MD Anderson IND Sponsor Cover Sheet

Protocol ID	2020-1212
Protocol Title	**A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Angiosarcoma**
Protocol Phase	II
Protocol Version	01
Version Date	08/24/2021
Protocol PI	Vinod Ravi
Department	Sarcoma Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	155134

Clinical Protocol

Study Title:	A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Angiosarcoma
Protocol Number:	2020-1212
Version and Date:	Version 01, 24th August 2021
Product Name:	Sintilimab (Recombinant Fully Human Anti-PD-1 Monoclonal Antibody Injection, R&D Code: IBI308)
Study Phase:	II
Sponsor:	MD Anderson Cancer Center

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Protocol Synopsis

Protocol Number	2020-1212
Sponsor	MD Anderson Cancer Center
Investigational Drug	Sintilimab (R&D Code: IBI308)
Active Ingredient	Recombinant fully human anti-PD-1 monoclonal antibody
Study Title	A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Angiosarcoma
Study Phase	II
Study Objectives	Primary Objectives: • To evaluate the efficacy of sintilimab in subjects with angiosarcoma ($PFR_{9cycles}$ by RECIST 1.1) Secondary Objectives: • To evaluate the ORR (CR+PR), stable disease rate (SDRstable disease for 9 cycles), progression-free survival (PFS), overall survival (OS), duration of response (DOR), quality of life (QOL) and safety of sintilimab in subjects with angiosarcoma Exploratory Objectives: • To evaluate the correlation between biomarkers in tumor tissue and efficacy, including but not restricted to PD-L1 expression level, presence of tertiary lymphoid structures (TLS), transcriptome sequencing, single-cell sequencing, and multicolor immunohistochemistry (IHC) analyses;

	• To evaluate the correlation between biomarkers in peripheral blood and efficacy, including but not restricted to soluble PD-L1, circulating tumor DNA (ctDNA), identification/quantification of immunologic changes and cytokine analyses.
Study Design	This is a Phase 2 clinical trial evaluating the efficacy and safety of sintilimab in subjects with angiosarcoma. A total of 30 subjects with Angiosarcoma will be enrolled. Subjects will be treated with sintilimab (200 mg IV on Day 1 Q3W). The treatment will repeat every 3 weeks until progressive disease (PD), intolerable toxicity, initiation of new anti-tumor therapy, withdrawal of consent, lost to follow-up, death, completion of therapy, or any other investigator-determined reasons for treatment discontinuation (whichever occurs first). Treatment will continue for a maximum period of 24 months (starting from the first dose). During the trial, tumor imaging evaluation will be initially performed once Q9W (± 7 days) and will be based on RECIST 1.1. After the completion or discontinuation of the study treatment, safety follow-up and survival follow-up will be performed.
Inclusion Criteria	1. Histopathologically confirmed unresectable, locally advanced, recurrent or metastatic angiosarcoma. 2. Intolerant to or progressed on at least one line of systemic chemotherapy. Patient ineligible for cytotoxic chemotherapy are eligibile. 3. Aged ≥ 18. 4. ECOG PS of 0 or 1. 5. Should be able to provide archival or fresh tissues for correlative analysis. 6. Have at least one measurable lesion as per RECIST v1.1. 7. Adequate organ and bone marrow functions, as defined below:

	1) Complete blood count: absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L, platelet (PLT) count ≥ 75 × 10^9/L, hemoglobin (HGB) ≥ 8.0 g/dL. Note: Subjects cannot receive blood transfusion, erythropoietin (EPO), or Granulocyte-colony stimulating factor (GSF) within 7 days prior to the blood collection. 2) Hepatic function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN in subjects without hepatic metastasis; TBIL ≤ 1.5 × ULN, ALT and AST ≤ 5 × ULN in subjects with hepatic metastasis. Exception: Patients with known Gilbert disease: serum bilirubin level ≤ 3 × ULN. 3) Renal function: urine protein < 2+ from random sample or < 1 g from 24-hour urine collection, and creatinine clearance rate (Ccr) ⩾ 50 mL/min by Cockcroft-Gault formula: Female: $Ccr = \frac{(140-age)\times \text{weight(kg)}\times 0.85}{72\times \text{serum creatinine(mg/dL)}}$ Male: $Ccr = \frac{(140-age)\times \text{weight(kg)}\times 1.00}{72\times \text{serum creatinine(mg/dL)}}$ 4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 × ULN; if the subject is receiving anticoagulant therapy, the results of coagulation tests need to be within the acceptable range for anticoagulants. 8. Expected survival ≥ 12 weeks. 9. Subject (female subjects of childbearing age or male subjects whose partners are of childbearing age) must take effective contraceptive measures during the entire course of the trial and until 180 days after the last dose (see Section 4.3). 10. Signed the informed consent form (ICF) and be able to comply with the scheduled follow-up v1isits and related procedures required in the protocol.
Exclusion Criteria	1. Received treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other

	antibody or drug that specifically targets T-cell co-stimulation or immune checkpoint pathways. 2. Enrolled in another interventional clinical study, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study. 3. Received palliative therapy for a local lesion within 2 weeks prior to the first dose. 4. Received systemic treatment with anti-cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study treatment. 5. Received systemic immunosuppressants within 2 weeks, excluding local use of glucocorticoids administered by nasal, inhaled, or other routes, and systemic glucocorticoids at physiological doses (no more than 10 mg/day of prednisone or equivalents), or glucocorticoids to prevent allergies to contrast media. 6. Received a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or be scheduled to receive live attenuated vaccine during the study period. Note: Seasonal inactivated influenza virus vaccines within 4 weeks prior to the first dose of study treatment are permitted, but attenuated influenza vaccines are not. 7. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study treatment or is scheduled to receive major surgery during the course of the trial. 8. Any toxicity (excluding alopecia, events that are not clinically significant, or asymptomatic laboratory abnormalities) due to prior anti-tumor therapy that has not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade 0 or 1 prior to the first dose of study treatment.

	9. Known symptomatic central nervous system (CNS) metastasis or carcinomatous meningitis. Subjects with brain metastases who have received prior treatment can be enrolled if the disease is stable (no imaging evidence of PD for at least 4 weeks prior to the first dose of study treatment), there is no evidence of new brain metastases or progression of the existing metastatic lesion(s) upon repeated imaging, and corticosteroids have not been required for at least 14 days prior to the first dose of study treatment. Patients with carcinomatous meningitis are ineligible, regardless of whether the disease is clinically stable or not. 10. Subjects with bone metastases at risk of paraplegia. 11. Known active autoimmune disease requiring treatment or previous disease history within 2 years (subjects with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment, hypothyroidism only requiring thyroid replacement, or type I diabetes only requiring insulin can be enrolled). 12. Known history of primary immunodeficiency diseases. 13. Known active pulmonary tuberculosis. 14. Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation. 15. HIV-infected subjects (positive anti-HIV antibody). 16. Active or poorly controlled serious infections that require systemic therapy. 17. Symptomatic congestive heart failure (NYHA Class II–IV) or symptomatic or poorly controlled arrhythmia. 18. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite standard treatment. 19. Any arterial thromboembolic event within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack. 20. Significant malnutrition, such as those requiring continuous parenteral nutrition ≥7 days; excluding those having received

	intravenous treatment for malnutrition for more than 4 weeks before the first dose of study treatment. 21. History of clinically significant deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis or incidental PE detected on scan without symptoms or superficial venous thrombosis are not considered as "serious" thromboembolisms). 22. Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties. 23. Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C. 24. Bowel obstruction or history of the following diseases: inflammatory bowel disease, extensive bowel resection (partial colectomy or extensive small intestine resection accompanied with chronic diarrhea), Crohn's disease, or ulcerative colitis. 25. Known acute or chronic active hepatitis B (positive HBsAg and HBV DNA viral load $>10^4$ copies/mL or > 2000 IU/mL), or acute or chronic active hepatitis C (HCV RNA$>10^3$ copies/mL), or simultaneously positive for HBsAg and HCV antibody. 26. History of gastrointestinal (GI) perforation and/or fistula within 6 months prior to the enrollment, excluding gastrostomy or enterostomy. 27. Interstitial lung disease requiring corticosteroids. 28. History of other primary malignant tumors, excluding: • Malignant tumors that achieved a complete response (CR) at least 2 years prior to enrollment and expected to require no treatment during the trial. • Adequately treated nonmelanoma skin cancer or lentigo maligna with no sign of disease recurrence.

	• Adequately treated carcinoma in situ with no sign of disease recurrence. • Prostate cancer, CLL or other cancers where the indolent nature of tumor allows for and patient is under active surveillance. 29. Pregnant or breastfeeding female subjects. 30. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased investigational drug-related risks, interference with interpreration of trial results, or considered ineligible for participating in the trial by the investigators.
Study Drugs, Strengths, and Administrations	• Sintilimab – Administration: 200 mg IV D1 Q3W
Evaluation Criteria	**Efficacy evaluation:** • Primary endpoint: Confirmed $PFR_{9cycles}$ assessed by independent radiology review (IRR) per RECIST v.1.1 • Secondary endpoints: ORR (investigator assessed), SDR, DOR, PFS, OS and QOL **Safety evaluation:** • The incidence and severity of treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to death, and immune-related adverse events (irAEs). • Changes in vital signs, physical examination, and laboratory tests results before, during, and after treatment. **Biomarker evaluation:** • The correlation between biomarkers in the tumor tissue and efficacy, including PD-L1 expression level, presence of tertiary lymphoid structures (TLS), transcriptome sequencing, single-cell sequencing, and IHC analyses;

	• The correlation between biomarkers in peripheral blood and efficacy, including the soluble form of PD-L1, ctDNA, identification/quantification of immunologic changes and cytokines analyses.
Statistical Analysis Method	**Efficacy endpoints:** The $PFR_{9cycles,}$ ORR and SDR and the corresponding exact 95% CIs will be estimated. The DOR, PFS and OS will be analyzed using Kaplan-Meier Method. QOL will be assessed through scales and reported using descriptive statistics. **Safety data:** The incidence and severity of AEs will be summarized, and laboratory abnormalities will be presented. **Biomarkers:** PD-L1 expression levels and distribution, presence of TLS and other potential biomarkers will be analyzed, and the potential correlation between these biomarkers and efficacy will be explored.

Table 1 Schedule of visits

Phase	**Screening**		**Treatment**							**End-of-Treatment Visit[17]**	**Safety Follow-Up**		**Survival Follow-Up[20]**
			Cycle 1		**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**From Cycle 7 Onwards**				
Day	-28 to -1	-7 to -1	1	8 (± 3 days)	22 (± 3 days)	43 (± 3 days)	64 (± 3 days)	85 (± 3 days)	106 (± 3 days)	Every 3 weeks (± 3 days)	Within ±7 days after end of treatment	30th day (± 7 days) after the last dose[18]	90th day (±7 days) after the last dose[19]	Every 60 days (± 7 days)
General Study Procedures														
Written ICF[1]	×													
Inclusion/Exclusion Criteria	×													
Demographics/Medical	×													

History/Previous Medication[2]														
Vital Signs[3]	×		×		×	×	×	×	×	×	×			
Weight/Height[4]	×		×		×	×	×	×	×	×	×			
Physical Examination	×		×		×	×	×	×	×	×	×			
ECOG PS	×		×		×	×	×	×	×	×	×	×	×	
12-Lead ECG[5]		×			×	×	×	×	×	×	×	×		
Laboratory Tests														
CBC/Blood Biochemistry/Routine Urinalysis[6]		×	×		×	×	×	×	×	×	×	×	×	
Coagulation Function[7]		×												
Pregnancy Test[8]	×				×		×		×	×	×			
Thyroid Function[9]	×				×	×	×	×	×	×	×			
HIV, HBV, and HCV[10]	×													
Safety Evaluation														

AE Evaluation[11]	×		×	×	×	×	×	×	×	×	×	×	×	
Concomitant Medication	×		×		×	×	×	×	×	×	×	×		
Survival Status			←											→
Subsequent Anti-Tumor Therapy											×	×	×	×
Efficacy Evaluation														
Tumor Imaging Evaluation[12]	×						×			×	×			
Study Drug Infusion														
Sintilimab[13]			×		×	×	×	×	×	×				
Quality of Life Evaluation[14]														
EQ 5D-5L + QLQ-C30			×				×			×	×	×		
PRO-CTCAE™			×		×	×	×	×	×	×	×	×		
Biomarker Study														
Optional Archival/Fresh Tumor	×						×				×			

Tissue Sample[15]														
Blood[16]			×	×	×		×			×	×			
PK/Antidrug antibodies (ADA)														
PK/ADA Sample[21]			×	×	×		×			×				

Note:

1. The ICF should be signed by subjects prior to any procedures outlined in the protocol.
2. Medical history includes all active diseases and diseases that are clinically significant as determined by the investigator, including history of cigarette use, alcohol use, surgery, and drug allergy. All autoimmune diseases should be documented, regardless of the date of onset. All medications (including replacement/supplement drugs) used within 30 days prior to the first dose of study treatment, including any washout requirements specified in the protocol, should be documented.
3. Vital signs: body temperature, pulse, respiratory rate, and blood pressure.
4. Height will only be measured during screening.
5. 12-lead ECG: within 7 days prior to the first dose during screening, within 3 days prior to administration of study treatment in each cycle (except Cycle 1), during end-of-treatment visit, and during the first safety follow-up.
6. Complete blood count: red blood cell (RBC) count, HGB, white blood cell (WBC) count, PLT count, WBC differentials [lymphocyte (LYM) count and ANC]. Blood biochemistry: hepatic function [TBIL, ALT, AST, alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactate dehydrogenase (LDH)], renal function [urea (UREA) and Cr], electrolytes (Na, K, Cl, Mg, Ca, and P), amylase, lipase and fasting blood glucose (FBG). Routine urinalysis: pH (PH), urine white blood cell (UWBC), urine protein (UPRO), urine red blood cell (URBC), and urine glucose (UGLU). complete blood count, blood biochemistry, and routine urinalysis are performed within 7 days prior to the first dose during screening, within 3 days prior to each dose, during the end-of-treatment visit, and during the first safety follow-up. Tests will be conducted in each local lab.
7. Coagulation function tests: PT and INR. The test will be conducted within 7 days prior to the first dose. Tests will be conducted in each local lab.

8. Women of childbearing potential will undergo a blood pregnancy test within 3 days prior to the first dose and during the end-of-treatment visit and a urine pregnancy test will be done prior to every other cycle from Cycle 2 onwards. If the urine pregnancy test is not conclusive, then a blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted in each local lab.
9. The tests will be conducted during screening, within 3 days prior to the administration of the study drug from Cycle 2 onwards, and during end-of-treatment visit. Thyroid function tests: thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free tetraiodothyronine (FT4). Tests will be conducted in each local lab.
10. Hepatitis B panel (HBsAg, HBsAB, HBcAB, HBeAg, and HBeAb), HCV antibody, and HIV antibody will be tested during screening. If the result shows HBsAg positive, then HBV DNA test should be further conducted. If the result shows HCV antibody positive, then HCV RNA test should be further conducted. The results obtained within 28 days prior to start of therapy can be accepted. Prophylactic antiviral therapy is suggested to be performed according to the local treatment guidelines for HBV carriers. HBV activity should be monitored regularly during the trial. Tests will be conducted in each local lab.
11. AE assessment on C1D8 will be collected via a telephone call. AE and laboratory safety evaluations will be performed according to NCI CTCAE v5.0. Refer to Section 8 for AE and SAE definitions, recording, determination of causal relationship, severity, reporting deadlines, and processing.
12. Tumor evaluations will be performed based on RECIST v1.1 and the same imaging method (CT/MRI) should be used for the same subject during the trial. Baseline evaluation will be conducted within 28 days prior to enrollment. After the first dose of study treatment, tumor imaging evaluation will be performed once Q9W (± 7 days) until initiation of a new anti-tumor therapy, PD, withdrawal of informed consent, lost to follow up, completion of treatment, or death. If the subject has confirmed or suspected bone metastatic lesion presents at baseline, a PET scan is recommended within 28 days prior to the first dose. If the bone metastasis is confirmed at baseline, PET scan with contrast can be used for imaging evaluation every 9 weeks or as clinically indicated. For subjects who discontinue the treatment for reasons other than imaging-confirmed PD, if the subject's last imaging evaluation is greater than 4 weeks prior to discontinuation, the imaging evaluation should be performed at the end-of-study treatment visit and be reperformed Q12W (± 7 days) thereafter until one of the followings occurs: start of new anti-tumor therapy, PD, withdrawal of informed consent, lost to follow-up or death.
13. Sintilimab: 200 mg, IV Q3W, for up to 24 months (starting from the first dose), or until PD, death, intolerable toxicity, withdrawal of informed consent, completion of treatment, or any other investigator-determined reason for treatment discontinuation. Treatment can be delayed for up to 1 week if the administration day is on a holiday. The study treatment can be administered 3 days before or 3 days after the scheduled day of administration.
14. Quality of life evaluation: on the day of the first dose, during each imaging evaluation, and during the first safety follow-up, including EQ 5D-5L, EORTC QLQ-C30. PRO-CTCAE™ will be administered day 1 of every cycle.

