least one post-baseline tumor assessment for objective response. Subjects who discontinue the study due to death or clinical progression without a post-baseline tumor assessment will also be considered complete.

Treatment with tislelizumab may continue until one of the following events occurs:

- Confirmed disease progression (refer to Section 8.5.1)
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse experiences (see Section 5.1.2)
- Need for >2 dose delays due to toxicity as per the dose modification guidelines described in Section 5.1.2
- Subject withdraws consent
- If in the opinion of the Investigator, a change or discontinuation of therapy would be in the best interest of the subject
- Subject is lost to follow-up
- Pregnancy in subject

If a subject discontinues from the study, the procedures will be followed as described in Section 5.2.5.2.

Subject reaches 24 months of treatment (measured from start of study treatment):

- Subjects may continue on study therapy beyond 2 years if the Investigator considers this to be in the best interest of the subject based on an assessment of clinical benefit and potential risks. Continuation of study therapy beyond 2 years has to be explicitly approved by the Sponsor, and will be contingent on the continued availability of tislelizumab drug product. The study assessment and procedures schedule will remain the same.
- If subjects have confirmed CR, PR, or SD after 2 years of tislelizumab, the treatment can be stopped if the subject wishes. The decision should be based on the Investigator's evaluation, with the subject's clinical benefit and risk taken into consideration. A treatment-interruption informed consent form must be signed by subjects who stop treatment. The Investigator should notify the Sponsor that treatment will be stopped prior to the event. In such a case, the study assessments and procedures will be performed every 12 weeks (in conjunction with repeat radiographic imaging, as described in Section 8.5) rather than every cycle. If a subject has evidence of PD within 1 year of treatment interruption, the Investigator can consider restarting tislelizumab therapy after discussion with the Sponsor, contingent on the continued availability of tislelizumab drug product.

5.2.5.2 Subject Withdrawal/Discontinuation

Subjects/patients may withdraw at any time (consent withdrawal) or be dropped from the study at the discretion of the Investigator should any untoward effects occur. In addition, a

subject/patient may be withdrawn by the Investigator or the Sponsor (drug withdrawal) if he/she violates the study plan or for administrative and/or other safety reasons. The Investigator or study coordinator must notify the Sponsor immediately when a subject/patient has been discontinued/withdrawn (drug withdrawal) due to an adverse experience. When a subject/patient discontinues/withdraws (drug withdrawal) prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal (drug withdrawal) should be followed in accordance with the safety requirements outlined in Section 8.3.

The reason for discontinuation of tislelizumab will be recorded in the electronic case report form (eCRF). These reasons include:

- Withdrawal of consent by the subject
- Discontinuation of tislelizumab by the Sponsor
- Pregnancy
- Any significant AE that compromises the subject's ability to participate in the study
- The Investigator or Sponsor determines it is in the best interest of the subject
- Intercurrent illness
- Treatment failure
- Confirmed progression of disease at any time during the study (refer to Section 8.5.1)
- Need for prohibited medication
- Lack of compliance with the study and/or study procedures (eg, administration instructions, study visits
- Significant deviation from the protocol by the Investigator without the consent of the Sponsor

Subjects withdraw prior to documentation of PD:

Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who

withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging.

6.0 STUDY TREATMENTS

6.1 Description of Investigational Product

Tislelizumab is a monoclonal antibody drug which is formulated for IV injection in a single-use vial (20R glass, United States Pharmacopoeia type I) containing a total of 100 mg antibody in 10 mL of isotonic solution. See Section 6.5 below for handling and product storage conditions.

6.2 Product Preparation and Administration

Tislelizumab will be administered by IV infusion, using a volumetric pump through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, subjects who receive the first and second infusion of Tislelizumab must be observed for 2 hours after infusion, in an area with resuscitation equipment and emergency agents.

Tislelizumab will be diluted to a concentration between 1 mg/mL to 10 mg/mL up to 100 mL in sterile normal saline (0.9% sodium chloride) as described below. For the 0.5 mg/kg dose, deliver first infusion over 60 min; if well-tolerated, second and subsequent infusions may be administered over 30 min. For 2 mg/kg dose and above, along with flat doses, deliver first infusion (Cycle 1 Day 1) over 60 min; if well-tolerated, second infusion and each subsequent infusion may be administered over 30 min if 60 min infusion tolerated. Do not co-administer other drugs through the same infusion line.

1. Slowly swirl solution in the vial. Allow up to 5 minutes for bubbles to clear. Do not shake the vial.
2. Visually inspect the solution for particulate matter and discoloration prior to preparation. The antibody drug solution is a clear to slightly opalescent, colorless to slightly yellow solution
3. Quarantine the vial for investigation if extraneous particulate matter other than translucent to white proteinaceous particles is observed

4. Aseptically withdraw the required volume from the vial(s) of tislelizumab into a syringe, and transfer into an IV bag (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on). Visually inspect used vial(s) and quarantine the vial(s) for investigation if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

5. Please use the following example to guide study drug preparation. The total dose to be administered will be diluted to a total volume of **not more than** 100 mL in sterile normal saline (0.9% sodium chloride). In case where the total volume is more than 100 mL, no additional dilution is necessary.

   Prepare tislelizumab solution for infusion per the example provided below:

For 2 mg/kg dose and assume subject body weight of 70 kg (other dose levels and body weights can be calculated similarly):

Total drug to be administered:	2 mg/kg x 70 kg =140 mg
Drug needed for dose preparation:	140 mg / 10 mg/mL = 14 mL
0.9% sodium chloride needed for dilution:	50 mL – 14 mL = 36 mL
Target final concentration:	140 mg / 50 mL = 2.8 mg/mL

For flat dose 200 mg:

Drug needed for dose preparation:	200 mg / 10 mg/mL = 20 mL
0.9% sodium chloride needed for dilution:	50 mL – 20 mL = 30 mL
Target final concentration:	200 mg / 50 mL = 4 mg/mL

The detail of drug preparation is presented for reference in Appendix 4. Site can adjust preparation process according to common practice in consultation with Sponsor.

6. Mix diluted solution by gentle inversion

7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be quarantined for further investigation (according to the instruction in Section 6.5) and documented on the Drug Accountability Log

8. Record the time tislelizumab was prepared on the IV bag label

9. Attach the IV bag containing the tislelizumab solution to the infusion set, 0.2 μm in line filter, and infusion pump

10. At the end of the infusion period, flush the line with a sufficient quantity of normal saline

For management of toxicity refer to Section 5.1.2.

6.3 Treatment Assignment

Subjects will be identified by a subject number. Each subject enrolled in this study will receive a unique subject number after signing the informed consent. Each subject receiving tislelizumab will also receive a treatment allocation number. Subject and treatment numbers will be assigned in chronological order starting with the lowest number. Once a subject number and treatment number have been assigned to a subject, it cannot be reassigned to any other subject.

6.4 Packaging and Labelling

tislelizumab was aseptically filled in 20R glass vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial contains 10 mL of the drug solution. The vials were packaged in a carton.

The primary labeling on the vials contain following information: protocol number, content and quantity of tislelizumab, batch number, expiry date, storage instructions, and administration instructions. The contents of the label will be in accordance with all applicable regulatory requirements.

6.5 Handling and Storage

The investigational product will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the Sponsor's procedures.

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the Investigator and authorized study center personnel and under physical conditions that are consistent with investigational product-specific requirements. The Investigational product must be kept at 2-8ºC.

The investigational product does not contain a preservative. The diluted solutions of tislelizumab cannot be frozen, and must be stored at:

- Either room temperature at 20°C to 25°C (68°F to 77°F) for no more than 4 hours from the time of reconstitution. This includes room temperature storage of drug product vials, storage of the infusion solution in the IV bag, and the duration of infusion.
- Or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

6.6 Product Accountability

The Investigator is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study center personnel must maintain investigational product accountability records throughout the course of the study. This person(s) will document the amount of investigational product received from the Sponsor, the amount supplied and/or administered to and returned by subjects, if applicable.

After completion of the study, all unused tislelizumab will be inventoried and destroyed on site, after receiving written Sponsor approval.

6.7 Assessment of Compliance

On all visits to the study center, subjects will be questioned in regard to compliance with study instructions.

6.8 Treatment of Investigational Product Overdose

Overdose is defined as: the subject has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%. Subjects with a suspected overdose should be managed with appropriate supportive therapy as determined by the Investigator in consultation with the Medical Monitor. Any adverse effects occurring as a result of an overdose should be reported to the medical monitor as well as being included in standard AE reporting.

6.9 Medical Care of Subjects after the End of Trial

After a subject has completed the trial or has withdrawn early, usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice, and depending on the subject's individual medical needs.

6.10 Occupational Safety

The investigational product is not expected to pose significant occupational safety risk to the study center personnel under normal conditions of use and administration. A material safety data sheet describing occupational hazards and recommended handling precautions will be provided to the Investigator, where this is required by local laws, or is available upon request from the Sponsor.

7.0 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

7.1 Concomitant Medication(s)/Treatment(s)

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

All concomitant medications received within 30 days before the first dose of study medication and 30 days after the last infusion of study medication should be recorded.

The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medication.

7.2 Prohibited Medications

Subjects may receive other medications that the Investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy (palliative radiotherapy on non-target lesions for emergent symptom relief is allowed, such as palliative radiation on bone lesions for pain control), immunotherapy, anti-neoplastic biological therapy or investigational agents other than tislelizumab. Subjects who in the assessment by the Investigator require the use of any of the aforementioned treatments for clinical management should be removed from the study. Bisphosphonates or Denosumab is allowed as long as the subject is on a stable dose for at least 14 days prior to investigational drug administration. The Investigator should discuss with the Sponsor or designated medical monitor if the subject has already been given Bisphosphonates or Denosumab right before the investigational drug administration or will be given while on study.

Subjects with active autoimmune disease or history of autoimmune disease that might recur, who require immune suppressive treatment including systemic corticosteroids, should be

excluded; these include but are not limited to subjects with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, SLE, connective tissue diseases, scleroderma, inflammatory bowel disease, Crohn's, ulcerative colitis, hepatitis, TEN, Stevens-Johnson syndrome, or phospholipid syndrome.

Subjects are prohibited from receiving live vaccines within 28 days prior to the first dose of study therapy and while participating in study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

Section 5.2.2 of the protocol (Exclusion Criteria) describes other medications which are prohibited in this study.

7.2.1 Other Drugs to be Used in the Study

Subjects may be pretreated with H1 blockers (diphenhydramine 50 mg IV, or equivalent), and acetaminophen (500 to 650 mg oral or IV), 30 to 60 minutes prior to each tislelizumab infusion. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered over at least 1 month and be at non-immunosuppressive doses (≥10 mg/day of prednisone or equivalent) before the next study drug administration. The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.

7.2.2 Other Study Considerations

The following nondrug therapies must not be administered during the study (within 28 days before the start of study treatment):

- Major surgery (excluding prior diagnostic biopsy)
- Herbal remedies with immunostimulating properties (ie, mistletoe extract) or known to potentially interfere with major organ function (ie, hypericin)
- Subjects should not abuse alcohol or other drugs during the study

7.3 Special Precautions

As a routine precaution, subjects who receive the first and second infusion of tislelizumab must be observed for 2 hours after infusion, in an area with resuscitation equipment and emergency agents.

