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Investigational Drug: Sintilimab

MD Anderson Cancer Center & Innovent Biologics

Protocol # 2020-0902

MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2020-0902
Protocol Title	A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Advanced Rare Cancers (SiARa Cancer Study) – Cancer of Unknown Primary (SiARa-CUP)
Protocol Version	02
Version Date	March 23, 2021
Protocol PI	Kanwal Raghav, MD
Department	Gastrointestinal Medical Oncology
IND Sponsor	The UT MD Anderson Cancer Center (MD Anderson)
IND #	155013

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Clinical Protocol

Study Title:	A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Advanced Rare Cancers (SiARa Cancer Study) – Cancer of Unknown Primary (SiARa-CUP)
Protocol Number:	2020-0902
Product Name:	Sintilimab (Recombinant Fully Human Anti-PD-1 Monoclonal Antibody Injection, R&D Code: IBI308)
Study Phase:	2
Sponsor(s):	UT MD Anderson Cancer Center and Innovent Inc.
Medical Monitor:	UT M.D. Anderson IND Office
Principal Investigator:	<p>Kanwal Raghav, MD</p> <p>1515 Holcombe Blvd, Unit 426, Houston, TX 77030</p> <p>Telephone: 713-792-2828; Fax: 713-745-1163</p> <hr/> <p>E-mail: kpraghav@mdanderson.org</p>

Protocol Synopsis

Protocol Number	2020-0902
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 Advanced Rare Cancers (SiARa Cancer Study) – Cancer of Unknown Primary (SiARa-CUP)
Study Phase	2
Study Objectives	<p>Primary Objectives:</p> <ul style="list-style-type: none"> To evaluate the safety and efficacy of sintilimab in subjects with CUP <p>Secondary Objectives:</p> <ul style="list-style-type: none"> To evaluate the overall objective response rate (ORR) (investigator assessed), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and Quality of Life (QOL) on sintilimab in subjects with CUP <p>Exploratory Objectives:</p> <ul style="list-style-type: none"> To evaluate the correlation between biomarkers in tumor tissue and efficacy, including but not restricted to PD-L1 expression level, transcriptome sequencing, single-cell sequencing, and multicolor immunohistochemistry (IHC) analyses; To evaluate the correlation between biomarkers in peripheral blood and drug efficacy, including but not restricted to soluble PD-L1, circulating tumor DNA (ctDNA), and cytokine analyses.
Study Design	This is a Phase 2 clinical trial evaluating the efficacy and safety of sintilimab in subjects with CUP.

	<p>Up to 45 subjects with CUP will be enrolled. Subjects will be treated with sintilimab at 200 mg via intravenous (IV) administration on Cycle 1 Day 1. 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).</p> <p>During the trial, tumor imaging evaluation will be initially performed once every 9 weeks (\pm 7 days) and will be based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. After the completion or discontinuation of the study treatment, safety follow-up and survival follow-up will be performed.</p> <p>Considering the rareness of the disease, the patient accrual rate is expected to be approximately 2 patients per month. The total study duration is expected to be between 24-27 months with 6-month follow up.</p>
Inclusion Criteria	<ol style="list-style-type: none"> 1. Has histopathologically confirmed unresectable, locally advanced, recurrent or metastatic CUP. Patients must have undergone standard work-up to attempt to identify the primary tumor prior to enrollment. 2. Is refractory or intolerant to at least one line of systemic chemotherapy. Patient ineligible for cytotoxic chemotherapy due to contraindications will be eligible. 3. Is age \geq 18 years. 4. Has an ECOG PS of 0 - 2. 5. Must be unsuitable for definitive treatment, such as definitive chemoradiotherapy and/or surgery. For subjects who have received (neo)adjuvant or definitive chemotherapy/chemoradiotherapy, time from the completion of last treatment to disease recurrence must be $>$ 3 months. 6. Is able to provide archival or fresh tissues for correlative analysis with obtainable results. 7. Has at least one measurable lesion as per RECIST v1.1.

	<p>8. Has adequate organ and bone marrow functions, as defined below:</p> <p>1) Complete blood count: absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/\text{L}$, platelet (PLT) count $\geq 75 \times 10^9/\text{L}$, hemoglobin (HGB) $\geq 9.0 \text{ g/dL}$. Note: Subjects cannot receive blood transfusion, erythropoietin (EPO), or Granulocyte-colony stimulating factor (GSF) within 7 days prior to the blood collection.</p> <p>2) Hepatic function: total bilirubin (TBIL) $\leq 1.5 \times$ upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN in subjects without hepatic metastasis; TBIL $\leq 1.5 \times$ ULN, ALT and AST $\leq 5 \times$ ULN in subjects with hepatic metastasis.</p> <p>Exception: Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN.</p> <p>3) Renal function: urine protein $< 2+$ from random sample or $< 1 \text{ g}$ from 24-hour urine collection, and creatinine clearance rate (CrCl) $\geq 30 \text{ mL/min}$ by Cockcroft-Gault formula:</p> <p>Female: $CrCl = \frac{(140 - \text{age}) \times \text{weight}(\text{kg}) \times 0.85}{72 \times \text{serum creatinine}(\text{mg/dL})}$</p> <p>Male: $CrCl = \frac{(140 - \text{age}) \times \text{weight}(\text{kg}) \times 1.00}{72 \times \text{serum creatinine}(\text{mg/dL})}$</p> <p>4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) $\leq 1.5 \times$ ULN; if the subject is receiving anticoagulant therapy, the results of coagulation tests need to be within the acceptable range for anticoagulants.</p> <p>9. Is expected to survive ≥ 12 weeks.</p> <p>10. 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).</p> <p>11. Is able to sign the informed consent form (ICF) and is able to comply with the scheduled follow-up visits and related procedures required in the protocol.</p>
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Exclusion Criteria	<ol style="list-style-type: none"> 1. Has 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. Is enrolled in another interventional clinical study. Current enrollment in an observational study (non-interventional) or in the follow-up phase of an interventional study is allowed. 3. Has received palliative therapy for a local lesion within 2 weeks prior to the first dose. 4. Has received systemic treatment with Chinese traditional medicines with anti-cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study treatment. 5. Has received systemic immunosuppressants within 2 weeks. Allowed are 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. Has received a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or is 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. Has undergone 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. Has 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.
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	<p>9. Has 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.</p> <p>10. Has bone metastases and is at risk for paraplegia.</p> <p>11. Has known active autoimmune disease requiring treatment or a previous autoimmune 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).</p> <p>12. Has a known history of primary immunodeficiency diseases.</p> <p>13. Has a known active pulmonary tuberculosis.</p> <p>14. Has a known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.</p> <p>15. Is human immunodeficiency virus (HIV)-infected (has positive anti-HIV antibody).</p> <p>16. Has an active or poorly controlled serious infections.</p> <p>17. Has symptomatic congestive heart failure (NYHA Class II–IV) or symptomatic or poorly controlled arrhythmia.</p> <p>18. Has uncontrolled hypertension (systolic blood pressure \geq 160 mmHg or diastolic blood pressure \geq 100 mmHg) despite standard treatment.</p> <p>19. Had any arterial thromboembolic event within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack.</p>
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	<p>20. Has significant malnutrition, such as those requiring continuous parenteral nutrition ≥ 7 days. Allowed are those who received intravenous treatment for malnutrition that ended more than 4 weeks before the first dose of study treatment.</p> <p>21. Has a history of clinically significant deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (having an implantable port or catheter-related thrombosis or incidental pulmonary embolism detected on scan without symptoms or superficial venous thrombosis is not considered to be a "serious" thromboembolisms).</p> <p>22. Has 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.</p> <p>23. Has severe pulmonary dysfunction.</p> <p>24. Has hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C.</p> <p>25. Has bowel obstruction or history of any 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.</p> <p>26. Has known acute or chronic active hepatitis B (positive HBsAg and hepatitis B (HBV) DNA viral load $\geq 10^3$ copies/mL or > 200 IU/mL), or acute or chronic active hepatitis C (positive hepatitis C [HCV] antibody and detectable HCV RNA).</p> <p>27. Has history of gastrointestinal (GI) perforation and/or fistula within 6 months prior to study enrollment (having a gastrostomy or enterostomy is allowed).</p> <p>28. Has interstitial lung disease requiring corticosteroids.</p> <p>29. Has history of other primary malignant tumors, excluding:</p>
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	<ul style="list-style-type: none"> • 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. <p>30. Is pregnant or breastfeeding.</p> <p>31. Has an acute or chronic diseases, psychiatric disorders, or laboratory abnormality that may lead to the following consequences: increased investigational drug-related risks, or interference with interpretation of trial results, or is otherwise considered ineligible for participating in the trial by the investigators.</p>
Study Drugs, Strengths, and Administrations	<p>Sintilimab</p> <p>200 mg IV on day 1 and then every 3 weeks</p>
Evaluation Criteria	<p>Efficacy evaluation:</p> <ul style="list-style-type: none"> • Primary endpoint: Confirmed ORR assessed by independent radiology review per RECIST v.1.1 • Secondary endpoints: ORR (investigator assessed), DCR, DOR, PFS, OS, QOL <p>Safety evaluation:</p> <ul style="list-style-type: none"> • The incidence and severity of treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), serious adverse events (SAEs), adverse events (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. <p>Biomarker evaluation:</p>