15. During screening, 20 slices of archival tissue will be collected(optional) or optional biopsy will be performed to obtain fresh tumor tissue samples for correlative studies. Optional biopsy will also be performed at C4D1 +/- 7 days and confirmed PD + 30 days for correlative studies.
16. 60 mL whole blood samples are required to be provided by subjects for biomarker testing at the following time points: prior to the first dose, C1D8, C2D1, C4D1, C7D1, C10D1, when first PD is recorded, and EOT/when PD is confirmed.
17. The end-of-treatment visit should be conducted within ±7 days after the end of treatment is confirmed. If the visit in which PD is confirmed is the end of treatment, then that visit can replace the end of treatment visit and it need not be repeated. However, all procedures for the need of treatment visit must be completed.
18. Safety follow-up at 30th day (± 7 days) after the last dose or before initiation of a new anti-tumor therapy. If the safety follow-up is performed within 7 days of the end-of-treatment visit, then the safety follow-up may be replaced by the end-of-treatment visit and does not need to be repeated. However, all procedures for the safety follow-up should be completed.
19. Safety follow-up at 90th day (±7 days) after the last dose. All AEs including SAEs and irAEs will be collected within 90 days (±7 days) after the last dose if new anti-tumor therapy has not been initiated. Only irAEs and sintilimab- or procedure-related SAE will be collected if a new anti-tumor therapy has been initiated.
20. Survival follow-up: once every 60 days (± 7 days) after the safety follow-up until death or for a duration of 3 years after last patient is enrolled. Telephone visits are allowed.

21. PK/ADA sample (5 ml each) will be collected at the following time points: within 1h before, any point within 2-24h after, any point within 120-264h after Sintilimab infusion in Cycle 1, within 1h before sintilimab infusion in Cycle 2/4, and then within 1h before sintilimab infusion with every 4 cycles thereafter starting cycle 7 (e.g. Cycle 7, 11, 15 etc.).

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List of Abbreviations

Abbreviations	Full Name
ADA	Anti-drug antibody
AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATG	Antithymocyte globulin
AUC	Area under the curve
β-hCG	β-human chorionic gonadotropin
Ccr	Endogenous creatinine clearance rate
CK	Creatine Kinase
CRA	Clinical Research Associate
CRO	Contract Research Organization
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-lymphocyte-associated protein 4

Abbreviations	Full Name
Cr	Creatinine
DCR	Disease control rate
DoR	Duration of response
DMARD	Disease-modifying antirheumatic drug
EC	Ethics committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FAS	Full analysis set
FBG	Fasting blood glucose
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
γ-GT	γ-glutamyltransferase
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody

Abbreviations	Full Name
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HGB	Hemoglobin
HR	Hazard ratio
ICF	Informed consent form
ICPi	Immune Checkpoint inhibitor
iDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
INR	International normalized ratio
irAE	Immunity-related adverse event
ITT	Intention to treat
IV	Intravenous
IRR	Independent radiology review
LCSS	The Lung Cancer Symptom Scale
MRI	Magnetic resonance imaging
NAb	Neutralizing antibody

Abbreviations	Full Name
NGS	Next-generation sequencing
NSAIDS	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PEX	Physical Examimation
PFR	Progression free rate
PFS	Progression free survival
PK	Pharmacokinetics
PLT	Platelet count
PPS	Per-protocol set
PR	Partial response
PT	Prothrombin time
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviations	Full Name
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SD	Stable disease
SS	Safety set
TCR	T-cell receptor
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TP	Total protein
TPS	Tumor Proportion Score
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
UGLU	Urine glucose
UPRO	Urine protein
URBC	Urine red blood cell
UREA	Urea
UWBC	Urine white blood cell
VEGF	Vascular endothelial growth factor

Abbreviations	Full Name
WBC	White blood cell count

1 Background

1.1 Disease Background

1.1.1 Scope of Problem

Sarcomas are rare tumors that originate from mesenchymal tissues (eg, bone, cartilage, fat and muscle). In the US, the incidence of bone and soft tissue sarcomas (STS) is approximately 13,000 new cases per year, leading to more than 5,000 deaths annually.[1] According to the World Health Organization (WHO) classification of 2002, over 70 different types of sarcoma have been described.[2] Localized tumors are curable but patients with metastatic disease have a median survival of approximately 12 months.[3] Standard systemic chemotherapy regimens are poorly tolerated, and of limited usefulness with response rates in the range of 10%-40%.[3] Angiosarcomas are rare, aggressive, and heterogeneous tumors of endothelial cell origin accounting for approximately 2% of STS.[4] Angiosarcoma can arise in any soft-tissue structure or viscera. About half of patients present with a primary cutaneous lesion (skin, scalp). The pathogenesis of this presentation includes prior radiation exposure as well as inflammatory damage in chronically sun-exposed skin. Non-cutaneous angiosarcoma (soft tissue, bone, viscera) can occur in the setting of prior radiation exposure or other unknown causes. Angiosarcoma has also been associated with prolonged lymphedema from any cause. Although complete resection with curative intent followed by adjuvant radiotherapy is the treatment of choice for localized disease amenable to surgery, approximately 50% of these patients will develop metastasis and die from the disease. Furthermore, metastases are frequently present at the time of diagnosis.[5] The surgical removal of metastatic lesion is rarely feasible.[6] Treatment options are limited for advanced disease and of modest benefit. The median overall survival is <12 months for patients with metastatic disease.[5,7,8] No standard of care or FDA approved agents specific to this subtype exist. There is an urgent unmet and critical need to develop novel agents for this orphan disease.

1.1.2 Rationale for use of Immunotherapy in Angiosarcoma

Checkpoint inhibitors have not been formally evaluated for AS. No patients with AS were enrolled in SARC028, a phase II study evaluating pembrolizumab in patients with advanced STS and bone sarcomas.[9] Likewise, only three patients with AS were treated in the Alliance A091401, a phase II trial investigating nivolumab monotherapy or in combination with ipilimumab in patients with advanced sarcomas.[10] Of the patients enrolled in the vascular sarcoma arm of the

phase II trial of durvalumab and tremelimumab in advanced or metastatic sarcomas, the cutaneous agiosarcoma histology was reported to derive benefit.[11] A preliminary review of data from patients with angiosarcoma treated with checkpoint inhibitors at M D Anderson Cancer Center has shown promising results. Based on this information, we propose a study to explore activity of Sintilimab in angiosarcoma.

Study Hypothesis: Sintilimab, fully humanized anti-PD1 antibody, can result in durable tumor responses in angiosarcoma.

1.2 Investigational Drug (Sintilimab)

1.2.1 Mechanism of action

Immune checkpoints are a type of immune inhibitory molecule, whose physiological function is to regulate the intensity and extent of the immune response and to avoid damage and destruction of normal tissues. Cancer cells often manipulate these immune checkpoints to escape immune surveillance. The efficacy of drugs designed to block the actions of immune checkpoints such as, CTLA-4 and PD-1/PD-L1, has been validated clinically.

PD-1, the receptor primarily expressed on activated T-cells, has two ligands, PD-L1 and PD-L2. PD-L1 is the main ligand that is expressed on activated T-cells, antigen-presenting cells, and tumor cells.[12] The binding of PD-1 with PD-L1 plays an important role in regulating T cell activation and maintaining peripheral immune tolerance. When T cells do not express PD-1, they interact with antigen-presenting cells to enable the activation and proliferation of T cells as well as the secretion of activated cytokines, which can kill tumor cells. Activated T cells begin to express PD-1. After PD-1 binds to the ligand PD-L1 expressed on the surface of antigen-presenting cells or tumor cells, the inhibitory signal transmitted by PD-1 inhibits the proliferation of T cells and the secretion of activated cytokines, thus weakening the function of T cells. Most tumor cells evade the attack from immune cells through this mechanism. The activity of T cells and their ability to kill cancer cells can be restored by blocking the PD-1/PD-L1 interaction with drugs.[13]

Sintilimab is a recombinant fully human IgG4 anti-PD-1 monoclonal antibody (R&D code: IBI308). Multiple preclinical in vitro and in vivo studies have demonstrated the ability of sintilimab to block the PD-1 pathway. The anti-tumor activity of murine analogs of sintilimab has also been demonstrated in various murine tumor models.

1.2.2 Clinical study results of sintilimab

A Phase 1a dose-escalation trial was initiated in Sep. 2016 to evaluate 4 dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg) of sintilimab. The Phase 1a trial has enrolled 9 subjects (3 for each arm) in 3 treatment arms (1 mg/kg, 3 mg/kg, and 200 mg), and evaluated the dose-limiting toxicities specified in the protocol for each arm. No dose-limiting toxicities were observed.

The preliminary pharmacokinetic (PK) results of sintilimab in subjects with multiple tumors demonstrated a typical IgG4 PK with a slow elimination ($t_{1/2} \approx 17.3$ d). The elimination half-life is similar to the physiological half-life of IgG4.

The pharmacodynamic (PD) results showed that: a dose of sintilimab at 1 mg/kg rapidly (24 h) saturated peripheral PD-1 (95.8 ± 2.3%) and maintained the receptor occupancy with decreasing concentrations throughout the study. The minimum concentration at steady state was 13 μg/mL and peripheral PD-1 receptor occupancy was maintained.

Following completion of the dose escalation trial, clinical studies of sintilimab for the treatment of lymphomas and solid tumors were subsequently conducted. A total of 595 Chinese subjects and 36 US subjects received ≥ 1 dose of sintilimab, of which 534 Chinese subjects and 36 US subjects received sintilimab monotherapy, and 61 Chinese subjects received sintilimab in combination with chemotherapy. Over 93% of the subjects completed at least 2 cycles of treatment, 83.5% completed at least 3 cycles of treatment, 73.6% completed at least 4 cycles of treatment, and 65.9% completed at least 5 cycles of treatment. The median treatment duration for subjects that received 200mg Q3W was 24.29 weeks (range: 9.57~57.86 weeks).

Overall, a total of 77.3% of Chinese subjects (460/595) experienced a sintilimab-related adverse events (TRAE), the three most common (≥10%) TRAE including fever (15.0%), hypothyroidism (14.1%), and increased AST (13.6%). A total of 18.7% (111/595) of subjects had TRAE ≥ grade 3, among which the most common (incidence ≥ 1%) were decreased platelet count (1.2%), decreased neutrophil count (1.0%), and decreased lymphocyte count (1.0%). A total of 55.6% of US subjects (20/36) experienced sintilimab-related adverse events (TRAE), the most common (≥ 10%) included fatigue (16.7%), nausea (13.9%), and diarrhea (13.9%).

A total of 29.4% of Chinese subjects (175/595 subjects) experienced treatment-emergent SAEs during the study. The most common treatment-emergent SAEs included lung infection (4.0%), pneumonia (2.5%), and pulmonitis (2.5%). A total of 36.1% of US subjects (13/36 subjects) experienced treatment-emergent SAEs during the study. The most common treatment-emergent

SAEs included urinary tract infection (8.3%), pleural effusion (5.6%), and hypotension (5.6%). The overall safety profile of sintilimab is comparable with current globally marketed PD-1/PD-L1 products.

In US, one Phase 1b study (IND #136159) is ongoing that enrolls patients with solid tumors, and a Phase 3 trial in patients with first line esophageal squamous cell carcinoma (IND #145675) has also been initiated.

1.3 Risk/Benefit Assessment

1.3.1 Potential risks

Considering the mechanism of action and the clinical safety information available for IBI308, the additional adverse events (AEs) in the sintilimab arm that occur during this clinical trial are expected to be the immune-mediated inflammatory response resulting from the activation of immune system, e.g. pneumonitis, colitis, hepatitis, renal insufficiency, and endocrine events. According to the available clinical data, anti-PD-1 monoclonal antibodies are well-tolerable despite a high incidence of adverse reactions. Treatment discontinuation due to adverse reactions only occurs in a small number of subjects, and most events resolve after appropriate interventions. As early symptoms of immune-related adverse events (irAEs) vary, the investigators should pay extra attention to early signs and symptoms of irAEs during the trial, make decisions promptly, adjust the dose according to Section 5.2 in the protocol, and provide effective treatment measures to reduce the subject's risk.

1.3.2 Potential benefits

Pharmacological and safety data from multiple clinical trials showed that sintilimab has clear pharmacological activity and good tolerability in subjects with advanced cancers. Similar drugs have shown significant anti-tumor activity in subjects with advanced AS, supporting the conduct of clinical trials in subjects with advanced AS.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of sintilimab in subjects with angiosarcoma (Progression- free rate PFR at 9 cycles by RECIST 1.1)

2.2 Secondary Objectives

- To evaluate the ORR, SDR, PFS, OS, QOL, safety and DOR of sintilimab in subjects with angiosarcoma

2.3 Exploratory Objectives:

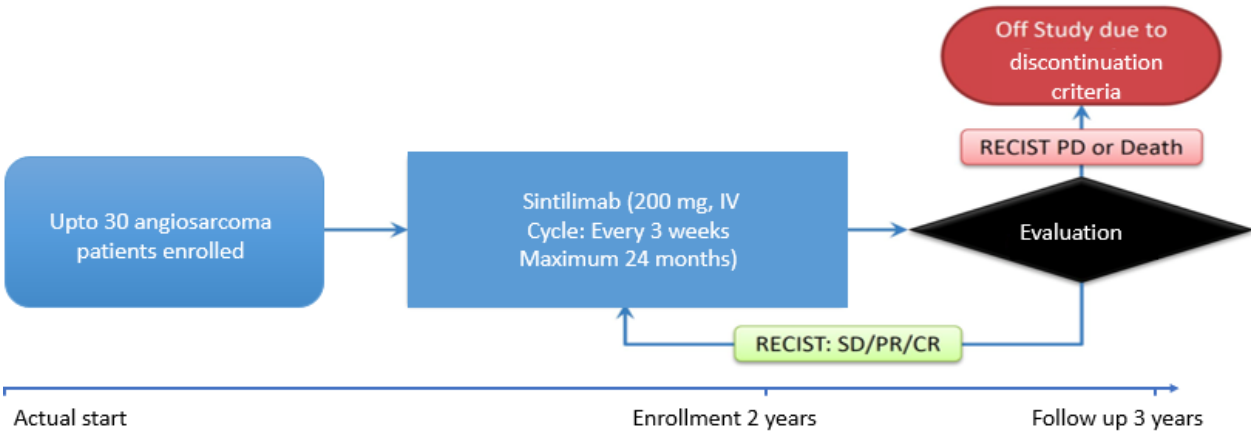
- To evaluate the correlation between biomarkers in tumor tissue and efficacy, including but not restricted to PD-L1 expression level, tertiary lymphoid structures (TLS), transcriptome sequencing, single-cell sequencing, and multicolor immunohistochemistry (IHC) analyses;
- To evaluate the correlation between biomarkers in peripheral blood and efficacy, including but not restricted to soluble PD-L1, circulating tumor DNA (ctDNA), identification/quantification of immunologic changes and cytokine analyses.