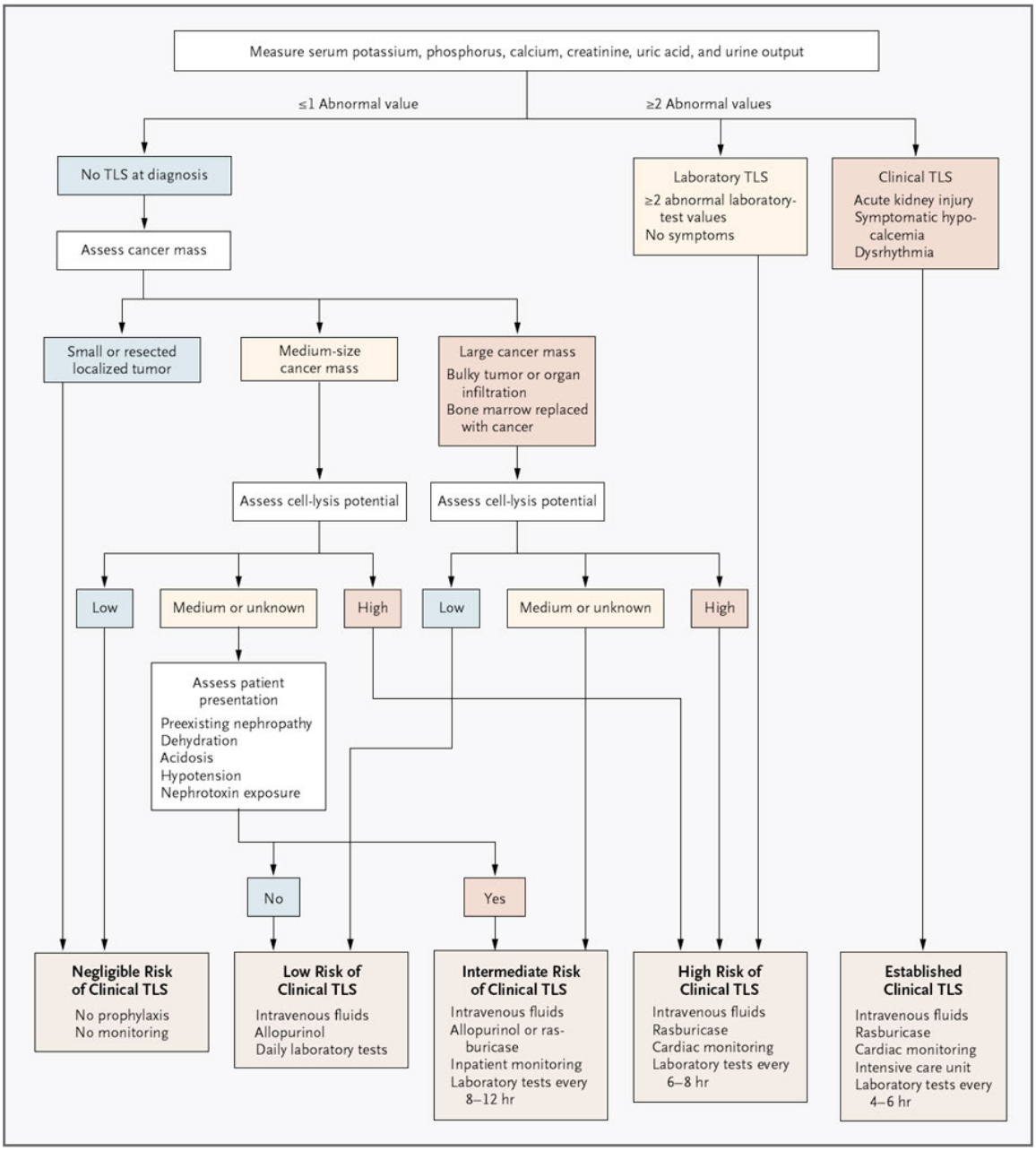
Infusion of tislelizumab will be discontinued in case of Grade 2 or greater hypersensitivity, inflammatory response, or infusion-related reaction. The treatment recommendations for

infusion-related reactions, severe hypersensitivity reactions, and tumor lysis syndrome according to the NCI are outlined in Sections 7.3.2, 7.3.3, and 7.3.1 respectively.

7.3.1 Tumor Lysis Syndrome

A potential risk of tumor lysis syndrome exists since tislelizumab can induce cytotoxicity. As published by Howard et al 2011, once tumor lysis syndrome occurs, subjects should be treated as per the local guidelines and the management algorithm (Figure 7-1).

Figure 7-1 Assessment and Initial Management of Tumor Lysis Syndrome



7.3.2 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. Subjects should be closely monitored for such reactions. Treatment modification for symptoms of infusion-related reactions due to tislelizumab is presented in Table 12.

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. Infusion of tislelizumab will be discontinued in case of Grade ≥2 infusion-related, allergic, or anaphylactoid reactions. Following the first and second infusion of tislelizumab, subjects must be observed for 2 continuous hours post-infusion for potential infusion-related reactions.

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical care. Subjects should be instructed to report any delayed reactions to the Investigator immediately based on a complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK).

Table 12 Treatment Modification for Symptoms of Infusion-Related Reactions Due to Tislelizumab

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to at least grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Grade 3: 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. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, 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 subject has a second infusion-related reaction (Grade ≥ 2) on the slower infusion rate, infusion should be discontinued and the subject should be withdrawn from tislelizumab treatment.

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

CTCAE Grade 3 or 4 infusion reaction: Immediately stop the infusion. 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 anti-histamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

If a subject experiences a Grade 4 infusion-related reaction at any time, tislelizumab must be discontinued.

In the event of a Grade 3 infusion reaction, continuation of study therapy is at the discretion of the Investigator after consultation with the Sponsor. If continued, the infusion time of tislelizumab in the next cycle should be at least 1 hour. Subjects should receive oral premedication with an anti-histamine (eg, diphenhydramine or equivalent) and an anti-pyretic (eg, paracetamol or equivalent), and in addition premedication with methylprednisolone 100 mg or its equivalent IV approximately 30 minutes before start of the infusion. Subjects should be closely monitored for clinical signs and symptoms of an infusion reaction.

7.3.3 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject 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). Subjects 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 subject discontinued from the study**.

The subjects will be administered epinephrine injection and dexamethasone infusion if a hypersensitivity reaction is observed and then the subject should be placed on monitor immediately and ICU is 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 (NSAID) (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of tislelizumab IV infusion. Alternative treatments for fever (ie, paracetamol) may be given to subjects at the discretion of the Investigator.

7.3.4 Immune-Related Adverse Events

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, metabolic, toxin, disease progression or other neoplastic causes) with appropriate diagnostic tests, which may include but is 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 list of potential irAEs is shown below in Table 13. 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 a recent European Society for Medical Oncology (ESMO) guideline (Haanen et al, 2017) and common immune-related toxicities are detailed in Appendix 10. For any AEs not included in Appendix 10, please refer to the recent ESMO guideline (Haanen et al, 2017) for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 13 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

Dose modification and management for irAEs are detailed in Appendix 10.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug should be discontinued after consultation with the Sponsor. Patients who experience a recurrence of any event at the same or higher severity grade with rechallenge should permanently discontinue treatment.

7.3.5 Hepatic Abnormalities

Patients with advanced HCC generally have underlying cirrhosis with decreased hepatic function. Special attention is needed because they may also have a concomitant chronic viral infection. Therefore, when a hepatic event, such as liver function laboratory abnormalities, is observed, the Investigator must evaluate for re-activation of viral hepatitis, consider other drug-related toxicity, and exclude PD involving the liver. For diagnosis and management of

patients with AST or ALT values ≥ Grade 1 at baseline, please see Section 7.3.4 and refer to Appendix 10.

In patients with Grade 2 AST/ALT abnormalities at baseline, therapeutic interventions with a steroid treatment may be required with rising AST and ALT laboratory abnormalities. The following algorithm is proposed for the use of steroid treatment:

- If AST or ALT increases by ≥ 50% relative to baseline and lasts for at least 1 week, start oral prednisolone 1 mg/kg/day and taper over at least 2-4 weeks; re-escalate dose if liver function tests (LFTs) worsen, depending on clinical judgment (manage as per Appendix 10). Study treatment should be held until AST/ALT increase resolved/improved to baseline and prednisolone tapered to ≤ 10 mg.
- If any ALT or AST increases meets Grade 3 criteria, initiate steroid therapy promptly per Appendix 10. Study treatment will be held until AST or ALT improves to value ≤ Grade 2. Study drug may be reintroduced only after discussion with the Sponsor.
- If any ALT or AST increases meets Grade 4 criteria, initiate steroid therapy promptly per Appendix 10. Study treatment will be discontinued permanently

8.0 SAFETY, PHARMACOKINETIC, PHARMACODYNAMIC, AND OTHER ASSESSMENTS

A signed, written informed consent must be obtained prior to screening assessments and before any study specific assessments are initiated. The study specific assessments and procedures for Phase 1A Part 1 are shown in Table 5, Phase 1A Part 2 are shown in Table 7 (Q2W) and Table 8 (Q3W) respectively, Phase 1A Part 3 are shown in Table 9, Phase 1B are shown in Table 11. The PK sampling time points for Phase 1A Part 1 and Part 3 are presented in Table 6 and Table 10, respectively.

8.1 Demographic and Baseline Assessments

Demographic data will include date of birth, race, height (in cm), body weight (in kg), and body mass index (body mass index in kg/m^2). For height and weight measurements, the subject will be allowed to wear indoor daytime clothing with no shoes. This data will be captured in the eCRF and database.

Having given consent, subjects will be required to undergo a medical screen to determine whether they are eligible to participate in the study according to the criteria listed in Section 5.2. Screening assessments will be completed within 28 days prior to the first dose of the investigational product. In Phase 1B, subjects who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer should 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. Screening assessments completed within 72 hours of administration can be used as Day 1 assessments as indicated in the schedule of assessment tables. Please refer to Table 5, Table 7, Table 8, and Table 9 for Phase 1A, and Table 11 for Phase 1B. The screening assessments for Phase 1A and 1B will include:

- Baseline demographics
- Medical history including diagnosis, date of first diagnosis, histology, prior anti-neoplastic therapy, and current sites of disease
- Concurrent medications
- Disease assessments within past 4 weeks (28 days)
- Vital signs
- Physical examinations

- Ophthalmologic examinations
- Evaluation of AEs
- ECOG performance status
- Electrocardiogram (ECG)
- Laboratory tests: hematology, chemistry, urinalysis, pregnancy test, and PT/aPTT
- Collection of archival tumor specimen or new tumor biopsy
- Standard tumor markers (eg, AFP for HCC and CA 125 for ovarian cancer, as appropriate for a given tumor type)
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), HCV antibody and HIV 1/2 antibodies
- CT/magnetic resonance imaging (MRI) scan
- Bone scan (for patients with mCRPC as described in Section 8.2.4 or when clinically indicated)

The above mentioned data will be captured in the source documents. Any results falling outside the normal range will be repeated at the discretion of the Investigator.

The Investigator will obtain the patient's medical history at the Screening visit. Medical history will include all active conditions, and any condition that are considered to be clinically significant by the Investigator. History of treatment for the primary diagnosis, including prior systemic, radiation treatment, and surgical treatment will be recorded. Date of and response to last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Complete medication history for 30 days prior to the first dose (C1D1) of study mediation needs to be reported.

Date of and response to last platinum-containing chemotherapy treatment for patients with ovarian cancer must be documented unless no platinum-containing treatment has been received before. Subjects are defined as platinum-sensitive if disease progression by RECIST or GCIG criteria had occurred more than 6 months after their last platinum chemotherapy, as platinum-resistant if disease progression occurred less than 6 months after their last platinum chemotherapy but after their post-treatment evaluation, and as platinum-refractory if they experienced disease progression while receiving platinum chemotherapy, up to the date of their post-treatment evaluation.

8.2 Assessments During Treatment

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 5, Table 7, Table 8, and Table 9 for Phase 1A, and Table 11 for Phase 1B, respectively.

8.2.1 Laboratory Evaluation

Laboratory assessments should be performed at a local certified laboratory on Day 1 before the investigational product administration. Laboratory assessments need not be repeated on Cycle 1 Day 1 if these assessments were completed for screening within 72 hours of the first administration. Required laboratory assessments are listed in Appendix 2.

Routine laboratory tests (eg, hematology, chemistry, and urinalysis) will be performed by the local study site laboratory. Subject treatment and overall management decisions will be based on local laboratory data. Details regarding the amount of blood drawn for laboratory testing are provided in Appendix 3.

Clinical chemistry, hematology, coagulation, and urinalysis will be performed at the time points specified in Table 5, Table 7, Table 8, and Table 9 for Phase 1A and Table 11 for Phase 1B respectively. In the event of neutropenia (ANC <1000/mm^3), thrombocytopenia (platelets <50,000/mm^3), or Grade 3 clinical chemistry toxicity, the relevant assessments will be conducted every other day until toxicity resolves to ≤Grade 2 toxicity. If warranted, additional testing can also be done, or the relevant tests done more frequently in accordance with institutional guidelines. All subjects who have any Grade 3 or Grade 4 laboratory abnormalities at withdrawal from the study must be followed up until they have returned to Grade 1 or Grade 2, unless these are not likely to improve due to the underlying disease.

On routine urinalysis, if urine protein is ≥2+ by dipstick, a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine will be obtained. Subjects should NOT be dosed until the result of 24-hour urine protein is confirmed. If urine protein is >2 g/24 hours, the investigational product administration will be interrupted until it returns to ≤2 g/24 hours. If urine protein is ≤2 g/24 hours, further clinical evaluation and/or more frequent testing may be performed as clinically indicated. A random urine protein to creatinine ratio can serve as a reliable surrogate for the 24-hour urine protein when following subjects with urine protein of ≤2 g, documented by a 24-hour urine collection. In such cases, the 24-hour urine for total protein should be repeated only if a clinically significant increase is observed in the random urine protein to creatinine ratio.

8.2.2 Physical Examination, Ophthalmologic Examination, Vital Signs, and Hepatitis B and C Testing

A complete physical examination, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and respiratory rate), and weight will be performed at the time points specified in Table 5, Table 7, Table 8, and Table 9 for Phase 1A, and Table 11 for Phase 1B, respectively. During the treatment period, symptom-directed physical examinations should be performed. If there are no complaints and no abnormal findings from the previous visit for a particular organ system, a physical examination of that organ system is not required.