	<ul style="list-style-type: none"> Correlation between biomarkers in the tumor tissue and efficacy, including PD-L1 expression level, transcriptome sequencing, single-cell sequencing, and IHC analyses; Correlation between biomarkers in peripheral blood and efficacy, including the soluble form of PD-L1, ctDNA, and cytokines analyses.
Statistical Analysis Method	<p>Primary efficacy endpoint:</p> <p>The primary efficacy endpoint will be confirmed ORR (confirmed complete response (CR) or partial response (PR) determined by RECIST 1.1). A Simon's two-stage Minimax design will be used. The null hypothesis involves an ORR of 10% that will be tested against an ORR of 25%. In the first stage, 22 patients will be treated. If there are ≤ 2 patients who achieve objective response the study will be terminated. If the study moves forward to second stage, an additional 18 patients will be treated in stage 2 leading to a total of 40 patients. Eight or more responders out of the 40 treated patients will be considered clinically relevant. The power of this design is 80% under the 1-sided type I error rate of 5%. Assuming a 10% dropout rate, we will need to enroll up to a total of 45 patients. The ORR and DCR and the corresponding 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.</p> <p>Safety data:</p> <p>The incidence and severity of AEs will be summarized, and laboratory abnormalities will be presented.</p> <p>Biomarkers:</p> <p>PD-L1 expression levels and distribution, and other potential biomarkers will be analyzed, and the potential correlation between these biomarkers and efficacy will be explored.</p> <p>Pharmacokinetics (PK) data:</p> <p>The PK analysis will include but is not limited to descriptive statistical analysis of trough concentrations of sintilimab.</p>

Table 1 Schedule of visits

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				
Visits	1	2	3	4	5	6	7	8	9–N	Within ±7 days after end of treatment	30 th day (± 7 days) after the last dose ¹⁸	90 th day (±7 days) after the last dose ¹⁹	Every 60 days (± 7 days)
Day	-28 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)				
General Study Procedures													
Signed ICF ¹	×												
Inclusion/Exclusion Criteria	×												
Demographics/Medical History/Previous Medication ²	×												
Vital Signs ³	×	×		×	×	×	×	×	×	×			
Weight/Height ⁴	×	×		×	×	×	×	×	×	×	×		
Physical Examination ⁴	×	×		×	×	×	×	×	×	×			
ECOG PS ⁴	×	×		×	×	×	×	×	×	×	×	×	
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	×												
PK/ADA													
PK	×	×		×	×	×	×	×	×	×	×		
ADA	×	×		×	×	×	×	×	×	×	×		
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														
Archival/Fresh Tumor Tissue Sample ¹⁵	×			×						×				
Blood ¹⁶		×	×	×	×	×	×	×	×	×				
PK 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 diagnosed within the past 10 years that are clinically significant as determined by the investigator, including history of cigarette use, alcohol use, surgery, and drug allergy. Detailed disease information regarding cancer of unknown primary should be documented separately and not listed as a part of the disease history. 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. Weight, physical examination and PS need not be repeated if done previously within 7 days of C1D1. Comprehensive physical examination is needed at all day 1 visit for each cycle. Targeted physical examination can be performed for visit scheduled outside the protocol as clinically indicated.
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, platelet (PLT) count, WBC differentials [lymphocyte (LYM) count and absolute neutrophil count (ANC)]. Blood biochemistry: hepatic function [total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (γ -GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactate dehydrogenase (LDH)], renal function [urea (UREA) and creatinine (Cr)], electrolytes (Na, K, Cl, Mg, Ca, and P), amylase, 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: prothrombin time (PT) and international normalized ration (INR). The test will be conducted within 7 days prior to the first dose and during the safety follow-up. 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 including at end-of-treatment. 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, HBcAg, 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 treatment 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. Adverse events (AEs) 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 (CT chest/abdomen and pelvis w contrast unless contraindicated; MRI abdomen and pelvis w contrast can be used if CT contrast cannot be used; PET can be used as long as CT portion is done with contrast) will be performed based on RECIST v1.1 and the same imaging method 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 every 9 weeks (\pm 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 should be performed within 28 days prior to the first dose. If the bone metastasis is confirmed at baseline, PET scan with contrast is recommended every 9 weeks or as clinical 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. A baseline evaluation with MRI of the brain should be done for all patients to rule out brain metastases.

13. Sintilimab: 200 mg, IV is given on cycle 1 day 1 and then every 3 weeks 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.
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. Subjects are required to provide at least 10 slides of archived or fresh tumor tissue samples during screening for biomarkers. If not available, a fresh biopsy will be performed. A mandatory biopsy (if clinically feasible) within 7 days prior to C2D1 and an optional biopsy at progression will be performed with patient consent.
16. Whole blood samples are required to be provided by subjects for biomarker testing at the following time points: prior to the first dose, C1D8, 1st day of every cycle, at each efficacy evaluation, and when PD is confirmed.
17. The end-of-treatment visit should be conducted within ± 7 days after the end of treatment is confirmed.
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 end of study [section 6.2.6]). Telephone visits are allowed.
21. PK sample (10 ml) 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
CK	Creatine Kinase
CNB	Core needle biopsy
CR	Complete response
CRA	Clinical Research Associate
CrCl	Endogenous creatinine clearance rate
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating cell-free tumor DNA

Abbreviations	Full Name
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
CUP	Cancer of unknown primary
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
EPO	Erythropoietin
FAS	Full analysis set
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
FT3	Free triiodothyronine

Abbreviations	Full Name
FT4	Free thyroxine
GSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
γ -GT	γ -glutamyltransferase
H&E	Hematoxylin and eosin
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
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council on Harmonisation
ICPi	Immune Checkpoint inhibitor
IF	Immunofluorescence
iDMC	Independent Data Monitoring Committee

Proprietary Information of MD Anderson

Investigational Drug: Sintilimab

MD Anderson Cancer Center & Innovent Biologics

Protocol # 2020-0902

Abbreviations	Full Name
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational New Drugs
INR	International normalized ratio
IO	Immuno-oncology
irAE	Immunity-related adverse event
IRB	Institutional review board
ITT	Intention to treat
IV	Intravenous
LPLV	Last patient last visit
IRR	Independent radiology review
LCSS	The Lung Cancer Symptom Scale
MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high
NCI	National Cancer Institute
NE	Not evaluable
NAb	Neutralizing antibody
NGS	Next-generation sequencing
NSAIDS	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NYHA	New York Heart Association

Proprietary Information of MD Anderson

Investigational Drug: Sintilimab

MD Anderson Cancer Center & Innovent Biologics

Protocol # 2020-0902

Abbreviations	Full Name
ORR	Overall 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
PET	Positron emission tomography
PEX	Physical Examination
PFS	Progression free survival
PI	Principal investigator
PK	Pharmacokinetics
PLT	Platelet count
PPS	Per-protocol set
PMBC	Peripheral mononuclear blood cells
PR	Partial response
PS	Performance center
PT	Prothrombin time
QOL	Quality of life
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event

Abbreviations	Full Name
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
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
VEGF	Vascular endothelial growth factor
WBC	White blood cell count
WES	Whole exome sequencing
WGS	Whole genome sequencing

1 Background

1.1 Disease Background

1.1.1 Scope of Problem

CUP is a rare malignancy which accounts for 3-5% of all cancers and is characterized by a heterogeneous group of cancers for which the anatomical site of origin remains occult after detailed investigations.¹ CUP has been traditionally treated in first-line with empiric/putative site-specified combination chemotherapies with limited response rates of 25-35% and survival ranging from 6 to 16 months.¹ Beyond, frontline therapy, no standard of care or FDA approved agents exist. Therefore, there is an unmet and critical need to develop novel agents for this orphan disease.

1.1.2 Rationale for use of Immunotherapy in CUP

Using a multiplex testing approach, 28% of CUP carry one or more predictive biomarkers (MSI-H, PD-L1 and/or TML-H) to the immune checkpoint blockade, providing a novel option for treatment in patients with CUP.² Our preliminary data has also shown, that using a 92-gene assay, as an objective platform, we can identify a subset of CUP patients (33%) who have the potential of responding to ICIs by identifying their gene-expression signature to known primaries where ICIs have established efficacy and FDA approved indication.^{Raghav and Varadhachary (unpublished)} Two studies, with Nivolumab and Pembrolizumab in CUP have shown preliminary activity with RR of 21% and 23%, respectively.^{3,4} However, no immunotherapy drug is approved for use in CUP patients.

Based on this information, we propose a study to explore activity of Sintilimab in CUP.

Study Hypothesis: Sintilimab, fully humanized anti-PD1 antibody, can result in durable tumor responses in both advanced refractory CUP.

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.⁵ 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.⁶

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 ($95.8 \pm 2.3\%$) and maintained the receptor occupancy with decreasing concentrations throughout the study. The minimum concentration at steady state was 13 $\mu\text{g/mL}$ 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 every 3 weeks 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 ($\geq 10\%$) TRAE including fever (15.0%), hypothyroidism (14.1%), and increased AST (13.6%). A total of 18.7% (111/595) of subjects had TRAE \geq grade 3, among which the most common (incidence $\geq 1\%$) 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 ($\geq 10\%$) 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 pneumonitis (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 the 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 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 esophageal cancer, supporting the conduct of clinical trials in subjects with advanced cancers.

2 Study Objectives

2.1 Primary Objectives

- To evaluate the safety and efficacy of sintilimab in subjects with CUP

2.2 Secondary Objectives

- To evaluate the ORR (investigator assessed) and DOR, PFS, OS, DCR, DOR, and QOL of sintilimab in subjects with CUP who receive Sintilimab.

2.3 Exploratory Objectives:

- To evaluate the correlation between biomarkers in tumor tissue and efficacy, including but not restricted to PD-L1 expression level, 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), 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 CUP. Subjects with unresectable, locally advanced, recurrent or metastatic CUP will be enrolled. Up to of 45 subjects will be enrolled. Subjects will be treated with sintilimab at 200 mg IV on Day 1 every 3 weeks. 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

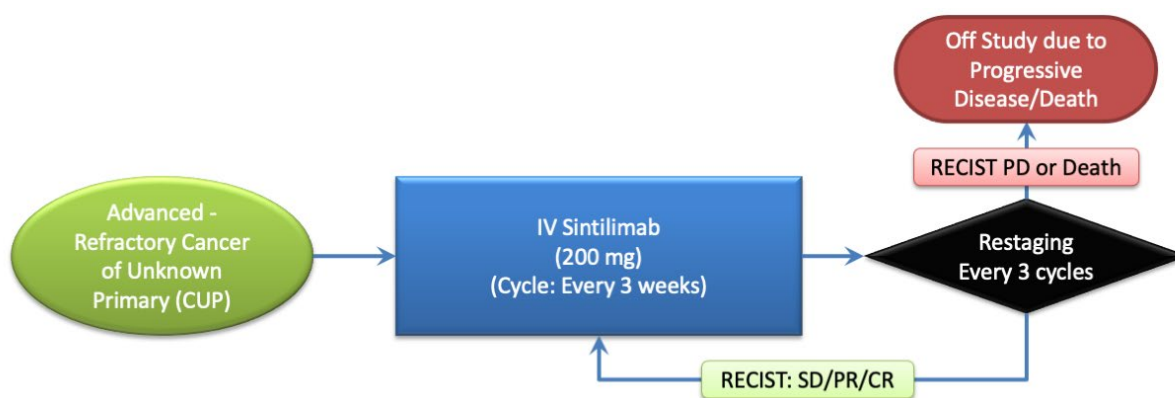
treatment discontinuation (whichever occurs first). Treatment will be infused for a maximum period of up to 24 months (starting from the first dose). During the trial, tumor imaging evaluation will be initially performed once every 9 weeks (± 7 days) and will be based on RECIST 1.1 per independent radiology review, 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 ORR assessed by IRR per RECIST v.1.1. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. All patients will be followed for survival unless consent is withdrawn.

Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy (especially during the flare time-window of the first 12 weeks of treatment to account for expected delayed response). In such cases confirmation of progression is recommended at a minimum of 4 weeks after the first immune-related PD assessment. Such subjects must discontinue therapy when further progression is documented.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. The NCI CTCAE v5.0 will be used to characterize the toxicity profile of the study treatments for all patients.

After discontinuation of study treatment, patients may receive any subsequent line therapy as directed by their treating physician.

Figure 1 Schematic of SiARa-CUP study design and administration



3.2 End of Study and Length of Study

The final analysis will occur after full enrollment, which is expected approximately 24-27 months after the first patient is enrolled. The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., ORR) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 30-33 months after the first patient is enrolled. In addition, the PI may decide to terminate the study at any time.

3.3 Rationale for Study Design

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

3.3.1 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti-PD-1 and anti-PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of sintilimab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, prior to start of treatment and then after 3 weeks of therapy and an optional biopsy at the time of first evidence of radiographic disease progression. Tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of sintilimab may be analyzed.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as cytokines associated with T cell activation, circulating tumor DNA (ctDNA) concentration, and lymphocyte subpopulations may provide evidence of biologic activity of sintilimab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from sintilimab.

Tumor tissue and blood samples collected at baseline and, if deemed clinically feasible, tumor tissue collected at 3 weeks of therapy and at the time of progression will enable NGS and RNA profiling to identify germline and/or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing (WGS) provides a comprehensive characterization of the genome and, along

with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches.

3.3.2 Rationale for Allowing Patients to Continue Treatment until Loss of Clinical Benefit

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents as increase in tumor size does not consistently reflect therapeutic failure (Wolchok et al. 2009). The phenomena of pseudo-progression or infiltration of the tumor by immune cells may mimic tumor progression. Therefore, as this study is evaluating an immunotherapy, we will allow patients to continue to receive study treatment after documented RECIST v1.1–defined radiographic disease progression, provided the benefit-risk ratio for the patient remains favorable as assessed by the physician and study monitor. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving sintilimab will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data.
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease.
- Absence of decline in ECOG Performance Status that can be attributed to disease progression.
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.

3.4 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.

3.5 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 (PI) 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 of efficacy at the time of the interim analysis;
- The subjects are unable to meet protocol requirements for compliance;
- The data are 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. Has histopathologically confirmed unresectable, locally advanced, recurrent or metastatic CUP. Patients must have undergone standard work-up to attempt to identify the primary tumor prior to enrollment.
2. Is refractory or intolerant to at least one line of systemic chemotherapy. Patient ineligible for cytotoxic chemotherapy due to contraindications will be eligible.
3. Is aged ≥ 18 years.
4. Has an ECOG PS of 0 - 2.
5. Must be unsuitable for definitive treatment, such as definitive chemoradiotherapy and/or surgery. For subjects who have received (neo)adjuvant or definitive chemotherapy/radiochemotherapy, time from the completion of last treatment to disease recurrence must be > 3 months.
6. Is able to provide archival or fresh tissues for correlative analysis with obtainable results.
7. Has at least one measurable lesion as per RECIST v1.1.
8. Has an adequate organs and bone marrow functions, as defined below:
 - 1) Complete blood count: absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$, platelet (PLT) count $\geq 75 \times 10^9/L$, hemoglobin (HGB) ≥ 9.0 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) $\leq 1.5 \times$ upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN in subjects without hepatic metastasis; TBIL $\leq 1.5 \times$ ULN, ALT and AST $\leq 5 \times$ ULN in subjects with hepatic metastasis. Exception: Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN.
- 3) Renal function: urine protein $< 2+$ from random sample or < 1 g from 24-hour urine collection, and creatinine clearance rate (CrCl) ≥ 30 mL/min by Cockcroft-Gault formula:

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

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

- 4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) $\leq 1.5 \times$ ULN; if the subject is receiving anticoagulant therapy, the results of coagulation tests need to be within the acceptable range for anticoagulants.
9. Is expected to survive ≥ 12 weeks.
10. 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).
11. Is able to sign the ICF and be able to comply with the scheduled follow-up visits and related procedures required in the protocol.

4.2 Exclusion Criteria

1. Has 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. Is 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. Has received palliative therapy for local lesion within 2 weeks prior to the first dose.
4. Has received systemic treatment with Chinese traditional medicines with anti-cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study treatment.

5. Has received systemic immunosuppressants within 2 weeks prior to treatment, 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. Has 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. Has undergone 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. Has 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. Has 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. Has bone metastases and is at risk for paraplegia.

11. Has known active autoimmune disease requiring treatment or a previous autoimmune 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. Has a known history of primary immunodeficiency diseases.

13. Has known active pulmonary tuberculosis.

14. Has a known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.

15. Is HIV-infected subjects (has positive anti-HIV antibody).

16. Has an active or poorly controlled serious infections.

17. Has symptomatic congestive heart failure (NYHA Class II–IV) or symptomatic or poorly controlled arrhythmia.
18. Has uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite of standard treatment.
19. Has any arterial thromboembolic event within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack.
20. Has 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. Has a 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. Has 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. Has severe pulmonary dysfunction.
24. Has hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C.
25. Has 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.
26. Has known acute or chronic active hepatitis B (positive HBsAg and HBV DNA viral load $\geq 10^3$ copies/mL or > 200 IU/mL), or acute or chronic active hepatitis C (positive HCV antibody and positive HCV RNA).
27. Has a history of gastrointestinal (GI) perforation and/or fistula within 6 months prior to the enrollment, excluding gastrostomy or enterostomy.
28. Has interstitial lung disease requiring corticosteroids.
29. Has a 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.

30. Is pregnant or breastfeeding.

31. Has an acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased investigational drug-related risks, or interference with interpretation of trial results, or is otherwise considered inappropriate 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 Method of Treatment Assignment

After written informed consent has been obtained and eligibility established, each patient will be assigned an identification number and enrolled on study and will receive study medications in this single-arm study. All participants will be registered in the Clinical Oncology Research System (COrE).

4.4 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 and whose luteinizing hormone and follicle stimulating hormone levels are within the postmenopausal range are considered menopausal;
- 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 luteinizing 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

4.5 Criteria for Discontinuation/Withdrawal

4.5.1 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.

4.5.2 Subject withdrawal

A subject has the right to withdraw from the study at any time for any reason. 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. However, the investigator should make every effort to persuade him / her to complete all the examinations specified for the end-of-treatment visit.

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.

4.5.3 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 study team is unable to contact the subject.

5 Study Drugs and Other Treatments

The study drug is sintilimab. The first dose of study treatment should start on Day 1 of Cycle 1. For the rest of the treatment cycles, the study treatment can be administered 3 day before or 3 days 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 ¹	200 mg	Every 3 week	IV infusion	on Day 1, every 21 days thereafter

The study drugs in [Table 3](#) is provided by the supporting company. The local labs are 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 supporting company'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°C 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 the supporting company.