3 Study Design

3.1 Overall Design

This is a Phase 2 clinical trial evaluating the efficacy and safety of sintilimab in subjects with angiosarcoma. Subjects with unresectable, locally advanced, recurrent or metastatic angiosarcoma will be enrolled. A total of upto 30 subjects will be enrolled. Subjects will be treated with sintilimab (200 mg IV on Day 1 Q3W). The treatment will be repeated every 3 weeks until progressive disease (PD), intolerable toxicity, initiation of new anti-tumor therapy, withdrawal of informed consent, lost to follow-up, completion of therapy, death, or any other investigator-determined reasons for treatment discontinuation (whichever occurs first). Treatment will be infused for a maximum period of up to 24 months (starting from the first dose). During the trial, tumor imaging evaluation will be initially performed once Q9W (± 7 days) and will be based on RECIST 1.1 per IRR, until PD, initiation of new anti-tumor therapy, withdrawal of informed consent, lost to follow-up, death, or completion of the study (whichever comes first). After the completion or discontinuation of the study treatment, safety follow-up (30 days ± 7 days and 90 days ± 7 days after the last dose) and survival follow-up (every 60 days ± 7 days) will be performed. The primary endpoint of the trial will be confirmed PFR at 9 cycles assessed by IRR per RECIST v.1.1.

Figure 1 Schematic of SiARa-angiosarcoma study design and administration



3.2 Definition of Study Completion

The subject is considered to have completed the study if the survival follow-up is completed or the subject withdraws consent.

The trial is completed if the last subject has completed the survival follow-up, been treated for 24 months, or the sponsor decides to discontinue the trial early and/or the agreement between sponsor and health authority.

3.3 Criteria for Study Discontinuation

This study may be interrupted temporarily or discontinued prematurely if there are sufficient reasons to do so. The party who discontinues or interrupts the study should provide written notification to the subjects, investigators, funding agencies, and regulatory authorities, with documented reasons for interruption or discontinuation. If the study is discontinued prematurely or interrupted, the principal investigator should notify the subjects, Ethics Committee (EC), and sponsor immediately, and provide the reasons for discontinuation or interruption. Where applicable, the investigators should contact the subjects and inform them of the changes in the visit schedule.

Reasons for study discontinuation or interruption include but are not limited to:

- Unexpected, significant, or unacceptable risks to the subjects are identified;

- The study is discontinued or interrupted based on overwhelming lack in efficacy at the time of the interim analysis;
- The subjects are unable to meet protocol requirements for compliance;
- The data is incomplete and/or insufficient for evaluation;
- The primary endpoint has been met.

The study may be resumed only if the safety, protocol compliance, and data quality issues have been addressed, and the requirements of the sponsor, EC, and US Food and Drug Administration are met.

4 Study Population

4.1 Inclusion Criteria

1. Histopathologically confirmed unresectable, locally advanced, recurrent or metastatic angiosarcoma.
2. Intolerant to or progressed on at least one line of systemic chemotherapy. Patient ineligible for cytotoxic chemotherapy are eligibile.
3. Aged ≥ 18.
4. Can provide archival or fresh tissues for optional correlative analysis.
5. Have at least one measurable lesion as per RECIST v1.1.
6. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
7. Adequate organs and bone marrow functions, as defined below:
    1) Complete blood count: absolute neutrophil count (ANC) ≥ 1.0×10^9/L, platelet (PLT) count ≥ 75×10^9/L, hemoglobin (HGB) ≥ 8.0 g/dL.
    2) Hepatic function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN in subjects without hepatic metastasis; ALT and AST ≤ 5 × ULN in subjects with hepatic metastasis, gamma-glutamyl transferase (GGT) ≤ 10 × ULN

3) Renal function: urine protein < 2+ from random sample or < 1 g from 24-hour urine collection, serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance rate (Ccr) ≥ 50 mL/min by Cockcroft-Gault formula:

$$\text{Female: } Ccr = \frac{(140-age)\times \text{weight(kg)}\times 0.85}{72\times \text{serum creatinine(mg/dL)}}$$

$$\text{Male: } Ccr = \frac{(140-age)\times \text{weight(kg)}\times 1.00}{72\times \text{serum creatinine(mg/dL)}}$$

4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 × ULN; if the subject is receiving anticoagulant therapy, the results of coagulation tests need to be within the acceptable range for anticoagulants.

8. Expected survival ≥ 12 weeks.
9. Subject (female subjects of childbearing age or male subjects whose partners are of childbearing age) must take effective contraceptive measures during the entire course of the trial and until 180 days after the last dose (see Section 4.3).
10. Signed the informed consent form (ICF) and be able to comply with the scheduled follow-up visits and related procedures required in the protocol.

4.2 Exclusion Criteria

1. Received treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug that specifically targets T-cell co-stimulation or immune checkpoint pathways.
2. Enrolled in another interventional clinical study for angiosarcoma, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study.
3. Received palliative radiation therapy for local lesion within 2 weeks prior to the first dose.
4. Received systemic treatment with anti-cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study treatment.
5. Received systemic immunosuppressants within 2 weeks prior to first dose, excluding local use of glucocorticoids administered by nasal, inhaled, or other routes, and systemic glucocorticoids at physiological doses (no more than 10 mg/day of prednisone or equivalents), or glucocorticoids to prevent allergies to contrast media.
6. Received a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or be scheduled to receive live attenuated vaccine during the study period.

Note: Seasonal inactivated influenza virus vaccines within 4 weeks prior to the first dose of study treatment are permitted, but attenuated influenza vaccines are not.

7. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study treatment or is scheduled to receive major surgery during the course of the trial.
8. Any toxicity (excluding alopecia, events that are not clinically significant, or asymptomatic laboratory abnormalities) due to prior anti-tumor therapy that has not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade 0 or 1 prior to the first dose of study treatment.
9. Known symptomatic central nervous system (CNS) metastasis or carcinomatous meningitis. Subjects with brain metastases who have received prior treatment can be enrolled if the disease is stable (no imaging evidence of PD for at least 4 weeks prior to the first dose of study treatment), there is no evidence of new brain metastases or progression of the existing metastatic lesion(s) upon repeated imaging, and corticosteroids have not been required for at least 14 days prior to the first dose of study treatment. Patients with carcinomatous meningitis are ineligible, regardless of whether the disease is clinically stable or not.
10. Subjects with bone metastases at risk of paraplegia.
11. Known active autoimmune disease requiring treatment or previous disease history within 2 years (subjects with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment, hypothyroidism only requiring thyroid replacement, or type I diabetes only requiring insulin can be enrolled).
12. Known history of primary immunodeficiency diseases.
13. Known active pulmonary tuberculosis.
14. Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.
15. HIV-infected subjects (positive anti-HIV antibody).
16. Active or poorly controlled serious infections that require systemic therapy.
17. Symptomatic congestive heart failure (NYHA Class II–IV) or symptomatic or poorly controlled arrhythmia.
18. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite of standard treatment.

19. Any arterial thromboembolic event within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack.
20. Significant malnutrition, such as those requiring continuous parenteral nutrition ≥ 7 days; excluding those having received intravenous treatment for malnutrition for more than 4 weeks before the first dose of study treatment.
21. History of clinically significant deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis or incidental PE detected on scan without symptoms or superficial venous thrombosis are not considered as "serious" thromboembolisms).
22. Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties.
23. Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C.
24. Bowel obstruction or history of the following diseases: inflammatory bowel disease, extensive bowel resection (partial colectomy or extensive small intestine resection accompanied with chronic diarrhea), Crohn's disease, or ulcerative colitis.
25. Known acute or chronic active hepatitis B (positive HBsAg and HBV DNA viral load $\geq 10^4$ copies/mL or > 2000 IU/mL), or acute or chronic active hepatitis C (HCV RNA>10^3 copies/mL), or simultaneously positive for HBsAg and HCV antibody.
26. History of gastrointestinal (GI) perforation and/or fistula within 6 months prior to the enrollment, excluding gastrostomy or enterostomy.
27. Interstitial lung disease requiring corticosteroids.
28. History of other primary malignant tumors, excluding:
    - Malignant tumors that achieved a complete response (CR) at least 2 years prior to enrollment and expected to require no treatment during the trial.
    - Adequately treated nonmelanoma skin cancer or lentigo maligna with no sign of disease recurrence.
    - Adequately treated carcinoma in situ with no sign of disease recurrence.
    - Prostate, CLL or other cancers where the indolent nature of tumor allows for and patient is cancer under active surveillance.
29. Pregnant or breastfeeding female subjects.

30. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased investigational drug-related risks, interference with interpreration of trial results, or considered ineligible for participating in the trial by the investigators.

    - If there are any uncertainties regarding the inclusion/exclusion, please contact the sponsor immediately and provide a complete medical history of the subject. The sponsor and principal investigator will discuss and determine the eligibility of the subject.

4.3 Restrictions During the Study

For women of childbearing potential who are sexually active with male partners who have not undergone sterilization, and men who have not undergone sterilization and are sexually active with women of childbearing potential, the subjects and their partners must use one of the acceptable methods of contraception listed in **Table 2** during the entire course of the trial and until 180 days after the last dose of study treatment. Periodic abstinence, a calendar-based method, and withdrawal are not acceptable forms of contraception. Women of childbearing potential are defined as females who have experienced menarche, have not undergone surgical sterilization (bilateral tubal ligation, bilateral salpingectomy, or panhysterectomy), and are not postmenopausal.

Menopause is defined as 12 months of amenorrhea of a woman without any other medical reasons. Age requirements are as follows:

- Females ≥ 50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy;
- Females < 50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy, who have undergone radiation-induced ovariectomy or chemotherapy-induced amenorrhea, and whose luteining hormone and follicle stimulating hormone levels are within the postmenopausal range are considered menopausal.

Table 2 Effective methods of contraception

Single method (must use one)	Double barrier (must use two)
Intrauterine device	Condom
Contraceptive implant	Diaphragm/cervical cap with spermicide
	Hormonal contraceptives including: Oral contraceptive, contraceptive patch, contraceptive ring, injection

4.4 Criteria for Discontinuation/Withdrawal

4.4.1 Treatment discontinuation

Treatment discontinuation is not the same as withdrawal from the study. Since data on some clinical events after treatment discontinuation may be important to the study, these data must be collected until the subject's last scheduled visit, even if the treatment has already been discontinued.

A subject must discontinue the treatment in the case of any of the following, but can continue to be monitored during the study:

- Disease progression as per RECIST v1.1
- Treatment discontinuation required by the subject or his/her legal representative;
- Occurrence of an AE that requires discontinuation due to protocol-specified reasons (refer to Section 5.2);
- Onset of another malignant tumor that requires active treatment;
- Onset of a concurrent disease that interferes further treatment;
- Positive serum pregnancy test results;
- Poor compliance of the subject;
- Inappropriate to continue participating in the study when continued participation would result in unacceptable risk to the subject, as determined by the investigator and/or sponsor;
- Completion of 24-month of treatment with the study drugs.

All the visits and procedures presented in the study schedule (**Table 1**) should be completed for

subjects who discontinued treatment but continue to be followed.

4.4.2 Subject withdrawal

A subject has the right to withdraw from the study at any time for any reasons. A subject must withdraw from the study if the subject or his/her legal representative withdraws informed consent.

A subject can withdraw from the study for the following:

- Screen failures;
- A subject or his/her legal representative withdraws informed consent;
- Death;
- Lost to follow-up;
- Study completion.

A subject who withdraws from the study will no longer receive the treatment and protocol-specified follow-up visits.

The reasons for withdrawal should be documented in the electronic case report forms (eCRFs). A subject who has signed the ICF and received any study interventions cannot be replaced after withdrawal or treatment discontinuation.

4.4.3 Lost to follow-up

A subject is considered lost to follow-up when he/she fails to return to the study site for 2 consecutive scheduled visits and the site personnel are unable to contact the subject.

The following actions must be taken if a subject does not return to the study site for a scheduled visit:

- The study site should try to contact the subject, reschedule the missed visits, reiterate the importance of complying with the schedule of visits, and confirm whether he/she is willing and/or should continue to participate in the study.
- Before a subject is considered lost to follow-up, the investigator or designee should make every effort to recontact the subject (at least 2 phone calls should be made; if the subject is still out of contact, a letter should be mailed to the subject's last known address). These

attempts to contact the subject should be documented in the subject's medical records or study documents.

The subject is considered lost to follow-up and determined to have withdrawn from the study if the subject is still unable to be contacted.

5 Study Drugs and Other Treatments

The study drug is sintilimab. The first dose of study treatment would be designated Day 1 of Cycle 1. For the rest of the treatment cycles, the study treatment can be administered 3 days before or after the scheduled day of administration. Treatment can be delayed for up to 1 week if the administration day is on a holiday or if the subject is otherwise unavailable.

Table 3 Dosage and administration

Study Drug	Dose	Frequency	Route	Treatment Cycle
Sintilimab	200 mg	Q3W	IV infusion	on Day 1, every 21 days

The study drugs in

Table 3 is provided by Innovent. The administering institution (M D Anderson Cancer Center) is responsible for recording the batch numbers, manufacturers, and expiration dates.

5.1 Treatment Regimens of Study Drugs

5.1.1 Sintilimab

The main active ingredient of sintilimab is the recombinant fully human anti-PD-1 monoclonal antibody at a concentration of 10 mg/mL. This product is a clear, colorless or light yellow liquid free of foreign matter. The excipients include 30.06 mg/L mannitol, 3.73 mg/L histidine, 5.88 mg/L dihydrate sodium citrate, 2.92 mg/L sodium chloride, 0.0075 mg/L disodium edetate (ethylenediaminetetraacetic acid disodium salt), and 0.2 mg/mL polysorbate 80, with a pH of 6.0.

The smallest packaging unit is one box, with each box containing 2 vials of sintilimab (IBI308) injection. The package contains the drug name, dosage form, strength, drug code, batch number, expiration date, storage conditions, and Innovent’s information, etc. The label on the vial contains the same information as the outer package except for dosage form, precautions, and

dosage and administration. The package and vial should both be labeled "for clinical study use only". Sintilimab should be stored at 2–8℃ away from light. The shelf life is 24 months. If quality issues such as turbidity and precipitation are observed in the vial, seal the vial immediately and notify Innovent. The preparation and administration of sintilimab is as follows:

1. Calculate the required dose of sintilimab (200 mg IV Q3W).
2. Calculate the volume of 0.9% (weight/volume) sodium chloride solution needed to dilute the sintilimab. The final concentration should be between 1.5 and 5 mg/mL. Then, calculate the redundant volume in the 0.9% (weight/volume) sodium chloride solution containing IV infusion bag, draw and discard the redundant volume.
3. Warm the vial of sintilimab injection to room temperature (25℃) and draw the required dose of sintilimab (step 1) completely and transfer it into the IV infusion bag in step 2 at one time. Record the time when the preparation process starts.
4. Gently invert the IV bag to mix the solution, ensuring the uniformity of the contents. Do not shake vigorously so as to avoid bubbles. If a large amount of bubbles appear, allow the IV bag to stand until the bubbles disappear.
5. Administer with a 0.2 μm in-line filter (infusion time is 30–60 min). Document the start and stop time of infusion.

Note: Before preparation, make sure that the sintilimab injection is clear without any quality issues such as turbidity or precipitation. To avoid medication errors and to ensure sterility, make sure that the required dose of sintilimab is drawn and transferred into the IV infusion bag at one time. Do not draw and transfer several times. Make sure that the time from sintilimab drawing to the end of infusion is no more than 6 h. The prepared solution can be stored for 24 h at 2-8℃ protected from light, and can be stored up to 6 h at 20 -25℃ under indoor lighting (including the duration of dosing). Avoid mixing with other drugs. Do not administer as an IV push.