To the extent feasible, blood pressure will be taken on the same arm throughout the study. A large cuff should be used for obese patients. Subjects must be resting in a sitting position for 10 minutes prior to obtaining vital signs. If blood pressure is >150/100 in a subject without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a subject with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

Ophthalmological examinations (such as eyesight/visual acuity, fundoscopy, slit lamp microscopy, and optical coherence tomography [or equivalent diagnostic test]) will be performed at the time points specified in Table 5, Table 7, Table 8, and Table 9 for Phase 1A and Table 11 for Phase 1B, respectively. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an appropriate specialist at Screening. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used for the Screening evaluation. Subjects dosed on a Q2W schedule will then undergo ophthalmologic examinations by an appropriate specialist on Cycle 1 Day 15 (± 7 days) (Phase 1 A Part 1 only), Cycle 3 Day 1 (± 7 days), and thereafter every 4 cycles/16 weeks (± 7 days) during study treatment. Subjects dosed on a Q3W schedule will undergo an ophthalmologic examination by an appropriate specialist at the end of Week 9 (± 7 days), and thereafter every 5 cycles/15 weeks (± 7 days) during study treatment. Subjects in all groups will undergo a final assessment <30 days after the last dose of study treatment. For those subjects who have already received 2 or 3 more doses of study drug, respectively, the examination should be repeated at the subject's next visit and then approximately either every 4 cycles/16 weeks (± 7 days) for subjects dosed on a Q2W schedule or every 5 cycles/15 weeks (± 7 days) for subjects dosed on a Q3W schedule, according to the schedule from first dose (Cycle 1 Day 1).

In addition, Investigators should solicit subjects 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 (see Appendix 10).

Subjects enrolled in the study who had detectable HBV DNA or HCV RNA at Screening should be tested for HBV or HCV viral load, respectively, every 4 cycles (± 7 days) throughout the study, eg Screening, Cycle 5, Cycle 9, and so on (and whenever clinically indicated). For subjects who already received 4 or more doses of study drug, the viral load test should be repeated at the subject's next visit and every 4 cycles according to the schedule from first dose (Cycle 1 Day 1), and whenever clinically indicated. HCC subjects who test positive for HCV will not be discontinued. HCC subjects who test positive for HBV should be treated as per local guidelines at the investigator's discretion.

8.2.3 Electrocardiogram

Electrocardiograms will be obtained at the time points specified in Table 5, Table 7, Table 8, and Table 9 for Phase 1A, and Table 11 for Phase 1B, respectively. If prolongation of QT or QT interval corrected for heart rate (QTc) is noted during the first 15 days (for Q2W schedule) or 21 days (for Q3W schedule) of tislelizumab treatment, ECGs will be performed weekly during the first cycle, and then within 30 min after the end of every subsequent tislelizumab administration, and at the mandatory Safety Follow-up visit.

Significant QTc prolongation will be defined as an interval ≥500 msec or an interval which increases by ≥60 msec over baseline. Either of these conditions should be documented on two or more ECG tracings separated by at least 5 minutes. The ECG tracing should be examined and a manual measurement by a trained physician to assess the accuracy of the equipment being used.

If a subject has significant QTc prolongation:

- He/she will be withdrawn from the investigational product administration if the Investigator and/or the medical monitor determine the subject is at risk.
- The subject will be monitored, treated appropriately, and closely followed (ECGs at least three times per week) until the QT and QTc interval return to within 30 msec of baseline.
- The medical monitor will be consulted prior to administering further doses or re-challenging.

The medical monitor will be consulted prior to administering higher doses.

8.2.4 Computed Tomography

A computed tomography (CT) scan of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate, including bone scan for subjects with bone metastasis, will be performed to assess all known disease. All known disease must be documented at baseline as target or non-target lesions using RECIST v 1.1. 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. The CT scan will be used for the evaluation of RECIST v 1.1 by the Investigator at each study center.

Unless contraindicated, intravenous contrast product must be used to maximize visualization of all lesions. Five millimeter (mm) contiguous scans at baseline and subsequent scanning approximately every 8 weeks for Q2W and 9 weeks for Q3W in the first 12 months and approximately every 12 weeks thereafter (as calculated by the date of the first administration of the investigational product) until progression, with mandatory imaging coverage from thoracic inlet to symphysis pubis should be performed. Subjects who cannot tolerate enhanced CT due to increased risk of allergic reaction to iodinated contrast media should follow local practice to obtain diagnostic quality images with an appropriate imaging modality and the same imaging modality should be utilized consistently.

Technetium bone scans will be used to assess bone lesions. In patients with prostate cancer baseline bone scans will be performed during the screening window. Repeat bone scans will be performed every 16 weeks (Q2W) or 18 weeks (Q3W) to keep with the schedule of the CT scans. Bone scan results will be reported as either no lesions or lesions present along with the number of bone lesions. Disease progression by bone scan will be defined per the PCWG2 criteria as presented in Appendix 9; progression is defined as 2 new bone lesions at the first ‘progression’ scan, confirmed by a subsequent scan at least 6 weeks later with the presence of 2 additional lesions.

Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments during the study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging.

Lesions that are expected to require palliative radiotherapy while in the study should not be included as target lesions, but should be listed as non-target lesions.

8.2.5 Adverse Events

All AEs and SAEs, regardless of the relationship to the investigational product, will be collected from signing the informed consent form and throughout the study.

8.3 Safety Assessments

Vital signs, weight, physical examinations, ophthalmologic examinations, ECOG performance status, ECGs and laboratory safety tests (eg, PT/aPTT, urinalysis, hematology, serum chemistry, autoantibodies, thyroid function, viral antigen reactions, cytokine / chemokine panels) will be obtained and assessed at designated intervals throughout the study (see Table 5, Table 7, Table 8, and Table 9 for Phase 1A, and Table 11 for Phase 1B, respectively). Special attention will be given to immune-related adverse effects (eg, gut, skin, lung, liver, kidney endocrine organs, others).

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE v 4.03. Characterization of toxicities will include severity, duration, and time to onset. Safety endpoints will include all types of AEs, in addition to laboratory safety assessments, ECOG performance scale status, ECGs, and vital signs.

The continuous safety evaluation will be performed by the Sponsor, the Coordinating Investigator, and Investigators. An SMC will be established for the determination of dose levels to be administered during dose escalation and dose regimens in this study. Details of the safety monitoring process will be specified in a dedicated SMC charter.

8.3.1 Phase 1A Part 1

The SMC consists of the Coordinating Investigator, selected recruiting Investigators, the Sponsor's medical monitor, and the contract research organization (CRO)'s medical monitor. Ad hoc members will be consulted as needed and may include, but are not restricted to the biostatistician and pharmacokineticist.

Before moving to the next dose level, the SMC will review all safety data available to determine whether recruitment to the next cohort should be initiated. At the conclusion of the dose escalation phase, the SMC will determine the RP2D(s) to be further investigated.

The SMC will determine when no further dose escalation is appropriate and whether the MTD will be defined as a preceding dose or an intermediate dose.

The SMC will meet for cohort safety reviews after all subjects in a dosing cohort have completed the first treatment cycle. All available safety data will also be provided for subjects who discontinue prior to this time. Safety data from prior cohorts may also be presented. The decision to escalate dose and the determination of the MTD will be based on

the cohort safety reviews. The SMC will review any protocol violations that may have impacted evaluation of potential DLT. The SMC may weigh collective evidence and may determine a DLT for reasons in addition to those explicitly stated in the final protocol.

Response from all SMC members, including Investigators with subjects enrolled in the Phase 1 stage, or their designees, shall be required for each escalation/review.

Adequate time for review of results will be given to SMC members (approximately 1 to 2 business days). Enrollment in subsequent dose levels will be put "on hold" during each review period, pending the decision of the SMC.

The SMC decision points may fall into one of the categories detailed below:

- Escalate to a higher dose
- Recruit an additional 3 subjects into existing dose level
- Stop escalation and investigate lower dose(s)
- End part of the study
- End the overall study

Decisions will be made using the criteria defined within the protocol (see Section 5.1.3.1). The SMC will make the dose escalation decisions.

8.3.2 Phase 1A Part 2 and Part 3

In order to adequately monitor safety during in the Phase 1A Part 2 and Part 3 stages of the study, data review will be routinely conducted by the SMC. The SMC consists of the Coordinating Investigator, representative recruiting Investigators, the Sponsor's Medical Monitor, and the CRO's Medical Monitor. Ad hoc members will be consulted as needed and may include, but are not restricted to the biostatistician and pharmacokineticist.

The SMC will review safety data (including but not limited to, AEs, SAEs, laboratory parameters, investigational product logs, treatment delays or reductions, and treatment discontinuation due to toxicity), when all the subjects have completed the first cycle of treatment in each stage, or withdrew due to any reason (PD, adverse event, or death). The SMC will make the decision using the criteria as described in Section 5.1.4.1 (Part 2) or Section 5.1.5.1 (Part 3). Any treatment-related death will also trigger review by the SMC. The SMC will determine whether it is safe to proceed.

8.3.3 Phase 1B

In order to adequately monitor safety during the Phase 1B stage of the study, data review will be routinely conducted by the CRO and Sponsor medical and safety monitors. Serious safety issues such as treatment-related death will be reviewed by the SMC. The SMC consists of the Coordinating Investigator, representative recruiting Investigators, the Sponsor's medical monitor, and the CRO's medical monitor. Ad hoc members will be consulted as needed and may include, but are not restricted to the biostatistician and pharmacokineticist.

8.4 Follow-up Assessments

All subjects have to be followed for at least 30 days after their last dose of study drug or until initiation of a new anti-cancer treatment, whichever occurs first. Telephone contacts with patients should be conducted to assess irAEs 90 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. All drug-related SAEs will be recorded by the Investigator after treatment discontinuation until patient death or loss to follow-up, whichever occurs first.

Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

Subjects who stop treatment prior to documentation of PD will undergo repeated imaging for tumor response assessments approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter **until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial, whichever occurs first**. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD will be requested to undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging. Following completion of the treatment and safety follow-up periods, all subjects will be followed for survival status. Subjects will have their survival status assessed approximately every 3 months ± 2 weeks by either a telephone or in-person contact until subject death or termination by the Sponsor. With the exception of the collection of irAE data through 90 days post-treatment (as described above), no other data (eg subsequent therapies, performance status etc.) beyond survival will be collected during these calls/visits.

8.5 Efficacy Assessments

This study includes preliminary assessments of efficacy as outlined in the sections below.

Disease assessment by radiographic imaging (CT or MRI, with a preference for CT) will be performed and recorded at screening within 28 days before enrollment and while on study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately every 12 weeks thereafter according to the RECIST Guidelines as shown in Appendix 5. The same imaging technique as used at baseline has to be used throughout the study.

After first documentation of CR or PR, imaging performed at the next regularly scheduled time point will be used for response confirmation.

8.5.1 Treatment Beyond Disease Progression

Patients must be re-consented to continue treatment beyond initial documentation of disease progression.

There is evidence that a minority of subjects treated with anti-PD1 therapies such as tislelizumab may derive clinical benefit despite initial documentation of PD by RECIST v 1.1. Pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions (Wolchok et al, 2009). These patients may go on to exhibit a partial response at a later time point. It is the responsibility of the Investigator to determine if the patient should be considered for treatment beyond progression due to clinical benefit. This decision should be considered carefully so as to permit patients who are likely to be benefiting to continue treatment while at the same time preventing prolonged exposure of a futile therapy in patients who may not be benefitting. Any decisions to continue treatment beyond initial progression must be discussed with the medical monitor and documented in the study records.

Thus subjects with documented progression in tumor burden or the appearance of new lesions in the absence of significant clinical deterioration (decline in performance status and/or laboratory values) are permitted to continue with treatment (after re-consenting in Phase 1) until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point. The next imaging to confirm disease progression must not exceed 12 weeks from initial documentation of PD. In addition, the following criteria must be met:

- Absence of clinical symptoms and signs of disease progression (including worsening laboratory values)

- Stable ECOG performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg cord compression) that necessitates urgent alternative medical intervention

In rare cases, a subject with unequivocal radiographical PD may be allowed to continue study treatment if, in the judgment of the investigator, the subject is benefiting from the treatment. Prior consultation with the Sponsor is required.

8.5.2 Efficacy Endpoints

Efficacy measures include:

- The ORR, defined as the percentage of subjects in the study whose best overall response was either CR or PR, as assessed by Investigators based on RECIST v 1.1.
- The PFS and DCR (CR + PR + SD) as assessed by RECIST v 1.1; and CBR (CR + PR + durable SD [SD ≥24 weeks])
- DOR for responders (CR or PR)

PCWG2 criteria (Scher et al, 2008) may also be used to evaluate responses in patients with prostate cancer enrolled in the study as presented in Appendix 9.

GCIG criteria (Rustin et al, 2011), in addition to RECIST v 1.1 may also be used to evaluate response in patients with ovarian cancer enrolled in the study.

RANO criteria (Wen et al, 2010) may also be used to evaluate response in patients with GBM enrolled on the study.

8.6 Pharmacokinetics

Blood will be collected to describe the PK profile of tislelizumab for Phase 1A and 1B stages of the study. PK analysis will include but is not limited to $AUC_{0\text{-}14\ day}$, C_{max} and T_{max}, C_{trough}, $T_{1/2,}$ Cl, and V_d.

Details concerning handling of PK serum samples, including labeling and shipping instructions will be provided in the Lab Manual. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Blood samples (3.5 mL) for PK analysis will be collected according to the Lab Manual and serum will be separated and immediately frozen. Samples must remain frozen in a freezer set at or below -70°C and in a box with dry ice during shipping.

Prior to collection, the collection tube and serum storage tube must be labeled with the corresponding labels provided by the sponsor. The labels must be placed along the length of the tube so they can be read easily. Tape must not be used to secure the labels as the tube will not fit into the auto-analyzer test tube rack. The labels are of high quality and will not peel off of the tube even under extreme conditions.