The preparation and administration of sintilimab is as follows:

1. The dose and regimen of sintilimab is 200 mg IV every 3 weeks.
2. Calculate the volume of 0.9% (weight/volume) sodium chloride solution needed to dilute the sintilimab to a final concentration between 1.5 and 2 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°C) 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: 60 minutes for first infusion and if tolerated, 30 minutes thereafter). 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 hours. The prepared solution can be stored for 24 hours at 2-8°C protected from light, and can be stored up to 6 hours at 20 -25°C 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 weight loss
- All the dose adjustments should be documented, including the reasons and actions taken.
- If further concerns exist about resolution of toxicities, the investigator should discuss these concerns with the sponsor prior to drug administration.

5.2.2 Sintilimab dose adjustments

Dose adjustments for sintilimab are not permitted during the entire course of the study. Attached below is the reference table for sintilimab dose adjustments (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

Drug-Related Toxicities	Severity	Management
		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 Dermatoses	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.
	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)	/

Drug-Related Toxicities	Severity	Management
	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 high-strength 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, starting with 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 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

Drug-Related Toxicities	Severity	Management
		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
	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

Drug-Related Toxicities	Severity	Management
	Grade 3–4	Interrupt study treatment until clinically stable, consult an endocrinologist, and provide symptom management
Hyperthyroidism	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Interrupt study treatment until clinically stable, consult an endocrinologist, and provide symptom management
Primary Adrenocortical Insufficiency	Grade 1–2	<p>Continue and monitor closely.</p> <p>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) for mineralocorticoid replacement in primary adrenal insufficiency.</p> <p>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.</p> <p>Taper stress-dose corticosteroids down to maintenance doses over 5-10 days</p> <p>Maintenance therapy as in G1.</p>
	Grade 3–4	<p>Interrupt study treatment until clinically stable, consult an endocrinologist, and provide 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.</p> <p>Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge.</p> <p>Maintenance therapy as in G1</p>
Hypophysitis	Grade 1–2	Continue, monitor closely, and hormonal supplementation

Drug-Related Toxicities	Severity	Management
	Grade 3–4	Interrupt study treatment until clinically stable, consult an endocrinologist, and provide 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	Interrupt study treatment until clinically stable and consult an endocrinologist to determine whether to resume the treatment
5. Musculoskeletal Toxicities		
Inflammatory Arthritis	Grade 1	Continue
	Grade 2	<p>Interrupt until the symptoms are controlled and prednisone requirement is ≤ 10 mg/day.</p> <p>If inadequately controlled by NSAIDs, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks.</p> <p>If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3.</p> <p>If unable to lower corticosteroid dose to 10 mg/d after 3 months, consider DMARD</p> <p>Consider intra-articular corticosteroid injections for large joints</p>
	Grade 3–4	<p>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</p> <p>If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD</p> <p>Synthetic: methotrexate, leflunomide</p> <p>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</p>

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Drug-Related Toxicities	Severity	Management
		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;
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

Drug-Related Toxicities	Severity	Management
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. Initiate 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)
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

Drug-Related Toxicities	Severity	Management
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 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 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 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

Drug-Related Toxicities	Severity	Management
		If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology
Transverse Myelitis	Grade 1–4	<p>Permanently discontinue. Methylprednisolone 2 mg/kg</p> <p>Strongly consider higher doses of 1 g/d for 3-5 days</p> <p>Strongly consider IVIG</p>
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	<p>Permanently discontinue, IV prednisone corticosteroids 1-2 mg/kg/d</p> <p>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</p>
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
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	<p>Interrupt, treat with growth factors, horse ATG plus cyclosporine and monitor daily.</p> <p>If no response, repeat immunosuppression with rabbit ATG plus</p>

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Drug-Related Toxicities	Severity	Management
		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	<p>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.</p> <p>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</p> <p>IVIG used with corticosteroids when a more-rapid increase in platelet count is required</p> <p>If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary</p> <p>If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression</p>
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/m ² 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

Drug-Related Toxicities	Severity	Management
		improvement add cyclosporine or immunosuppression/immunosorption
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 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 referral. Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per

Drug-Related Toxicities	Severity	Management
		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
For more detailed management guidelines regarding immune-related adverse events, please refer to ASCO guidance document (https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/2018-management-of-irAEs-summary.pdf).		

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 may 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 in the following two cases:

- Sintilimab hold > 12 weeks due to glucocorticoid taper while treating immune-related adverse events (irAEs): Consult the sponsor's medical monitor 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 monitor 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 hours 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	<p>Stop the infusion and monitor symptoms.</p> <p>Other appropriate treatments include but are not limited to:</p> <ul style="list-style-type: none"> IV fluids Antihistamines NSAIDS Acetaminophen Consider bronchodilators Consider corticosteroids <p>Monitor the subject, including vital signs, closely until the subject is stable as determined by the investigator.</p> <p>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).</p> <p>If symptoms recur with resumption of the infusion, discontinue further treatment at that visit. Monitor the subject closely until the subject is stable.</p> <p>If symptoms resolve in > 1 h, discontinue the treatment at that visit.</p>	<p>Pre-medications should be given for subsequent infusions.</p> <p>The following pre-medications are recommended within 1.5 h (± 30 min) prior to sintilimab infusion:</p> <p>Diphenhydramine 50 mg PO (or equivalent antihistamines)</p> <p>Acetaminophen 500–1000 mg PO (or equivalent antipyretics)</p> <p>If grade 2 toxicities occur despite of adequate pre-medications, the study drugs should be permanently discontinued.</p>
Grade 3 or 4	Discontinue the infusion.	Not applicable.

NCI CTCAE Grades	Treatments	Premedications for Subsequent Infusions
<p>Grade 3</p> <p>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)</p> <p>Grade 4</p> <p>Life threatening; pressors or ventilatory support indicated</p>	<p>Other appropriate treatments include but are not limited to:</p> <p>Epinephrine**</p> <p>IV fluids</p> <p>Antihistamines</p> <p>NSAIDS</p> <p>Acetaminophen</p> <p>Oxygen</p> <p>Bronchodilators</p> <p>Pressors</p> <p>Corticosteroids</p> <p>Monitor the subject, including the vital signs, closely until the subject is stable as determined by the investigator.</p> <p>Hospitalization may be indicated.</p> <p>**Epinephrine should be used immediately for allergic reactions.</p>	<p>The study drugs should be permanently discontinued.</p>
<p>Appropriate first-aid equipment should be provided in the ward and physicians should be available at all times during the administration.</p> <p>For more information, refer to CTCAE v5.0 (http://ctep.cancer.gov).</p>		

5.2.4 Dose Modification Criteria for Hematological and Non-Hematological Toxicities that are Not Immune-related

Dose adjustments for sintilimab are not permitted during the entire course of the study. Dose delay is allowed for any non-immune related hematological and non-hematological toxicities as per the following principles.

- For grade 1-2 toxicity, treatment should continue with close follow-up of toxicities.
- For grade 3-4 toxicity, interrupt treatment until toxicity resolves to grade ≤ 2 . A thorough work-up should be initiated to ensure that the toxicity is not immune/sintilimab related. Once confirmed, treatment can be restarted once toxicity has resolved to grade ≤ 2 .

Sintilimab treatment may 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.

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 during the treatment. The investigators are encouraged to review every potential hepatotoxic drug via 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.
- If a grade 3 or higher neutropenia occurs, prophylactic treatment with a granulocyte colony-stimulating factor is permitted starting from the next cycle.

5.4.3 Drug-drug interactions

- Sintilimab: No interaction information is currently available.

5.5 Drug Management

Sintilimab should be refrigerated at 2–8°C in a dry place and away from light (also see section 5.1.1). Do not freeze. Cold-chain management 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 in a timely manner and follow the advice of the sponsor.

All the study drugs provided by the supporting company 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.

Used sintilimab should be stored under the same storage conditions before verification by the monitor.

5.5.1 Return and destruction

In this trial, the containers of used sintilimab should be returned.

Upon the completion or discontinuation of the study, all unused or expired study drugs must be returned to the supporting company for destruction. Arrangements for the return of study drugs

will be made by the research team in GI Medical Oncology.

5.6 Study Drug Records

The designee of the study sites 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. 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 monitor 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 (within 3 days prior to the first dose)
- Thyroid function (results obtained within 28 days prior to treatment are also accepted)
- 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 treatment are also accepted.
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation
- 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 within the past 10 years 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 in medical record and CRF.

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 in medical record and CRF.

6.2.2 Baseline (prior to Day 1 of Cycle 1)

- Recording the vital signs
- Weight (no need to repeat if done previously within 7 days prior to the first dose)
- ECOG PS (no need to repeat if done previously within 7 days prior to the first dose)
- AE evaluation
- Concomitant medications
- EQ 5D-5L
- EORTC QLQ-C30
- PRO-CTCAE
- Blood sampling for biomarkers and PK sampling (for C1D1 and C1D8)
- 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

- Thyroid function
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation (if applicable)
- Administration of study drugs (tumor imaging evaluation should be performed prior to administration)
- EQ 5D-5L (if applicable)
- EORTC QLQ-C30 (if applicable)
- PRO-CTCAE (if applicable)
- Blood sampling for biomarkers and PK sampling (for C2D1)
- Fresh tumor tissue (C2D1) (if clinically feasible)
- 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 visits

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
- Coagulation function
- Thyroid function
- Pregnancy test
- Tumor imaging evaluation (if applicable)

- AE evaluation
- Concomitant medications
- Survival status
- Optional biopsy (can be done within 21 days but prior to any subsequent treatment)
- Blood sampling for biomarkers (if applicable) and PK sampling
- EQ 5D-5L
- EORTC QLQ-C30
- PRO-CTCAE
- Subsequent anti-tumor therapy

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
- AE evaluation
- Concomitant medications (for the 30-day safety follow-up only)
- Document subsequent anti-tumor therapy
- Survival status
- 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)

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. However, immunogenicity sampling should be obtained.

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 (\pm 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 end of study.

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 4 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 neck (if applicable), 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. A baseline evaluation with MRI of the brain should be performed for all patients to rule out brain metastases.

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 of 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 every 9 weeks (± 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 discontinue treatment, treatment beyond disease progression is not allowed. 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 suspected PD was initially observed. Definition of clinical stability is as follows:

- Absence of clinically significant signs and symptoms suggesting PD (including absence of 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, PET scan is recommended at baseline and for follow-up.

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, attribution/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, including the respiratory tract, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal system and nervous system. 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 treatment 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. Blood pressure and pulse are measured in the supine/sitting position after resting for at least 5 min. 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 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, and document the results on the ECG. 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) and PK/ADA sampling

Refer to [Table 6](#) for laboratory tests including complete blood count, routine urinalysis, and blood biochemistry. Separately, serum samples from 1 mL of blood will be collected and stored for future PK/ADA analysis.

Table 4 Routine laboratory safety evaluation

Complete blood count	RBC, HGB, WBC, PLT, LYM, and ANC
Blood Biochemistry	TBIL, ALT, AST, γ -GT, ALP, ALB, TP, LDH, UREA, Cr, Na, K, Cl, Mg, Ca, P, amylase, 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; γ -GT = γ -glutamyltransferase; 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 (starting 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 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, 3.5 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.

7.4 Biomarker Analysis

7.4.1 Tissue and Serum biomarkers

All the eligible subjects must provide blood samples and tumor tissue samples for exploratory research on biomarkers (See Appendix 6).

- a. Fresh tumor tissue sample (or archival tissue) will be collected at baseline for determination of PD L1 expression and for exploratory research on biomarkers
 - Tissue should be collected by excisional or core needle biopsy, typically using a 21-18 gauge needle. The biopsy should include at least 5 cores, 2 will be formalin-fixed paraffin-embedded (FFPE) and 3 will be fresh frozen. Tissue should be collected within 28 days prior to initiation of protocol therapy.
 - For archival tissue: a representative FFPE tumor specimen in a paraffin block (preferred) or at least 10 slides containing unstained, freshly cut, serial sections need to be submitted along with an associated pathology report. Samples collected via resection, core-needle biopsy (CNB) (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable.
 - Considering the benefit seen with immunotherapy in MSI-H cancer, we will perform MSI tests on all patients.
- b. Tumor tissue sample will also be collected at week 3 for exploratory research on biomarkers
 - Biopsies at week 3 should be performed within 7 days before administration of C2D1 of study therapy. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

- c. Tumor tissue sample will also be collected at time of progression for exploratory research on biomarkers
 - Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.

Blood and tissue collections will be tracked by Tissue Station. Collection requests will be placed in the system, prior collections, and updated once completed including details of the process.

Exploratory biomarker research may include, but will not be limited to, immunohistochemistry for PD-L1, multiplexed immunofluorescence for immune markers, flow cytometry, analysis of ctDNA concentration, genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocyte subpopulations, T-cell receptor repertoire, or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of germline or somatic mutations, and use of WGS or NGS.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final manuscript has been completed, with the following exceptions:

- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- ***Blood, plasma, serum, and tumor tissue*** samples collected for biomarker research will be destroyed no later than 5 years after the final manuscript has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law.

7.5 Storage and Destruction of Biological Samples

If needed, certain analyses such as selectivity with incurred sample, parallelism with incurred sample, in-study cut point determination, et al., using pooled or individual samples which are

necessary for further evaluation and validation of analytical methods may also be performed. Results of these analysis may be included in the Clinical Study Report (CSR) or published separately from the CSR.

Incured samples reanalysis will be assessed simultaneously with the biological samples. The results of these evaluations will not be recorded in the CSR, but will be presented separately in a biological analysis report.

After all necessary analyses, subject information will be desensitized (including anonymized and pooled) and then disposed or destroyed.

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 followings:

- 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. Any adverse event should be evaluated the attribution/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 must also be evaluated for severity, and 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 5 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 investigational 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 hospitalization ; (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 investigational product to be discontinued?	
Relationship to Sponsor's Product	<p>Did the investigational 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.</p> <p>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.</p> <p>The following components are to be used to assess the relationship between the Investigational product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the investigational product caused the adverse event (AE):</p>	
	Exposure	Is there evidence that the subject was actually exposed to the investigational 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	<p>Did the AE follow in a reasonable temporal sequence from administration of the investigational product?</p> <p>Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</p>
	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	<p>Was the investigational product discontinued or dose/exposure/frequency reduced?</p> <p>If yes, did the AE resolve or improve?</p> <p>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.</p> <p>(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the investigational product; or (3) the trial is a single-dose drug trial); or (4) investigational product(s) is/are only used one time.)</p>
	Rechallenge Tests	<p>Was the subject re-exposed to the investigational product in this study?</p> <p>If yes, did the AE recur or worsen?</p> <p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p>

		(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) investigational 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 the investigational product or drug class pharmacology or toxicology?
The assessment of attribution/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.		
Attribution/causality	<p>Attribution is the determination of whether an adverse event is related to a medical treatment or procedure.</p> <p>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a investigational product relationship).</p> <ul style="list-style-type: none"> • 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. All the AEs (including SAEs) should be documented 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 III	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 III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II 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 does not resolve, a reasonable explanation should be documented in the eCRF. The outcome and date of an AE/SAE should be documented in the medical record and recorded in the eCRF, 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), 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 drug(s).

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 (that requires treatment/intervention) 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 that happen during the entire course of the study, and after the last dose (including those that occur before Day 90), should be documented in the patient's medical record, captured in the eCRF 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 eCRF and reported to the sponsor and supporting company in a timely manner, according to the specific SAE reporting guidelines.

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 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 a 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 event 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 Serious 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 following

outcomes:

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 30 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 30 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 The investigator must fill out the SAE Report Form provided by the supporting company, regardless of whether it is the initial report or a follow-up report. Besides, the investigator must report the SAE to the sponsor (drugsafety@innoventbio.com) by the time within 24 hours after noticing the event.

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

The investigator must submit the completed SAE report form to the supporting company within 24 hours after noticing the event. The investigator should urgently collect all missing information and provide a complete SAE report.

For an SAE, the investigator should 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 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 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.

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 who exposed to the study drugs becomes pregnant, the subject will continue with the study. The investigator must report the sponsor and the supporting company, within 24 hours 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 the sponsor.

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 6 Liver injuries required to be reported as SAEs

Baseline	Normal (AST/ALT and TBIL)	Abnormal (AST/ALT and TBIL)
Treatment Period	ALT or AST $\geq 3 \times$ ULN with TBIL $\geq 2 \times$ ULN	ALT or AST $\geq 8 \times$ ULN and the increased value of TBIL $\geq 1 \times$ ULN

	and $ALP \leq 2 \times ULN$ and no hemolysis	or $TBIL \geq 3 \times ULN$
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After being notified of the abnormalities, the subject must return to the study site promptly (ideally within 48 hours) 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. These 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 investigators will conduct regular safety review for the irAEs.

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.

9 Statistics

9.1 Statistical Analysis Plan

This is a Phase II, open label, single arm study, evaluating the efficacy and safety of sintilimab in subjects with CUP. Up to 45 subjects with CUP will be enrolled. The goal for the number of evaluable subjects is 40.

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 have measurable lesions at baseline and have at least one restaging evaluation. This analysis set is used for ORR analysis.

Safety analysis set (SS): all treated 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 major protocol violations that affect the efficacy evaluation. The PPS is used for the sensitivity analyses of primary efficacy endpoints 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. Attribute 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.

All the statistical analyses will be performed with SAS 9.2 (or higher).

9.3.1.1 Analysis of primary efficacy endpoints

The primary efficacy endpoint is confirmed ORR, defined as the proportion of subjects with a best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR), assessed by the IRR based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1) in the evaluable population. A 95% confidence interval will be provided for

observed ORR.

Design and sample size/power

The primary efficacy endpoint will be confirmed ORR. A patient will be considered as a responder to the treatment if he/she has achieved confirmed complete response (CR) or partial response (PR) determined by RECIST 1.1.

A Simon's two-stage Minimax design will be used to monitor the efficacy of sintilimab. The null hypothesis involves an ORR of 10% that will be tested against an ORR of 25%, i.e. a 15% improvement. In the first stage, 22 patients will be treated. If there are ≤ 2 patients who achieve objective response in these 22 patients (by end of 6 cycles in the last enrolled patient), the study will be terminated. If the study moves forward to second stage, an additional 18 patients will be treated leading to a total of 40 patients. Eight or more responders out of the 40 treated 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 62% if the ORR is 10% and the average sample size would be 28.8. Assuming a 10% dropout rate, we will need to enroll up to a total of 45 patients.

9.3.1.2 Stopping Rule Monitoring

The Investigator is responsible for completing efficacy/safety summary reports and submitting them to the IND Office Medical Affairs and Safety Group, for review. These should be submitted after the first 22 evaluable subjects, complete 6 cycles of study treatment, and again after the total of 40 evaluable subjects, complete 6 cycles of therapy.

9.3.1.3 Analysis of key and other secondary efficacy endpoints

The key secondary efficacy endpoints are ORR (investigator assessed), DCR, DOR, PFS and OS in the evaluable and ITT populations.

The ORR, DCR (defined as proportion of patients with CR+PR+SD) and corresponding exact 95% CIs of the sintilimab arm will be estimated using binomial distribution.

PFS is the time from treatment initiation to first date of progression (by imaging), or to death due to any cause. OS is the time from treatment initiation to death due to any cause. Subjects who neither progress nor die will be censored at the date of their last tumor imaging evaluation.

Subjects who do not have any tumor imaging evaluation after baseline will be censored on the date of registration. The mPFS and mOS and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted.⁷ Log-rank test will be performed to

test the difference in survival between groups.⁸ Regression analyses of survival data based on the Cox proportional hazards model (Cox, 1972) will be conducted on PFS 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 (Jiang, 2007). Appropriate methods will be applied to analyze correlative data. Other statistical analyses may be performed as appropriate.

DOR: subjects who have achieved CR or PR: from first date of Investigator-determined response to Investigator-determined PD or death; subjects who neither progress nor die: be censored at the date of their last tumor imaging evaluation. The mDoR will be estimated via the Kaplan-Meier method and survival plots will be presented.

9.3.2 Safety analysis

The safety analysis will use the SS. Safety parameters include AEs, laboratory tests, vital signs, ECG, immunogenicity, etc. Unless otherwise stated, all the safety analyses will be summarized .

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, 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.

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 \geq 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.

Other important baseline information such as region, choice of chemotherapies and time of enrollment will also be summarized.

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 changes in quality of life on treatment.

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

The University of Texas MD Anderson Cancer Center will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the electronic data capture (EDC) system. The PI will perform oversight of the data management of this study.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at The University of Texas MD Anderson Cancer Center and records retention for the study data will be consistent with The University of Texas MD Anderson Cancer Center's standard procedures, which mandate that data be maintained indefinitely.

11 Data Management and Record Keeping

11.1 Electronic Case Report Forms

eCRFs are to be completed through use of the MD Anderson Cancer Center Prometheus EDC system. All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee. SAE data will be captured via eSAE in accordance with Sponsor policy.

11.2 Source Data Documentation

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 11.4.

To facilitate source data verification and review, the investigators must provide the Sponsor direct access to applicable source documents and reports for trial related monitoring, Sponsor audits, and IRB/EC review. The study site will allow inspection by applicable health authorities.

11.3 Use of Computerized Systems

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified,

the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

11.4 Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of the investigational medical product (IMP), including eCRFs, electronic patient-reported-outcomes (PRO) data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator indefinitely, in accordance with the current policy of the MD Anderson Cancer Center IND office.

Written notification should be provided to the Sponsor and Innovent Inc prior to transferring any records to another party or moving them to another location.

11.5 Monitoring

During the study, a study monitor from the University of Texas MD Anderson Cancer Center Investigational New Drug Office will have regular contacts with the investigator and team.

12 Ethics

12.1 Compliance with Laws and Regulations

This study will be conducted in full conformance with the International Council on Harmonization (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

12.2 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

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

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

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

12.3 Institutional Review Board or Ethics Committee

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 13.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety related communications from the Sponsor. Investigators are responsible for ensuring that such reports

are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

12.4 Confidentiality

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the policy on study data publication (see Section 13).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

13 Study Documentation, Monitoring and Administration

13.1 Study Documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

The Investigator is responsible for completing the cohort summary report and submitting it to the IND office Medical Monitor for review. This should be submitted after the first 5 evaluable patients per cohort, and every 5 evaluable patients per cohort, thereafter.

13.2 Protocol Deviations

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and Innovent Inc and to the IRB/EC in accordance with established IRB/EC policies and procedures.

13.3 Administrative Structure

This trial will be supported via the rare disease strategic alliance between The University of Texas MD Anderson Cancer Center and Innovent. The University of Texas MD Anderson Cancer Center will be the sole site, responsible for enrolling patients. The MD Anderson Cancer Center IND office will provide oversight of safety.

After written informed consent has been obtained, the study team will generate a unique study identification number for the patient.

Patient data will be recorded via an EDC system with use of eCRFs.

Central laboratories, including those at Innovent collaborators and at The University of Texas MD Anderson Cancer Center, will be used for PD-L1 expression status determination and will provide kits for pharmacogenomic, tissue, whole blood, serum, and plasma sample analyses to be conducted at central laboratories or Innovent.

Treatment decisions will be made on the basis of the local reading of ECGs obtained during the study.

Imaging data will be retained at The University of Texas MD Anderson Cancer Center.

13.4 Publication of Data and Protection of Trade Secrets

Regardless of the outcome of a trial, the Sponsor and Innovent Inc is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the PI aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the PI aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to Innovent Inc prior to submission for publication or presentation. This allows Innovent Inc to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Innovent Inc personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Innovent Inc personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Innovent Inc, except where agreed otherwise.

13.5 Protocol Amendments

Any protocol amendments will be prepared by the PI. Protocol amendments will be submitted to the MD Anderson IRB/EC and to regulatory authorities in accordance with local regulatory requirements. Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in contact information).

14 References

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5. Chang GC, Yang TY, Shih CM, Lin LY, Lee HS, Chiang CD. Serial-measured versus estimated creatinine clearance in patients with non-small cell lung cancer receiving cisplatin-based chemotherapy. *J Formos Med Assoc.* 2003;102(4):257–261.

15 Appendix

Appendix 1: Signature Page for Investigator

Protocol Title: A Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab for Advanced Rare Cancers (SiARa Cancer Study) – Cancer of Unknown Primary (SiARa-CUP)

Protocol Number: MD 2020-0902

This protocol is a trade secret owned by The UT MD Anderson Cancer Center and 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: _____

Appendix 2: Schedule of Biomarker Samples

Visit	Timepoint	Sample Type
Screening (Day -28 to Day -1)	Baseline	Biomarker (blood, plasma, and serum)
Day 1 of Cycle 3	Prior to infusion	Biomarker (blood, plasma, and serum)
Progression (≤ 40 days after progression is radiographically determined ¹)	NA	Biomarker (blood, plasma, and serum)

Appendix 3: 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

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Appendix 4: 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, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor 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 ≥ 15 mm 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 non-cystic 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, sagittal 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 13](#) 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 14](#) 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 15](#).

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 13](#) to [Table 15](#).

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 7 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
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 8 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 9 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

Overall response first time point	Overall response subsequent time point	Best overall response
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 5: Immune-Modified Response Evaluation Criteria in Solid Tumors (Immune-Modified RECIST)

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like sintilimab, which can produce delayed responses that may be preceded by initial apparent radiographic progression, including the appearance of new lesions. Therefore, immune-modified response criteria have been developed to incorporate new lesions into the assessment of total tumor burden and allow radiographic progression to be confirmed at a subsequent assessment. Immune-modified Response Evaluation Criteria in Solid Tumors (RECIST), as described within this appendix, were adapted from RECIST, Version 1.1 (v1.1) (Eisenhauer et al 2009), in the same manner that immune-related response criteria were adapted from WHO criteria (Wolchok et al. 2009) and RECIST v1.0 (Nishino et al. 2014). When not otherwise specified, RECIST v1.1 conventions will apply. Differences between immune-modified RECIST and RECIST v1.1 are summarized in Table 1.

Table 1 Comparison of RECIST v1.1 and Immune-Modified RECIST

	RECIST v1.1	Immune-Modified RECIST
Measurable new lesions	Always represent progression	Incorporated into the total tumor burden ^a and followed
Non-measurable new lesions	Always represent progression	Do not represent progression, but preclude CR
Non-target lesions	Contribute to defining CR, PR, SD, and PD	Contribute to defining CR only
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease in sum of diameters of target lesions, in the absence of CR, new lesions, and unequivocal progression in non-target lesions	≥ 30% decrease in tumor burden, ^a in the absence of CR
PD	≥ 20% increase in sum of diameters of target lesions, unequivocal progression in non-target lesions, and/or appearance of new lesions	≥ 20% increase in tumor burden ^a
SD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CR = complete response; PD = progressive disease; PR = partial response;

RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

^a Tumor burden is the sum of diameters of target lesions and measurable new lesions.

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor 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 as follows:

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval \leq 5 mm)

10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be \geq 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be \leq 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions," "New Lesions," and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis \geq 10 mm but $<$ 15 mm) 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, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring 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 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 malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Lesions may include hepatic lesions previously treated with hepatic arterial therapy, or other solid masses previously treated with external beam radiotherapy.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (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.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions

on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

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.

IDENTIFICATION 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 that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend

itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that 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. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm \times 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

NEW LESIONS

New lesions identified after baseline will be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST (e.g., non-lymph node lesions must be ≥ 10 mm on the longest diameter; new lymph nodes must be ≥ 15 mm on the short axis [see note below]). All new lesions (measurable or non-measurable) must be assessed and recorded at the time of identification and at all subsequent tumor assessment timepoints.

Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden that is performed as part of the tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the calculation of tumor burden and thus will not affect overall tumor response evaluation. New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint can be included in the tumor response evaluation from that point on, if the maximum number of measurable new lesions has not been reached.

Note regarding new lymph node lesions: If at first appearance the short axis of a lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion. If at first appearance the short axis of a lymph node lesion is ≥ 10 mm and < 15 mm, the lymph node will not be considered measurable but will still be considered a new lesion and should be identified as a non-measurable new lesion. If at first appearance the short axis of a lymph node is < 10 mm, the lymph node

should not be considered pathological and should not be considered a new lesion. A lymph node can subsequently become measurable, when the short axis is ≥ 15 mm.

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline as a measure of tumor burden. At each subsequent tumor assessment, a sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions plus measurable new lesions (up to five new lesions, with a maximum of two new lesions per organ) that have emerged after baseline. Hence, each net percentage change in tumor burden per assessment accounts for the size and growth kinetics of both old lesions and new lesions as they appear.

Measuring Lymph Nodes

If at first appearance the short axis of a new lymph node lesion is ≥ 15 mm, it will be considered a measurable new lesion and may be included in the sum of the diameters. If the new lymph node lesion is included in the sum of diameters, it will continue to be measured and included in the sum of diameters at subsequent timepoints, even if the short axis decreases to < 15 mm (or even < 10 mm). However, if it subsequently decreases to < 10 mm and all other lesions are no longer detectable or have also decreased to a short axis of < 10 mm (if lymph nodes), a response assessment of complete response may be assigned.

Lymph nodes should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included in the sum of diameters, the sum 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.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions and up to five measurable new lesions (lymph node and non-lymph node) should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

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 and "too small to measure" should be ticked. (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 and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS AND NON-MEASURABLE NEW LESIONS

Measurements are not required for non-target lesions or non-measurable new lesions. Non-target lesions should be noted at baseline, and non-measurable new lesions should be noted at the time of identification. At subsequent evaluations, non-target lesions and non-measurable new lesions will be categorized as "present" or "absent."

After baseline, changes in non-target lesions or non-measurable new lesions (or measurable new lesions in excess of five total or two per organ) will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions and non-measurable new lesions) and will not be used to assess progressive disease.

RESPONSE CRITERIA

Definitions of the criteria used to determine objective tumor response are provided below:

Complete response (CR): Disappearance of all lesions

Any pathological lymph nodes must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the baseline sum of diameters, in the absence of CR

Progressive disease (PD): At least a 20% increase in the sum of diameters of all target lesions plus measurable new lesions (up to a maximum of five total or two per organ), taking as reference the smallest sum of diameters on study (including baseline)

In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is factored into the sum of the diameters, which is used to determine the overall immune-modified RECIST tumor response.

Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions and Measurable New Lesions ^a	Non-Target Lesions and Non-Measurable New Lesions ^b	Overall Response
CR	Absent	CR
CR	Present or not all evaluated	PR
PR	Any	PR
SD	Any	SD
Not all evaluated	Any	NE
PD	Any	PD

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

^a Up to a maximum of five measurable new lesions total (and a maximum of two lesions per organ) can be included in the calculation of tumor burden, in addition to the target lesions identified at baseline.

^b Also includes measurable new lesions in excess of five total or two per organ.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target or measurable new lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic

deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions, as well as new lesions, as shown in Table 1.

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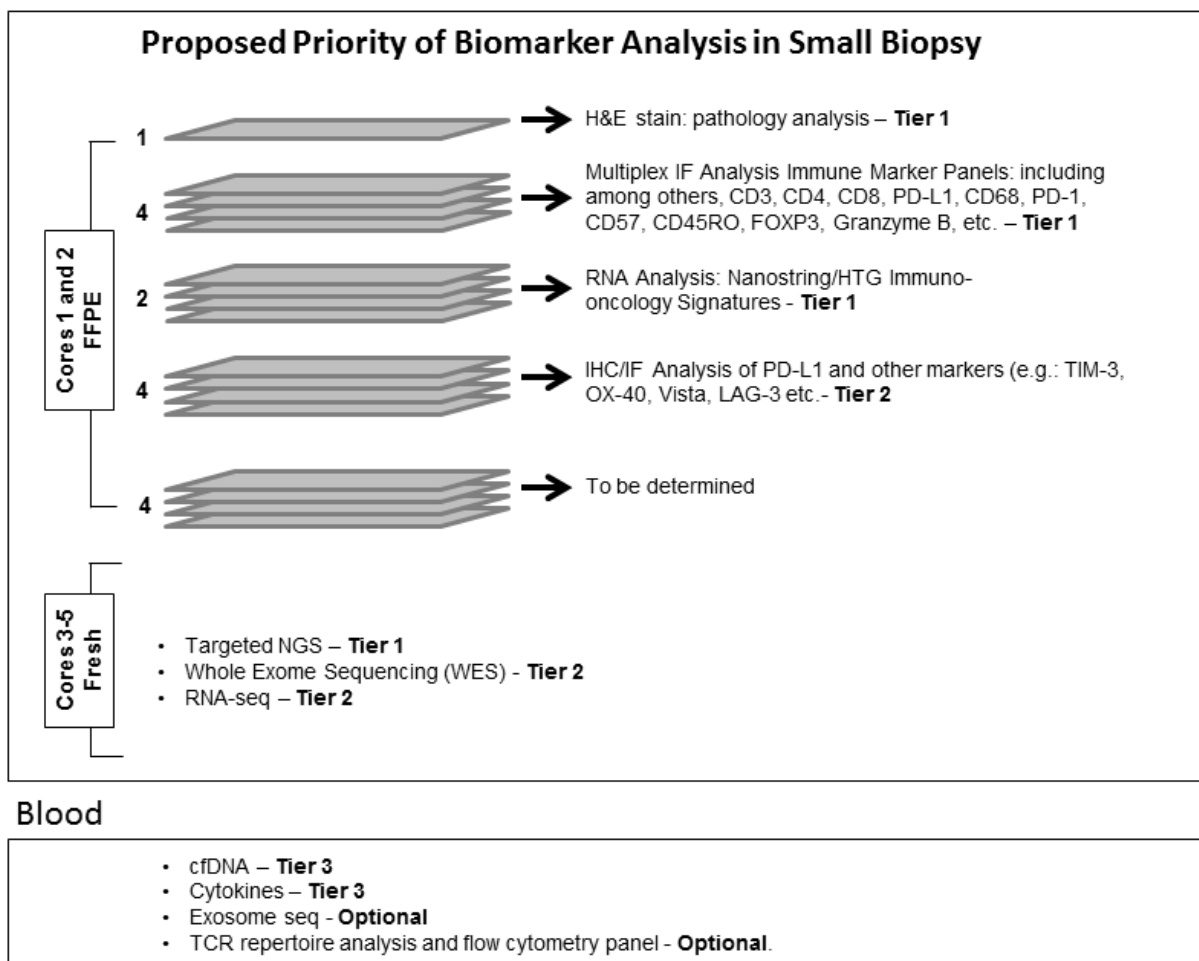
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Appendix 6: Biomarker Analysis

• Samples Collection and Processing:

- **Core needle biopsy (CNB) or excisional biopsy:** A fresh CNB or excisional biopsy will be obtained with the purpose of research studies before and after treatment and sent to the MD Anderson Institutional Tissue Bank (ITB) immediately after collection. At least 5 tissue cores will be obtained from the CNB/surgical procedure. The number of cores obtained will be affected by the patient clinical condition at the time of biopsy and determined by the radiologist who is performing the procedure. It is important to note that in some patients, the biopsy sample will also be required for clinical diagnosis. In such case, the first specimen will be prioritized for clinical specimen processing. In most instances, a rapid on-site evaluation (ROSE) is available locally to evaluate the adequacy of clinical sample, thus additional biopsies may be procured for this research project. Nevertheless, the amount tissue available for correlative studies can be variable. Core biopsy is typically performed using 21-18 gauge needle and with condition permitting, up to 5 cores should be collected.
- These cores/surgical excision pieces will be processed for (Figure 1):



- Cores or excision pieces 1 and 2: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples). The FFPE sample is important as it also provides a histological confirmation for the presence and cellularity of tumor cells. FFPE samples will also be prioritized for immune gene expression profiling by NanoString or other to be determined assays (Figure 1)
 - Cores or excision pieces 3 to 5: Flash freezing in liquid nitrogen will be obtained for RNA (RNA-sequencing) and DNA (targeted or whole exome sequencing (WES), among other analysis. Potentially, flow cytometry from fresh tissue tumor tissues could be performed in selected cases.
- The tissue and blood will be processed as follows:
 - FFPE Tissues: Immediate and overnight fixation in 10% buffered formalin for paraffin embedding, usually within 20-24 hour after fixation. For biopsies performed on Friday, fixation time may extend to 48 hours (FFPE samples). For pathology evaluation, at least one sample per 1-cm of diameter will be submitted for FFPE processing and pathology analysis. Hematoxylin and eosin (H&E)-stained sections from all FFPE diagnostic slides (tumor and adjacent normal level) will be scanned in Aperio image analysis for pathological evaluation and biomarker analysis
 - Fresh Tissues: Flash freezing in liquid nitrogen for genomic studies including RNA-sequencing and Whole Exome Sequencing (WES).
- **Blood Specimens**: 40 ml of blood will be collected at several time points (pre-treatment or baseline, cycle 1 day 15, and at the time of disease progression [+/- 1 week]) for:
 - Isolation of germ-line DNA from peripheral mononuclear blood cells (PMBCs) and TCR- T-cell receptor repertoire.
 - Isolation of plasma for cell free DNA analysis of genomic abnormalities using gene panels or analysis of cytokines associated with T-cell activation.
 - Isolation of circulating tumor cells (CTCs).
 - Potential flow cytometry analyses for phenotypic and functional studies.
- **Biomarker Analysis**:
 - **Histology evaluation of tumor tissue**: H&E-stained sections from CNBs and surgical excisions will be used to confirm the presence of tumor cells, as well as their abundance (tumor cellularity), stromal components and lymphocytic infiltrates. Hematoxylin and eosin (H&E)-stained sections from all FFPE diagnostic slides (tumor, normal and lymph nodes) will be scanned in Aperio™ digital pathology scanner analysis for

pathological evaluation and selection of 1 or 2 blocks (depending on tumor availability) for biomarker analysis.

From the tumor tissue specimens, the following pathological analysis will be performed: 1) tumor diagnosis using the World Health Organization (WHO) classification; 2) lowest degree of tumor differentiation; 3) percentage of areas of necrosis; 4) percentage of areas of fibrosis; 5) percentage of viable tumor tissue; and, 6) percentage of viable malignant cells.

Central Review: The scanned H&E-stained slides will be available for pathology analysis at the Translational Molecular Pathology and Biomarker Lab chaired by Dr. Ignacio I. Wistuba, MD Anderson Cancer Center.

- **Quality Control (QC) of tumor tissue**: All tissue specimens collected will be reviewed by reference pathologists. At least, three types of QC activities for specimens collected will be performed: a) histology/cytology examination of the tissues and cells; b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and immunofluorescence; and, c) quality assessment of DNA, RNA and protein extracted. All histology stained samples will be scanned and digital images will be available for review.
- **Immunohistochemistry (IHC) and Immunofluorescence (IF) analyses**: Fresh frozen and FFPE tissues will be used for analysis of immune markers. For immunohistochemistry (IHC) and multiplex immunofluorescence (IF) analyses, histology sections obtained from FFPE samples will be utilized (Figure 1). IHC and IF will be performed using autostainers. All antibodies used will be optimized for IHC/IF by examination of positive and negative controls and testing of the antibodies standard methods, including Western blotting. All pathology slides will be scanned into a digital image scanner and analyzed using image analysis software; IHC analysis will be performed using the Aperio Image Toolbox™ (Leica Biosystems) and IF analysis using, among others, the Vectra Inform™ (Perkin-Elmer) software. The following markers will be performed using optimized and validated protocols, as follows:
 - **IHC assays**: Staining of tumor tissue for PD-L1 will be conducted before and after treatment and be performed using the proper IHC assay. Briefly, 4µm-thick histology sections will be used for IHC will be performed on autostainers (Leica Bond Max, Leica Biosystems, Vista, CA). All antibodies have been optimized for IHC by examination of positive and negative controls and testing of the antibodies by Western blotting. To perform quantitative image analysis if the expression of each marker, all IHC slides will be scanned into a digital image scanner (Aperio™ AT Turbo, Leica Biosystems, Buffalo Grove, IL), and analyzed using the Aperio Image Genie Toolbox™ software (Leica Biosystems,

Buffalo Grove, IL). Five random 1-mm square areas within the tumor region will be selected for analysis. The expression of IHC marker(s) in malignant cells will be evaluated using the Aperio™ digital H-score system which includes the percentage of positive cells (0 to 100) and intensity (0 to 3+), with a total score ranging from 0 to 300. The expression of markers in inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area.

- **Multiplex IF Analysis:** Up to 20 immune markers distributed in 3-4 panels will be utilized. For multiplex IF analysis, we will use the Opal chemistry and multispectral microscopy Vectra system (Perkin-Elmer) which includes the Nuance software; analysis will be performed using the InForm software. The expression of protein markers and inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area. The data and digital images will be deposited in a central database for review by pathologists. Among other markers, we will study the expression of the following CD3, CD4, CD8, PD-L1, PD-1, FOXP3, CD45RO, CD57, CD68, and Granzyme B; additional markers will be selected according the results of the gene expression analysis and may include other immunotherapy targets (e.g., OX-40, Vista, GITR, TIM-3, LAG-3, NKp46/CD16, etc.) and proliferation markers (e.g., Ki67).
- **Nucleic acids and protein extraction:** Blood (plasma and PMBCs), tumor (CNB and surgical excision specimens) samples will be subjected to DNA, RNA and protein extraction using standard methods. DNA and RNA quantity and integrity will be assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analyses. Also, protein lysate will be extracted using standard methods.
- **Molecular analysis of tumor tissues:** Using FFPE and/or fresh frozen for CNBs/surgical excisions (Figure 1), the following analysis will be performed:
 - **Immuno-oncology (IO) gene expression signatures:** Using FFPE tumor tissues, IO panels of genes will be examined using the Nanostring technology (nCounter). This assay will be used to measure expression levels of drug targets, tumor infiltrate composition, and total immune cell composition using a single section of FFPE tumor tissue. The Nanostring methodology offers a cost-effective way to analyze the expression levels of up to 800 genes simultaneously, with precision superior to qPCR. The current Nanostring PanCancer Immune Profiling Panel includes 770 genes and combines markers for 24 different immune cell types and populations, 30 common cancer antigens and genes that represent all categories of immune responses including key checkpoint blockade genes. Alternatively, we will apply the HTG Edge Seq technology, also known as quantitative nuclease

protection assay or HTG Edge Chemistry that enables extraction and amplification-free quantitation of mRNA from FFPE tissues without RNA extraction. Their Immuno-Oncology Assay examines the expression of 549 genes implicated in the host immune response to tumors.

- Next Generation Sequencing (NGS) analysis: To study tumor molecular abnormalities, fresh, and alternatively, FFPE tumor tissues before and after treatment will be examined for targeted gene panel NGS (analysis of mutations, copy number, indels, translocations), whole exome sequencing (WES) and RNA sequencing. Targeted NGS: Different sequencing platforms can be used to sequence DNA extracted from clinical samples. These platforms have a minimum input of 10ng of sample which make it amenable to sequencing with minimal DNA. The panels available are, among others, CMS50, CMS400, Oncomine and Foundation Medicine. They range from 50 to 409 oncogenes and tumor suppressor genes, with coverage of hotspots and whole exomes. All these platforms are available at facilities at MD Anderson Cancer Center. WES and RNA-seq: Illumina Hi-seq platform is available at the Sequencing Facilities at MD Anderson Cancer Center
- Flow cytometry Analysis: This type of analysis may be applied to two types of specimens.
 - Cryopreserved PBMCs: High order flow cytometry panels are available for analysis of tumor tissue and blood specimens. The panels will focus on 1) delineation of major immune cell types (T cells, B cells, NK cells, DC), 2) determination of T cell differentiation status and limited functionality (IFN γ , TNF α , GB) and 3) defining the expression level of costimulatory and co-inhibitory molecules on T cells. The proposed studies may be conducted retrospectively on cryopreserved PBMCs. Briefly, 40 cc of heparinized peripheral blood from patients prior to the initiation of treatment, and at 3 time points throughout treatment (2 weeks, 8 weeks and at time of progression) will be processed fresh (within 24h of being drawn) for PBMC isolation. PBMCs will be cryopreserved and stored in liquid nitrogen until use.
 - Flow cytometry of freshly disaggregated tumor tissue. In selected cases, fresh tissue will be available for flow cytometry analysis. Tumor tissue will be stored in HBSS for up to 24h before processing for flow cytometry. Fresh tissue will be mechanically disaggregated or digested according to needs and panel design. The cells will be processed as a single cell suspension and stained according to each customized panel.
- Liquid biopsy analysis: Liquid biopsies are non-invasive blood tests that detect tumor cell free DNA (cfDNA) that are shed into the blood from the primary tumor and from

metastatic sites. cfDNA testing offers the opportunity to take serial samples in order to monitor tumor genomic changes in real time. There are several platforms available at MD Anderson Cancer Center, including the application of droplet digital PCR (ddPCR) platform in a small panel of hot spots/genes or a larger panel of genes using NGS platform. Additionally, isolation of circulating tumor cells (CTCs) and exosomes for genotyping DNA purposes are available as optional analysis of blood compartments.

- **TCR receptor repertoire:** TCR sequencing analysis may be performed using DNA from tumor tissues as well as PBMC. Briefly, 500 ng tumor DNA or 3-6 ug PBMC DNA will be subjected to high throughput TCR V β CDR3 sequencing on an Illumina HiSeq sequencer with at least 5-fold coverage by ImmunoSEQ™ sequencing (Adaptive Biotechnologies, Seattle, WA). TCR profile generated from treatment-refractory tumors at the time of disease progression will be compared to data from pre-treatment tumor samples to explore the TCR repertoire evolution of these tumors under therapeutic pressure. The dynamic changes of TCR from PMBC, when longitudinal blood samples are available, will be correlated to response to immune checkpoint blockade or chemotherapy and survival.
- **Cytokines analysis:** For the detection of soluble factors in plasma we may use the SQ120 instrument from Meso Scale Discovery (MSD). This and other technologies allow for the detection of up to 40 analytes per well and uses a very low sample volume, with a sensitivity up to 1000-fold higher than traditional ELISA assays with a large linear range of 3-4 logs. These technologies can be utilized for either single agent detection or in multiplex format.