5.2 Dose Adjustments

5.2.1 General principles

- The subject's hematologic, hepatic, and renal function must meet the requirements for study drug administration prior to Day 1 of each cycle. All the toxicities related to the study drug must resolve to NCI CTCAE v5.0 grade 0 – 1 or baseline levels, excluding the following cases:

- Alopecia
- Grade 2 fatigue
- Hemoglobin (HGB) ⩾ 8.0 g/dL
- Grade 2 neurotoxicities*
- Grade 2 weight loss*

- All the dose delays should be documented, including the reasons and actions taken.
- The investigator should discuss with the sponsor to determine administration for any further concerns.

* refer to section 5.2.2 for more details

5.2.2 Sintilimab dose adjustments

Dose reductions for sintilimab are not permitted during the entire course of the study. Attached below is the reference table for sintilimab dose delays (only for sintilimab-related AEs determined by the investigator). If the administration delay occurs in a 3-week treatment cycle for sintilimab, all the subsequent administration should be delayed to ensure a dosing interval of 21 ± 3 days.

Sintilimab administration under special circumstances:

- An administration delay is not required for grade 3 lymphopenia.
- An administration delay is not required for any drug-related Grade 3 amylase or lipase abnormalities if it is not related to symptoms or clinical manifestations of pancreatitis.
- Administration can be continued for grade 3–4 drug-related endocrine AEs, such as adrenocortical insufficiency, hypophysitis, hyperthyroidism, hypothyroidism, and type I diabetes, that are adequately controlled with physiologic hormone replacement therapy (corticosteroids or thyroid hormone).

Table 4 Sintilimab dose adjustments

Drug-Related Toxicities	Severity	Management
1. Skin Toxicities		
Rash/Inflammatory Dermatitis	Grade 1	Continue, Consider topical emollients and/or mild-moderate potency topical corticosteroids
	Grade 2	Consider interruption, Treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids, Consider initiating prednisone 1 mg/kg, tapering over ≥ 4 weeks
	Grade 3	Interrupt and consult a dermatologist to decide whether and when to resume the treatment, Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids, Initiate (methyl)prednisolone or equivalent 1-2 mg/kg/d, tapering over ≥ 4 weeks
	Grade 4	Interrupt and consult a dermatologist to decide whether and when to resume the treatment after resolving and prednisone requirement ≤ 10 mg/day, Initiate (methyl)prednisolone or equivalent 1-2 mg/kg with slow tapering when toxicity resolves, Initiate topical therapies recommended by a dermatologist
Bullous Dermatosis	Grade 1	Interrupt and consult a dermatologist to decide whether and when to resume the treatment
	Grade 2–3	Interrupt and consult a dermatologist to decide whether and when to resume the treatment. For Grade 2 toxicity, Initiate class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement and Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks; For Grade 3 toxicity, Administer IV (methyl) prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks. If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE.

Drug-Related Toxicities	Severity	Management
	Grade 4	Permanently discontinue. Administer IV (methyl) prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves. If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE
Serious Skin Adverse Reactions: SJS, TEN, AGEP, and DRESS	Grade 1 (not applicable)	
	Grade 2	Interrupt and consult a dermatologist to decide whether and when to resume the treatment. Initiate therapy with topical emollients, oral antihistamines, and medium- to highstrength topical corticosteroids. Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
	Grade 3	Interrupt and consult a dermatologist to decide whether and when to resume the treatment. Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum. Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks
	Grade 4	Permanently discontinue. Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid unresponsive cases
2. GI Toxicities		
Colitis	Grade 1	Continue, or interrupt until resolve to grade 0–1
	Grade 2	Interrupt until resolve to grade 1. Administer corticosteroids, unless diarrhea is transient, startingwith initial dose of 1 mg/kg/day prednisone or equivalent when symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may

Drug-Related Toxicities	Severity	Management
		also be an option after an evaluation of the risks and benefits
	Grade 3	Interrupt until resolve to grade 1. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent). If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab).
	Grade 4	Permanently discontinue. Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks. Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days
Hepatitis	Grade 1	Continue and monitor
	Grade 2	Interrupt, resume after resolving to grade 0–1 and prednisone requirement ≤ 10 mg/day. For grade 2 hepatic toxicity with symptoms,may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days. In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month
	Grade 3–4	Permanently discontinue. Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent. Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency).
3. Pulmonary Toxicities		
Pneumonitis	Grade 1	Interrupt if exacerbation confirmed by imaging

Drug-Related Toxicities	Severity	Management
	Grade 2	Interrupt until resolve to grade 0–1 Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks.
	Grade 3–4	Permanently discontinue. Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks
4. Endocrine Toxicities		
Primary Hypothyroidism	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Continue, consult an endocrinologist, and symptom management
Hyperthyroidism	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Continue, consult an endocrinologist, and symptom management
Primary Adrenocortical Insufficiency	Grade 1–2	Continue and monitor closely. For Grade 1, replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon). May require fludrocortisone (0.1 mg/d) formineralocorticoid replacement in primary adrenal insufficiency. For Grade 2, initiate outpatient treatment at two to three times maintenance. (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in G1.

Drug-Related Toxicities	Severity	Management
	Grade 3–4	Continue, consult an endocrinologist, and symptom management. emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg. Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge. Maintenance therapy as in G1
Hypophysitis	Grade 1–2	Continue, monitor closely, and hormonal supplementation
	Grade 3–4	Continue, consult an endocrinologist, hormonal supplementation and initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Diabetes	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Continue and consult an endocrinologist to determine whether to resume the treatment
5. Musculoskeletal Toxicities		
Inflammatory Arthritis	Grade 1	Continue
	Grade 2	Interrupt until the symptoms are controlled and prednisone requirement is ≤ 10 mg/day. If inadequately controlled by NSAIDS, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks. If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3. If unable to lower corticosteroid dose to 10 mg/d after 3 months, consider DMARD

Drug-Related Toxicities	**Severity**	**Management**
		Consider intra-articular corticosteroid injections for large joints
	Grade 3–4	Interrupt, consult a rheumatologist to decide whether to resume the treatment after resolving to grade 0–1. Initiate oral prednisone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD Synthetic: methotrexate, leflunomide Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment
Myositis	Grade 1	Continue
	Grade 2	Interrupt until the symptoms are controlled and CK is normal. If CK is elevated three times or more, initiate prednisone or equivalent at 0.5-1 mg/kg.
	Grade 3–4	Interrupt until resolve to grade 0–1 without immunosuppression; permanently discontinue if there are signs of myocardial involvement. Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) Consider plasmapheresis Consider IVIG therapy Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks;

Drug-Related Toxicities	**Severity**	**Management**
Polymyalgia Rheumatica-Like Syndrome	Grade 1	Continue
	Grade 2	Consider interruption until symptoms are controlled. prednisolone < 10 mg;
	Grade 3–4	Interrupt, consult a rheumatologist to decide whether to resume the treatment after resolving to grade 0–1. Initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time,may offer a corticosteroid-sparing agent, such as methotrexate or IL-6 inhibition with tocilizumab
6. Nephrotoxicities		
Nephritis	Grade 1	Consider interruption, make judgment based on other possible causes and the baseline renal function
	Grade 2	Interrupt, administer 0.5-1mg/kg/d prednisone equivalents. If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment. If improved to G1 or less, taper corticosteroids over 4-6 weeks
	Grade 3	Permanently discontinue. Inititate 1 to 2 mg/kg/d prednisone equivalents
	Grade 4	Permanently discontinue, Consult a nephrologist. Administer corticosteroids (initial dose of 1-2mg/kg/d prednisone or equivalent)
Symptomatic Nephritis: Follow-Up	Grade 1	Resume routine creatinine monitoring if resolve to baseline values
	Grade 2	If resolve to grade 1, taper glucocorticoid dose for at least 3 weeks; If elevations persist. 7 days or worsen and no other cause found, treat as G3
	Grade 3–4	If resolve to grade 1, taper glucocorticoid dose for at least 4 weeks. If elevations persist >3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate)

Drug-Related Toxicities	Severity	Management
7. Neurotoxicities		
Myasthenia Gravis	Grade 1 (not applicable)	/
	Grade 2	Interrupt until resolve. Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom improvement
	Grade 3–4	Permanently discontinue. Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days
Guillain-Barré Syndrome	Grade 1 (not applicable)	/
	Grade 2–4	Permanently discontinue. Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Or methylprednisolone 2-4 mg/kg/d, followed by slow corticosteroid taper. Or pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) for G3-4 along with IVIG or plasmapheresis
Peripheral Neurotoxicity	Grade 1	Lower the criteria for interruption and monitor the symptoms for 1 week; closely monitor the symptoms if continue the treatment
	Grade 2	Interrupt until resolve to grade 0–1. Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild).
	Grade 3–4	Permanently discontinue. Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barre´syndrome management.
Autonomic Neuropathy	Grade 1	Lower the criteria for interruption and monitor the symptoms for 1 week; closely monitor the symptoms if continue the treatment
	Grade 2	Interrupt until resolve to grade 0–1. Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild).
	Grade 3–4	Permanently discontinue. Initiate methylprednisolone 1 g daily for 3

Drug-Related Toxicities	Severity	Management
		days followed by oral corticosteroid taper.
Aseptic Meningitis	Grade 1–4	Permanently discontinue. Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1mg/kg if moderate/severe symptoms
Encephalitis	Grade 1–4	Permanently discontinue. Once bacterial and viral infection are negative, trial of methylprednisolone 1-2 mg/kg. If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology
Transverse Myelitis	Grade 1–4	Permanently discontinue. Methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days Strongly consider IVIG
8. Hematotoxicities		
Autoimmune Hemolytic Anemia	Grade 1	Continue and monitor closely
	Grade 2	Interrupt and consider permanently discontinuing. Administer 0.5-1 mg/kg/d prednisone equivalents
	Grade 3–4	Permanently discontinue, IV prednisone corticosteroids 1-2 mg/kg/d If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporin A, and mycophenolate mofetil
Acquired Thrombotic Thrombocytopenic Purpura	Grade 1–4	Interrupt. Administer 0.5-1 mg/kg/d prednisone for Grade 1-2. For Grade 3-4, administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX

Drug-Related Toxicities	**Severity**	**Management**
Hemolytic Uremic Syndrome	Grade 1–2	Continue and monitor closely
	Grade 3–4	Permanently discontinue. Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, the 1,200 mg every 2 weeks
Aplastic Anemia	Grade 1–2	Interrupt, treat with growth factors, and monitor closely. For Grade 2, administer ATG + cyclosporine
	Grade 3–4	Interrupt, treat with growth factors, horse ATG plus cyclosporine and monitor daily. If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, cyclophosphamide
Lymphopenia	Grade 1	Continue
	Grade 2–3	Continue and monitor the complete blood count and CMV weekly
	Grade 4	Interrupt
Immune Thrombocytopenia	Grade 1	Continue and monitor closely
	Grade 2–4	Interrupt, resume the treatment after resolving to grade 1. For Grade 2, administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose. For Grade 3-4, Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms). If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor

Drug-Related Toxicities	Severity	Management
		agonists, or more-potent immunosuppression
Acquired Hemophilia	Grade 1–2	Interrupt, For Grade 1, administer 0.5-1 mg/kg/d prednisone; For Grade 2, administer 1 mg/kg/d prednisone 6 rituximab (dose, 375 mg/m2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab v cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks
	Grade 3–4	Permanently discontinue. Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) 6 rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or (dose, 1-2 mg/kg/d). If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption
9. Cardiovascular Toxicities		–
Myocarditis, Pericarditis, Arrhythmia, Ventricular Insufficiency with Heart Failure and Vasculitis	Grade 1	Interrupt
	Grade 2–4	Permanently discontinue. High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms). In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin.
Venous Thromboembolism	Grade 1–3	Continue
	Grade 4	Permanently discontinue
10. Ocular Toxicities		
Uveitis/Iritis	Grade 1	Continue
	Grade 2	Interrupt until after consulting an ophthalmologist. Topical corticosteroids, cycloplegic agents, systemic corticosteroids May resume ICPi treatment once off systemic corticosteroids, which

Drug-Related Toxicities	Severity	Management
		are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity. Re-treat after return to G1 or less
	Grade 3–4	Permanently discontinue. Emergent ophthalmology feferral. Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion.
Episcleritis	Grade 1	Continue
	Grade 2	Interrupt and consult an ophthalmologist. Topical corticosteroids, cycloplegic agents, systemic corticosteroids
	Grade 3–4	Permanently discontinue. Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents
Blepharitis	No grades available	Continue, unless the symptoms are persistent and serious

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis; DRESS: drug rash with eosinophilia and systemic symptoms; NSAIDs: Non-Steroidal Anti-Inflammatory Drug; DMARD: Disease-modifying antirheumatic drug; IVIG: Intravenous Immunoglobulin; CK: Creatine Kinase; PEX: Physical Examination; ATG: Antithymocyte Globulin; ICPi: Immune Checkpoint inhibitor.

Sintilimab treatment is allowed to be held for up to 12 weeks. If the symptoms do not resolve and treatment cannot be resumed within 12 weeks, the subject must permanently discontinue sintilimab treatment and enter the follow-up phase of the study except for the following two cases:

- Sintilimab hold > 12 weeks due to glucocorticoid taper while treating immune-related adverse events (irAEs): Consult the sponsor's medical manager prior to resuming sintilimab. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and will be performed as scheduled.
- Sintilimab hold > 12 weeks due to AEs unrelated to sintilimab: Consult the sponsor's medical manager prior to resuming sintilimab. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and will be performed as scheduled.

5.2.3 Management of sintilimab-related infusion reactions

Sintilimab may cause severe or life-threatening infusion reactions, including severe hypersensitivity reactions or allergic reactions. Signs and symptoms usually occur during or after drug infusion and usually resolve within 24 h after the infusion completion. Refer to **Table 5** for the guidelines for management of sintilimab-related infusion reactions.

Table 5 Guidelines for the management of sintilimab-related infusion reactions

NCI CTCAE Grades	Treatments	Premedications for Subsequent Infusions
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Monitor the subject, including vital signs, closely until the subject is stable as determined by the investigator.	Not applicable.
Grade 2 Treatment or infusion interruption required, but responds promptly to timely symptomatic treatment (e.g. antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], anesthetics, IV fluids); prophylactic medications indicated for ≤ 24 h	**Stop the infusion and monitor symptoms.** Other appropriate treatments include but are not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Consider bronchodilators Consider corticosteroids Monitor the subject, including vital signs, closely until the subject is stable as determined by the investigator.	Premedications should be given for subsequent infusions. The following premedications are recommended within 1.5 h (± 30 min) prior to sintilimab infusion: Diphenhydramine 50 mg PO (or equivalent antihistamines) Acetaminophen 500–1000 mg PO (or equivalent antipyretics) **If grade 2 toxicities occur despite of adequate**

NCI CTCAE Grades	Treatments	Premedications for Subsequent Infusions
	If symptoms resolve within 1 h after interrupting the infusion, then the infusion will be resumed at 50% of the original infusion rate (e.g. from 100 mL/h to 50 mL/h). If symptoms recur with resumption of the infusion, discontinue further treatment at that visit. Monitor the subject closely until the subject is stable. If symptoms resolve in > 1 h, discontinue the treatment at that visit.	**premedications, the study drugs should be permanently discontinued.**
Grade 3 or 4 Grade 3 Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltration) Grade 4 Life threatening; pressors or ventilatory support indicated	**Discontinue the infusion.** Other appropriate treatments include but are not limited to: Epinephrine** IV fluids Antihistamines NSAIDS Acetaminophen Oxygen Bronchodilators Pressors Corticosteroids Monitor the subject, including the vital signs, closely until the subject is stable as determined by the investigator. Hospitalization may be indicated. **Epinephrine should be used immediately for allergic reactions.	Not applicable. **The study drugs should be permanently discontinued.**
Appropriate first-aid equipment should be provided in the ward and physicians should be available at all times during the administration. For more information, refer to CTCAE v5.0 (http://ctep.cancer.gov).		