Samples will be shipped to the central laboratory where all samples will be analyzed for serum tislelizumab concentrations using a validated method.

8.6.1 Phase 1A Part 1

Cannulation for blood sampling for PK in Phase 1A Part 1 stage will be performed. PK samples should not be drawn from the infusion line or from the same arm of infusion. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 6.

Cycle 1 and Cycle 4

For subjects in the dose-escalation cohorts, 8 blood samples (3.5 mL each) will be collected on Day 1, 2, 4 (or 5), 8 and 15 at the following time points: predose (within 1 hour before the investigational product administration) and 0.5 (end infusion to 30 min), 1.5, 6, 24, 72 (or 96), 168 and 336 hours postdose (the 336-hour PK sample will be collected on Day 15 within 1 hour before the investigational product administration). In addition, a postdose sample (end infusion to 30 min) on Cycle 1 Day 15 will be collected.

Cycle 2 and Additional Cycles except Cycle 4 during the First 12 Months of Study

Two blood samples (3.5 mL each) will be collected on Day 1 of each cycle at the following time points: predose (within 1 hour before the investigational product administration) and postdose (end infusion to 30 min).

Safety Follow-up

One blood samples (3.5 mL) will be collected at the mandatory Safety Follow-up Visit.

Other Blood Samples

Unscheduled blood samples may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related. Blood samples (3.5 mL) should be obtained, when possible, for analysis of serum tislelizumab in the event of a DLT or any Grade 3 or above irAE (refer to Section 7.3.4). The Investigator must record the time the blood samples obtained and the time of the previous administration in the eCRF.

Should a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction as decided by the Investigator in consultation with the Sponsor.

Total Blood Volume

The maximum total amount of blood collected during the study (including screening safety assessments) is presented in Appendix 3.

8.6.2 Phase 1A Part 2

For the Phase 1A Part 2 stage of the study, the approximate amount of blood taken for PK assessments and other assessments is listed in Appendix 3. These samples will be collected at the time points presented in Table 7 (Q2W) and Table 8 (Q3W). Predose (within 60 min before start infusion) and postdose (within 30 min after the end of infusion) samples should be collected at Cycle 1 Day 1, Day 15 (only for Q2W), Day 1 of Cycle 2 and subsequently every cycle in the first 12 months, then approximately every 6 months thereafter; additional PK samples should be collected at Cycle 1 Day 4 (or 5), Day 8, Day 15 (only for Q3W) and the mandatory Safety Follow-Up Visit. Should a subject present with a DLT or any Grade 3 or above irAE (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

8.6.3 Phase 1A Part 3

For the Phase 1A Part 3 stage of the study, the approximate amount of blood taken for PK assessments and other assessments is listed in Appendix 3. These samples will be collected at the time points presented in Table 10. Predose (trough, within 24 hours before start infusion) and postdose (within 30 min after the end of infusion) samples should be collected at Day 1 of Cycle 1, Cycle 2, Cycle 3, Cycle 5 and every 2 cycles in first 6 months, every 4 cycles in the next 6 months, approximately every 6 months thereafter; additional PK samples should be collected at Day 2, Day 4 (or 5), Day 8 and Day 15 of Cycle 1 and Cycle 5; a predose sample on Cycle 5 Day 22 (Cycle 6 Day 1) should also be collected; additional PK samples should be collected at the mandatory Safety Follow-Up Visit. All trough samples should be drawn at the same time as blood collection for anti-tislelizumab antibodies. Should a subject present with a DLT or any Grade 3 or above irAE (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

8.6.4 Phase 1B

For the Phase 1B stage of the study, the approximate amount of blood taken for PK assessments and other assessments is listed in Appendix 3. These samples will be collected

at the time points presented in Table 11. Predose (trough, within 24 hours before start infusion) and postdose (within 30 min after the end of infusion) samples should be collected at Day 1 of Cycle 1, and subsequent every 2 cycles in the first 6 months, every 4 cycles in next 6 months, then approximately every 6 months thereafter; additional PK samples should be collected at the mandatory Safety Follow-Up Visit. All trough samples should be drawn at the same time as blood collection for anti-tislelizumab antibodies. Should a subject present with a DLT (Section 5.1.1) or any Grade 3 or above irAE (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

8.7 Anti-Drug Antibody

Immunogenic responses to tislelizumab will be assessed to determine occurrence of anti-tislelizumab antibody. For subjects in Phase 1A Part 1 stage, as specified in Table 5, 2 mL of blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every cycle in the first 6 months, every 2 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. For subjects in Phase 1A Part 2 stage, as specified in Table 7 and Table 8, 2 mL of blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every cycle in the first 6 months, every 2 cycles (Q2W) or 3 cycles (Q3W) in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. For subjects in Phase 1A Part 3 stage, as specified in Table 9, 2 mL of blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every 2 cycles in the first 6 months, every 4 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. For subjects in Phase 1B stage, as specified in Table 11, 2 mL of blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion of Cycle 1 and subsequent every 2 cycles in the first 6 months, every 4 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for C_{trough}. Samples will be processed according to the Lab Manual and shipped to a central laboratory for analysis using a validated method.

8.8 Pharmacodynamics Assessments

Pharmacodynamic measurements include effects of tislelizumab on immune cell subtypes and cytokine/chemokine in the blood. At the specified time points (Table 5), 40 mL of blood in ACD will be collected and transported at room temperature to the central laboratory within 8 hours according to the instructions in the Lab Manual. Due to sample logistics issue, this

assay will only be performed on subjects enrolled in Phase 1A Part 1 of the study in Melbourne area.

PD-1 receptor occupancy assay will only be performed in subjects enrolled in Arm 2 in Phase 1B stage of the study in Melbourne area. PD-1 receptor occupancy on circulating T cells will be measured as an indication of target engagement. 30 mL of blood will be collected at the specified time points (Table 11). Details on collection of blood samples, processing, storage, and shipping details are provided in the Lab Manual.

Other pharmacodynamic biomarkers could include changes in tumor microenvironment, including but not limited to PD-L1 expression and TILs. These are detailed in the following Section 8.9.

8.9 Biomarker Assessments

Tumor biopsy and plasma samples for the development of exploratory biomarkers will be collected as stated in Table 5, Table 7, Table 8, and Table 9 for Phase 1A, and Table 11 for Phase 1B, respectively.

The archival tumor tissues are mandatory for all subjects who consent to participate in the study and have available archival tumor tissue samples, although a fresh baseline tumor biopsy (within 8 weeks before starting treatment) is strongly recommended. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is mandatory. For these subjects, an optional biopsy for biomarker analysis after approximately 2 cycles of treatment is strongly recommended.

For Arm 2 (ovarian cancer), Arm 3 (gastric cancer), and Arm 4 (HCC) of Phase 1B study, a fresh baseline biopsy within 8 weeks before starting treatment is mandatory for biomarker analysis

For Arm 9 (melanoma) of Phase 1B study, a fresh baseline biopsy within 8 weeks before starting treatment and one approximately on Cycle 3 Day 1 are mandatory for biomarker analysis.

All other subjects who have easily accessible lesions are strongly recommended for baseline or the paired biopsy.

Optional biopsy will also be taken at the safety follow up visit for the subjects who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions

(eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). Risk assessment of tumor biopsy must be evaluated by investigators to ensure that only non-significant risk procedures (ie, those procedures associated with an absolute risk of mortality or major morbidity of less than 2% based on institutional experience, biopsy location, and patient's clinical status) will be performed for protocol-mandated biopsies. From the baseline biopsy or archived tumor tissue, either a formalin-fixed paraffin-embedded block with tumor tissue (preferred) or at least 10 unstained slides must be sent to the central laboratory. If performed, a core or excisional biopsy of the tumor (cytologic or fine-needle aspiration samples are not acceptable) should be obtained that has proper size for histological examination and biomarker.

Specific instructions for tissue/plasma collection and shipment are provided in the Lab Manual. The maximum amount of blood collected during the study is presented in Appendix 3.

The primary biomarker objective is to assess the relationship between PD-L1 expression levels, TILs in the tumor tissues and anti-tumor activity of tislelizumab.

Other candidate biomarkers which will be investigated in the study may include, but are not limited to, the following:

- PD-L2 expression levels
- RNA and DNA profiling, including but not limiting to neoantigens, in tumor tissue
- Proteomics and cfDNA profiling in peripheral blood

8.10 Appropriateness of Measurements

All efficacy, safety and PK assessments used in this study are standard, ie, widely used and generally recognized as reliable, accurate, and relevant.

9.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the ICH GCP Guidelines, 1996, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Local certified laboratories for laboratory measurements and ECGs
- Study center initiation visit
- Early study center visits post-enrollment
- Routine study center monitoring
- Ongoing study center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, the sponsor and/or the CRO clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to the study center, study center visits, PK laboratories, local laboratories, vendors, clinical database, and the final clinical study reports. When audits are conducted, access must be authorized for all study- related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

9.1 Monitoring

In accordance with applicable regulations, GCP, and sponsor procedures, the Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. Monitors will work in accordance with the Sponsor or CRO SOPs and have the same rights and responsibilities as monitors from the Sponsor's organization. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification

- Identify any issues and address their resolution

This will be done in order to verify that the:

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

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 13.1.

9.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of Quintiles.

An electronic data capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study center personnel prior to the study being initiated and any data being entered into the system for any subjects.

The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections

to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate study center personnel will answer queries sent to the Investigator.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives the investigational product, regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Concomitant diseases/medical history will be coded using the most current version of MedDRA.

9.3 Quality Assurance Audit

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after

completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

10.0 SAFETY MONITORING AND REPORTING

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the Investigator or study center personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

10.1 Definition of an Adverse Event

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational product.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study. See Section 10.3 for additional information.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product 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 investigational product or a concurrent medication (overdose per se should not be reported as an AE or SAE)
- Significant failure of expected pharmacological or biological action. See Section 10.3 for additional information

Examples of an AE do not include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

10.2 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 event in which the subject was at risk of death at the time of the event. It does not refer to an event, 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 subject 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 out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- 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
- Medically Significant: A medical or scientific judgment regarding that the event, such as important medical events that may not be immediately life-threatening or result in death or hospital admission but may jeopardize the subject or may require medical or surgical intervention (in the office or an Emergency Department visit with treatment) to prevent one of the other outcomes listed in the above definitions. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3 Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

10.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (eg, clinical chemistry, hematology, coagulation, urinalysis) or other abnormal assessments (eg, ECGs, X-rays, vital signs, etc.) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 10.1, or an SAE, as defined in Section 10.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study or require a medical intervention for treatment will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.5 Time Period, Frequency, and Method of Detecting Adverse Events and Serious Adverse Events

Subjects will be assessed for AEs and SAEs beginning immediately after signing the informed consent form and continuing through to follow-up which is 30 ± 3 days of last dose of investigational drug. Telephone contacts with patients should be conducted to assess irAEs 90 days after the last dose of tislelizumab 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 drug-related SAEs will be recorded by the Investigator after treatment discontinuation until patient death or loss to follow-up, whichever occurs first.

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?

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs will be reported in the eCRF.

10.6 Recording of Adverse Events and Serious Adverse Events

When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The Investigator will then record all relevant information regarding an AE or SAE in the eCRF. It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the appropriate AE or SAE eCRF pages. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the Sponsor or designee.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE or SAE and not the individual signs/symptoms. Adverse events are independent components of the study.

10.7 Evaluating Adverse Events and Serious Adverse Events

10.7.1 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study, at the time the event is reported. When applicable, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v 4.03. In addition to performing the CTCAE assessment, the intensity of each AE and SAE recorded in the eCRF should also be assigned to one of the following categories based on the Investigator's clinical judgment:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.2.

10.7.2 Assessment of Causality

The Investigator is obligated to assess the relationship between the investigational product and the occurrence of each AE or SAE, at the time the event is reported. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The Investigator will also consult the IB and/or Product Information, for marketed products, 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 or designee. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE eCRF to the Sponsor or designee. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Investigator will provide the assessment of causality as per instructions on the SAE eCRF.

10.8 Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the Investigator is required to proactively follow each subject and provide further information to the Sponsor or designee on the subject's condition.

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

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. 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, or consultation with other health care professionals.

The Sponsor or designee 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 subject dies during participation in the study or during a recognized follow-up period, the Sponsor or designee will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE eCRF. The updated SAE eCRF should be resubmitted to the Sponsor or designee within the time frames outlined in Section 10.9.

10.9 Prompt Reporting of Serious Adverse Events

10.9.1 Timeframes for Submitting Serious Adverse Events

Serious AEs will be reported promptly to the Sponsor or designee as described in Table 14 once the Investigator determines that the event meets the protocol definition of an SAE.

Table 14 Timeframe 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
All SAEs	Within 24 hours of first knowledge of the AE	SAE Report	As expeditiously as possible	SAE Report

Abbreviations: AE, adverse event; SAE, serious adverse event.

10.9.2 Completion and Transmission of the Serious Adverse Event Report

Once an Investigator becomes aware that an SAE has occurred in a subject, he/she will report the information to the Sponsor or designee within 24 hours as outlined in Table 14. The SAE eCRF will always be completed as thoroughly as possible with all available details of the event. The SAE should be recorded by the Investigator (or designee) and reported to the Sponsor within the designated timeframes. The data alert letter will be automatically submitted to sponsor or designee immediately by EDC system. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor or designee of the event and completing the form. The form will be updated when additional information is received.

The Investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.7.2.

In case EDC is down, facsimile transmission of the paper SAE form is the preferred backup method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the paper SAE form sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator to complete and sign the paper SAE form within the time frames outlined in Section 10.9.1.

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

10.10 Regulatory Reporting Requirements for Serious Adverse Events

The Investigator will promptly report all SAEs to the Sponsor or designee in accordance with the procedures detailed in Section 10.9.1. 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. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

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

This protocol may be filed under an Investigational New Drug (IND) application with the US FDA. Once active, a given SAE may qualify as an IND safety report if the SAE is both

attributable to the investigational product and unexpected. In this case, all Investigators filed to the IND (and associated INDs for the same compound) will receive an expedited Investigator safety report, identical in content to the IND safety report submitted to the FDA.

Expedited Investigator safety reports are prepared according to the Sponsor's policy and are forwarded to Investigators as necessary. Such a report is prepared for an SAE that is both attributable to investigational product and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the Sponsor or designee, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

10.11 Post-study Adverse Events and Serious Adverse Events

A post-study AE or SAE is defined as any event that occurs outside of the AE/SAE detection period, defined in Section 10.5.

Investigators are not obligated to actively seek AEs or SAEs in former subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify the Sponsor or designee.

10.12 Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly to the Sponsor or designee (see Section 10.9).

10.13 Pregnancy

10.13.1 Contraception and Pregnancy Testing

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 12 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

A serum pregnancy test will be performed at screening in women of childbearing potential. Any female subject who is pregnant will not be eligible for the study (see Section 5.2.1). A urine or serum pregnancy test must be performed if any woman suspects that she has become pregnant during the study.

10.13.2 Time Period for Collecting Pregnancy Information

The time period for collecting information on whether a pregnancy occurs is from screening until 30 days after the last investigational product administration. Information on pregnancies identified prior to the investigational product administration does not need to be reported to sponsor.

10.13.3 Action to be Taken and Reporting if a Pregnancy Occurs

A subject who has a positive pregnancy test result at any time after the investigational product administration will be immediately withdrawn from participation in the study. All post-study assessments will be collected at the time of discontinuation as described in Section 5.2.5.2.

The Investigator, or his/her designee, will collect pregnancy information on any female subject or a female partner of a male subject who becomes pregnant while participating in this study. The Investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor or designee. Generally, follow-up will be no longer than 8 weeks following the delivery date. Any premature termination (spontaneous or elective abortion prior to 20 weeks or stillbirth after 20 weeks gestational age) of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE, as described in Section 10.6 and will be followed as described in Section 10.8.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 10.0. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the investigational product by the Investigator, will be reported to the Sponsor or designee as described in Section 10.11. While the Investigator is not obligated to actively seek this information in former subjects, he/she may learn of an SAE through spontaneous reporting.

11.0 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1 Sample Size Considerations

11.1.1 Sample Size Considerations for Phase 1A

In the Phase 1A stage, the number of dose levels and schedules examined and the emerging tislelizumab toxicities will determine the sample size. It is anticipated that approximately 24 subjects will be required to establish the RP2D(s) of tislelizumab when administered as a single agent. In addition, 10 to 20 subjects will be enrolled in each of the schedule expansion and flat dose cohort at one or more dose level (up to 10 mg/kg Q2W or Q3W in schedule expansion cohort; 200 mg Q3W in flat dose cohort) not exceeding MTD to further evaluate safety, tolerability, PK and preliminary efficacy of tislelizumab. In total approximately 120 subjects are planned for the study.

11.1.2 Sample Size Considerations for Phase 1B

In the Phase 1B stage, approximately 330 subjects (approximately 20, 30 or 50 subjects for each arm except arm 9) will be evaluated for efficacy as well as safety and tolerability of tislelizumab in select tumor types. One or more arms may be closed early due to difficulty in patient recruitment.

Using binomial approach, the 95% confidence interval (CI) width of an observed ORR of 10% is reduced by 12%, from 30.5% to 18.5%, when sample size increases from 20 to 50. The 95% CI width of an observed ORR=50% is reduced by 16.6%, from 45.6% to 29.0%, when sample size increases from 20 to 50. There is approximately 88% chance to observed at least one responder in an expansion arm of size 20 when the underlying ORR is 10%; and such chance increases while sample size expands.

11.2 General Considerations for Data Analysis

Data will be listed and summarized using SAS® v 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) according to Sponsor agreed reporting standards, where applicable. Complete details will be documented in the reporting and analysis plan. Primary safety and efficacy analyses will be conducted approximately 6 months after the last subject being enrolled.

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

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum

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

Efficacy and safety data will be summarized by stage and arm, unless otherwise specified. Further description of the statistical methods and analyses will be provided in the statistical analysis plan.

11.2.1 Analysis Populations

All Subjects Enrolled Set (ENR)

The all subjects enrolled (ENR) set will include all subjects who provide informed consent for this study. The ENR analysis set will be used to summarize and describe the subject disposition, and deaths, unless stated otherwise.

Safety Analysis Set (SAF)

The safety analysis set (SAF) will include all subjects in the ENR set who receive at least one dose of tislelizumab. The SAF will be used for all efficacy and safety summaries (except DLTs, PK and PD analyses).

DLT Analysis Set (DLT)

The DLT Analysis Set includes all subjects who experienced a DLT during Cycle 1 plus subjects who received at least 90% of the planned doses of treatment during the DLT observation period (Cycle 1).

PK Analysis Set (PKS)

The PK Analysis Set will include subjects who have received at least the first dose of tislelizumab and provided PK samples as per protocol following first dosing on Day 1.

PD Analysis Set (PDS)

The PD Analysis Set will include subjects who have received at least the first dose of tislelizumab and have evaluable pharmacodynamic data.

11.2.2 Interim Analysis

Phase 1A stage of this study is a dose escalation and schedule expansion study, safety, PK and pharmacodynamic data will be evaluated on an ongoing basis. The interim analysis will be performed once the Phase 1A stage is completed.

11.2.3 Efficacy Analyses

Efficacy is not a primary objective of the Phase 1A stage of this study. Objective response is the primary endpoint of the Phase 1B stage. There is no formal statistical testing for the efficacy endpoints in Phase 1B. The efficacy analyses will be descriptive only.

Response based on Investigators' judgment will be collected at screening and while on study approximately every 8 weeks or 9 weeks depending on dosing schedules in the first 12 months and approximately 12 weeks thereafter in the simple form of four categories: PD, SD, CR, and PR (according to RECIST v 1.1).

PCWG2 criteria (Scher et al, 2008) may also be used to evaluate responses in patients with prostate cancer enrolled in the study.

GCIG criteria (Rustin et al, 2011), in addition to RECIST v 1.1 may also be used to evaluate response in patients with ovarian cancer enrolled in the study.

RANO criteria (Wen et al, 2010) may also be used to evaluate response in patients with GBM enrolled on the study.

Listing of the data will be provided. If data warrant, a summary by category will be provided.

Objective Response

The number and proportion of subjects who achieve objective tumor response (CR or PR) or SD will be summarized. The ORR will be determined along with 95% CI.

Progression Free Survival

Progression-free survival is defined as the time from the date of first study dose to disease progression or death whichever occurs first. Subjects without an event (no disease progression or death) will be censored at the date of "last tumor assessment". Subjects with no baseline or post-baseline tumor assessments will be censored at Day 1.

Kaplan-Meier methodology will be used to estimate median PFS and 95% CI. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

Duration of Response

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. For subjects who are alive without progression following the qualifying

response, DOR will be censored on the date of last evaluable tumor assessment or last follow-up for progression of disease.

Kaplan-Meier methodology will be used to estimate median time and 95% CI for DOR.

Disease Control Rate

The DCR is defined as the proportion of subjects who achieve CR, PR, and SD based on RECIST v 1.1 in subjects with select tumor types. The DCR will be calculated for each tumor type with 95% CI estimated.

Clinical Benefit Rate

The CBR is defined as the proportion of subjects who achieve CR, PR, and durable SD [SD ≥24 weeks] based on RECIST v 1.1 in subjects with select tumor types. The CBR as well as 95% CI will be estimated for each tumor type.

Overall Survival

Overall survival is defined as the time interval between the date of the first study drug dose to the date of death for any cause. Kaplan-Meier methodology will be used to estimate OS at various time points.

11.3 Safety Analyses

All subjects who are exposed to (or started receiving) tislelizumab will be evaluated for safety. Safety data will be summarized separately for the Phase 1A and 1B portions of the study.

11.3.1 Dose Limiting Toxicity

For Phase 1A, the number and proportion of subjects experiencing DLTs will be reported by dose level, based on DLT observations during the first cycle. The DLT Analysis Set will be used for this analysis.

There is no DLT analysis in Phase 1B.

11.3.2 Adverse Events

The AE verbatim descriptions (Investigator's description from the eCRF) will be classified into standardized medical terminology using MedDRA®. All AEs will be coded to MedDRA® (v 18.1 or later) lower level term closest to the verbatim term. All TEAEs will be summarized.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy. The TEAE classification also applies to irAEs that are recorded up to 90 days after discontinuation from tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. The SAEs, deaths, TEAEs of Grade 3 or above, related TEAEs and TEAEs that led to treatment discontinuation, and AEs of particular interest will be summarized.

11.3.3 Laboratory Assessments

Hematology, clinical chemistry, coagulation, and urinalysis values will be flagged as high or low relative to the normal range, where applicable. Predose values will be used to assess laboratory shifts occurring at postdose. A comparison of pre-study and post-study values will be performed to identify any parameters that have not returned to pre-study levels.

11.3.4 Electrocardiogram

All ECG parameters including the QT interval corrected for heart rate (QTc) will be listed for each subject and summarized by dose level and assessment time. Change from baseline will also be summarized. Relationship between dose level and QTc changes will be explored by graphs. QTc will be calculated using Fridericia's formula.

11.3.5 Vital Signs

Blood pressure, pulse, respiratory rate, temperature and weight will be summarized and listed. The change from baseline will also be displayed.

11.3.6 Extent of Exposure

Extent of exposure to tislelizumab will be summarized descriptively as the number of doses received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (in mg/3 weeks), and relative dose intensity.

The number (percentage) of patients requiring drug discontinuation due to AEs will be summarized.

11.3.7 Physical Examination

Physical examination results will be listed.

11.3.8 Ophthalmologic Examination

Ophthalmologic examination results will be listed by subject.

11.3.9 Immunogenicity Analysis

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 subjects. The effect of immunogenicity on PK, efficacy and safety may be evaluated if data allow.

11.3.10 Hepatitis A and B Analysis

Hepatitis B and C analysis results will be listed.

11.4 Pharmacokinetic Analyses

Pharmacokinetic parameters will be derived using standard non-compartmental methods with WinNonlin Professional v 5.2 or higher (Pharsight Corp., Mountain View, California) or SAS® v 9.2 or higher (SAS Institute, Inc., Cary, North Carolina).

tislelizumab PK variables (eg, C_{max}, T_{max}, C_{trough}, AUC, Cl, and V_d) will be calculated as appropriate and summary statistics will be provided [redacted].

11.5 Pharmacodynamic Analyses

Summary statistics will be provided for immune cell subtype, chemokine/cytokine modulation and PD-1 receptor occupancy in the blood. [redacted].

11.6 Biomarker Analyses

The primary predictive biomarker analysis is based on a subset of the subjects with both a valid PD-L1 expression and/or TILs measurement and at least one disease assessment post-treatment. A supportive analysis is based on subjects with a valid PD-L1 expression and/or TILs measurement, irrespective of the availability of post-treatment disease assessments. In this analysis, those without post-treatment disease assessments will be imputed with the worst outcome in tumor response [redacted]

[redacted]

[redacted].

12.0 ETHICS

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 before the study is initiated at a study center in that country.

12.2 Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, current version of the Declaration of Helsinki.

The Investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential subjects (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The Investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The Sponsor will provide the Investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the investigational product(s) can be shipped to the study center, the Sponsor must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

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

12.3 Informed Consent

Informed consent(s) will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent(s) will be in accordance with all applicable regulatory requirements.

12.4 Investigator Reporting Requirements

As indicated in Section 10.10, the Investigator (or Sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the Investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor.

13.0 STUDY ADMINISTRATION

13.1 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
- Data queries
- Accountability, reconciliation, and arrangements for unused investigational product(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 temporarily suspend or prematurely discontinue this study 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 non-compliance. 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 for safety reasons, and will also inform the

regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the 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 all unused investigational product(s) in accordance with the applicable Sponsor procedures for the study.

Financial compensation to Investigators and/or institutions will be in accordance with the agreement established between the Investigator and the Sponsor.

13.2 Records Retention

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 back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that 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 15 years.

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

13.3 Provision of Study Results and Information to Investigators

When the interim clinical study report for Phase 1 and the final clinical study report is completed, the Sponsor will provide the major findings of the study to the Investigator.

In addition, details of the study treatment assignment will be provided to the Investigator to enable him/her to review the data to determine the outcome of the study for his/her subjects.

The Sponsor will not routinely inform the Investigator or subject of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

13.4 Information Disclosure and Inventions

All information provided by the Sponsor and all data and information generated by the study center as part of the study (other than a subject's medical records) are the sole property of the Sponsor.

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 subject's medical records) 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 which becomes publicly available through no fault of the Investigator or study center personnel
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose in order to provide appropriate medical care to a subject
- Study results which may be published as described in Section 13.4.1

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

13.4.1 Publication Policy

For multi-center studies, the first publication or disclosure of study results shall be a complete, joint multi-center publication or disclosure coordinated by the Sponsor. Thereafter, any secondary publications will reference the original publication(s).

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

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

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

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15.0 APPENDICES

APPENDIX 1: SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 1A/1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors

PROTOCOL NO: BGB-A317_Study_001

This protocol is a confidential communication of BeiGene Research and Development. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. 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 Research and Development.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to Quintiles.

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: _____

_____

_____

_____

APPENDIX 2: CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	RBC count	Prothrombin time	pH
Alanine aminotransferase	Hematocrit	Activated Partial thromboplastin Time	Specific gravity
Aspartate aminotransferase	Hemoglobin	International Normalized Ratio	Glucose
Albumin	MCH		Protein
Total bilirubin	MCHC		Ketones
Bicarbonate[1]	MCV		Blood
Blood urea nitrogen or urea	Platelet counts		24-hour protein[2]
Calcium	WBC count with differential		Random urine protein to creatinine ratio
Chloride	Neutrophil count		
Creatinine	Lymphocyte count		
Glucose	Monocyte count		
Lactate dehydrogenase	Basophil count		
Phosphate	Eosinophil count		
Total protein			
Creatine kinase (CK)[3]			
Creatine kinase – cardiac muscle isoenzyme (CK-MB)[3]			
Potassium			
Sodium			

Abbreviations: CK-MB, creatine kinase cardiac muscle isoenzyme; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration;
MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.

1. Blood CO_2 or HCO_3 is acceptable.
2. On routine urinalysis, if urine protein is ≥2+ by dipstick, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio.
3. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

APPENDIX 3: BLOOD REQUIREMENTS

Phase 1A Part 1

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 1 stage (dose escalation cohorts)
Screening		
	Serum chemistry	5
	Hematology	2.5
	Coagulation	3
	HIV, Hepatitis B and C	5
	Serum tumor markers[1]	3
	Total	18.5
Cycle 1 Day 1		
	Serum chemistry	5
	Hematology	2.5
	Immune cell subtyping and cytokine/chemokine panel[2]	40
	Thyroid function	3
	Immunoglubulins[3]	5
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6]	14
	Total	76.5
Day 2		
	Pharmacokinetics[6]	3.5
	Total	3.5
Day 4 (or 5)		
	Pharmacokinetics[6]	3.5
	Total	3.5
Day 8		
	Serum chemistry	5
	Hematology	2.5
	Pharmacokinetics[6]	3.5
	Total	11

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 1 stage (dose escalation cohorts)
Day 15		
	Serum chemistry	5
	Hematology	2.5
	Immune cell subtyping and cytokine/chemokine panel[2]	40
	Pharmacokinetics[6]	7
	Total	54.5
Cycle 2 and Additional Cycles (except for Cycle 4) Day 1		
	Serum chemistry	5
	Hematology	2.5
	Immune cell subtyping and cytokine/chemokine panel[2]	40
	Thyroid function	3
	Immunoglubulins[3]	5
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6]	7
	Serum tumor markers[1]	3
	Total	72.5
Day 15		
	Serum chemistry	5
	Hematology	2.5
	Total	7.5
Cycle 4 Day 1		
	Serum chemistry	5
	Hematology	2.5
	Immune cell subtyping and cytokine/chemokine panel[2]	40
	Thyroid function	3
	Immunoglubulins[3]	5

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 1 stage (dose escalation cohorts)
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6]	14
	Total	76.5
Day 2	Pharmacokinetics[6]	3.5
	Total	3.5
Day 4 (or 5)	Pharmacokinetics[6]	3.5
	Total	3.5
Day 8	Pharmacokinetics[6]	3.5
	Total	3.5
Day 15	Serum chemistry	5
	Hematology	2.5
	Pharmacokinetics[6]	3.5
	Total	11
Cycle 5 Day 1 **(and every 4 cycles thereafter)**	Hepatitis B and C	3-5
Safety Follow-up	Serum chemistry	5
	Hematology	2.5
	Coagulation	3
	Immune cell subtyping and cytokine/chemokine panel[2]	40
	Thyroid function	3
	Immunoglubulins[3]	5
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6]	3.5
	Serum tumor markers[1]	3

	Total	72
Other blood samples[7]		

1. Standard tumor markers (eg, AFP for HCC and CA 125 for ovarian cancer, as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter, and at the mandatory Safety Follow-Up Visit.
2. **Only for the dose-escalation subjects treated in Melbourne sites due to sample and assay logistics.** Blood in ACD will be collected and transported at room temperature within 8 hours according to the instructions in the Lab Manual at the time points specified in Table 5.
3. Analysis of IgG and IgM at predose of Day 1 of every cycle in the first 12 months, approximately every 8 weeks thereafter, and at the Safety Follow-Up Visit.
4. Blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every cycle in the first 6 months, every 2 cycles in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose.
5. Blood collected at predose on Day 1 of every cycle until 6 months of study, and at the safety follow up visit for the subjects who have confirmed disease progression during the study to explore resistance mechanism.
6. Cannulation for blood sampling for pharmacokinetics will be performed. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 6.
7. Unscheduled blood samples for pharmacokinetic (PK) analysis may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related. Blood samples (3.5 mL) should be obtained, when possible, for analysis of serum tislelizumab in the event of a DLT.

   Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

Phase 1A Part 2

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 2 stage (Q2W schedule)	Blood volume (mL) for subjects in the Phase 1A Part 2 stage (Q3W schedule)
Screening			
	Serum chemistry	5	5
	Hematology	2.5	2.5
	Coagulation	3	3
	HIV, Hepatitis B and C	5	5
	Serum tumor markers[1]	3	3
	Total	18.5	18.5
Cycle 1 Day 1			
	Serum chemistry	5	5
	Hematology	2.5	2.5
	Thyroid function	3	3
	Immunoglubulins[2]	5	5
	Anti-tislelizumab antibodies[3]	2	2
	Proteomics and genomics biomarkers in blood[4]	5	5
	Pharmacokinetics[5]	7	7
	Total	29.5	29.5
Day 4 (or 5)			
	Pharmacokinetics[5]	3.5	3.5
	Total	3.5	3.5
Day 8			
	Serum chemistry	5	5
	Hematology	2.5	2.5
	Pharmacokinetics[5]	3.5	3.5
	Total	11	11
Day 15			
	Serum chemistry	5	5
	Hematology	2.5	2.5
	Pharmacokinetics[5]	7	3.5
	Total	14.5	11

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 2 stage (Q2W schedule)	Blood volume (mL) for subjects in the Phase 1A Part 2 stage (Q3W schedule)
Cycle 2 and Additional Cycles Day 1			
	Serum chemistry	5	5
	Hematology	2.5	2.5
	Thyroid function	3	3
	Immunoglubulins[2]	5	5
	Anti-tislelizumab antibodies[3]	2	2
	Proteomics and genomics biomarkers in blood[4]	5	5
	Pharmacokinetics[5]	7	7
	Serum tumor markers[1]	3	3
	Total	32.5	32.5
Day 15			
	Serum chemistry	5	N/A
	Hematology	2.5	N/A
	Total	7.5	0
Cycle 5 Day 1 **(and every 4 cycles thereafter)**	Hepatitis B and C	3	3-5
Safety Follow-up			
	Serum chemistry	5	5
	Hematology	2.5	2.5
	Coagulation	3	3
	Thyroid function	3	3
	Immunoglubulins[2]	5	5
	Anti-tislelizumab antibodies[3]	2	2
	Proteomics and genomics biomarkers in blood[4]	5	5
	Pharmacokinetics[5]	3.5	3.5
	Serum tumor markers[1]	3	3
	Total	32	32
Other blood samples[6]			

1. Standard tumor markers (eg, AFP for HCC and CA 125 for ovarian cancer, as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1 Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter, and at the mandatory Safety Follow-Up Visit.
2. Analysis of IgG and IgM at predose of Day 1 of every cycle in the first 12 months, approximately every 8 weeks thereafter, and at the Safety Follow-Up Visit.
3. Blood for anti-tislelizumab antibodies should be collected within 24 hours before start of Day 1 infusion every cycle in the first 6 months, every 2 cycles (Q2W) or 3 cycles (Q3W) in the next 6 months, approximately every 6 months thereafter, and at the mandatory Safety Follow-Up Visit. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose.
4. Blood collected at predose on Day 1 of every cycle until 6 months of study, and at the safety follow up visit for the subjects who have confirmed disease progression during the study to explore resistance mechanism.
5. Cannulation for blood sampling for pharmacokinetics will be performed. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 7 and Table 8.
6. Unscheduled blood samples for pharmacokinetic (PK) analysis may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related. Blood samples (3.5 mL) should be obtained, when possible, for analysis of serum tislelizumab in the event of a DLT.

   Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

Phase 1A Part 3

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 3 stage
Screening		
	Serum chemistry	5
	Hematology	2.5
	Coagulation	3
	HIV, Hepatitis B and C	5
	Serum tumor markers[1]	3
	Total	18.5
Cycle 1 Day 1		
	Serum chemistry	5
	Hematology	2.5
	Thyroid function	3
	Immunoglubulins[2]	5
	Anti-tislelizumab antibodies[3]	2
	Proteomics and genomics biomarkers in blood[4]	5
	Pharmacokinetics[5]	7
	Total	29.5
Day 4 (or 5)		
	Pharmacokinetics[5]	3.5
	Total	3.5
Day 8		
	Serum chemistry	5
	Hematology	2.5
	Pharmacokinetics[5]	3.5
	Total	11
Day 15		
	Serum chemistry	5
	Hematology	2.5
	Pharmacokinetics[5]	3.5
	Total	11
Cycle 2 and Additional Cycles (except Cycle 5) Day 1		
	Serum chemistry	5

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 3 stage
	Hematology	2.5
	Thyroid function	3
	Immunoglubulins[2]	5
	Anti-tislelizumab antibodies[3]	2
	Proteomics and genomics biomarkers in blood[4]	5
	Pharmacokinetics[5]	7
	Serum tumor markers[1]	3
	Total	32.5
Cycle 5 Day 1		
	Serum chemistry	5
	Hematology	2.5
	Thyroid function	3
	Immunoglubulins[3]	5
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6] Hepatitis B and C	7 3-5
	Total	32.5 – 35.5
Cycle 9 Day 1 **And every 4 cycles thereafter**	Hepatitis B and C	3-5
Day 2		
	Pharmacokinetics[6]	3.5
	Total	3.5
Day 4 (or 5)		
	Pharmacokinetics[6]	3.5
	Total	3.5
Day 8		
	Pharmacokinetics[6]	3.5
	Total	3.5
Day 15		
	Pharmacokinetics[6]	3.5
	Total	3.5

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1A Part 3 stage
Day 22 (Cycle 6 Day 1)		
	Pharmacokinetics[6]	3.5
	Total	3.5
Safety Follow-up		
	Serum chemistry	5
	Hematology	2.5
	Coagulation	3
	Thyroid function	3
	Immunoglubulins[2]	5
	Anti-tislelizumab antibodies[3]	2
	Proteomics and genomics biomarkers in blood[4]	5
	Pharmacokinetics[5]	3.5
	Serum tumor markers[1]	3
	Total	32
Other blood samples[6]		

1. Standard tumor markers (as appropriate for a given tumor type) will be collected as specified in Table 9 footnote 17.
2. Analysis of IgG and IgM will be performed as specified in Table 9 footnote 12.
3. Blood for anti-tislelizumab antibodies should be collected as specified in Table 9 footnote 13.
4. Blood will be collected at the time points specified in Table 9 footnote 14.
5. Cannulation for blood sampling for pharmacokinetics will be performed. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 10.
6. Unscheduled blood samples for pharmacokinetic (PK) analysis may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related. Blood samples (3.5 mL) should be obtained, when possible, for analysis of serum tislelizumab in the event of a DLT.

   Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

Phase 1B

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1B stage
Screening		
	Serum chemistry	5
	Hematology	2.5
	Coagulation	3
	HIV, Hepatitis B and C	5
	Serum tumor markers[1]	3
	Total	18.5
Cycle 1 Day 1		
	Serum chemistry	5
	Hematology	2.5
	Thyroid function[2]	3
	Immunoglubulins[3]	5
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6]	7
	PD-1 receptor occupancy[7]	30
	Total	59.5
Day 2		
	PD-1 receptor occupancy[7]	30
	Total	30
Cycle 2 and Additional Cycles Day 1		
	Serum chemistry	5
	Hematology	2.5
	Thyroid function[2]	3
	Immunoglubulins[3]	5
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6]	7
	PD-1 receptor occupancy[7]	30
	Serum tumor markers[1]	3

Time point	Assessment	Blood volume (mL) for subjects in the Phase 1B stage
	Total	62.5
Cycle 5 Day 1 **(and every 4 cycles thereafter)**	Hepatitis B and C	3-5
Safety Follow-up	Serum chemistry	5
	Hematology	2.5
	Coagulation	3
	Thyroid function[2]	3
	Immunoglubulins[3]	5
	Anti-tislelizumab antibodies[4]	2
	Proteomics and genomics biomarkers in blood[5]	5
	Pharmacokinetics[6]	3.5
	Serum tumor markers[1]	3
	Total	32
Other blood samples[8]		

1. Standard tumor markers (as appropriate for a given tumor type) will be collected as specified in Table 11 footnote 18.
2. Thyroid testing will be performed as specified in Table 11 footnote 11.
3. Analysis of IgG and IgM will be performed as specified in Table 11 footnote 12.
4. Blood for anti-tislelizumab antibodies should be collected as specified in Table 11 footnote 13.
5. Blood will be collected at the time points specified in Table 11 footnote 14.
6. Cannulation for blood sampling for pharmacokinetics will be performed. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 11 footnote 15.
7. **Only for subjects in Arm 2 in the Phase 1B stage if enrolled by Melbourne sites.** Procedures for collection of samples are described in the Procedures Manual. Blood will be collected via the intravenous cannula at the time points specified in Table 11 footnote 16.
8. Unscheduled blood samples for pharmacokinetic (PK) analysis may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related. Blood samples (3.5 mL) should be obtained, when possible, for analysis of serum tislelizumab in the event of a DLT.

   Should a subject present with a DLT or any Grade 3 or above immune-related adverse event (refer to Section 7.3.4), additional blood PK samples will be taken to determine the plasma concentration of tislelizumab.

APPENDIX 4: DRUG DILUTION CALCULATION

Dose Level: 0.5 mg/kg

Body Weight (kg)	Total Administered Drug (mg)	Total Dose Volume (mL)	DP Volume (mL)	DP Volume (vial)	Aspirated 0.9% NaCl Volume (mL)	Target Final Concentration (mg/mL)
40	20	20	2.0	1	2.0	1.00
42	21	20	2.1	1	2.1	1.05
44	22	20	2.2	1	2.2	1.10
46	23	20	2.3	1	2.3	1.15
48	24	20	2.4	1	2.4	1.20
50	25	20	2.5	1	2.5	1.25
52	26	20	2.6	1	2.6	1.30
54	27	20	2.7	1	2.7	1.35
56	28	20	2.8	1	2.8	1.40
58	29	20	2.9	1	2.9	1.45
60	30	20	3.0	1	3.0	1.50
62	31	20	3.1	1	3.1	1.55
64	32	20	3.2	1	3.2	1.60
66	33	20	3.3	1	3.3	1.65
68	34	20	3.4	1	3.4	1.70
70	35	20	3.5	1	3.5	1.75
72	36	20	3.6	1	3.6	1.80
74	37	20	3.7	1	3.7	1.85
76	38	20	3.8	1	3.8	1.90
78	39	20	3.9	1	3.9	1.95
80	40	20	4.0	1	4.0	2.00
82	41	20	4.1	1	4.1	2.05
84	42	20	4.2	1	4.2	2.10
86	43	20	4.3	1	4.3	2.15
88	44	20	4.4	1	4.4	2.20
90	45	20	4.5	1	4.5	2.25
92	46	20	4.6	1	4.6	2.30
94	47	20	4.7	1	4.7	2.35
96	48	20	4.8	1	4.8	2.40
98	49	20	4.9	1	4.9	2.45
100	50	20	5.0	1	5.0	2.50

DP, drug product; NaCl; sodium chloride

Dose Level: 2 mg/kg

Body Weight (kg)	Total Administered Drug (mg)	Total Dose Volume (mL)	DP Volume (mL)	DP Volume (vial)	Aspirated 0.9% NaCl Volume (mL)	Target Final Concentration (mg/mL)
40	80	50	8.0	1	8.0	1.60
42	84	50	8.4	1	8.4	1.68
44	88	50	8.8	1	8.8	1.76
46	92	50	9.2	1	9.2	1.84
48	96	50	9.6	1	9.6	1.92
50	100	50	10.0	1	10.0	2.00
52	104	50	10.4	2	10.4	2.08
54	108	50	10.8	2	10.8	2.16
56	112	50	11.2	2	11.2	2.24
58	116	50	11.6	2	11.6	2.32
60	120	50	12.0	2	12.0	2.40
62	124	50	12.4	2	12.4	2.48
64	128	50	12.8	2	12.8	2.56
66	132	50	13.2	2	13.2	2.64
68	136	50	13.6	2	13.6	2.72
70	140	50	14.0	2	14.0	2.80
72	144	50	14.4	2	14.4	2.88
74	148	50	14.8	2	14.8	2.96
76	152	50	15.2	2	15.2	3.04
78	156	50	15.6	2	15.6	3.12
80	160	50	16.0	2	16.0	3.20
82	164	50	16.4	2	16.4	3.28
84	168	50	16.8	2	16.8	3.36
86	172	50	17.2	2	17.2	3.44
88	176	50	17.6	2	17.6	3.52
90	180	50	18.0	2	18.0	3.60
92	184	50	18.4	2	18.4	3.68
94	188	50	18.8	2	18.8	3.76
96	192	50	19.2	2	19.2	3.84
98	196	50	19.6	2	19.6	3.92
100	200	50	20.0	2	20.0	4.00

DP, drug product; NaCl; sodium chloride

Dose Level: 5 mg/kg

Body Weight (kg)	Total Administered Drug (mg)	Total Dose Volume (mL)	DP Volume (mL)	DP Volume (vial)	Aspirated 0.9% NaCl Volume (mL)	Target Final Concentration (mg/mL)
40	200	100	20.0	2	20.0	2.00
42	210	100	21.0	3	21.0	2.10
44	220	100	22.0	3	22.0	2.20
46	230	100	23.0	3	23.0	2.30
48	240	100	24.0	3	24.0	2.40
50	250	100	25.0	3	25.0	2.50
52	260	100	26.0	3	26.0	2.60
54	270	100	27.0	3	27.0	2.70
56	280	100	28.0	3	28.0	2.80
58	290	100	29.0	3	29.0	2.90
60	300	100	30.0	3	30.0	3.00
62	310	100	31.0	4	31.0	3.10
64	320	100	32.0	4	32.0	3.20
66	330	100	33.0	4	33.0	3.30
68	340	100	34.0	4	34.0	3.40
70	350	100	35.0	4	35.0	3.50
72	360	100	36.0	4	36.0	3.60
74	370	100	37.0	4	37.0	3.70
76	380	100	38.0	4	38.0	3.80
78	390	100	39.0	4	39.0	3.90
80	400	100	40.0	4	40.0	4.00
82	410	100	41.0	5	41.0	4.10
84	420	100	42.0	5	42.0	4.20
86	430	100	43.0	5	43.0	4.30
88	440	100	44.0	5	44.0	4.40
90	450	100	45.0	5	45.0	4.50
92	460	100	46.0	5	46.0	4.60
94	470	100	47.0	5	47.0	4.70
96	480	100	48.0	5	48.0	4.80
98	490	100	49.0	5	49.0	4.90
100	500	100	50.0	5	50.0	5.00

DP, drug product; NaCl; sodium chloride

Dose Level: 10 mg/kg

Body Weight (kg)	Total Administered Drug (mg)	Total Dose Volume (mL)	DP Volume (mL)	DP Volume (vial)	Aspirated 0.9% NaCl Volume (mL)	Target Final Concentration (mg/mL)
40	400	100	40.0	4	40.0	4.00
42	420	100	42.0	5	42.0	4.20
44	440	100	44.0	5	44.0	4.40
46	460	100	46.0	5	46.0	4.60
48	480	100	48.0	5	48.0	4.80
50	500	100	50.0	5	50.0	5.00
52	520	100	52.0	6	52.0	5.20
54	540	100	54.0	6	54.0	5.40
56	560	100	56.0	6	56.0	5.60
58	580	100	58.0	6	58.0	5.80
60	600	100	60.0	6	60.0	6.00
62	620	100	62.0	7	62.0	6.20
64	640	100	64.0	7	64.0	6.40
66	660	100	66.0	7	66.0	6.60
68	680	100	68.0	7	68.0	6.80
70	700	100	70.0	7	70.0	7.00
72	720	100	72.0	8	72.0	7.20
74	740	100	74.0	8	74.0	7.40
76	760	100	76.0	8	76.0	7.60
78	780	100	78.0	8	78.0	7.80
80	800	100	80.0	8	80.0	8.00
82	820	100	82.0	9	82.0	8.20
84	840	100	84.0	9	84.0	8.40
86	860	100	86.0	9	86.0	8.60
88	880	100	88.0	9	88.0	8.80
90	900	100	90.0	9	90.0	9.00
92	920	100	92.0	10	92.0	9.20
94	940	100	94.0	10	94.0	9.40
96	960	100	96.0	10	96.0	9.60
98	980	100	98.0	10	98.0	9.80
100	1000	100	100.0	10	100.0	10.00

DP, drug product; NaCl; sodium chloride

APPENDIX 5: THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES

The text below was obtained from 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, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- 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 locoregional 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 x 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 CR 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 subject 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 PSA 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 one 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.

Complete Response (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).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to 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 III trials when it is not a criterion of trial entry to have measurable disease. The same

general concept apply 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 subject 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 disease progression; 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 disease progression. An example of this is the subject who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The subject'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 fluorodeoxyglucose (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 best overall response is the best response recorded from the start of the study drug treatment 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 best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response 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 subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response 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 subject's best response depends on the subsequent assessments. For example, a subject 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 subject 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

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

Note:

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 subjects 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 subject 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 disease progression 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 non-randomized 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 II or III) 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 (in randomized trials, from date of randomization) 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 subjects 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 two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 6: COCKCROFT-GAULT FORMULA

FOR SERUM CREATININE CONCENTRATION (SCr) IN MG/DL[a]

Cl_{cr} for males (mL/min) $= \frac{(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$

CL_{cr} for females (mL/min) $= \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$

FOR SERUM CREATININE CONCENTRATION (SCr) IN µMOL/L[a]

Cl_{cr} for males (mL/min) $= \frac{(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$

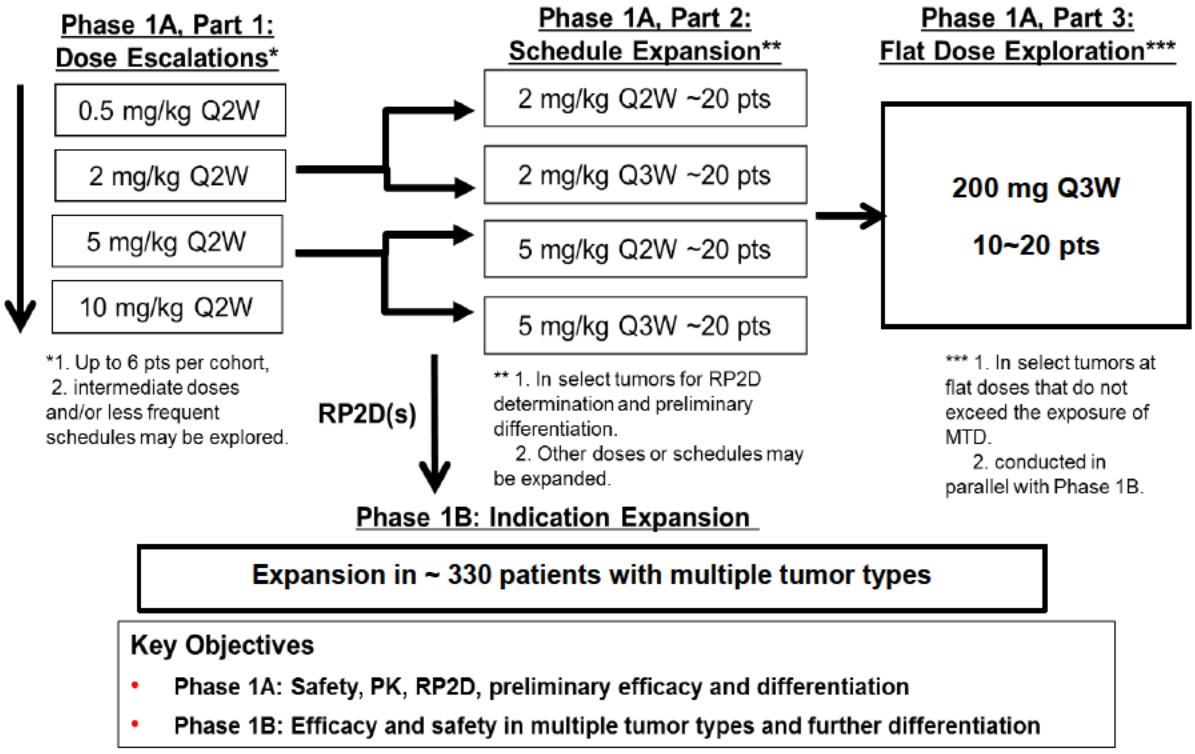
CL_{cr} for females (mL/min) $= \frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$

a Age in years and weight in kilograms.