5.3 Principles for Managing Immune Checkpoint Inhibitor Toxicities

The mechanism of sintilimab is to stimulate T-cell activation and proliferation, which may lead to autoimmune disease involving multiple systems. Autoimmune AEs such as immune-related pneumonitis, diarrhea/enterocolitis, renal insufficiency, rash, hepatitis, endocrine disorders, and peripheral or central neuritis have been observed with checkpoint inhibitors including ipilimumab, nivolumab, pembrolizumab, and atezolizumab. If subjects experienced the irAEs described above, the signs and symptoms should be monitored, relevant examinations should be performed, and the cause should be identified. If an alternative cause is not found (such as PD, concomitant medications, or infections) and glucocorticoids and/or other immunosuppressants are required, then any AE described above is considered related to sintilimab-induced immune hyperfunction, which should be diagnosed as an irAE. Endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type I diabetes, and adrenal insufficiency may not require immunosuppressants, but are still considered as immune-related events.

See**Table 4**, **Table 5** and the latest NCCN guidelines for management of immune-related toxicity in cancer immunotherapy for dose adjustments and management of toxicity.

5.4 Concomitant Treatments

5.4.1 Prohibited treatments

The following treatments are prohibited throughout the trial:

- Any systemic chemotherapy or biotherapy (except for cytokine drugs to treat chemotherapy-induced AEs), as well as herbal and proprietary Chinese medicines, with anti-tumor effects other than sintilimab.
- Immunomodulators, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulin, and gamma globulin) as well as herbal and proprietary Chinese medicines with immunomodulating effects;
- Radiotherapy to control tumors (palliative radiotherapy is allowed if not directed towards the target lesion, such as radiotherapy for relieving pain from bone metastasis and symptoms of brain metastasis);
- Inoculation with live vaccine within 30 days prior to the first dose of study treatment and throughout the trial. Live vaccines include but are not limited to measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette Guerin, and typhoid (oral) vaccines;

Seasonal inactivated influenza virus vaccines are permitted, but live attenuated influenza vaccines are not;

- Corticosteroids. Inhaled steroids for subjects with asthma or chronic obstructive pulmonary disease (COPD) are permitted; temporary use of corticosteroids for dyspnea are permitted; corticosteroids are permitted for the treatment of immune-related AEs; corticosteroids of physiologic dose are permitted after consulting the sponsor.

Note: Prophylactic corticosteroids as pretreatment of allergic reactions (e.g. premedication prior to IV contrast agent or chemotherapy) are permitted.

Based on the assessment of the investigator, subjects requiring any one of the treatment methods above must be excluded from the trial. Subjects may receive other medications that the investigator considers medically necessary.

It is very important for the investigator to review every drug (prescription and non-prescription) used by the subject prior to the trial and during each visit.

- During each visit, subjects must be asked about any new medications received.
- To minimize the risk of drug-drug interactions, the concomitant medications should be limited to those that are really necessary.
- Drugs with hepatotoxicity (i.e. those with warnings in the prescribing information) should be avoided if possible during the treatment. The investigators are encouraged to review every potential hepatotoxic drug via http://www.livertox.nih.gov" .
- Prohibited drugs listed in the exclusion criteria are not permitted.

5.4.2 Permitted treatments

- Medications that meet the protocol requirements, as determined by the investigator (e.g. concomitant medication used for disease-related symptoms and treatment-related AEs);
- Subjects with underlying diseases such as hypertension and diabetes requiring chronic medications can continue these treatments;
- Local surgery or radiotherapy used for isolated lesions (excluding target lesions);
- Supportive care for relieving tumor-related symptoms, such as bisphosphonate treatment for bone metastases;

- Use of corticosteroids by topical administration, such as dermal, ocular, nasal, and inhaled;
- Prophylactic antiviral therapy is permitted for hepatitis B carriers. Refer to treatment guidelines for dosage and administration.

5.4.3 Drug-drug interactions

- Sintilimab: No interaction information is currently available.

5.5 Drug Management

Sintilimab should be refrigerated at 2–8℃ in a dry place and away from light. Do not freeze. Cold-chain should be maintained during transport, and the study drug should be maintained and dispensed by a designee.

The study drugs should be stored in a refrigerator only accessible to the authorized personnel. After receiving the study drugs, the investigator should ensure that the temperature during the transport is maintained within the specified range, sign for receipt upon verification, and store the study drugs at the specified temperature. If abnormalities of the storage temperature during either the transport or storage at the study site arise, the study drugs should be moved to an environment in the specified temperature as soon as possible and should not be administered. Notify the sponsor and Innovent in a timely manner and follow the advice of the sponsor.

All the study drugs provided by Innovent should only be used for this clinical trial. Any purposes other than those specified in the protocol are not permitted. The investigator must agree not to provide the study drugs to any patients not in the trial.

5.5.1 Return and destruction

Upon the completion or discontinuation of the study, all unused or expired study drugs will be destroyed locally in accordance with all applicable institutional standard operating procedures, local and federal laws.

5.6 Study Drug Records

The designee of the study site(s) should keep accurate and complete records for receiving, dispensing, using, storing, returning, and destroying study drugs in accordance with the relevant regulations and guidelines and the operational requirements of this study.

6 Study Procedure

6.1 Enrollment

6.1.1 Enrollment

The investigator will enroll subjects using the following steps:

1. Obtain the ICF signed by the subjects prior to any study-related procedures;
2. Register patients in Clinical Oncology Research System (CORe) website;
3. Confirmation of the subjects' eligibility by the principal investigator or trained designee after reviewing the inclusion/exclusion criteria;

Subjects who do not meet the criteria (screen failures) may be re-screened. If re-screening is considered, the investigator must contact the study PI. Each subject can be re-screened once. The subject must sign the ICF again and be assigned a new identification number when re-screening.

6.1.2 Enrollment error handling

The inclusion/exclusion criteria must be followed strictly. If an ineligible subject is enrolled, the sponsor's medical manager and investigator must discuss whether the subject is allowed to continue the study and whether the subject can be treated with the study drugs. If it is determined by the investigator that allowing the subject to continue the study is medically appropriate and this is agreed to by the sponsor's medical monitor, then the subject will continue the study and receive the study drugs. On the other hand, if the medical monitor does not agree, the subject should not continue the study (regardless of receiving the study drugs or not). The investigator may not allow the improperly enrolled subject to continue with the study until they receive the written approval from the sponsor.

6.2 Study Plan and Schedule

6.2.1 Screening

The following procedures must be completed during the screening (Day -28 to -1) to ensure subject eligibility:

- Signing the ICF
- Confirming the inclusion/exclusion criteria
- Recording the demographics, medical history, and prior medications

- Recording the vital signs, height, and weight
- Physical examination
- ECOG PS
- 12-lead ECG (within 7 days prior to the first dose)
- Complete blood count/blood biochemistry/routine urinalysis (within 7 days prior to the first dose)
- Coagulation function (within 7 days prior to the first dose)
- Pregnancy test (where applicable within 3 days prior to the first dose)
- Thyroid function (results obtained within 28 days prior to first dose)
- HIV antibody, hepatitis B panel (test HBV DNA for subjects with positive HBsAg), and HCV antibody (test HCV RNA for subjects with positive HCV antibodies). Results obtained within 28 days prior to first dose are also accepted.
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation
- Optional archival or fresh tumor tissue

Refer to Sections 7.1 and 7.2 for details regarding tumor evaluation and safety evaluation.

6.2.1.1 Medical history

A medical history should be obtained by the investigator or qualified designee. It includes all active diseases and diseases diagnosed that are clinically significant, as determined by the investigator, including but not limited to history of cigarette use, alcohol use, surgery, and drug allergy. All autoimmune diseases should be documented, regardless of the date of onset.

6.2.1.2 Prior medications

All medications (including over-the-counter supplements) used within 30 days prior to the first dose of study treatment, including any washout requirements specified in the protocol, will be reviewed by the investigator or qualified designee and should be documented.

6.2.1.3 Concomitant medications

The investigator or qualified designee will document all the medications used throughout the trial (from the signing of the ICF to the safety follow-up). Concomitant medications related to SAEs and irAEs should be documented. All concomitant medications will be recorded in the EMR only.

6.2.2 Day 1 of Cycle 1)

- Recording the vital signs
- Weight
- ECOG PS
- Complete blood count/blood biochemistry/routine urinalysis
- AE evaluation
- Concomitant medications
- Administration of study drugs
- EQ 5D-5L
- EORTC QLQ-C30
- PRO-CTCAE
- Blood sampling for biomarkers and PK sampling (if applicable)
- Survival status

6.2.3 Treatment visits

- Recording the vital signs
- Weight.
- Physical examination
- ECOG PS
- 12-lead ECG
- Complete blood count/blood biochemistry/routine urinalysis

- Urine pregnancy test (every other cycle from cycle 2 onwards)
- Thyroid function (from cycle 2 onwards)
- AE evaluation
- Concomitant medications
- EQ 5D-5L (if applicable)
- EORTC QLQ-C30 (if applicable)
- PRO-CTCAE (if applicable)
- Tumor imaging evaluation (if applicable)
- Administration of study drugs (tumor imaging evaluation should be performed prior to administration)
- Optional fresh biopsy (if applicable on C4D1)
- Blood sampling for biomarkers and PK sampling (if applicable)
- Survival status

Refer to **Table 1** for the study schedule during the treatment.

Refer to Sections 7.1, 7.2, 7.3 and 7.4 for details regarding tumor imaging evaluation, safety evaluation, immunogenicity sampling, and PK sampling, respectively.

6.2.4 End-of-treatment visit

The following should be completed within ± 7 days after confirming the end of treatment:

- Recording the vital signs
- Physical examination
- Weight
- ECOG PS
- 12-lead ECG
- Complete blood count/blood biochemistry/routine urinalysis

- Thyroid function
- Blood pregnancy test
- Tumor imaging evaluation (if applicable)
- AE evaluation
- Concomitant medications
- EQ 5D-5L
- EORTC QLQ-C30
- PRO-CTCAE
- Optional fresh biopsy
- Blood sampling for biomarkers
- Survival status
- Subsequent anti-tumor therapy

If the visit in which PD is confirmed is the end of treatment, then that visit can replace the end of treatment visit and it need not be repeated. However, all procedures for the end of treatment visit must be completed.

6.2.5 Safety follow-up

The safety follow-up will be performed at the 30th day (± 7 days) and 90th day (± 7 days) after the last dose and will include the following procedures:

- ECOG PS
- 12-lead ECG (for the 30-day safety follow-up only)
- Complete blood count/blood biochemistry/routine urinalysis
- AE evaluation
- Concomitant medications (for the 30-day safety follow-up only)
- Document subsequent anti-tumor therapy
- EQ 5D-5L (for the 30-day safety follow-up only)
- EORTC QLQ-C30 (for the 30-day safety follow-up only)

- PRO-CTCAE (for the 30-day safety follow-up only)
- Survival status

If the safety follow-up is less than 7 days after the end-of-treatment visit, then the safety follow-up may be replaced by the end-of-treatment visit and does not need to be repeated.

If the subject initiates a new anti-tumor therapy within 30 days after the last dose, then the safety follow-up must be performed before initiation of the new therapy.

6.2.6 Survival follow-up

After completing the safety follow-ups, the subject should be contacted (telephone visits are allowed) once every 60 days (± 7 days) to obtain the survival information, any subsequent systemic anti-tumor therapy, and PD information. Long-term follow-up should be continued until death or for a duration of 3 years after the last patient is enrolled.

6.2.7 Subsequent anti-tumor therapy

The investigator or qualified designee will collect all the information about new anti-tumor therapies initiated after the last dose of the study drugs and the corresponding efficacy. If the subject initiates a new anti-tumor therapy within 30 days after the last dose, then the safety follow-up must be performed before initiation of the new therapy.

The subject should be followed for survival after initiation of a new anti-tumor therapy. Refer to Section 6.2.6– Survival follow-up for details regarding survival follow-up.

6.2.8 Unscheduled visits

Unscheduled visits may be performed if requested by the subject or investigator. The investigator will carry out relevant examinations based on the subject's status, which includes but is not limited to the vital signs, targeted physical examination, ECOG PS, complete blood count/blood biochemistry/routine urinalysis, and tumor imaging evaluation. Test results from the unscheduled visits should be documented in the eCRFs.

7 Study Evaluation

7.1 Efficacy Evaluation

Tumor evaluations will be performed based on RECIST v1.1. Refer to Appendix 3 for the

evaluation methods.

All the decisions made during the study will be based on the imaging evaluations by the independent and investigator radiology review, subject's clinical status, and relevant examination results.

7.1.1 Tumor imaging and disease evaluations

Tumor imaging examinations usually include contrast-enhanced CT or MRI of the chest, abdomen, and pelvis. Contrast-enhanced MRI should also be performed on the brain at baseline for subjects with signs and symptoms of CNS metastasis. The imaging method should be consistent for a given subject during the trial.

During the screening, the investigator of the study site will confirm the presence of measurable lesions based on RECIST v1.1 to determine the eligibility of the subject. According to RECIST v1.1, a maximum or 5 lesions in total and 2 lesions per organ will be recorded.

7.1.2 Tumor imaging during the study

The imaging method used for the evaluation of tumor burden during each visit should be the same as the one used at baseline. Other affected sites should be examined based on the signs and symptoms of each subject. Baseline evaluation will be conducted within 28 days prior to the first dose of the study treatment, which means the investigator can evaluate the imaging results within 28 days prior to the enrollment.

After the first dose of study treatment, tumor imaging evaluation will initially be performed once Q9W (± 7 days) until initiation of a new anti-tumor therapy, PD, withdrawal of informed consent, lost to follow-up, death, or completion of the study (whichever comes first).

Patients who have radiographic PD will be allowed to continue therapy if clinically stable till next scheduled scans. If PD is confirmed on the next scan, patient will discontinue therapy. For certain cases which PD cannot be determined, especially on those with equivocal non-target lesions enlargement or equivocal new lesions, the treatment may be continued until signs of clinical instability develop or when PD is confirmed by the investigator in the next scheduled scan. Once PD is confirmed, the disease progression date will be recorded as the date when the suspective PD was initially observed. Definition of clinical stability is as follows:

- Absence of clinically significant signs and symptoms suggesting PD (including worsening laboratory values);
- No reduction in ECOG PS score;
- No rapid PD;
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g. spinal cord compression) that requires urgent medical interventions.

Tumor evaluations should be performed as scheduled and should not be delayed due to treatment delays, holidays, or any other reasons.

Further tumor evaluations are not required for subjects who discontinue the treatment due to radiographic PD.

For subjects who discontinue the treatment for reasons other than radiographic PD, tumor evaluation should be performed Q12W (± 7 days) until one of the followings occurs: start of new anti-tumor therapy, PD, withdrawal of informed consent, or death. A scan at the end of the treatment is not mandatory if it were less than 4 weeks after the last tumor evaluation.

If the subject has confirmed or suspected bone metastatic lesion(s) present at baseline, a contrast enhanced PET/CT can be used for efficacy assessment.

7.2 Safety Evaluation

The investigator or qualified designee should evaluate each subject, as specified in the schematic of the study design, to identify the potential new or worsening AEs. Safety evaluations can be performed more frequently if clinically indicated. AEs are graded and documented according to NCI CTCAE v5.0 during the study and follow-up. Toxicities will be characterized by severity grade, causality, and actions taken with the study treatment.

All AEs with unknown causes after exposure to the study treatment must be evaluated to determine whether the event is potentially immune-related.

Refer to Sections 8.2 and 8.3 for details regarding AE evaluation and documentation.

Refer to the schedule of visits in **Table 1** for the timing of the evaluations. Refer to Appendix 2 for ECOG PS criteria.

7.2.1 Physical Examination

7.2.1.1 Comprehensive physical examination

A comprehensive physical examination will be performed by the investigator or designee during the screening. All the clinically significant abnormalities should be documented in the disease history. After the first dose of study treatment, any new clinically significant abnormalities should be documented as AEs.

7.2.1.2 Targeted physical examination

In cycles where a comprehensive physical examination is not required by the study protocol, targeted physical examination should be performed by the investigator or qualified designee if clinically indicated. The examination should be scheduled prior to administration on Day 1 of each treatment cycle. All of the clinically significant abnormalities should be documented as AEs.

7.2.1.3 ECOG PS

The investigator or qualified designee will evaluate PS during screening, prior to administration on Day 1 of each treatment cycle, during the end-of-treatment visit, and during safety follow-up in accordance with the instructions in the Schedule of Visits.

7.2.1.4 Vital signs

Vital signs will be examined in accordance with the schedule of visits in **Table 1**, including temperature, pulse, respiratory rate, and blood pressure. The time and date of measurement should be documented in the appropriate section of the eCRF. Temperature, pulse, respiratory rate, and blood pressure should be measured within 15 minutes prior to the administration of study drugs.

Additional monitoring of vital signs is allowed based on standard clinical practice or clinical need, and should be documented in the eCRF when an AE/SAE occurs (if applicable). The time and date of measurement should be documented in the appropriate section of the eCRF.

7.2.1.5 12-lead ECG

A resting 12-lead ECG will be performed at the local laboratory in accordance with the schedule of visits in **Table 1**.

The subject must be resting in a supine position for at least 5 min prior to 12-Lead ECG. All the

12-lead ECG results should be recorded in the supine position. Further ECGs (or other related tests) should be performed if clinically indicated, such as a cardiac AE. The investigator should review the ECG on the day it is performed. The evaluation method should be consistent throughout the trial.

The investigator should evaluate all the ECGs as either normal, clinically significant abnormalities, or clinically insignificant abnormalities. If it is a clinically significant abnormality(s), the investigator should document an AE in the eCRF.

7.2.2 Routine laboratory safety evaluations

See below for the specific laboratory procedures/evaluations. Refer to the Procedure Manual for the total amount of blood/tissues extracted/collected throughout the trial (from pre-trial to post-trial visits), including the amount of each subject's blood/tissues extracted/collected for each specimen type during each visit. Refer to the section on laboratory evaluations in the Schedule of Visits.

7.2.2.1 Laboratory safety evaluation (complete blood count, routine urinalysis, and blood biochemistry)

Refer to **Table 6** for laboratory tests including complete blood count, routine urinalysis, and blood biochemistry.

Table 6 Routine laboratory safety evaluation

Complete blood count	RBC, HGB, WBC, PLT, LYM, and ANC
Blood Biochemistry	TBIL, ALT, AST, ALP, ALB, TP, LDH, UREA, Cr, Na, K, Cl, Mg, Ca, P, amylase, lipase and FBG
Routine Urinalysis	PH, UWBC, UPRO, URBC, and UGLU
Thyroid Function	FT3, FT4, and TSH
Coagulation Function	PT and INR
Viral Serological Test	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV DNA, HCV antibody, HCV RNA, and HIV antibody

ALB = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; Cr = serum creatinine; FBG = fasting blood glucose; FT3 = free triiodothyronine; FT4 = free thyroxine; HBcAb = hepatitis B core antibody; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e

antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HGB = hemoglobin; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LYM = lymphocyte count; PH = pH; PLT = platelet; PT = partial thromboplastin time; TBIL = total bilirubin; TP = total protein; TSH = thyroid stimulating hormone; RBC = red blood cell; UGLU = urine glucose; UPRO = urine protein; URBC = urine red blood cell; UREA = urea; UWBC = urine white blood cell; WBC = white blood cell.

7.2.2.2 Pregnancy test

Serum β-human chorionic gonadotropin (β-hCG) pregnancy tests should be performed in women of childbearing potential (refer to Section 4.3 for definition) within 3 days prior to the first dose of study treatment and at the end-of-treatment visit. At every other cycle (strating cycle 2) a urine pregnancy test should be performed ONLY in women of childbearing potential. If the result of urine β-hCG is positive or inconclusive, then serum β-hCG pregnancy test should be performed. Result of the serum pregnancy test is determinative. If the serum β-hCG result is positive, the subject is not eligible and must be excluded from the study.

7.3 Biomarker Analysis

Refer to the Laboratory Manual for sampling methods, sample storage, transportation, and analysis.

7.3.1 Tissue biomarkers

Eligible subjects can provide tumor tissues for optional tissue biomarker analysis. Acceptable tumor tissues include archival specimens or at least 20 unstained, 4–5 μm sections from a fresh specimen (tissue should have a surface area of 25 mm^2 containing greater than 20% of tumor cells) for evaluating PD-L1 expression, transcriptome sequencing, single-cell sequencing, and multicolor IHC. Optional archival specimens or fresh tissue through optional biopsy will be collected at screening, C4D1 and at EOT/ confirmed PD.

7.3.2 Serum biomarkers

Subjects need to provide a 60 mL of whole blood sample for serum biomarker detection at the following time points: Prior to first dose, C1D8, C2D1, C4D1, C7D1, C10D1, when first PD is recorded and when PD is confirmed. (See **Table 1** and **Appendix 4**)

Refer to the Laboratory Manual for sampling methods, sample storage, transport, and analysis.

7.4 Pharmacokinetics (PK)

PK samples will be collected at the following time points: within 1 h before, any point within 2-24 h after, any point within 120-264 h after sintilimab infusion in Cycle 1, within 1 h before sintilimab infusion in Cycle 2/4, and then within 1h before sintilimab infusion with every 4 cycles thereafter starting cycle 7 (e.g. Cycle 7, 11, 15 etc.).

For PK analysis, 5 mL of whole blood will be collected using vacutainers with clot activator. Serum is then separated and frozen in aliquots. Refer to the Laboratory Manual provided by the supporting company's designated central laboratory for sampling methods, sample storage, transportation, and analysis.

8 Safety Reports and AE Management

8.1 Definition of AEs

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study treatment.

AEs include but are not limited to the following:

- Deterioration of pre-existing (prior to enrollment) medical conditions/diseases (including symptoms, signs, and laboratory abnormalities);
- Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
- Clinically significant laboratory abnormalities, changes in the vital signs, ECG abnormalities, and findings on physical examination.

All AEs that are observed by the Investigator, staff or mentioned by the subject either spontaneously or upon questioning will be recorded in Prometheus.

8.2 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events and determine the relationship with study therapy. Any adverse event should be evaluated according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

The severity of the adverse events (AEs) will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Table 7 Detailed rules of AE evaluation

Severity based on CTCAE V.5.0 **Grade** **Events not included in the NCI CTCAE will be scored as follows:**	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; medical intervention not indicated**
	Grade 2	**Moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily life, but not bedridden**
	Grade 4	**Life-threatening consequences; urgent intervention indicated**
	Grade 5	**AE-related deaths**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Innovent's product that:	
	† **Results in death** (excluding those death due to PD);	
	† **Is life threatening;** or, places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.);	
	† **Results in a persistent or significant disability/incapacity;** (substantial disruption of one's ability to conduct normal life functions); or	
	† **Results in or prolongs an existing inpatient hospitalizatio**n; (hospitalization is defined as an inpatient admission, regardless of length of stay) (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Innovent product and is documented in the patient's medical history.); or	
	† **Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when,based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action Taken	Did the adverse event cause the Innovent's product to be discontinued?	
Relationship to Sponsor's Product	Did Innovent's product cause the adverse event? The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events; assigning the attribution and assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or drug. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution for all adverse events for subjects enrolled. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Innovent's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Innovent's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time course	Did the AE follow in a reasonable temporal sequence from administration of Innovent's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Possible causes	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?
	Dechallenge	Was Innovent's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of Innovent's product; or (3) the trial is a single-dose drug trial); or (4) Innovent's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study?

	Tests	If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Innovent's product(s) is/are used only one time).
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Innovent's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Attribution** is the determination of whether an adverse event is related to a medical treatment or procedure. **Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Innovent's product relationship).** • **Definite** - the adverse event is clearly related to the investigational agent(s). • **Probable** - the adverse event is likely related to the investigational agent(s). • **Possible** - the adverse event may be related to the investigational agent(s). • **Unlikely** - The adverse event is doubtfully related to the investigational agent(s). • **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s).

8.3 AE Documentation

The investigator should document AEs and SAEs from the time of the first protocol intervention until 90 days after the last study drug administration, using medical terms and concepts. Avoid colloquialisms and abbreviations. AEs (including SAEs) should be recorded on the AE forms in the eCRFs.

8.3.1 Collection and time of AEs

The investigator should use non-leading questions when asking the subjects about AEs.

AEs will be recorded in Prometheus, following the NCI recommended Adverse Event Recording Guidelines for Phase II studies:

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II	Phase I Phase II	Phase I Phase II	Phase I Phase II

		Phase III	Phase III	Phase III	Phase III

All AEs including SAEs and irAEs will be collected within 90 days after the last dose if new anti-tumor therapy has not been initiated. Only irAEs and study treatment- or procedure-related SAE will be collected if a new anti-tumor therapy has been initiated.

After 90 days since the last dose, investigator should report sintilimab-related or procedure-related SAEs.

8.3.2 Follow-up of AEs

The AEs should be followed until the events return to the baseline values or grade 0–1, or until the investigator believes that no further follow-up is required for reasonable reasons (if the event cannot resolve or has already been improved). If the event cannot resolve, a reasonable explanation should be documented in the eCRF. The outcome and date of an AE/SAE should be documented in the eCRF and medical record, regardless of whether the event is related to the study drugs.

8.3.3 Contents of AE documentation

The investigator must document all the AEs, including the diagnosis (document signs and symptoms including the laboratory abnormalities if there is no diagnosis), time and date of occurrence (if applicable), CTCAE grade and changes in severity, whether it is an SAE, irAE or not, measures taken for the study drugs, treatment for the AE and outcome of the event, and relationship between the event and study drugs.

For an SAE, the investigator should also provide the date when the AE meets the criteria for an SAE, the date when the investigator is informed of the SAE, the reason that it is considered an SAE, date of hospitalization, date of hospital discharge, possible cause of death, date of death, whether an autopsy has been performed, causality assessment (the drug being investigator or other drugs included in the regimen), and other possible causes of the SAE. The investigator should provide their rationale for the causality and a description of the SAE. In the SAE description, the following should also be included: the subject number, age, gender, height, and weight; indication for receiving the investigational drug, cancer staging, and overall condition; SAE occurrence, development, outcome, and result; laboratory results related to the SAE (the time of the examination, units, and normal ranges must be provided); medical history, onset and duration of concurrent diseases related to the SAE; medication history and initiation, duration,

and dosage of concomitant medications related to the SAE; initiation, duration, and dosage of the study drugs.

Descriptions of the AE are as follows:

Diagnosis, signs, and symptoms

Document the definite diagnosis, if there is one, rather than just listing the independent signs and symptoms (e.g. hepatic failure rather than jaundice, elevated transaminase, and asterixis). Signs and symptoms should be reported as separate AEs/SAEs if they cannot be attributed to the diagnosis. If it is determined that the signs and symptoms are caused by the diagnosis, then only the diagnosis should be reported, which has the signs and symptoms included in. The record of signs and symptoms should then be deleted. A follow-up SAE report should be submitted.

AEs secondary to other events

Generally, for AEs secondary to other events (such as result of another event or clinical sequelae), the primary event should be documented. However, clinically significant secondary events should be recorded as independent AEs in the eCRFs if they occur at different time from the primary event. If the relationship between events is unclear, document them as separate events in the eCRFs.

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs.

Recurrent AEs refer to AEs that have resolved between the two time points of assessment but subsequently occur again. These events should be independently documented in the eCRFs.

Laboratory abnormalities

Any abnormal laboratory finding that is clinically significant should be reported as an AE. The investigator is responsible for reviewing all the laboratory abnormalities and determine whether the findings should be reported as AEs.

Death

All deaths (including those that occur before Day 90) that happen during the entire course of the study, and after the last dose should be documented in the patient’s medical record, captured captured in the database and reported as an SAE to the sponsor and supporting company, in a

timely manner, according to the specific SAE reporting guidelines, regardless of the causality with the study drugs.

If the cause of death is known, record the cause of death as an AE and the outcome of the event as a death and submit an SAE report; if the cause of death is unclear, the AE should be recorded as Death of Unknown Cause in the AE form, and submit the SAE report as Death of Unknown Cause. The exact cause of the death should be further investigated and, when feasible, updated in the eCRF and SAE report.

If the cause of death is confirmed to be PD then the event may not be documented or reported as an SAE, but the event should be documented in the database and reported to the sponsor and supporting company within 24 hours.

If the subject initiates a new anti-tumor therapy within the 90 days after the last dose, the death after the initiation of new therapy should not be reported as an SAE, unless the death is believed to be related to study drugs or study procedures.

Pre-existing medical conditions

Symptoms/signs presenting during the screening period will be recorded and reported as AEs only if their severity or frequency becomes aggravated (except for worsening of the studied disease). The relative change should be documented, such as increased frequency of headaches.

Hospitalization, prolonged hospitalization, or surgery

Any AE that results in hospitalization > 24 hours or prolonged hospitalization should be documented and reported as an SAE, except for the following situations:

- Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration or efficacy evaluation).
- Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.

However, elective surgery/therapy required because of the exacerbated condition during the study (e.g. surgery/therapy required earlier than scheduled) should be considered as an AE.

Progressive disease

A PD is defined as the worsening of the subject's condition caused by the primary tumor that the study drug is targeting, the appearance of new lesions, or the progression of the primary lesion.

PD will not be reported as an AE. Any life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by PD will not be reported as an SAE.

Overdose

An overdose is the administration of a drug at more than 20% of the dose specified in the study protocol. All the occurrences of overdose must be documented in the eCRF. Any adverse events resulting from the overdose should be recorded. If the adverse events met the serious criteria, it should be reported as a SAE.

New anti-tumor therapy

All irAEs and study treatment- or procedure-related SAEs occurred within 90 days after the last dose are required to be documented and reported if a new anti-tumor therapy has been initiated.

8.4 Serious Adverse Events

8.4.1 Serioud Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsor Single Site IND Protocols

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the followingoutcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon

appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent.

Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office within 5 working days of knowledge of the event regardless of the attribution.

Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office within 24 hours of knowledge of the event

Additionally, any serious adverse events that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.

All events reported to the supporting company must also be reported to the IND Office

Reporting to FDA:Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

8.4.2 Serious Adverse Event (SAE) Reporting to the Supporting Company

All the SAEs that occur from the first protocol specific intervention through Day 90 (inclusive) after the last dose must be reported within 24 hours. The investigator must fill out the SAE Report Form provided by Innovent or MDACC e-SAE form, regardless of whether it is the initial report or a follow-up report. Besides, the investigator must report the SAE to Innovent. (drugsafety@innoventbio.com) within 24 hours after noticing the event. In accordance with the laws and regulations of corresponding regions and countries, the investigator should also report the SAE to the regulatory authorities and EC/IRB

For SAEs occurring beyond the above period, those considered related to sintilimab should also be reported.

The investigator must submit the completed MDACC e-SAE report form to Innovent within 24 h after noticing the event. The investigator should urgently collect all missing information and provide a complete SAE report.

For an SAE, the investigator should also provide the date when the AE meets the criteria for an SAE, the date when the investigator is informed of the SAE, the reason that it is considered an SAE, date of hospitalization, date of hospital discharge, possible cause of death, date of death, whether an autopsy has been performed, causality assessment (the drug being investigator or other drugs included in the regimen), and other possible causes of the SAE.

8.4.3 Pregnancy

The risk of embryotoxicity exists for similar drugs. All the subjects with childbearing potential must take effective contraceptive measures.

During the study, if a female subject exposed to the study drugs becomes pregnant, she must be excluded from the study. The investigator must report the sponsor and the supporting company,

within 24 h of noticing the event and submit the Innovent Clinical Study Pregnancy Report/Follow-Up Form.

During the study, if a female partner of a male subject exposed to the study drugs becomes pregnant, the subject will continue with the study. The investigator must report the sponsor within 24 h of noticing the event and submit the Innovent Clinical Study Pregnancy Report/Follow-Up Form.

The investigator must continuously monitor and visit on the outcome of the pregnancy until the 8th week after the subject gives birth. The outcome should be reported to Innovent.

If the outcome of the pregnancy is stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defect), or medical abortion, it should be considered as an SAE and the event is required to be reported to the sponsor and the supporting company, in accordance with SAE procedures and time limits.

If the subject also experienced an SAE during the pregnancy, the event should be reported according to SAE procedures.

8.5 Abnormal Hepatic Function

Drug-induced liver injury is considered if abnormal AST and/or ALT levels are accompanied with abnormal elevation of TBIL, and the following conditions are met without other possible causes. Such cases should always be considered as important medical events.

Table 8 Liver injuries required to be reported as SAEs

Baseline	**Normal (AST/ALT and TBIL)**	**Abnormal (AST/ALT and TBIL)**
Treatment Period	ALT or AST ≥ 3 × ULN with TBIL ≥ 2 × ULN and ALP ≤ 2 × ULN and no hemolysis	ALT or AST ≥ 8 × ULN and the increased value of TBIL ≥ 1× ULN or TBIL ≥ 3× ULN

Once being notified with the abnormalities, the subject must return to the study site promptly (ideally within 48 h) and receive an assessment. The assessment must include the laboratory tests, detailed medical history, and physical assessment. The possibility of hepatic tumor (primary or secondary) should be considered.

Other than repeated AST and ALT tests, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-GT, PT/INR, and ALP should also be tested. Detailed medical history includes history of alcohol, acetaminophen, soft drugs, various supplements, traditional Chinese medicine, chemical drug exposure, family diseases, occupational exposure, sexual behavior, travel, contact with subjects with jaundice, surgery, blood transfusion, hepatic diseases or allergies, cardiac diseases, and immune diseases. Further tests may include the detection of acute hepatitis A, B, C and E, hepatic imaging (such as biliary tract), autoantibodies, and echocardiography. If a retest showed consistency with the criteria outlined in **Table 8** and there is no other possible cause, the possibility of drug-induced liver injury should be considered before all the results of etiological tests are accessible. This potential drug-induced liver injury should be reported as SAEs. Additional dosing with the study drugs should follow the Dose Modification Criteria included in Section 5.2.2.

8.6 Management of Drug-Related Toxicities

During the course of the trial, the Innovent will conduct blinded safety review for the irAE regularly.

8.6.1 irAEs

Since the mechanism of sintilimab involves T-cell activation and proliferation, irAEs are likely to be observed during this study. Signs and symptoms of irAEs should be monitored. If there are no alternative causes (e.g. infections), signs and symptoms of the subjects during the study may be related to the immune system.

Refer to Section 5.2 for dose adjustments of sintilimab and principles of AE management. Refer to the latest version of NCCN guideline for Management of Immunotherapy-Related Toxicities for a detailed guide on irAE management.

Innovent will continue to collect irAEs until 90th day after the last dose. An irAE should be followed up until it resolves to Grade 0-1 or baseline level, or investigators decide not to follow up anymore with acceptable reasons (e.g. cannot fully recover or getting better).

9 Statistics

9.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will begin after the first enrollment and will be

finalized prior to database locking. The SAP should contain details of all analyses and the presentation of results.

9.2 Statistical Analysis Population

Intention-to-treat set (ITT): all enrolled subjects who are treated.

Evaluable set (EP): all enrolled subjects who have measurable lesions at baseline and have at least one restaging evaluation. This analysis set is used for PFR analysis.

Safety analysis set (SS): all subjects who received at least one dose of study treatment. The SS is used for all the safety evaluations.

Per-protocol set (PPS): A subset of ITT, refers to subjects who do not have protocol violations that affect the efficacy evaluation. The PPS is used for the sensitivity analyses of primary efficacy endpoint and key secondary efficacy endpoints.

9.3 Statistical Analysis Methods

9.3.1 General statistical analysis

Continuous data will be summarized using mean, standard deviation, median, maximum, and minimum. Categorical data will be described using frequency and percentage. Student t-test/Wilcoxon test and ANOVA/Kruskal-Wallis test will be used to compare continuous variables between different patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables.

9.3.1.1 Design and sample size/power

The primary efficacy endpoint will be PFR at 9 cycles ($PFR_{9cycles}$). A patient will be considered as a responder to the treatment if he/she has no confirmed progressive disease (PD) determined by RECIST 1.1 after 9 cycles of therapy. Patients who died from any cause, or discontinued treatment for any reason (for example toxicity, patient preference, or initiation of new treatment without documented disease progression) prior to 9 cycles will be considered inevaluable for primary endpoint

A Simon's two-stage Minimax design will be used to monitor the efficacy of sintilimab. The null hypothesis involves a $PFR_{9cycles}$ of 15% that will be tested against a $PFR_{9cycles}$ of 35%, i.e. a 20% improvement. In the first stage, 15 patients will be treated. If there are ≤ 2 patients who achieve

response in these 15 patients, the study will be terminated. If the study moves forward to second stage, an additional 13 patients will be treated leading to a total of 28 evaluable patients (maximum accrual 30 patients; 28 evaluable, potential 5% drop out rate). Eight or more progression- free patients out of the 28 evaluable patients will be considered clinically relevant to justify further investigation. The power of this design is 80% under the 1-sided type I error rate of 5%. The early stopping probability is 60% if the $PFR_{9cycles}$ is 15% and the average sample size would be 20.1.

9.3.1.2 Analysis of primary efficacy endpoint

The primary efficacy endpoint is confirmed Progression- Free Rate (PFR), defined as the proportion of subjects with no confirmed progressive disease (PD) at 9 cycles assessed by the IRR based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1) in the evaluable population. If the study is stopped early, this agent will not be considered of interest for future study for this cohort of patients. If the study's accrual is complete, we will estimate the $PFS_{6cycles}$ along with a 95% exact confidence interval.

9.3.1.3 Analysis of key and other secondary efficacy endpoints

The key secondary efficacy endpoints are ORR, SDR, DOR, QOL, PFS and OS in the evaluable and ITT populations.

DOR is defined as from first date of Investigator-determined response to Investigator-determined PD or death in the subjects who have achieved CR or PR. PFS is defined as the time from treatment onset to either disease progression as defined by RECIST or death from any cause, or discontinuation of treatment for any reason (for example toxicity, patient preference, or initiation of new treatment without documented disease progression), whichever occurs first. Overall survival (OS) is defined as the time from treatment onset to death. For events that have not occurred by the time of data analysis, times will be censored at the last contact at which the patient was known to be progression-free for DOR and PFS or the last time the patient was known to be alive for OS. PFS, DOR and OS will be estimated using the Kaplan-Meier method.[15] Log-rank test[16] will be performed to test the difference in survival between groups. Regression analyses of survival data based on the Cox proportional hazards model[17] will be conducted on PFS, DOR or OS. The proportional hazards assumption will be evaluated

graphically and analytically, and regression diagnostics (e.g., martingale and Shoenfeld residuals) will be examined to ensure that the models are appropriate. For repeated measures, linear mixed model will be used for continuous outcomes and GEE model will be fit for binary outcomes.[18] Appropriate methods will be applied to analyze correlative data. Other statistical analyses may be performed as appropriate.

The ORR(CR+PR), SDR (SD for 9 cycles) and corresponding exact 95% CIs will be estimated using binomial distribution. QOL will be assessed through scales and reported using descriptive statistics.

9.3.2 Safety analysis

The safety analysis will use the SS. Safety parameters include AEs, laboratory tests, vital signs, ECG, immunogenicity, etc.

9.3.2.1 Drug exposure

The amount of drug exposure and duration of treatment (number of treatment cycles) will be summarized.

9.3.2.2 AEs

The incidence (frequency) of AEs, TEAEs, TRAEs, irAEs, SAEs, AEs resulting in treatment discontinuation, and AEs resulting in death will be summarized. The severity distribution of TEAEs, TRAEs, and irAEs will be summarized using NCI CTCAE v5.0 presented via SOC/PT.

Subjects who discontinue the treatment due to AEs, develop SAE, or die will be listed (include at least the followings: start and end dates of the AEs, severity grades, relationship with study drugs, measures taken, and outcomes).

9.3.2.3 Laboratory tests

Abnormalities in hematology and biochemistry will be assessed through laboratory parameters. Each laboratory test result will be graded according to NCI CTCAE v5.0. The number of subjects with laboratory abnormalities at baseline will be presented by severity grade. Laboratory parameters measured on the day of first dose of study treatment (Day 1 of Cycle 1) will be considered as baseline measurements. The treatment phase for all laboratory parameters begins on Day 1 of study treatment.

The frequency of laboratory abnormalities of each subject during the treatment phase will be

summarized by severity grade. The worst grade (most severe) for each subject will be used if the same laboratory parameter was found to be abnormal repeatedly. All the laboratory parameters will be summarized by the worst NCI grade.

Cross-classification tables describing changes in frequency of any given laboratory parameter before and after treatment based on NCI grades will be provided.

Lists of subjects with laboratory abnormalities ≥ grade 3 will be provided.

For any given laboratory parameter, a subject is considered evaluable if at least one measurement is available.

Routine urinalysis: A cross-classification table is used to describe changes between normalities and abnormalities before and after the treatment.

9.3.2.4 ECG

Descriptive statistics are used for ECG and changes from baseline. A cross-classification table is used to describe ECG changes in PR and QTc from baseline before and after the treatment and data lists will be provided for other abnormalities.

9.3.2.5 Vital signs, physical examinations, and other safety-related examinations

Descriptive statistics of vital signs and relative changes from baseline will be shown.

Abnormal changes from baseline in physical examination will be listed.

9.3.3 Compliance

The frequency and proportion of subjects who violate the treatment regimen will be presented.

The proportion of subjects administered study drugs of doses between 80–110% of the dose specified in the protocol, who complete the study in accordance with study protocol, and who complete different number of treatment cycles will also be summarized.

9.3.4 Baseline characteristics and concomitant medications

Subjects' demographics (sex, race, ethnicity and age), tumor diagnosis information (pathological diagnosis, tumor staging, prior treatment), baseline tumor evaluation (target lesion, number of non-target lesions, sites, total diameter, etc), and other baseline information [height and weight (BMI, BSA), vital signs, laboratory tests, past/concomitant medications] will be analyzed using descriptive statistics.

9.3.5 Data lists of eligible subjects

In addition to subjects' data lists, tumor evaluations (date of evaluation, lesion status, and evaluation results) and efficacy endpoints of subjects who have achieved CR and PR will be listed separately.

Data including the PFS and OS of all the subjects at the end of the study (date of progression, date of death, PFS, and OS) will be also be presented.

9.3.6 Exploratory analysis

Evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1 expression level, transcriptome sequencing, single-cell sequencing, and multicolor IHC analyses;

Evaluate the correlation between biomarkers in peripheral blood and efficacy, including soluble PD-L1, ctDNA, and cytokines analyses.

10 Quality Assurance and Quality Control

In accordance with the Good Clinical Practice (GCP), the sponsor is responsible for the implementation and maintenance of quality assurance and quality control systems as per appropriate standard operating procedures, to ensure the study is implemented and the authentic data is collected, documented, and reported in accordance with the requirements of the protocol, GCP, and applicable regulations.

10.1 Clinical Monitoring

The MD Anderson IND Office will conduct clinical monitoring of this study. The monitor should perform the monitoring in accordance with the standard operating procedures, and has the same rights and responsibilities as the sponsor's medical monitor. The monitor must maintain regular communication with the investigator, authorized research personnel, and sponsor.

During the course of the study, the monitor is responsible for the monitoring according to the monitoring plan. The monitor should compare the data recorded in the databases with the raw data, and inform the investigator of any errors or omissions. Besides, the monitor should also control the compliance of the protocol and study procedures for the study site, ensure that the drugs are kept under proper conditions and oversee drug accountability.

The monitoring visits should be conducted in accordance with relevant laws and regulations.

From the time the subjects are enrolled, site shall receive regular visits for the purpose of monitoring. After each visit to the investigator, the monitor should submit a written report to the sponsor.

The study will be monitored by the MD Anderson External Data and Safety Monitoring Board (EDSMB).

11 Data Management and Record Keeping

This study will use an electronic data collection (EDC) system, and the research data will be recorded in the eCRFs by the investigators or its authorized personnel. Before the initialization of the study site or data entry, the investigators and authorized personnel should be properly trained and appropriate security measures should be applied for the computer and other equipment.

Data entry into the eCRFs should be completed as soon as possible during or after visiting. The eCRFs should be updated at any time to ensure that they reflect the latest conditions of the subjects. To avoid variations in outcome evaluations by different evaluators, it is recommended that the baseline and all subsequent efficacy and safety evaluations of a given subject should be performed by the same individual. The investigators are required to review the data to ensure the accuracy and correctness of all the data entered into the eCRFs. If no evaluations are conducted during the study, or some information obtained are not evaluable, not applicable, or unknown, the investigators should record the above information in the eCRFs.

The CRA will review the eCRFs, then evaluate the completeness and consistency by comparing them with the source document especially the key data. Data entry, corrections, and modifications should be performed by the investigator or designee. The data in the eCRFs is submitted to the data server and any modifications in the data should be recorded in the audit trail, including reasons, operator names, time, and dates of modifications. The roles and permission levels of the personnel responsible for data entry in the study site will be determined in advance. The CRA or data management personnel may raise an inquiry in the EDC for suspicious data. The study site personnel are responsible for dealing with such inquiry. The EDC system will record the audit trail of the inquiry, including the investigator name, time, and date.

Unless otherwise stated, the eCRFs should only be used as forms to collect data instead of source. The source documents are records that used by the investigators or hospital, including all those related to the subjects, which are able to demonstrate the presence, inclusion/exclusion

criteria, and participation of subjects (laboratory records, ECGs, pharmaceutical records, and subject folders etc.). Permanent copies of study visit records will be considered as source documents which is used to record the data of enrolled subjects. Data in the eCRFs should be retrieved from the source documents and consistent with source data.

The investigator is responsible for the maintenance of all source documents and should offer the documents to the study monitor for review during each visit. In addition, the investigator must submit a complete eCRF for each enrolled subject, regardless of the duration of participation. The protocol number and subject numbers of all supporting documents (such as laboratory records or hospital records) submitted with the eCRFs should be carefully verified. All the personal identities (including the subjects' names) should be deleted or made illegible to protect the privacy of the subjects.

AEs and concomitant diseases/history should be coded. The dictionary used for coding will be described in the CSR.

Records from the clinical trial (such as protocol and protocol revision, completed eCRFs, and signed ICFs) should be kept and managed in accordance with the GCP. The study sites should keep these documents for 5 years after the end of the study.

The study documents should be properly kept for future reviews or data tracking. Security and environmental risks should be considered for keeping documents.

No study documents can be destroyed without the written consent from the sponsor and investigator. The investigator/study site may transfer the study documents to other parties or another location that comply with the record-keeping requirements only after notifying the sponsor and obtaining the written consent.

12 Ethics

The sponsor or designee will prepare the relevant documents including the trial protocol, ICF, Investigator’s Brochure, subject recruitment materials or advertisements, and other documents required by regulations, which are to be submitted to the corresponding IRB in of the study site for approval. Prior to the start of the trial, written approval from the IRB must be obtained and submitted to the sponsor. The written approval from the IRB should specify the name, number, version number of the protocol and other documents (such as ICF), and the date of approval. The investigator is required to notify the sponsor of the IRB's written comments regarding delay, interruption, and re-approval of the study.

The study site must follow the requirements of the corresponding IRB. The modifications of protocol, ICF, or recruitment materials should be submitted to the IRB for approval. Local safety reports should be drafted and updated regularly in accordance with the regulations from the IRB, and the final report should be submitted. All the above documents with IRB approvals must be provided to the sponsor or designee.

12.1 Implementation of Ethics

The study process and ICF aquisition are subject to the Declaration of Helsinki, GCP requirements, as well as laws and regulations of drug and data protection in any related countries.

GCP provides ethical, scientific, global quality standards for the design, implementation, documentation, and report of clinical studies involving human subjects. This study will be conducted in accordance with the GCP and relevant national regulations and in accordance with the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the subjects.

The investigator is required to follow the procedures specified in this protocol and cannot change the procedures without the permission from the sponsor. Any protocol violations must be reported to the IRB, sponsor, or regulatory authorities.

12.2 Informed Consent

Before the start of any study process, the ICF is introduced to explain the risks and benefits of this study to potential participants, and the language in the ICF should be straightforward. The ICF statement should clarify that this ICF signing is voluntary, and the risks and benefits of participating in this study should be clearly outlined. The subject can withdraw from the study at any time. Subjects can only be enrolled if he/she fully understands the study in detail, has received satisfactory answers to his/her inquiries, and has sufficient time for consideration. Written consent must be obtained from the subject. All signed ICFs must be kept in the investigator's files or in the subject's folder.

The investigator is responsible for the interpretation of the ICF of the subject, obtaining informed and dated ICF from the subject prior to the start of the study. After signing, the investigator should send the subject a copy of the signed ICF. The investigator is required to document the process of ICF in the source study document.

12.3 Protection of Subjects' Data

An ICF should include (or in some cases, use separate files together) information about data and privacy protection.

Take precautions to ensure the confidentiality of the documents so as to prevent the disclosure of information that can determine the identity of the subject. However, under special circumstances, some personnel may be permitted to see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, designated physician, or investigator will have an access to the subject identification code and the subject's genetic data. In addition, relevant regulatory authorities may require access to relevant documents.

12.4 Protocol Violation

Protocol violation refers to any non-compliance with the study protocol, the International Conference on Harmonization Good Clinical Practice (ICH GCP), or operating manual. Non-compliance may come from the subjects, investigators, or study site personnel. Violations should be corrected promptly.

13 Publishing of Study Data

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish the study results. Information about the publishing policies between the sponsor and investigator will be described in the clinical trial agreement.

All the information about this trial (not limited to the protocol and Investigators Brochure) must be kept strictly confidential. The investigator should realize that the scientific or medical information derived from this trial may be of commercial value to the sponsor. The investigator should keep the information and data related to this study confidential. The sponsor must be consulted in advance and written consent must be obtained prior to publishing of any study-related information or conclusions. In order to protect the rights and interests, the sponsor may request the investigator not to publish the information from this trial before the investigational product is approved for marketing.

The sponsor has the right to announce or publish information or data related to the trial or to report it to the drug administration. The sponsor must obtain the consent of the investigator if the name of the investigator would be included in the content of the announcement, publication, or advertisements.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin*. 2010;60(5):277-300. doi:10.3322/caac.20073.
2. Hogendoorn PCW, Collin F, Daugaard S, et al. Changing concepts in the pathological basis of soft tissue and bone sarcoma treatment. *Eur J Cancer*. 2004;40(11):1644-1654. doi:10.1016/j.ejca.2004.04.004.
3. Kawaguchi S, Wada T, Tsukahara T, et al. A quest for therapeutic antigens in bone and soft tissue sarcoma. *J Transl Med*. 2005;3(1):31. doi:10.1186/1479-5876-3-31.
4. Fata F, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. *Cancer*. 1999;86(10):2034-2037. http://www.ncbi.nlm.nih.gov/pubmed/10570428 Accessed July 27, 2017.
5. Penel N, Italiano A, Ray-Coquard I, et al. Metastatic angiosarcomas: doxorubicin-based regimens, weekly paclitaxel and metastasectomy significantly improve the outcome. *Ann Oncol*. 2012;23(2):517-523. doi:10.1093/annonc/mdr138.
6. Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: A retrospective study of the EORTC soft tissue and bone sarcoma group. *Eur J Cancer*. 2008;44(16):2433-2436. doi:10.1016/j.ejca.2008.07.037.
7. Italiano A, Cioffi A, Penel N, et al. Comparison of doxorubicin and weekly paclitaxel activity in metastatic angiosarcomas. *Cancer*. 2012;118(13):3330-3336. doi:10.1002/cncr.26599.
8. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for Patients with Advanced Angiosarcoma: A Phase II Trial from the French Sarcoma Group (GSF/GETO). *Oncologist*. 2012;17(2):260-266. doi:10.1634/theoncologist.2011-0237.
9. Tawbi, Hussein A., et al. "Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial." *The Lancet Oncology* 18.11 (2017): 1493-1501.
10. D'Angelo, Sandra P., et al. "Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials." *The Lancet Oncology* 19.3 (2018): 416-426.
11. Somaiah, Neeta, et al. "A phase II multi-arm study of durvalumab and tremelimumab for advanced or metastatic sarcomas." (2020): 11509-11509.
12. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008,8:467-477.
13. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. Journal of Clinical Investigation 2015,125:3384-3391.
14. Woolson, Robert F., and William R. Clarke. *Statistical methods for the analysis of biomedical data*. Vol. 371. John Wiley & Sons, 2011.

15. Kaplan, Edward L., and Paul Meier. "Nonparametric estimation from incomplete observations." *Journal of the American statistical association* 53.282 (1958): 457-481.
16. Mantel, Nathan. "Evaluation of survival data and two new rank order statistics arising in its consideration." *Cancer Chemother. Rep.* 50 (1966): 163-170.
17. Cox, David R. "Regression models and life‐tables." *Journal of the Royal Statistical Society: Series B (Methodological)* 34.2 (1972): 187-202.
18. Jiang, Jiming. *Linear and generalized linear mixed models and their applications*. Springer Science & Business Media, 2007.

14 Appendix

Appendix 1: Signature Page for Investigator

Protocol Title: A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Angiosarcoma

Protocol Number: CIBI308A301

This protocol is a trade secret owned by Innovent Biologics (Suzhou) Co., Ltd.. I have read and fully understood this protocol, and agree to conduct this study in accordance with the requirements found in this protocol and the Good Clinical Practice, and in compliance with relevant laws and regulations and the Declaration of Helsinki. Also, I promise not to reveal any confidential information to a third-party without the written consent from Innovent Biologics (Suzhou) Co., Ltd..

Instructions for investigators: please sign and date this page, print the name of the investigator, position, and study site, and return the signed form to Innovent Biologics (Suzhou) Co., Ltd..

I have read the entire content of this study protocol and will perform the study as required:

Signature of Investigator: _____ Date: _____

Name (Print): _____

Title of Investigator: _____

Study Site/Address: _____

_____

_____

Appendix 2: ECOG PS

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Death

References

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

Appendix 3: Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

The following is an excerpt from the RECIST v1.1.

1. Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm by conventional instruments in clinical exam (lesions which cannot be accurately measured by calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodule: pathologically enlarged and measurable, single lymph nodule must be ≥ 15mm in short axis by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and during follow-up, only the short axis will be measured and followed.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodule with ≥ 10 mm to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses that cannot be diagnosed and followed by reproducible imaging techniques, and cystic lesions.

1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate 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 noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by methods of measurements

1.2.1. Measurements of lesions

All measurements should be recorded in metric notation when clinically assessed. All baseline measurements of tumor lesions should be performed as close as possible to the treatment start and must be within 28 days (4 weeks) before the beginning of the treatment.

1.2.2 Method of assessment

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 being followed cannot be imaged but is assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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. 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. 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 (e.g. for body scans).

Ultrasound: Ultrasound should not be used as a method of measurement to assess lesion size. Ultrasound examinations cannot be reproduced for 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 CR 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 (e.g. 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 SD) and PD.

2. Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether subjects having non-measurable disease only are also eligible.

2.2 Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured

reproducibly should be selected.

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 two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. Nodes with short axis ≥ 10 mm but < 15 mm should not be considered 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 for baseline level of disease.

All other lesions including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. These lesions should be followed as "present", "absent", or in rare cases "unequivocal progression". Multiple target lesions involving the same target organ may be recorded as a single item (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

2.3 Response Criteria

2.3.1 Evaluation of target lesions

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.

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, 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).

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.

2.3.2 Special notes on the assessment of target lesions

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 Electronic CRFs or other data collection methods may therefore be designed to have target nodal lesions 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 (e.g. 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 case report form. 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 should be the maximal longest diameter for the coalesced lesion.

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

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

PD: Unequivocal progression of existing non-target lesions. Note: the appearance of one or more new lesions is also considered progression.

2.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows: When the subject 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 subject only has non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease

assessment. 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 subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from "localized" to "widespread", or may be described in protocols as "sufficient to require a change in therapy". 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 increase must be substantial.

2.3.5 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. For example, progression should not be 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 subject’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the subject who has visceral disease at baseline and while on study 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 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.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study 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, it depends on the nature of the study, protocol requirements, and results. 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".

2.4.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 9** provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, **Table 10** is to be used.

2.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

The best overall response is determined once all the data for the subject 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.

Best response determination in trials where confirmation of CR or PR is required: CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in **Table 11**.

2.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that 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.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in **Table 9** to **Table 11**.

Conditions that define "early progression, early death and inevaluability" are study 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, a biopsy of the residual lesion is recommended 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 FDG-PET and biopsy may lead to false positive CR due to limitations of both approaches (resolution/sensitivity).

Table 9 Time point response: subjects with target (with or without non-target) disease.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-Cr/Non-PD	No	PR
CR	Not evaluated	No	PR

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response	PR = partial response	SD = stable disease	PD = progressive disease NE = inevaluable

Table 10 Time point response: subjects with non-target disease only.

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: "Non-CR/non-PD" is preferred over "stable disease" for non-target disease. Since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign Non-CR/non-PD when no lesions can be measured is not advised.

For equivocal findings of progression (e.g. 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.

Table 11 Best overall response when confirmation of CR and PR required.

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

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable. a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD is met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of Phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If "time to an event" (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory Measurement/Duration of Response

2.6.1 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, i.e. in randomized trials (Phase 2 or 3) or studies 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 studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a

minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 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 PD is objectively documented (taking as reference for PD 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.

2.6.3 Duration of SD

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 SD 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

2.7 PFS/TTP

2.7.1. Phase 2 trials

This guideline is focused primarily on the use of objective response endpoints for Phase 2 trials. In some circumstances, "response rate" may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases PFS/PPF at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as subject selection and not the impact of the intervention. Thus, Phase 2 screening trials utilizing these

endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

Appendix 4: EQ 5D-5L Paper Interviewer Administration V1.0



Health Questionnaire

English version for the USA

VERSION FOR INTERVIEWER ADMINISTRATION

Note to interviewer: although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on page 2 of the questionnaire, the precise wording must be followed.

If the respondent has difficulty regarding which response to choose, or asks for clarification, the interviewer should repeat the question word for word and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

INTRODUCTION

(Note to interviewer: please read the following to the respondent.)

We are trying to find out what you think about your health. I will explain what to do as I go along, but please interrupt me if you do not understand something or if things are not clear to you. There are no right or wrong answers. We are interested only in your personal view.

First, I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer best describes your health TODAY.

Do not choose more than one answer in each group of questions.

(Note to interviewer: first read all five options for each question. Then ask the respondent to choose which one applies to him/herself. Repeat the question and options if necessary. Mark the appropriate box under each heading. You may need to remind the respondent regularly that the timeframe is TODAY.)

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EQ-5D DESCRIPTIVE SYSTEM

MOBILITY

First, I would like to ask you about mobility. Would you say that:

1. You have no problems walking? ❑
2. You have slight problems walking? ❑
3. You have moderate problems walking? ❑
4. You have severe problems walking? ❑
5. You are unable to walk? ❑

SELF-CARE

Next, I would like to ask you about self-care. Would you say that:

1. You have no problems washing or dressing yourself? ❑
2. You have slight problems washing or dressing yourself? ❑
3. You have moderate problems washing or dressing yourself? ❑
4. You have severe problems washing or dressing yourself? ❑
5. You are unable to wash or dress yourself? ❑

USUAL ACTIVITIES

Next, I would like to ask you about usual activities, such as work, study, housework, family or leisure activities. Would you say that:

1. You have no problems doing your usual activities? ❑
2. You have slight problems doing your usual activities? ❑
3. You have moderate problems doing your usual activities? ❑
4. You have severe problems doing your usual activities? ❑
5. You are unable to do your usual activities? ❑

PAIN / DISCOMFORT

Next, I would like to ask you about pain or discomfort. Would you say that:

1. You have no pain or discomfort? ❑
2. You have slight pain or discomfort? ❑
3. You have moderate pain or discomfort? ❑
4. You have severe pain or discomfort? ❑
5. You have extreme pain or discomfort? ❑

ANXIETY / DEPRESSION

Finally, I would like to ask you about anxiety or depression. Would you say that:

1. You are not anxious or depressed? ❑
2. You are slightly anxious or depressed? ❑
3. You are moderately anxious or depressed? ❑
4. You are severely anxious or depressed? ❑
5. You are extremely anxious or depressed? ❑

2

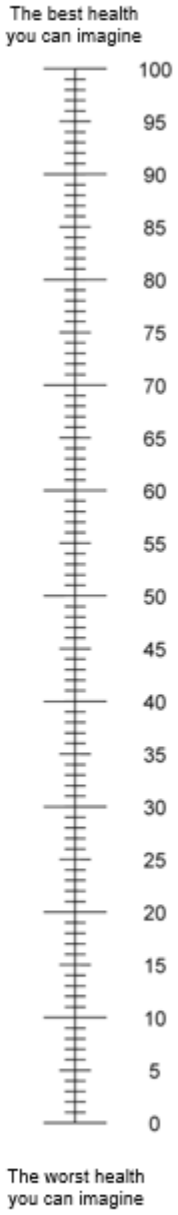
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EQ-5D VAS

- **Now, I would like to ask you to say how good or bad your health is TODAY.**
- **I would like you to try to picture in your mind a scale that looks like a thermometer.**
  (Note to interviewer: if interviewing face-to-face, please show the person the VAS scale.)
- **The best health you can imagine is marked 100 (one hundred) at the top of the scale and the worst health you can imagine is marked 0 (zero) at the bottom.**
- **I would now like you to tell me the point on this scale where you would put your health TODAY.**
  (Note to interviewer: mark the scale at the point indicating the respondent's 'health today'. Now, please write the number you marked on the scale in the box below.)

THE RESPONDENT'S HEALTH TODAY =

Thank you for taking the time to answer these questions.



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Appendix 5: EQ 5D-5L Self-Complete V1.1



Health Questionnaire

English version for the USA

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

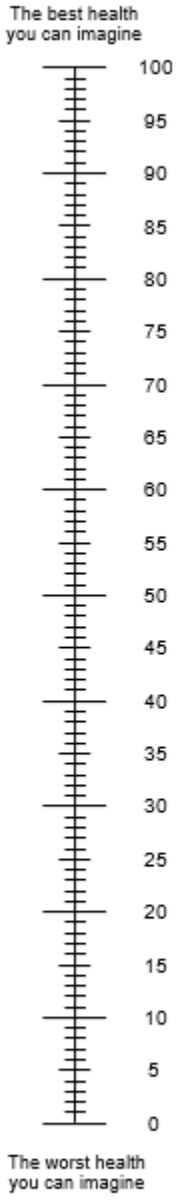
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

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

YOUR HEALTH TODAY = ☐



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Appendix 6: EORTC QLQ-C30

ENGLISH



EORTC QLQ-C30 (version 3)

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

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

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

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

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Appendix 7: PRO-CTCAE ™

NCI PRO-CTCAE ™ ITEMS

Item Library Version 1.0

English

Form Created on 28 October 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES attheir WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

3a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
4b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

6a. In the last 7 days, how OFTEN did you have LOOSE OR WATERYSTOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

7a. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7b. In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8a. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8b. In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9a. In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
9b. In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
9c. In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, did you have any RASH?	
O Yes	O No

11a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
11b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

12a. In the last 7 days, how OFTEN did you have PAIN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
12b. In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
12c. In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

13a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
13b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
13c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

14a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
14b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE withyour usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

15a. In the last 7 days, how OFTEN did you feel ANXIETY?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
15b. In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
15c. In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
O Yes	O No

Please list any other symptoms:	
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use.