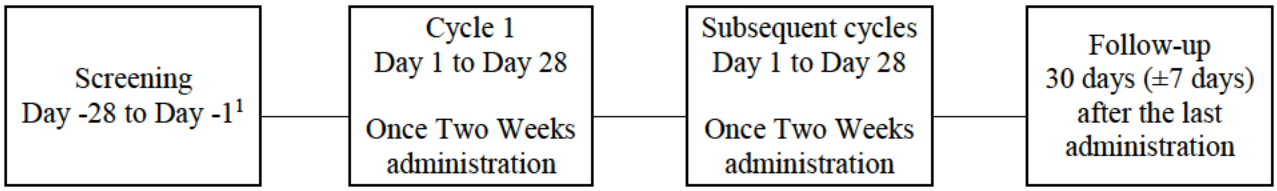
b If the subject is obese (>30% over ideal body weight), use ideal body weight in calculation of estimated CL_{cr}.

APPENDIX 7: FLOW CHARTS

Overall Study Design



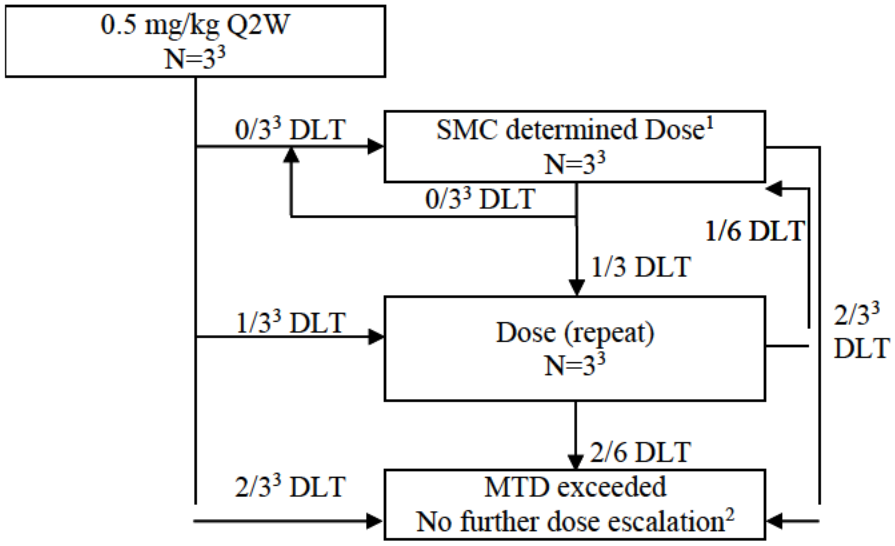
Flow Chart for Phase 1A Part 1



1. Screening assessments will be completed within 28 days prior to the first dose of the study drug. It is preferred that routine laboratory tests are conducted within 10 days prior to first dosing, although tests done within 28 days are acceptable.

Refer to Table 4 for Suggested Dose Escalation Scheme.

Dose Escalation for Phase 1A Part 1

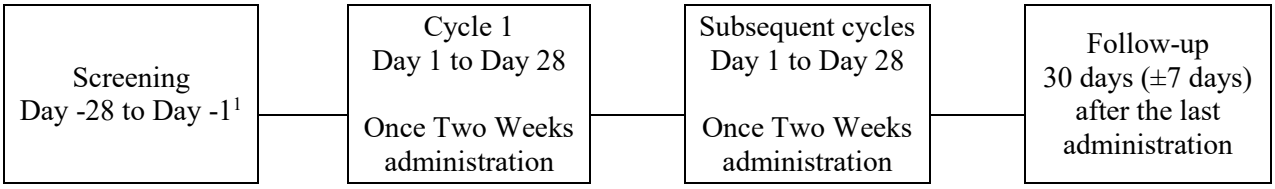


Abbreviations: DLT: dose-limiting toxicity; MTD: maximum tolerated dose; SMC: Safety Monitoring Committee.

1. If none (0) of the subjects in the cohort experience a DLT by the end of Cycle 1, escalation to the next dose will occur, as determined by the SMC. If one (1) out of six (6) subjects experience a DLT by the end of Cycle 1, escalation to the next dose will occur, as determined by the SMC.
2. No additional subjects will be treated at a given dose level if two (2) or more of the subjects in a cohort develop a DLT in Cycle 1. In this instance the MTD is considered to have been exceeded and as noted above, the MTD will be considered to be the dose level below this level or an intermediate dose level that has been evaluated and has not exceeded the MTD.

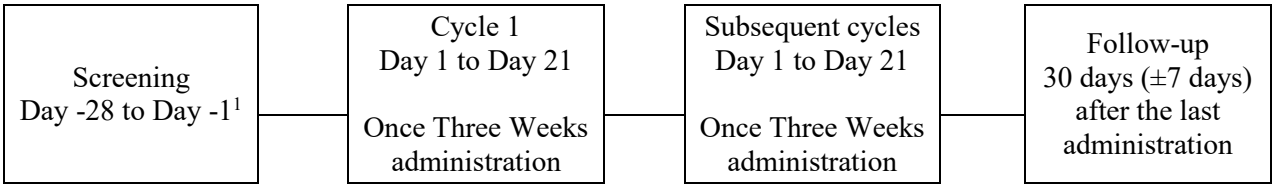
3. Additional subject(s), up to a maximum of six (6) subjects in total, will be enrolled if more than three (3) subjects have been screened and are eligible for the cohort. The DLT assessment and dose-escalation scheme will follow the rules stipulated in the modified 3 + 3 dose escalation scheme. For example, three (3) additional subjects will be enrolled if a DLT is observed in one (1) of three (3) subjects; additional two (2) subjects will be enrolled if a DLT is observed in one (1) of four (4) subjects; and additional one (1) subject will be enrolled if a DLT is observed in one (1) of five (5) subjects. No additional subjects are required if a DLT is observed in one (1) of six (6) subjects.

Flow Chart for Phase 1A Part 2 (Q2W schedule)



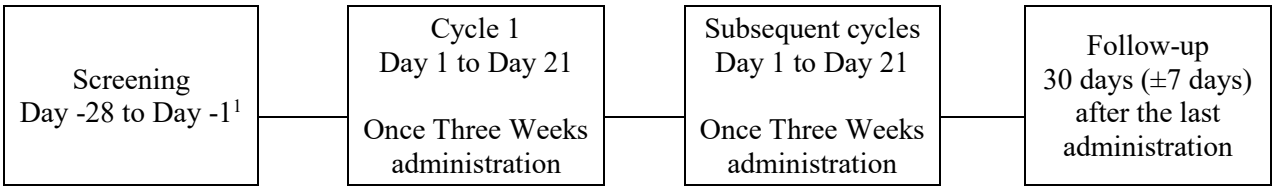
1. Screening assessments will be completed within 28 days prior to the first dose of the study drug. It is preferred that routine laboratory are conducted within 10 days prior to first dosing, although tests done within 28 days are acceptable.

Flow Chart for Phase 1A Part 2 (Q3W schedule)



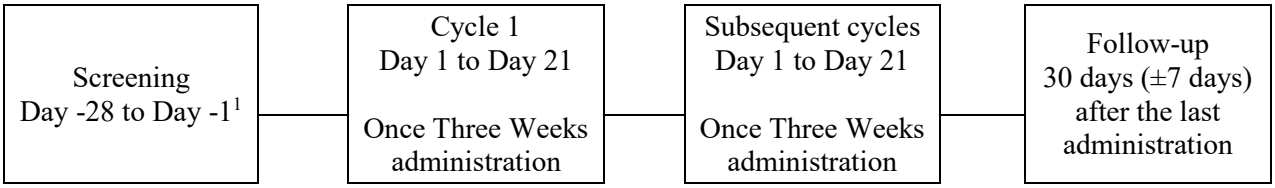
1. Screening assessments will be completed within 28 days prior to the first dose of the study drug. It is preferred that routine laboratory tests are conducted within 10 days prior to first dosing, although tests done within 28 days are acceptable.

Flow Chart for Phase 1A Part 3



1. Screening assessments will be completed within 28 days prior to the first dose of the study drug. It is preferred that routine laboratory tests are conducted within 10 days prior to first dosing, although tests done within 28 days are acceptable.

Flow Chart for Phase 1B



1. Screening assessments will be completed within 28 days prior to the first dose of the study drug. It is preferred that routine laboratory tests are conducted within 10 days prior to first dosing, although tests done within 28 days are acceptable.

APPENDIX 8: GUIDELINES FOR SUPPORTIVE CARE

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- Diarrhea: Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
    - In patients with severe enterocolitis, tislelizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
    - In patients with moderate enterocolitis, tislelizumab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with tislelizumab, see Section 5.1.2.
- All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.
- Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.
- Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Immune thrombocytopenic purpura should be ruled out before initiation of platelet transfusion.
- Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.
- Immune-related adverse events: Patients who develop a G2 or higher irAE (eg, colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, or any other), should be discussed immediately with the Sponsor. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.
- Infusion reaction: Infusion reactions may consist of 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 an infusion reaction during and immediately following drug infusion.
    - In the event of a Grade 1 or 2 infusion reaction, reduce the infusion rate by 50% for the entire remaining duration of that infusion. Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), anti-pyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen.
    - In the event of a Grade 3 or 4 infusion reaction, immediately stop the infusion. 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 anti-histamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.
    - Regarding continuation of study therapy after an infusion reaction has occurred, see the guidelines in Section 7.3.2.

APPENDIX 9: PROSTATE CANCER CLINICAL TRIALS WORKING GROUP 2 (PCWG2) CRITERIA TO GUIDE ASCRIBING DISEASE RESPONSE

Variable	PCWG2 (2007)
PSA	Record serial PSA. PSA partial response is defined as a ≥ 50% decline in PSA from screening (baseline) PSA value. This PSA decline much be confirmed to be sustained by a second PSA value obtained 4 or more weeks later.
Target Lesions	Nodal or visceral progression sufficient for trial entry independent of PSA Measurable lesions not required for entry Use RECIST to record soft-tissue (nodal and visceral) lesions as target or nontarget Only lymph nodes ≥ 2 cm in diameter should be used to assess for a change in size Record presence of nodal and/or visceral disease separately
Bone	≥ 2 new lesions at the first scheduled reassessment ≤13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post treatment scan (ie a total of ≥ 4 new lesions compared with the baseline bone scan). Confirm ambiguous results by other imaging modalities (eg, CT or MRI)
	≥ 2 new lesions at the first scheduled reassessment >13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared the baseline scan. (ie a total of ≥ 2 new lesions compared with the baseline bone scan). Confirm ambiguous results by other imaging modalities (eg, CT or MRI)

Abbreviations: PCWG2, Prostate Cancer Clinical Trials Working Group 2; PSA, prostate-specific antigen; PSA-DT; RECIST, Response Evaluation Criteria in Solid Tumors; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography

* Modified Table 2 from Scher et al, 2008.

APPENDIX 10: IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE are intended as a guidance. This document should be used in conjunction with expert clinical judgment (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, disease progression, 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 disease progression 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. 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 DLCO.

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

Immune-related Toxicity	Diagnostic Evaluation Guideline
	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.
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). 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 patients experience eye inflammation, blurred vision or other visual disturbance 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 and consider liver biopsy.
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

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

Immune-related Toxicity	Diagnostic Evaluation Guideline
	as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. 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/or T), 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; DLCO, 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 cystolic antigen; LFT, liver function test; 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

- Immune-related AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study 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 study 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 Judgment)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. 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 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities 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** 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 Judgment)	Study Drug Management
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV 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** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 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. 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 $\leqslant$ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV 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	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
		empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	
Neurological Toxicity	**1** Mild symptoms		Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 3 liquid stool per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If grade 1 persists for > 14 days manage as a grade 2 event.	Continue study treatment.
	2 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). 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	Initiate IV methylprednisolone 1-2mg/kg/day.	Hold study treatment; retreatment may be considered when

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	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. 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. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgment: • For moderate symptoms: oral prednisolone 0.5-1	Hold study treatment. Retreat when AE is resolved or improved to mild rash (grade 1-2) after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
		mg/kg/day for 3 days then taper over 2-4 weeks. • For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** 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. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; reescalate dose if LFTs worsen, depending on clinical judgment.	Hold study treatment, treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.
	3	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone	Hold study treatment until improved to baseline grade;

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	ALT or AST 5-20X ULN	1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (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.	reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone change to pulsed IV methylprednisolone • If on IV add mycophenolate mofetil (MMF) 500-1000 mg twice a day • If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3X baseline or > 1.5-3X 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. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3 Creatinine > 3X baseline or > 3-6X 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 IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 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** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160 - 250 mg/dL; 8.9 - 13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or grade 0-1.
	3 Fasting glucose value 250 - 500 mg/dL; 13.9 – 27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist	

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
		for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (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 study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or grade 0-1.
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guideline, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as grade 3.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 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
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 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	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular construction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CK-MB, creatine kinase – cardiac muscle isoenzyme; CHF, congestive heart failure; ECG = electrocardiogram; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 11: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

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 12: CONTRACEPTION GUIDLINES 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 (transdermal, implants or subcutaneous or intramuscular injections)
- Combined oral contraceptives (birth control pills) may be used, but only if a concurrent barrier method is employed
- 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 (with azoospermia demonstrated by a post-procedure medical examination of the semen)
- 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 another acceptable method 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 (FSH) 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 Faciliation Group (CFTG): Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014.
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf