CLINICAL STUDY PROTOCOL

An open-label, phase 1b multicenter study of IBI308 in subjects with advanced/metastatic solid malignancies.

This study will be conducted according to this protocol, including protocol amendments and in compliance with Good Clinical Practice, ethical principles, and other applicable regulatory requirements

Protocol Number:	**CIBI308A102**
Clinical Phase:	**Phase 1b**
IND Number:	**136159**
Sponsor:	**Innovent Biologics(Suzhou) Co.Ltd**
Version:	6
Effective Date:	**January 7, 2019**

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SPONSOR SIGNATURE

Study Title: An open-label, phase 1b multicenter study of IBI308 in subjects with advanced/metastatic solid malignancies

Study Number: CIBI308A102

Protocol Version: Version 6, Jan 07, 2019

Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, Innovent Biologics (Suzhou) Co. Ltd.

PRINTED NAME [redacted]
TITLE [redacted]

Signature_____

Date_____

INVESTIGATOR AGREEMENT

Protocol No.: CIBI308A102 **Version Date:** V 6, Jan 07, 2019

I have read the protocol CIBI308A102 and Investigators' Brochure for study conduct and regarding the risks and potential benefits of the trial. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.

I certify that I, and my research study staff, have received adequate training to conduct this research protocol.

I agree to maintain accurate and adequate records in accordance with institutional, company, Federal, state and local laws and regulations.

Principle Investigator

Name (printed)_____

Signature_____

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
aPTT	Partial thromboplastin time
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	Complete Response
CRF	case report form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
EOI	End of Infusion
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBeAg	Hepatitis B “e” antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HGB	hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application
INR	International normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRRC	Independent Radiology Review Committee
irAE	immunotherapy-related adverse events

IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	overall response rate
PD	disease progression
PK	pharmacokinetics
PO	Per os (by mouth, orally)
PR	partial response
PT	Prothrombin time
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
RBC	red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SD	standard deviation
TMB	Tumor Mutation Burden
ULN	upper limit of normal
WBC	white blood cell (count)

Synopsis

Title:	An Open-label, Phase 1b Multicenter Study of IBI308 in Subjects with Advanced/Metastatic Solid Malignancies
Sponsor	Innovent Biologics (Suzhou) Co. Ltd.
Study Drug	IBI308
Clinical Trial Phase	Phase 1b
Proposed Indication	Advanced/metastatic solid malignancies
Objectives:	Primary • To evaluate preliminary anti-tumor activity (overall response rate, ORR) of IBI308 monotherapy in subjects with advanced/metastatic solid malignancies.
	Secondary • To measure progression-free survival rate (PFS). • To measure duration of response (DOR). • To measure overall survival rate (OS). • To obtain safety and toxicity data. • To further evaluate pharmacokinetics (PK) of IBI308. • To further evaluate immunogenicity of IBI308. Exploratory Objectives • To explore the relationship between baseline markers (PD-L1, TMB etc.) and clinical response. • To explore the relationship between exposure and efficacy/safety. • To assess the impact of ADA on PK, efficacy/safety.
Study Population:	≥18 years, have a histologically or cytologically confirmed advanced/metastatic solid tumor and have progressed on available standard therapies or for which no standard therapy exists.
Number of Subjects planned	Up to 40 subjects with advanced/metastatic endometrial cancer (EC) will be enrolled in cohort 2. The original planned cohort 1 with 60 subjects with advanced/metastatic cancer and high tumor mutational burden (TMB) has stopped enrolling at the time of the protocol amendment.
Number of Study Centers Planned	Approximately 15 study sites located in the United States. Additional sites may be added if necessary.
Description of Study Intervention:	This is an open-label, phase 1b multicenter study of IBI308 in subjects with advanced/metastatic solid malignancies. Patients will be recruited for 2 cohorts: • Cohort 1: Advanced/metastatic cancers with TMB>10 mutations per megabase (mut/Mb). This enrollment of this cohort has been stopped per sponsor's communication with the sites. For patients who have already enrolled in this cohort, treatment and monitoring will be conducted as stipulated by the protocol. The patients will remain on study

	until disease progression or intolerable toxicity, death, withdrawal of consent, or end of study, whichever occurs first. • Cohort 2: Advanced/metastatic endometrial cancer (N=40) Please see **Table-5** for sample sizes. A fixed dose of 200 mg IBI308 will be administered as IV infusion for every three weeks (Q3W) to the patients until disease progression or intolerable toxicity, death, withdrawal of consent, or end of study, whichever occurs first.
Study participation Duration:	The maximum treatment duration is 2 years.
Pharmacokinetic (PK) evaluations	PK of IBI308 will be investigated extensively: PK will be assessed at predose, within 5 min after the end of infusion (EOI), at 1, 6, 24, 48, 168, 336 hours post EOI in Cycle 1, predose in Cycle 2 and every other cycle thereafter for the first 12 cycles, and at 30 days follow-up visit for the first 6 subjects in cohort 1 and first 12 subjects in cohort 2. PK will be sparsely assessed at predose in Cycle 2 and every other cycle thereafter for the first 12 cycles, and at 30 days follow-up visit for other subjects. The results of these analyses, if performed, may be reported separately.
Safety Evaluations	Safety will be assessed by physical examinations, vitals, ECG, laboratory tests, AE monitoring, and concomitant medication usage monitoring. AEs are graded according to the CTCAE v4.03. Investigators will report whether an AE is potentially immune related (irAE). irAEs are defined as AEs of unknown etiology potentially associated with an immune phenomenon. Follow up for SAEs, which are assessed as at least possibly related late irAEs, will be followed up to 3 months after the last dose of IBI308.
Efficacy Evaluations	Tumor assessment will be performed at baseline, every 2 cycles, and at the end of treatment by the investigator per RECIST v1.1. Efficacy evaluations will include the following: computed tomography (CT), magnetic resonance imaging (MRI), physical examination, and other procedures as necessary. If a patient is classified as having disease progression at a post-baseline tumor assessment, then confirmation by a second scan within 4-6 weeks in the absence of rapid clinical deterioration is required. Anti-cancer activity parameters that will be assessed include determination of the following: 1) Best overall response [complete response (CR), partial response (PR), stable disease (SD), or progressive disease] 2) Objective response rate (ORR) (CR + PR) 3) Duration of response (DOR) or duration of SD

	4) Disease control rate (DCR) (CR, PR or SD) 5) Progression-free survival (PFS) and overall survival (OS) efficacy evaluations
Immunogenicity	Blood samples for anti-drug antibody (ADA) analyses will be collected within 24 hours before start of infusion in Cycle 1 and Cycle 2 and then in every other subsequent cycle, and at the Safety Follow-up Visit or until start of a new anti-cancer therapy, whichever occurs first.
Statistical Analysis:	Summary statistics will be presented by cohort as well as overall for the trial. The number of subjects presenting with adverse events will be summarized by cohort and overall for the trial. Safety and tolerability will be evaluated by AEs/irAEs, laboratory assessments, vital signs, 12-lead electrocardiograms, physical examination, ECOG PS, and concomitant medication usage, using the safety analysis set. For laboratory data, changes over time will be described using descriptive statistics, and the percentage of subjects with values outside the normal range will be presented. All PK, immunogenicity, and safety data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. ORR and the associated 2-sided 95% exact confidence limits will be provided. The proportion of subjects who have experienced best response as CR, PR, SD or disease progression (PD) will be calculated. PFS and OS data will be analyzed by Kaplan-Meier method.

Schedule of Events

Table-1. Schedule of Events

Study Day/Visit Day	Screening -28 to 0 (±3 Day)	Cycle 1 Day 1	Each Subsequent Cycle Day1 (± 3 Day)	EOT Within 7 days[16] (±3 Days)	Safety FU 30 Days after last dose (±7) [17]	Survival FU (±7) Every 3 months after last dose[18]
Informed consent	X					
Inclusion/Exclusion Criteria	X					
Medical History	X					
Safety Assessment						
Vital Signs [1]	X	X	X	X	X	
Physical Examination	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	
Disease-Specific Staging Criteria[2]	X					
AE assessment	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	
CBC w/ Diff [3]	X	X	X	X	X	
Blood chemistry [4]	X	X	X	X	X	
Thyroid Function Tests [5]	X		X	X	X	
Coagulation [6]	X					
Pregnancy test (HCG)[7]	X				X	
Hepatitis and HIV screen[8]	X					

ECG (12 Lead)[9]	X	X	X	X	X	
Urine Analysis	X		X	X	X	
Efficacy Assessments						
Imaging (CT or MRI)[10]	X	every 2 cycles and at EOT				
Cardiac Assessment (ECHO, MUGA)[11]	X					
Bone scan[19]	X					
Administration of Investigational drug						
Administration of IBI308		X	X			
Biomarker Assessments						
Tissue[12]	X					
Blood samples[13]		X	X		X	
PK and Immunogenicity						
PK[14] (see Table 2)						
ADA[15]		X	X		X	

EOT: end of treatment

[1] Baseline conditions

[2] Disease-specific staging criteria (for CRF purposes, e.g.: TNM classification and etc.)

[3] Including CBC with differential and platelet count performed within 7 days prior to first dose (do not repeat Cycle 1 Day 1 CBC, if screening CBC is within 7 days of dosing) and 72 hours prior following doses on the schedule

[4] Including alkaline phosphatase, ALT/AST, total bilirubin, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides), amylase and lipase performed within 7 days prior to first dose (do not repeat Cycle 1 Day 1 Blood Chemistry, if screening Blood Chemistry is within 7 days of dosing) and 72 hours prior following doses on the schedule

[5] Thyroid function tests include Thyroid stimulation hormone (TSH), Free T3 and T4

[6] Including aPTT/INR performed within 7 days prior to first dose at day 1 on a schedule

[7] Pregnancy test needs to be performed within 72 hours before Cycle 1 dosing and at first Safety Follow-up visit

[8] Including HBsAg, HBsAb, HBcAb, Hep C RNA, HIV screen

[9] 12-lead ECG on screening, 72 hours prior each dose, EOT and at first Safety Follow-up visit

[10] Tumor imaging (either CT or MRI, with preference for CT) will be performed at screening, every 2 cycles and EOT. The same imaging technique should be used in a patient throughout the study. Tumor assessment should be performed according to RECIST 1.1 and to iRECIST 1.1

[11] Cardiac Assessments Echocardiogram (ECHO) and/or multiple-gated acquisition scan (MUGA) at screening phase, and as clinically indicated afterwards.

[12] May be archival or recent sample. Separate ICF is needed for collecting fresh tumor tissue biopsies. 1 formalin-fixed paraffin embedded tumor tissue block, or minimum of 10 FFPE unstained slides are needed. Evaluations include but are not limited to PD-L1 and TIL, please refer to 6.1.3 section for details. Specific instructions for tissue collection and shipment are provided in the procedures manual.

[13] Collected prior to first dose and every 2 cycles at predose until the Safety Follow-up Visit. Evaluations include but are not limited to factors induced by IFNγ signaling, antibodies to tumor-associated antigens, and soluble PD-L1 (PD-L1), please refer to 6.1.3 section for details. Specific instructions for sample collection and shipment are provided in the procedures manual.

[14] Please see details in specific PK (**Table-2**).

[15] Blood samples for anti-drug antibody (ADA) analyses will be collected within 24 hours before start of infusion in Cycle 1 and Cycle 2 and then in every other subsequent cycle, and at the Safety Follow-up Visit or until start of a new anti-cancer therapy, whichever occurs first.

[16] EOT visit should be completed within 7 days (±3 Days) if investigator decides to end the treatment for subject. If the physic al exams, lab tests and other relevant events which should be performed on the EOT have done within 7 days of next planned visit after previous dose of study medicine, these results could be recorded as EOT visit; if the above scheduled events have done within 21 to 30 days after the last dose of study medicine, these results could be recorded as the safety FU visit.

[17] The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study therapy or before the initiation of a new anti-cancer treatment, whichever occurs first. Patients who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

[18] After the Safety Follow-UP visits, subjects will have survival follow-ups every 3 months by clinical visits or telephone calls, until death, loss-to-follow-up, withdrawal of consent, or study termination by sponsor.

[19] Bone scan should be performed according to local clinical practice guideline by investigators' decision

Table-2. Details of Sampling for Pharmacokinetics (PK)

	Screening	**Treatment**												**Safety FU 30 Days (±7)**
		Cycle 1									[2]Cycle 2 and Additional Cycles (21 Days ±2 Days)			
Day	-28~-1	1					2	3	8	15	1			
		Predose			Post-dose						Predose			
[1]Time Points		-1h	infusion	Immediately at end of infusion	1h	6h	24h	48h	168h	336h	-1h	infusion	Immediately at EOI	
Window				+5min	±5min	±15min	±1h	±2h	±8h	±12h			+5min	
IBI308			X									X		
[4]PK		X		X	X	X	X	X	X	X	X [2]			X [3]

Please note:

1. Sample collection must be from opposite arm to that used for study drug infusion.
2. Cycle 2 and subsequently every other cycle for the first 12 cycles.
3. PK assays should be performed at the mandatory end of study visit.
4. PK will be intensively assessed at predose, within 5 min after the end of infusion (EOI), at 1, 6, 24, 48, 168, 336 hours post EOI in Cycle 1, predose in Cycle 2 and every other cycle thereafter for the first 12 cycles, and at 30 days follow-up visit for the first 6 subjects in cohort 1 and first 12 subjects in cohort 2. PK will be sparsely assessed at predose, within 5 min after the end of infusion (EOI) in cycle1, predose in Cycle 2 and every other cycle thereafter for the first 12 cycles, and at 30 days follow-up visit for other subjects.

1. INTRODUCTION

1.1 Background and Rational for Tumor Selection

Recently emerging data has shown, that immunotherapeutic treatment with check point inhibitors is efficient and well tolerated, with a favorable safety profile and less toxicity as compared to conventional chemotherapy. The interaction between the programmed cell death protein 1 (PD-1) and its ligands (programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), plays an important role in maintaining the balance between immune activation and tolerance, potentially including tumor tolerance. Blocking the interaction between PD-1 and PD-L1, has been reported to have antitumor effects in many malignancies. A number of checkpoint inhibitors including PD-1 or its ligand (PD-L1), have been approved by FDA for the treatment of multiple cancers including non-small cell lung cancer (NSCLC), melanoma, classical Hodgkin lymphoma (cHL), urothelial carcinoma, renal cell carcinoma (RCC), adult and pediatric microsatellite instability-high cancer(MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC), hepatocellular carcinoma (HCC), gastric cancer, and recurrent or metastatic head and neck squamous cell cancer (HNSCC) (OPDIVO®; KEYTRUDA®).

Endometrial cancer (EC)

EC is the 4th most common malignancy among women and the 6th leading cause of death in 2017. It is the most common gynecologic malignancy in the United States, with an estimated 61,380 new cases and 11,000 deaths in 2017 (ACS, 2016). The incidence of EC is increasing annually by an estimated 1-2%. Obesity is a strong risk factor for the development of EC, accounting for approximately 50% of cases in Europe and the United States; it also has been associated with a relative increased risk of death of up to 6.25. While most ECs present at an early stage, approximately 25 % of early stage and more than 50 % of advanced stage cancers will recur.

Current adjuvant therapies for advanced EC patients are not very effective and there are limited options for patients with metastatic disease. Patients with advanced stage disease at the time of diagnosis have a high risk for recurrence. The median survival after recurrence is ten months and the five-year overall survival for patients who have recurred is less than 15%. Unfortunately, recurrent disease is generally not curable, and response rates for hormone therapy are in the 15-20 % range (Lee et al., 2014). Therefore, efforts in finding effective treatments for this population need to be pursued. In a Phase1 Study (NCT02054806) in patients with EC after failure of prior systemic treatment, the confirmed response rate to pembrolizumab was 13 %, demonstrating a promising activity in this heavily pretreated PD-L1 positive EC patients.

Tumor mutation burden (TMB)

TMB was defined as the number of somatic, coding, base substitution, and indel mutations per megabase of genome examined. Retrospective data suggest that mutational load may potentially predict response more robustly than PD-L1 IHC, presence of tumor infiltrating lymphocytes, or clinical variables.

TMB-h cancer types, NSCLC, melanoma, bladder cancer patients and other indications where PD-1 is thought to play a role in tumor immune evasion, were allowed to be enrolled in this IBI308 study. The sponsor has made strategic decisions to stop enrolling into this cohort. This decision was not related to any safety or ethic concerns.

1.2 IBI308

IBI308 is a novel PD-1 antagonist that is being developed for the treatment of various tumors. It binds to and neutralizes PD-1 receptor mediated immune suppressive signals on T cells, and activates human immune response to kill tumor cells.

1.3 Rational of the study

1.3.1 Preclinical Studies

Comprehensive nonclinical studies had been conducted to study the pharmacological activities, pharmacokinetic-pharmacodynamics (PK/PD) relationships and safety profiles of IBI308. The *in vivo* nonclinical toxicology (4-week and 26-week) and pharmacokinetic studies in cynomolgus monkeys suggest that IBI308 is safe for use in clinical studies in cancer patients. Additional *in vitro* and *in vivo* pharmacology and toxicology studies conducted using nivolumab (an approved anti-PD-1 mAb) as a comparator further support the safety and efficacy of IBI308. In these studies, similar profiles were observed for IBI308 and nivolumab in terms of binding affinity, blockade of PD-1 receptor and ligand binding, enhancement of T cell activation in an allogenic MLR assay, anti-tumor activity in a mouse xenograft model, tissue cross reactivity, and cytokine release.

Refer to the IB for more detailed information on preclinical studies of IBI308.

1.3.2 Clinical Studies

IBI308 was first developed in China intended for treating advanced/metastatic tumors. In China, Innovent has completed phase 1 dose escalation trials, and currently is conducting 3 Phase 2 trials and 1 Phase 3 trial for IBI308 [redacted]. Innovent filed a BLA for IBI308 in China for recurrence / refractory Hodgkin's lymphoma in early December of 2017. Refer to the IB for more detailed safety and efficacy information on clinical studies of IBI308.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

2. OBJECTIVES

2.1 Primary Objectives

To evaluate preliminary anti-tumor activity (overall response rate, ORR) of IBI308 as a single treatment agent in selected populations

2.2 Secondary Objectives

- To measure progression-free survival rate (PFS).
- To measure duration of response (DOR).
- To measure overall survival rate (OS).
- To obtain toxicity data.
- To further evaluate PK parameters.
- To further evaluate immunogenicity of IBI308.

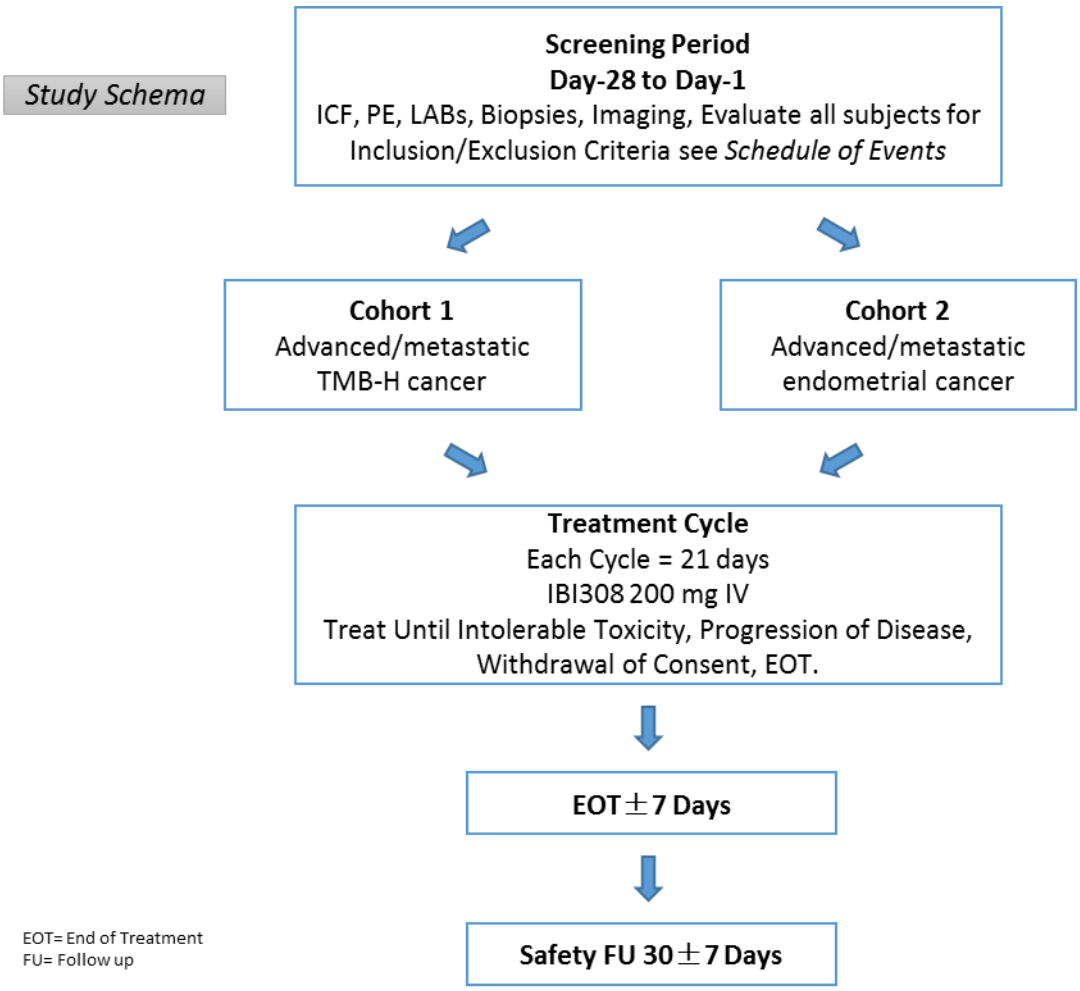
2.3 Exploratory Objective

- To explore the relationship between baseline markers (TMB) and clinical response
- To explore the relationship between exposure and efficacy/safety
- To assess the impact of ADA on PK, efficacy/safety

3. STUDY DESIGN

3.1 Scheme of The Study design

Study Schema



3.2 Overview

This is an open-label, phase 1b multicenter study of IBI308 in subjects with advanced/metastatic solid malignancies. The trial will recruit 2 cohorts: cohort 1 consisting of advanced/metastatic cancer patients with TMB>10 mut/Mb, and cohort 2 consisting of advanced endometrial cancer patients (refer to Study Design Scheme, and **Table-5** for sample sizes). Sponsor has made strategic decisions to stop enrollment in cohort 1 in this protocol amendment. In each cohort a fixed dose of 200 mg IBI308 will be administered Q3W to the patients. Additional cohorts may be added to this study via a new IND package or will be added with a protocol amendment submission during the clinical trial stage.

3.2.1 Rationale of Dose Selection

Innovent would like to initiate the Phase 1b expansion study with a fixed dose of 200 mg IBI308 Q3W, based on all nonclinical and clinical data obtained from Chinese studies, as well as the FDA approved clinical dose of similar anti-PD-1 products.

- The no observed adverse effect level (NOAEL) of 200 mg/kg observed in the pivotal 4-week toxicity study in monkeys was used to determine the maximum recommended starting dose (MRSD) for IBI308. Applying a 10-fold safety margin, the corresponding MRSD is 20 mg/kg (1/10 of NOAEL). The proposed Phase 1b dose (200 mg) is

equivalent to 3 mg/kg given an average body weight of 70 kg. This dose is 6-fold lower than the MRSD.

- A Phase 1 dose-escalation (3+3) study at doses of 1 mg/kg, 3 mg/kg, 200 mg (fixed dose), and 10 mg/kg Q3W was completed in Chinese patients with advanced malignancies (N=12). A Phase 1 dose expansion (200 mg as monotherapy or in combination with other chemotherapies in various cancer diseases) is ongoing in China. There were no DLT at any dose up to including 10mg/kg in the completed Phase 1a study. IBI308 was generally well tolerated after single and multiple dose administration in patients with advanced cancers.

- Currently, there are 5 clinical studies with IBI308 in China. As of October 30, 2017 (cutoff date), a total of 267 advanced cancer patients received ⩾1 dose of study drug, of whom 91.76 received ⩾2 cycles, 79.40% received ⩾3 cycles, 57.68% received ⩾4 cycles, and 40.45% received ⩾5 cycles of dosing. Among the total of 267 patients who received at least one dose of IBI308, 258 patients were treated at the 200 mg fixed dose as monotherapy or in combination with chemotherapeutic agents. Overall, the 200 mg fixed dose was very well tolerated in patients with various advanced cancers. Refer to the IB for more detailed information on clinical studies of IBI308.

- The CIBI308B201 Phase 2 study showed robust PD-1 receptor occupancy (RO) on peripheral blood CD3 + T cells by IBI308 was achieved in patients with recurrence/refractory Hodgkin's lymphoma treated with a 200 mg fixed dose. The overall response rate (ORR) per independent radiology review committee (IRRC) was 65.0% (N=60) following treatment with IBI308 at 200mg Q3W.

- Pharmacokinetics of IBI308 were characterized in solid cancer patients with an elimination half-life (geometric mean) of 14.4 days (ranged from 8.0-23.3 days) at the 1st cycle and 13.4 days (ranged from 10.6-14.7 days) at the 4th cycle (steady state).

- The proposed dose and dosing intervals are also based on the approved anti-PD-1/PD-L1 products. Based on literature reports and data obtained from other anti-PD-1 products, body size and race are less likely to affect PK or efficacy/safety of anti-PD-1 products at the therapeutic dose.

We therefore propose a fixed dose of 200 mg IBI308 for every 3 weeks (Q3W) in the US trial.

3.3 Randomization Procedures

Randomization and blinding procedures are not applicable in this open-label study. Eligible subjects will be registered and assigned to the available treatment cohorts. Subjects will be assigned to the cohort allocation after they have given their written informed consent and have completed the necessary baseline assessments. The subject will be assigned an identification number, which will be used on all case report forms (CRFs) and other study-related documentation

4. STUDY POPULATION

4.1 Patient Number/Study Sites

Approximately 50 subjects will be recruited for this study in the United States.

4.2 Eligibility Criteria

4.2.1 Overview

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment.

The following criteria apply to all patients enrolled in the study unless otherwise specified.

4.2.2 Inclusion Criteria

1) Subjects able to give voluntary informed consent, understand the study and are willing to follow and complete all the test procedures.
2) Subjects (males and females) of childbearing potential should be willing to use reliable contraception methods that are deemed effective by the investigator from visit 1 through 90 days following the last dose of study drug. Postmenopausal women must have been amenorrhea for at least 12 months to be considered of non-childbearing potential.
3) Male or female subjects ≥18 years
   a) At least one measurable lesion (per RECIST version 1.1)
   b) Eastern Cooperative Oncology Group (ECOG) Performance Status ≤1.
   c) Subjects with life expectancy of ≥ 3 month
4) If subject received anti-tumor therapy:
   a) Generalized radiation therapy must have been completed 3 weeks prior to enrollment, or local radiotherapy or radiation therapy for bone metastases for 2 weeks prior to enrollment. Treatment with radiopharmaceuticals must have been completed 8 weeks prior to enrollment.
   b) Previous chemotherapy, biotherapy (tumor vaccines, cytokines, or growth factors that control cancer), tyrosine kinase inhibitors, or approved targeting and other treatments should have completed at least 3 weeks prior to the first administered dose in this study;
5) Subjects must have adequate organ function (liver, kidney function and hematopoietic function tests) prior IBI308 administration
   a) Absolute neutrophil count (ANC) ≥1.5 x10^9/L
   b) Platelet count ≥ 100 x 10^9/L
   c) Hemoglobin ≥ 9 g / dL (whole blood or component transfusion within 7 days before 1st dose of study drug is prohibited)
   d) Renal function tests: serum creatinine ≤1.5 ×upper limit of normal range (ULN) or an estimated glomerular filtration rate (eGFR) ≥ 50 mL/min/1.73 m^2
   e) Liver function tests alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN, for patients with known liver cancer or liver metastases, AST and ALT ≤ 5 x ULN

f) Total bilirubin (TBil) ≤1.5 x ULN; If Gilbert's Syndrome may have Bilirubin> 1.5 x ULN
g) Coagulation tests: aPTT ≤ 1.5 x ULN and INR ≤2.0

6) Cohort Specific Inclusion Criteria:

Cohort 1: Advanced/metastatic cancers with high TMB expression

i. Advanced/metastatic cancers with TMB level > 10 mut/Mb
ii. Histologically or cytologically confirmed unresectable Stage III/IV NSCLC or other advanced/metastatic cancers (for example, melanoma, bladder cancer, SCLC, prostate cancer, colorectal cancer, gastric cancer)
iii. Separate informed consent is required for subjects who provide fresh biopsies for serial tumor biopsies for biomarker testing. TMB testing should be performed on the most recently obtained tumor sample.
iv. Subjects must be tested for TMB level before entering the study, and pre-screen informed consent is required for TMB testing. Subjects who have existing FoundationOne TMB testing results from within 6 months of study entry do not need to have repeat testing.
v. Refractory or intolerant to standard therapy or for whom no standard therapy exists. Subjects must have no available therapy likely to confer clinical benefit for their cancer. Subjects who experienced irAE grade ≥ 3, or grade 2 recurrent pneumonitis, or who had to discontinue prior anti-PD-1/PD-L1 treatment due to irAEs of any grade will not be eligible.
vi. NSCLC subjects with EGFR mutation and/or ALK rearrangement and/or ROS-1 positive, should have received appropriate targeted therapy and are refractory to targeted therapy prior to enrolling this trial.

Cohort 2: Advanced/metastatic endometrial Cancer

i. Histologically confirmed advanced/metastatic endometrial cancer.
ii. Refractory or intolerant to standard therapy, and no available therapy likely to confer clinical benefit for their cancer. Subjects who experienced irAE grade ⩾ 3, or who had to discontinue prior anti-PD-1/PD-L1 treatment due to irAEs of any grade will not be eligible.

4.2.3 Exclusion Criteria

1) Legal incapacity or limited legal capacity.
2) Pregnancy, lactation, breastfeeding.
3) Concurrent anticancer treatment (e.g., cytoreductive therapy or cytokine therapy except for erythropoietin) or use of other investigational product within 28 days before start of trial treatment; major surgery within 28 days before start of trial treatment (excluding prior diagnostic biopsy.
   Note: Small molecule or antibody targeted therapy < 3 weeks from start of trial treatment will be excluded.
4) Received a biologic (G-CSF, GM-CSF) within 14 days prior to the first dose of study drug.
5) Vaccination within 4 weeks of first dose of IBI308 and while on study except for administration of inactivated vaccines (e.g., inactivated influenza vaccines)
6) Failure to recover from adverse events from the most recent anti-tumor treatment to CTCAE ≤ grade 1 or baseline with the exception of alopecia;
7) Active autoimmune disease requiring systemic treatment within the past 1 year or a documented history of clinically severe autoimmune disease or a syndrome that requires

systemic steroids or immunosuppressive agents during the conduct of this study. Exceptions: - Vitiligo, eczema, psoriasis (<10% of body surface area (BSA) of skin eruption or systemic involvement) or resolved childhood asthma/atopy, autoimmune hypothyroidism stable on hormone replacement.

8) History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
9) Acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.
10) History of primary immunodeficiency, stem cell or organ transplant, or previous clinical diagnosis of tuberculosis.
11) Subject who have had severe infection within 4 weeks or signs and symptoms of any active infection within 2 weeks prior to the first dose administration.
12) Known allergies, hypersensitivity, or intolerance to protein-based therapies or with a history of any significant drug allergy (e.g., anaphylaxis, hepatotoxicity, immune-mediated thrombocytopenia or anemia
13) Subjects who experienced (irAE) grade ⩾ 3 immunotherapy-related adverse events. Subjects with CNS metastasis unless they are asymptomatic or adequately treated with radiotherapy and/or surgery and subjects are neurologically stable with minimal residual symptoms/signs 14 days prior to dosing.
14) Patients who require high dose of systemic corticosteroids (>10 mg/day prednisone or equivalents) for at least 2 weeks prior to treatment are not eligible.
15) Severe or uncontrolled cardiac disease requiring treatment, congestive heart failure (New York Heart Association) NYHA III or IV, unstable angina pectoris even if medically controlled, history of myocardial infarction during the last 3 months, serious arrhythmias requiring medication (with exception of atrial fibrillation or paroxysmal supraventricular tachycardia).
16) Any other serious underlying medical (e.g., uncontrolled hypertension, active uncontrolled infection, active gastric ulcer, uncontrolled seizures, cerebrovascular incidents, gastrointestinal bleeding, severe signs and symptoms of coagulation and clotting disorders, other serious cardiac conditions not listed in exclusion criteria), psychiatric, psychological, familial or geographical condition that, in the judgment of the investigator, may interfere with the planned staging, treatment and follow-up, affect patient compliance or place the patient at high risk from treatment-related complications.

4.3 Subject Screening Procedures

A written ICF must be obtained prior to initiating pre-screening for TMB status with the FoundationOne assay. TMB testing should be performed on the most recently obtained tumor sample. Specimen handling is described in the Biomarker section of this protocol (6.1.3.2). If the subject meets the TMB eligibility criteria for cohort 1, the subject will be asked to sign the main study ICF and will then undergo the complete screening. Subjects who have existing FoundationOne TMB testing results from within 6 months of study entry do not need to have repeat testing.

Written ICF must be obtained prior to any study-related procedures. Screening procedures will be conducted at qualified clinical research centers. Demographic data to be recorded in the eCRFs include subjects' gender, race, and date of birth.

Prior to participation in the study, all volunteers will have a routine history and physical along with screening blood tests. The screening procedures and assessments must be completed within 28 days of the study treatment visit Day 1 (Schedule of Events). Weight, height and vital signs will also be obtained upon screening. All female volunteers will have a urine pregnancy test and will be asked to participate only if the test is negative. In addition, female and male subjects will be asked to practice a reliable medically accepted form of birth control during participation in the study. In this proposed application, all subjects will have a baseline 12-lead ECG to exclude cardiovascular disease before entering the study. Subject's current medication schedule will be reviewed to ensure patients safety during the treatment.

After all the screening results are obtained eligibility criteria will be reviewed and a complete clinical evaluation will be performed. All screening assessments will occur within 28 days prior to the first dose of study drug.

If an assessment was performed as part of the subject's routine clinical evaluation and not specifically for this study, it does not need to be repeated after signed ICF has been obtained. However, the assessments must fulfill the study requirements and should be performed within the specified timeframe prior to the first dose of study drug. Retesting of abnormal screening values that lead to exclusion are allowed only once during the Screening Phase (to reassess eligibility). The last result obtained prior to the first dose of study drug will be used to determine eligibility.

The prospective subject's medical history will be assessed prior to the initial treatment for continued study eligibility and adherence to final inclusion/exclusion criteria. During the Treatment Period, a symptom-based assessment will be maintained. The recent medical history assessment will include recent medication changes that have occurred since the previous visit.

5. STUDY INTERVENTION

5.1 Study Drug

The IBI308 drug product (DP), is a 10 mg/mL solution for IV infusion, to be stored at 2-8 ℃, in single-use colorless and transparent 15 ml borosilicate glass Type I vials. Each vial of IBI308 DP contains 100 mg/10 mL of IBI308 drug substance in 30.06 mg/mL mannitol, 3.73 mg/mL L-histidine, 2.92 mg/mL sodium chloride, 0.0075 mg/mL ethylenediaminetetraacetic acid (EDTA-2Na), 0.2 mg/mL polysorbate 80, 5.88 mg/mL sodium citrate dehydrate. The DP vial is capped with polytetrafluoroethylene membrane chlorinated butyl rubber stopper and sealed with an aluminum cap. IBI308 will be supplied by the sponsor.

The storage and handling of the diluted DP should meet the following time and temperature limits:

- Storage time should be limited to 8 hours at room temperature following DP dilution into the infusion bag including infusion time.
- Storage time should be limited to 24 hours at 2-8 oC following DP dilution into the infusion bag including infusion time.

5.2 Treatment Compliance and drug accountability

The site should maintain accurate dosage preparation records and should ensure that all pertinent/required information on the preparation and administration of the dose is captured in

source documents, and appropriate dosing information is entered onto CRFs. This information should be readily available during the monitoring visits.

Upon termination of the study, or at the request of the sponsor, the pharmacist must return the study drugs to sponsor, unless it is destroyed at the site as agreed upon by both the sponsor and the site.

5.3 Dosage and Drug Administration

This is an open label study without blinding or randomization. Prior to use, DP is supplied as a solution for IV infusion packaged in single-use glass vials. Prior to administration, IBI308 will be diluted to the required volume to achieve a final concentration of 2mg/mL using 0.9% sodium chloride solution. Administer the infusion over 60 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

All dose administrations will be performed in the clinical center under the supervision of appropriately trained staff. Blood samples will not be collected from the arm used for the IV infusion for at least 24 hours after administration. Subjects should not receive prophylactic pre-medication, unless they have suffered an infusion reaction in a prior cycle of administration of study drug.

5.4 Dosing Procedure and Treatment cycles

This trial will include 2 cohorts, and total of approximately 50 subjects. Please see **Table-5**.

Each cycle will consist of 21 days and each subject will receive IBI308 on a Day1 of each cycle and continue treatment with IBI308 until disease progression or intolerable toxicity, withdrawal of consent, or end of study, whichever occurs first.

Table-5. Study population, sample size and treatment dose.

Cohort Number	Indication	Patient Number	IBI308 Dose
Cohort 1	Advanced/metastatic cancers with TMB level >10mut/Mb	2 enrolled as of 1/7/2019	200 mg
Cohort 2	Advanced/Metastatic Endometrial Cancer	40	200 mg

5.5 Duration of Treatment

Patients may continue to receive IBI308 until disease progression or intolerable toxicity, death, withdrawal of consent, or end of study up to 2 years, whichever occurs first.

5.6 Treatment Beyond Disease Progression

Subjects treated with IBI308 will be permitted to continue treatment beyond initial RECIST 1.1 defined disease progression as long as they meet the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression

2. Continue to meet all other study protocol eligibility criteria

3. Tolerance of study drug

4. Stable performance status

5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)

6. Subject provides written informed consent prior to receiving additional IBI308 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial progression should be discussed with the Sponsor Medical Manager and documented in the study records.

A radiographic assessment/scan should be performed within six (6) weeks of original disease progression to determine whether there has been a decrease in the tumor size, or continued disease progression. The assessment of clinical benefit should be assessed by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with IBI308.

If the investigator considers that the subject on IBI308 continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Schedule of Events. The decision to continue treatment should be discussed with the Sponsor Medical Manager and documented in the study records.

5.7 Dose Modification and Management of Withholding, Resuming or Discontinuation of the Study Drug

Dose modifications are not permitted during this study unless intolerable toxicities occur. If significant toxicity occurs, dosing may be delayed or permanently discontinued as described below. In the event of multiple toxicities, dosing management should be based on the worst toxicity observed (Refer to Section 5.8).

5.7.1 Criteria for Withholding Study Drug

1) Grade ≥2 non-skin, drug-related AEs with the following exceptions: Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
2) Grade ≥2 immune-mediated ocular disease will result in withholding study drug.
3) Any Grade 3 drug-related laboratory abnormalities with the following exceptions for lymphopenia, leukopenia, AST, ALT or total bilirubin
   a. Grade 3 lymphopenia or leukopenia does not require dose delay
   b. If a subject's baseline AST, ALT or total bilirubin was WNL, delay dosing for drug-related Grade ≥2 toxicity
   c. If a subject's baseline AST, ALT or total bilirubin was in a Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity

4) Any AE, laboratory abnormalities, or intercurrent illness, which in the judgment of the Investigator warrants delaying the dose of study drug.

5.7.2 Criteria to Resume Treatment

Subjects may resume treatment with study drug(s) when the drug-related AEs resolve to Grade ≤1 or baseline value or with the following:

1) Patients with Grade 2 fatigue
2) Patients with Grade 2 skin toxicity provided they have not experienced Grade 3 or higher skin toxicity
3) Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed
4) Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

5.7.3 Criteria for Drug Discontinuation

1) Discontinue treatment for Grade 3 or higher drug-related AEs of pneumonitis, creatinine, neuropathy, diarrhea/colitis that may lead to bowel perforation
2) Discontinue treatment for any other Grade 4 drug-related AEs or laboratory abnormality, except for the following events which do not require discontinuation.
   a. Isolated grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < grade 4 within 1 week of onset
   b. Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
3) Discontinue treatment for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks (except for endocrinopathies that are controlled with replacement hormones)
4) Grade 4 increases in liver function tests (subjects with liver involvement) or Grade 3 increases in liver function tests (subjects without liver involvement)
5) Discontinue treatment for persistent drug-related AE that does not recover to Grade 0-1 or baseline within 12 weeks unless otherwise agreed to by the sponsor representative and the investigator based on evidence of clinical benefit
6) Discontinue treatment for any recurrent Grade 2 pneumonitis or recurrence of same Grade 3 AEs
7) Discontinue treatment for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued investigational drug dosing.

Following treatment discontinuation, the subject should complete the EOT Visit as described in Schedule of Events.

5.8 Special Precautions and Clinical Interventions

5.8.1 Infusion Reactions

All therapeutic monoclonal antibodies (mAbs) used for cancer treatment have the potential to cause infusion reactions. Symptoms vary with a wide spectrum of severity, ranging from mild fever and chills to life-threatening anaphylaxis with bronchospasm, and hypotension. Typically, infusion reactions to monoclonal antibodies develop within 30-120 minutes after the initiation of drug infusion, although symptoms may not show up until 24 hours. The majority of reactions occur after the first or second exposure to drug, although it can also rarely occur during subsequent treatments. Additionally, the risk of infusion reaction declines with each subsequent course of therapy.

Most common symptoms or "standard infusion reactions" (SIRs) are fever/chills, nausea, vomiting diarrhea, itching/flushing, rash changes in blood pressure (BP) and heart rate (HR), dyspnea, chest discomfort, back and abdominal pain.

Although exact mechanism of SIRs caused by mAbs is not fully clear, most likely it is a result of antibody-antigen interactions resulting in cytokine release.

Although premedication can help to prevent and/or reduce the severity of infusion reactions, anaphylaxis generally cannot be prevented by premedication. Thus, the following supplies and equipment needs to be readily available in any area where chemotherapy is administered: IV fluids, epinephrine, antihistamines, oxygen, aerosolized bronchodilators, intubation and tracheostomy equipment, and a defibrillator.

The investigator will be responsible for managing infusion related and hypersensitivity reactions according to local standard procedure or follow the recommendations listed **Table-6**.

Table-6 Management of Infusion-Related Reactions/Hypersensitivity Reactions (NCI CTCAE Grade)

Grade 1 Mild transient reaction; infusion interruption NOT indicated; intervention NOT indicated	• Monitor subject closely until recovery from symptoms, Consider premedication with 50 mg diphenhydramine or 650 acetaminophen at least 30 minutes before additional study drug administration
Grade 2 Cessation of infusion or therapy is indicated. Responds promptly to symptomatic treatment.	• Stop infusion; start IV saline infusion; IV **50 mg diphenhydramine or 650 acetaminophen**; depending on symptoms, consider corticosteroids and bronchodilator therapy; remain at bedside and monitor subject until recovery from symptoms • Restart infusion at 50% of initial rate: if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate; monitor subject closely. • Prophylactic medication indicated for less than or equal to 24 hours • Symptoms recur: stop and discontinue further treatment at that visit; administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF.
Grade 3-4 Prolonged recurrence of symptoms, hospitalization indicated for other clinical sequelae, maybe life threatening and	• Stop infusion; start IV saline infusion; recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1: 1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1: 10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. • Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional

hospitalization may require. Should discontinuation from treatment	guidelines for the treatment of anaphylaxis. In the case of late-occurring hypersensitivity symptoms (for example, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.8.2 Extravasation

In the event of extravasation, infusion should be stopped immediately and the investigator needs to be consulted immediately. Treatment of extravasation should follow local standard of care.

5.8.3 Immune Related Adverse Events (irAE)

Checkpoint inhibition is associated with a wide spectrum of side effects defined as immune-related adverse events (irAE). IrAEs may include gastrointestinal, hepatic, endocrine, dermatologic and inflammatory events. Early recognition and management of these irAEs may mitigate more severe and subsequent toxicities.

General, treatment is based upon the severity of the observed toxicity. Recommendations for irAE treatment:

- Subjects should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and/or topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.

Immunosuppressive agents should be considered for events not responding to systemic corticosteroids.

5.8.3.1 Management of Gastrointestinal irAEs

Diarrhea/colitis is the most common GI symptom in patients treated with checkpoint inhibitors. Usually it presents approximately in six weeks after starting treatment.

The investigator will be responsible for managing GI irAEs according to local standard procedure or follow the recommendations listed **Table-7**.

Table-7 Management of Gastrointestinal irAEs

Grade 1	• **Symptomatic treatment (for example, loperamide) according to institutional standards;** • **Close monitoring; instruct subject to report worsening immediately and treat as Grade ≥2**
Grade 2	• ≤5 days: Symptomatic treatment according to institutional standards • >5 days or recurrence: 0.5–1.0 mg/kg/d methylprednisolone; consider prophylactic antibiotics; • Persistence or worsening despite steroids >3 days: treat as Grade 3/4

	• Improvement to ≤Grade 1: taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4 **permanent discontinuation from treatment**	• Immediately: 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower colonoscopy • Persistence >3 days or recurrence: add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) • Improvement to ≤Grade 2 within ≤3 days: taper steroids over at least 4 weeks

5.8.3.2 Management of Hepatic irAEs

The investigator will be responsible for managing hepatic irAEs according to local standard procedure or follow the recommendations listed **Table-8**:

Hepatic function test (transaminases and bilirubin) should be monitored prior each administration of the investigational drug.

Table-8 Management of Hepatic irAEs

Grade 1	• **Continue liver function monitoring** • **If worsens: Treat as Grade ≥2**
Grade 2	• Monitor every 3 days; • Returning to baseline: resume per protocol monitoring • Patients who experience grade 2 hepatitis regardless of duration should receive 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent; consider prophylactic antibiotics • LFT return to ≤Grade 1 or baseline: taper steroids over at least 4 weeks; resume routine monitoring and resume study treatment per protocol
Grade 3-4 Should be discontinued	• Monitor every ≤2 days; • Immediately: 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist • Persistence >3 days or recurrence: add mycophenolate mofetil 1g bid; if no response within ≤5 days, consider other immunosuppressants per local guidelines • LFT return to Grade 2: stop immunosuppressants • LFT return to ≤Grade 1: taper steroids over at least 4 weeks

5.8.3.3 Management of Dermatological irAEs.

The investigator will be responsible for managing dermatologic irAEs according to local standard procedure or follow the recommendations listed **Table-9**. For guideline of dose delay/discontinuation, refer to Section 5.7.

Anti-PD-1 antibodies can cause immune mediated rash, including Steven-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) that can also lead to fatal outcomes in some cases.

If SJS and TEN symptoms are suspected withhold IBI308 and refer to specialized care; if SJS and TEN confirmed permanently discontinue IBI308.

Table-9 Management of Dermatological irAEs.

Grade 1-2	• Symptomatic treatment (for example, antihistamines, topical steroids); • Persistence ≤2 weeks or recurrence: consider skin biopsy; consider 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics • Improvement to ≤Grade 1: taper steroids over at least 4 weeks • Worsening to >Grade 2: treat as Grade 3-4
Grade 3-4 Should discontinuation from treatment be warranted	• Consult dermatologist; consider skin biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics • Improvement to ≤ Grade 1: taper steroids over at least 4 weeks

5.8.3.4 Management of Endocrine irAEs

Endocrinopathies associated with checkpoint inhibitors include disorders of pituitary, thyroid, or adrenal glands, which often represents as with nonspecific symptoms such as nausea, headache, fatigue, and vision change.

Hypophysitis is often manifested by headaches and fatigue. It is diagnosed by reduced levels of pituitary hormones (TSH, follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), Adrenocorticotropic hormone (ACTH), and prolactin). In the event when hypohysitis is suspect investigational drug should be discontinued and high dose steroids need to be started to prevent the need for longer-term hormone replacement. In case of endocrine AEs endocrinology consults is recommended.

Hormone replacement needs be started as clinically indicated and corticosteroids should be administered at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis.

Permanently discontinue IBI208 if AE is ≥ Grade 3. Endocrinology consults is recommended.

In case of suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness) discontinue IBI308, rule out sepsis, and urgently initiate IV fluids, high dose of IV steroids with mineralocorticoid activity and consult endocrinologist. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency.

In addition to endocrine consult, when hypophysitis and adrenal insufficiency AE occur ≥Grade 2 withhold the dose until improves to grade 0 or 1 and permanently discontinue if≥Grade 3.

In the event of autoimmune hyper- or hypothyroidism thyroid functions needs to be monitored and hormone-replacement administered in case of hypothyroidism. No recommended dose adjustments are indicated during thyroid AEs.

5.8.3.5 Management of Pulmonary irAEs

Prior diagnosing drug-induced pneumonitis, alternative diagnoses, including infections needs to be excluded. Although pneumonitis is not a common complication, it is a potentially severe or fatal complication with checkpoint inhibitor immunotherapy treatment.

The investigator will be responsible for managing pulmonary irAEs according to local standard procedure or follow the recommendations listed **Table-10**.

Table-10 Management of Pulmonary irAEs.

Grade 1 **Asymptomatic; clinical or diagnostic observations only; intervention not indicated**	• **Withhold Investigational Drug for 2-4 weeks with close monitoring.** • **Monitor for symptoms every 2-3 days; consider pulmonary and infectious-disease consult; Re-image every 3 weeks.**
Grade 2 **Symptomatic; medical intervention indicated**	• **Withhold Investigational Drug** • Monitor symptoms daily; Consult to pulmonary and infectious-disease; consider bronchoscopy and lung biopsy; consider hospitalization • Immediately: start IV steroids or oral equivalent; prophylactic antibiotics • Additional immunosuppression may be used in patients with worsening of pneumonitis • Persistence for 2 weeks or worsening: treat as Grade 3-4 • Improvement to ≤ Grade 1 or baseline: taper steroids over at least 4 weeks
Grade 3-4 **Severe symptoms; limiting self-care ADL; oxygen indicated** **Discontinuation permanently**	• Hospitalize; pulmonary and infectious-disease consult; consider bronchoscopy and lung biopsy Immediately: 2-4 mg/kg/d methylprednisolone or IV equivalent; add prophylactic antibiotics; Persistence for 2 days or worsening: add immunosuppression (e.g., infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) Improvement to ≤ Grade 2: taper steroids over at least 6 weeks

5.8.3.6 Management of Renal irAEs

Immune-mediated nephritis and renal dysfunction is less commonly caused by PD-1/PD-L1 inhibitors. Patients need to be monitored periodically for elevated serum creatinine prior to and during treatment.

The investigator will be responsible for managing renal irAEs according to local standard procedure or follow the recommendations listed **Table-11**.

Table-11 Management of Renal irAEs.

Grade 1	**Monitor creatinine weekly** • **Creatinine returns to baseline: continue monitoring per protocol** • **Creatinine increases: treat as Grade ≥2**
Grade 2-3 **Permanently discontinue from treatment for Grade 3 nephritis regardless of duration**	**Withhold investigational Drug** • Monitor creatinine every ≤3 days • Immediately: 1-2 mg/kg/d prednisone or equivalent; consider prophylactic antibiotics and nephrology consult if no improvement to ≤Grade 1: taper steroids over at least 4 weeks. • Grade 3 nephritis regardless of duration will be permanently discontinued. • Persistence >7 days or worsening: treat as Grade 4
Grade 4 **Permanently discontinue from treatment regardless of duration**	Monitor creatinine daily • Immediately: consult nephrologist; consider renal biopsy; start 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; add prophylactic antibiotics • Improvement to ≤Grade 1: taper steroids over at least 4 weeks

5.8.3.7 Management of Pancreatic irAEs

Although elevated levels of serum amylase and lipase have been reported with check point inhibitors but often these laboratory findings do not fulfill the criteria for acute pancreatitis and most of these patients are asymptomatic. Withhold treatment if Grade 2 or 3 pancreatitis, or Grade 3 or 4 increases in amylase or lipase levels occurs (>2.0 times ULN). In asymptomatic patients close observation is recommended. PI should ensure that subjects do not exhibit pancreatitis associated symptoms, such as abdominal pain. Corticosteroid treatment is not indicated in asymptomatic patients with moderate pancreatic enzyme elevations, if no other signs or symptoms of pancreatic inflammation exists. In any case of recurrent pancreatitis or grade 3 pancreatitis discontinue treatment permanently.

5.8.3.8 Management of Cardiac irAEs

Cardiotoxicity may develop in the absence of cardiac risk factors and may be associated with a more general myositis and other irAEs. Treatment for cardiac toxicities is usually high dose steroids although in some cases symptoms might still progress despite aggressive treatment.
In case of elevated troponin and conductions abnormalities immediate transfer to a coronary care unit should be considered.

5.8.3.9 Management of Neurologic irAEs

A variety of neurologic syndromes have been associated with checkpoint blockade. Commonly reported neurologic cases includes but not limited to Guillain-Barre syndrome, myasthenia gravis, transverse myelitis, autoimmune encephalitis.

Serious neurologic irAEs should be treated with corticosteroids and consultation with neurology is indicated. Additionally, plasmapheresis and intravenous immunoglobulin treatments might be necessary.

5.8.3.10 Other Precautions

Uveitis, iritis, myositis, hemolytic anemia, seizures, vasculitis, polymyalgia rheumatica, facial and abducens nerve paresis were also associated with anti-PD-1 antibodies. The investigator will be responsible for managing irAE according to local standard procedure or refer to specialists.

5.9 Concomitant Medication

Some concomitant medications are allowed during the study to treat infusion-related reactions and other adverse events for symptomatic relief or management irAEs as specified in Section 5.8 above. Hormonal replacement therapy anticoagulation therapy, oral contraceptives, and inhaled corticosteroids/mineralocorticoids can be used or continue their use during the study at the discretion of the investigator.

5.10 End of Treatment (EOT)

An EOT Visit will be scheduled within 7days ±3 days after the last dose of study drug for all subjects, including those discontinuing treatment for any reason, except for patients lost to follow-up, death, or withdrawal of consent for study participation. The EOT Visit should be completed before starting any subsequent anticancer treatment. If a subject is unable to return to the site for the EOT Visit, the subject should be contacted to collect AEs and concomitant medications that occur up to 30± 7 days after the last dose of study drug.

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

5.11 Follow-up

For follow-up procedures see Schedule of Events. At least 30 days and no more than 37 days after discontinuation of treatment, subjects will return to undergo the assessments outlined in the Schedule of Events as well as a review of concomitant medications, vital signs, and assessment for resolution of any treatment related toxicity. Subjects continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

In the event a subject is unable to return to the clinic for the follow-up visit, telephone contact with the subject to assess AEs and concomitant medications and treatment is expected. If laboratory assessments are needed to follow-up unresolved AEs, retrieval of assessments performed at an institution local to the subject is acceptable.

To collect OS data, subjects will be contacted by telephone every 3 months (±7 days) post - EOT visit.

5.12 Removal from Study Treatment and off-Study Criteria

Participation in this research study is completely voluntary. Subjects are free to withdraw from this study at any time by informing the investigator. If a subject, for whatever reason, no longer appropriate to continue receiving study therapy, they will be notified and withdrawn from the study. Furthermore, if the subject is non-compliant (e.g. non-compliant with visits, concomitant medications.) they will be withdrawn from the study and a replacement subject may be recruited.

Additionally, prior to removal from study, efforts must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

5.12.1 Criteria for removal from study treatment

If subjects are taken off study treatment, they will be followed until meeting the Off-Study criteria in Section 5.12.2. When subjects are off protocol therapy, data will be still collected to meet protocol objectives.
Also, subjects who complete study treatment will be still followed for other study endpoints.
Below are Criteria for removal from study treatment:

- Death
- EOT
- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable toxicity
- Investigator discretion
- Positive pregnancy test

5.12.2 Off-Study Criteria

Once a subject is taken off study, no further data can be collected.

- Participant requests to be withdrawn from study
- Subject withdrawal from the follow-up period
- Subject completed all protocol required follow-ups
- Death
- Screen failure

5.13 Pregnancy/Contraception/Nursing

5.13.1 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 72 hours before Cycle 1 dosing and after the last dose of study drug. If a urine test is positive or borderline (unable to

confirm as negative), a serum β-hCG test will be required. Patients must be excluded in the event of a positive or borderline test result. The results of the pregnancy test will be recorded.

5.13.2 Contraception

IBI308 may have adverse effects on a fetus in utero. Furthermore, it is not known if IBI308 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ⩾45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) amenorrheaic for <1 year without a hysterectomy or oophorectomy and with a documented FSH value in the postmenopausal range, or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use 2 methods of birth control (which is also recommended for the female partners of male patients). The 2 birth control methods can be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1 through 90 days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 90 days after the last dose of study drug. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.13.3 Use in Pregnancy

IBI308 may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a female subject inadvertently becomes pregnant while on treatment with IBI308, the subject will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the SPONSOR. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the SPONSOR. See Section 9.6 for the details of pregnancy reporting.

5.13.4 Use in Nursing Women

It is unknown whether IBI308 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

6. STUDY ASSESSMENT AND EVALUATIONS

6.1 Specimen Collection and Evaluations

6.1.1 Pharmacokinetics (PK)

Intensive PK blood samples will be drawn from first 6 subjects in cohort 1 and first 12 subjects in cohort 2, PPK will be drawn from other subjects at the time points indicated in **Table-2**. Blood samples should be drawn from a site other than the infusion site on days of infusion. If the infusion is interrupted, the reason for interruption will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70ºC. Serum samples will be analyzed for IBI308 by a validated method. For each time point, 2 ml whole blood sample needs to be collected for PK testing. Further details on PK sample collection and processing will be provided to the site in a procedure manual.

6.1.2 Immunogenicity

Blood samples for anti-drug antibody (ADA) analyses will be collected at predose in Cycle 1 and Cycle 2 and then in every other subsequent cycle, and at the mandatory Safety Follow-up Visit or until start of a new anti-cancer therapy, whichever occurs first. Analysis will be performed by a central laboratory. For each time point, 4 ml whole blood sample needs to be collected, further details on ADA sample collection and processing will be provided to the site in a procedure manual.

6.1.3 Biomarkers

A variety of factors that could potentially predict clinical response to IBI308 will be investigated in tumor specimens obtained at screening, and in peripheral blood taken both at screening (prior to first dose of study drug) and during the study, from all subjects as outlined in Schedule of Events. Data from these investigations will be evaluated for associations with objective response, survival (OS, PFS).

6.1.3.1 Peripheral Blood Biomarkers

Serum will be obtained from all subjects prior to first dose of study drug, and during the study at every other cycle. Biomarkers measured in blood will focus on blood TMB and Serum-Soluble Factors.

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity of IBI308, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors will be evaluated by ELISA, serum chemistry, and/or other relevant multiplex-based protein assay methods. Examples of analytes

to be assessed include but are not limited to factors induced by IFN_{γ} signaling (e.g. T cell chemoattractants CXCL9; CXCL10), antibodies to tumor-associated antigens, and soluble PD-L1 (PD-L1), which may play an important role in immune tolerance and disease progression. For each time point, 10 ml whole blood sample needs to be collected for blood biomarkers testing. Further details on blood biomarker sample collection and processing will be provided to the site in a procedure manual.

6.1.3.2 Tissue Biomarkers

Before entry into study, every subject in cohort 1 must have testing for TMB by FoundationOne and the information of TMB level must be available. The FoundationOne assay was approved by The U.S. Food and Drug administration on Nov 30, 2017, and it was validated to detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type. Average sequencing depth of coverage was greater than 250x, with >100x at >99% of exons. For TMB, the number of somatic mutations detected on NGS (interrogating 1.2 Mb of the genome) are quantified and that value extrapolated to the whole exome using a validated algorithm. Alterations likely or known to be bona fide oncogenic drivers and germline polymorphisms are excluded. TMB is measured in mutations per megabase (Mb). In this study, only patients with TMB levels > 10 mut/Mb are eligible.

For FoundationOne testing specimens should follow the established FoundationOne Specimen Instruction documentation provided by Foundation Medicine. In summary the sample should either be a formalin-fixed, paraffin-embedded tumor tissue block and 1 original H&E slide, or 10 unstained 4-5 micron thick slides with 1 H&E slide. The surface area of the specimen should be 5-25 mm2. The tumor content of the specimen should be 20-30% estimated based on nuclei count. Cut formalin-fixed paraffin-embedded slides are stable for this analysis for at least 6 months.

Acceptable samples include formalin-fixed paraffin-embedded specimens, including core-needle biopsies, ne-needle aspirates, and effusion cytologies. Use standard fixation methods to preserve nucleic acid integrity. 10% neutral-buffered formalin for 6–72 hours is industry standard. Do not use other fixatives (Bouins, B5, AZF, Holland's). Do not decalcify. When decalcifcation is required, EDTA is recommended. Do not use strong acids (e.g., hydrochloric acid, sulfuric acid, picric acid).

For other biomarkers, a formalin-fixed, paraffin-embedded tumor tissue block or unstained slides (minimum 10 requested) of tumor sample (archival or recent) for biomarker evaluation will be obtained prior to subject enrollment. A reference laboratory will receive the samples for immunohistochemistry (IHC)-based analyses aimed at determining the abundance of the immunoregulatory proteins such as PD-L1. Additional immunohistochemical analysis may be completed to determine the abundance of other protein markers associated with TILS. The abundance of each protein monitored (or combinations of proteins) will be correlated with clinical endpoints. FFPET may be evaluated also by fluorescent in-situ hybridization (FISH), genetic mutation detection methods, and/or by RT-QPCR as part of additional exploratory analyses of putative biomarkers thought to be associated with response or resistance to therapeutics. Such analyses will be completed retrospectively and within the scope of informed consent.

Tumor samples: (meeting any of the following requirements)

Sample Type	Sample Collecting	Storage Temperature	Transportation	Remarks
Paraffin-embedded tissue (FFPE)	10~15 copies for surgical biopsy, at least 5 copies; >15 copies for puncture biopsy; Paraffin block 50mg (bean-size)	<37℃	Room temperature is acceptable	Paraffin unstained samples within 6 months.
Puncture biopsy	2 punctures recommended or at least once. 1-2mm diameter and more than 0.5cm length for each sample.	With preservation solution:<25℃ Without preservation solution:<-20℃	With dry ice	Try not to keep in formalin
Fresh tissue	No less than 60mg (bean-size)	With preservation solution:<25℃ Without preservation solution:<-20℃	With dry ice	Please ensure the tissue sample is completely immersed in liquid once preservation solution was used

6.1.4 Safety Laboratory Evaluations

Safety labs will be drawn to assess AEs. CBC with differential, blood chemistry, thyroid tests (TSH, free T3 and T4), urine analysis will be obtained prior to each dosing. Coagulation tests (INR, aPTT) will be obtained within 7 days prior to first dosing on Day 1.

AEs will be graded according to the CTCAE v4.03. Investigators will report whether an AE is potentially immune related (irAE).

7. DATA COLLECTION AND MANAGEMENT

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Hardcopies of the study visit worksheets will be used as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into EDC, which is a 21 CFR, Part 11-compliant data capturing system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Only individuals who have received training on the EDC are allowed to make eCRF entries, corrections, and alterations. Training must be documented and a log of all EDC users and their rights within the system be maintained. The data management team will raise queries in the

EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct.

Any outstanding entries must be completed immediately upon notice. No blank sections should be left on CRF and explanations have to be recorded for all missing data. All source documents should be retained. All essential documents should only contain subject coded identifiers and no personal identifying information should be transmitted.

7.1 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, study manuals, or ICH GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Compliance with Protocol
- Quality Assurance and Quality Control
- Noncompliance

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and if applicable, in eCRFs and study reports, in coordination with the sponsor or their designated CRO. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the requirements of the reviewing IRB.

7.2 Publication and Data Sharing

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee.

8. HUMAN SUBJECT PROTECTION AND REGULATORY OVERSIGHT

8.1 Informed Consent Processes and Documentation

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written ICFs and any other written information to be provided to the participants. Participants will be asked to read and review IRB-approved ICFs and other written information. ICF should include detailed description of study procedures, risk and benefits, directions, participant's rights, compensation if applicable, and contact of

Human Subject Protection Services. Additionally, investigator will explain the research study to the participant in terms suited to the participant's comprehension and answer any questions that may arise. Investigator should explain their rights as research participants, study procedures, risk and benefits, anticipated adverse effects. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. ICF should be signed prior to any interventions for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Participant will be given a copy of the signed consent form and the original consent form will be kept as a permanent record. Obtaining ICF should be documented in the source document.

8.2 Institutional Review Board Approval

The Sponsor/Investigator will obtain prospective approval of the clinical protocol and corresponding informed consent form(s), and any other written information to be provided to the participants from Institutional Review Board (IRB). Additionally, any modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment also requires IRB approval.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent forms may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject. In such circumstances, the Sponsor/Investigator will promptly notify the IRB of the deviation.

The Sponsor/Investigator has to operate in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event of modification of the protocol the sponsor/investigator will submit (i.e., in advance of implementing the change) a protocol amendment to the IND describing any change to the protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples such changes requiring a protocol amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

8.3 Case Report Forms (CRFs)

The Principal Investigator and/or appropriate designated staff, will prepare CRFs, and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific CRFs will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into standardized eCRFs in accordance with the study calendar, using single data entry with a secure access account. The Clinical Research

Team will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by study personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Case report forms (CRFs) should capture information on all immune-mediated adverse events, i.e.:

a) The criteria (under case definitions) which resulted in classification of an AE as an

immune-mediated adverse reaction

b) The treatment administered, including specific drugs, doses, and duration of immunosuppressive treatment

c) Information on dose modifications of, to include date when dose is modified, date dosing is resumed, and drug dose if reductions occur.

8.4 Confidentiality and Privacy

Participant's identification is concealed and a number is used as the identifier instead of the patient's name. Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following the discussions, participants will be asked to sign HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. Some designated research staff involved in the trial will have access to data. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

8.5 Conflict of Interest

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9. SAFETY REPORTING

9.1 Definitions

An adverse event **(AE)** is defined as any untoward medical occurrence associated with the use of a drug that occurs during the course of the clinical trial whether or not the event is considered related to the treatment or clinically significant.

For this clinical trial, AEs will include any events reported by the patient, any new medical conditions, symptoms, any new abnormal findings on physical examination or laboratory evaluation. Additionally, any worsening of a pre-existing condition or abnormality will also be considered as an AE.

AEs will be collected by the investigator from Informed Consent Form signed through 30 days after the last dose of study medication, or prior to initiate of new anti-cancer therapy whichever is earlier. AEs that occur outside of 30 days, following cessation of the study treatment, must also be reported within the same timeframe if considered related to study medication or procedure. All AEs must be recorded on CRF/eCRF. All AEs must be followed return to baseline or stabilizes.

Serious adverse events (SAE):

A serious adverse event is defined as any adverse experience that meets any of the following criteria:

- Results in death; death due to disease progression is not considered as SAE.
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization. Additionally, complications occurring during hospitalization are also considered AEs.
- Results in persistent or significant disability or incapacity (This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.);
- Consists of a congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious 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.

9.2 Causality AE

Causality assessment has become a common routine procedure in pharmacovigilance. Causality assessments can decrease disagreement between assessors, classify relationship likelihood and improvement of scientific evaluation.

- Limitations of causality assessment are following:
- It can NOT assess accurate quantitative measurement of relationship likelihood
- It can NOT distinguish valid from invalid cases
- It can NOT prove the connection between drug and event

- It can NOT quantify the contribution of a drug to the development of an adverse event

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the 2 categories below. In a clinical trial, the study product must always be suspect.

- **Related:** The AE is known to occur with the study product, there is a reasonable possibility that the study product caused the AE, or there is a temporal relationship between the study product and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- **Not Related:** There is not a reasonable possibility that the administration of the study product caused the event, there is no temporal relationship between the study product and event onset, or an alternate etiology has been established.

Protocol Deviation

Any change, divergence, or departure from the IRB-approved research protocol.

Non-compliance

The failure to comply with applicable IRB and other regulatory requirements, or regulatory requirements for the protection of human research subjects.

Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

(b) the characteristics of the subject population being studied; AND

- Is related or possibly related to participation in the research; AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.3 Categorizations of AEs

All AEs and clinically significant laboratory abnormalities will be graded according to Common Terminology Criteria for AEs, Version 4.03 dated 14 June 2010. For any term that is not specifically listed on the CTCAE scale, intensity will be assigned a grade of 1 through 5 using the following CTCAE guidelines:

Grade1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.

Grade2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade4: Life-threatening consequences; urgent intervention indicated.

Grade5: Death related to AE.

9.4 Reporting of SAEs

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported to sponsor (and/or IRB as required) **within 24 hours** of first becoming aware of the SAE. SAEs will be collected by the investigator from Informed Consent Form signed through 90 days after the last dose of study medication, or prior to initiation of new anti-cancer therapy, whichever is earlier. SAEs that occur outside of 90 days, following cessation of the study treatment, must also be reported within the same timeframe, if considered related to study medication or procedure. Any SAE that is judged by the investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor (or its designee) within 24 hours of receipt by the investigator. All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, reports of radiographic studies, and clinical laboratory reports should be obtained.

In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report, if performed. These records should be reviewed in detail, and the investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the investigator should consider whether the event is related or not related to study drug. All events determined to be non-serious should be reported on the eCRF.

9.5 IRB Reporting

The investigators will report to the IRB the following according to the requirements of reviewing IRB:

- All SAEs, except deaths due to progressive disease
- Non-compliance to GCP or protocol deviations as required by IRB

IND Safety Reports and any unexpected incidences or problems during the trial may be also reportable to the IRB as per IRB requirement.

9.6 Reporting of Pregnancy

For pregnancy including female subject pregnancy and male subject's female partner pregnancy, the investigator shall complete Pregnancy Report Form and submit the report to Innovent/ Innovent representative within 24 hours of the aware of pregnancy.

Maternal exposure

If a female subject becomes pregnant during the course of the study or within 120 days of the last dose of IBI308, the treatment must be discontinued immediately. The investigator or other site personnel must inform the appropriate Innovent representatives immediately but no later than 24 hours of when he or she becomes aware of it. The designated Innovent representative works with the investigator to ensure that all relevant information should be provided to the Innovent. Pregnancy is not regarded as an AE, however ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death must be reported and handled as SAEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) and normal birth/ congenital abnormality must be followed up 60 days after outcome of pregnancy, all related information should be documented even if the subject was discontinued from the study.

Paternal exposure

If a male subject's female partner becomes pregnant during the course of the study or within 120 days of the last dose of IBI308, The subject continued the treatment. Pregnancy of male subject's female partner is not considered to be an AE. However, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death must be reported and handled as SAEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) and normal birth/ congenital abnormality must be followed up 60 days after outcome of pregnancy, all related information should be documented even if the subject was discontinued from the study.

Related information about a pregnancy from the partner of a male subject should be captured. If so, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome; the male subject should not be asked to provide this information. A consent form specific to this situation must be used.

10. STATISTICAL CONSIDERATIONS AND EVALUATION OF RESULTS

10.1 General Statistical Consideration

Descriptive statistics will be utilized for all safety, efficacy, immunogenicity, and pharmacokinetic parameters. Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Time-to-event variables will be summarized using Kaplan-Meier methods and figures for the estimated median time. All data collected will be presented in subject listings. All data will be summarized by investigational drug dose level received. ORR will be calculated based on the full analysis set (FAS), including all patients who received at least one dose of drug.

10.2 Data Analysis

10.2.1 Pharmacokinetic Data

PK parameters will include, but not be limited to, AUC, C_{max}, $C_{min\ trough}$, $t_{1/2}$, CL, and V_{ss}. The concentration-time data will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, and geometric mean). PK parameters will be estimated using a non-compartmental method with WinNonlin (Pharsight Corp, Cary, North Carolina). Individual and mean serum concentration of investigational drug versus time data will be tabulated and plotted by dose level.

10.2.2 Immunogenicity

All samples will first be analyzed for ADAs in a screening assay. Study samples with results below the screening cut-off will be reported as negative for ADAs. In the event of a positive result in the screening assay, samples will be analyzed in the confirmatory assay. All samples confirmed positive will be reported as positive, and will be analyzed for presence of neutralizing antibodies (nAb).

The incidence of ADA will be summarized for all subjects who received at least one administration of investigational drug. Impact of ADAs on PK, efficacy/safety of investigational drug will be evaluated, if applicable.

10.2.3 Efficacy

ORR and the associated 2-sided 95% exact confidence limits will be provided. The proportion of subjects who have experienced best response as CR, PR, SD or disease progression (PD) will be calculated. PFS and OS data will be analyzed by Kaplan-Meier method.

10.3 Determination of Sample Size

For cohort 2: Assuming the true ORR in advanced/metastatic endometrial cancer patients receiving IBI308 is 25%, there is an approximately 80% chance to observe 8 or more than 8 responders in a total of 40 patients (i.e. observed ORR≥20%). With observing at least 8/40 responders, this study will approximately 96% confidence to exclude ORR≤10%. A preliminary evaluation of efficacy will be conducted after approximately 20 evaluable patients with at least post baseline 2 tumor assessments. If overwhelming efficacy is observed, this cohort might be further expanded beyond planned 40 patients to confirm the efficacy observed.

10.4 Subject Replacement Policy

In this study subject replacement is not permitted.

10.5 Safety Evaluations

Safety will be assessed by physical examinations, vitals, ECG, laboratory tests, AE monitoring, and concomitant medication usage monitoring (see Schedule of Events). AEs are graded according to the CTCAE v4.03. Investigators will report whether an AE is potentially immune related (irAE). irAEs are defined as AEs of unknown etiology potentially associated with an immune phenomenon. Follow up for SAEs assessed as at least possibly related late irAEs will occur until 3 months after the last dose of IBI308. The overall safety of IBI308 will be assessed by the Safety Monitoring Committee (SMC). SMC will be responsible for safety oversight, dose-escalation decisions, and other critical study decisions. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRATM).

10.6 Efficacy Evaluations

Tumor assessment will be performed at baseline, every 2 cycles thereafter, and at the end of treatment by the investigator per RECIST v1.1 (Appendix 11.2). Efficacy evaluations will include the following: CT/MRI, physical examination, and other procedures as necessary. Adequate/preferred imaging assessments include high resolution CT with contrast or contrast-enhanced MRI for evaluating radiographic tumor response. In subject with known severe contrast allergies, where pre-medication is not an option a non-contrast scan will suffice. Appearance of new malignant lesions denotes disease progression during the consistent scanning techniques. If a patient is classified as having disease progression at a post-baseline tumor assessment, then confirmation by a second scan in the absence of rapid clinical deterioration is required. If a lesion is identified on during the study in an anatomical location that was not scanned at baseline is will be considered as a new lesion and will indicate disease progression. Treatment response will also be assessed by iRECIST v1.1 criteria to assess the potential for pseudo progression.

Anti-cancer activity parameters that will be assessed include determination of the following:

1) Best overall response [complete response (CR), partial response (PR), stable disease (SD), or progressive disease]

2) Objective response rate (ORR) (CR + PR)

3) Duration of response (DOR) or duration of SD

4) Disease control rate (DCR) (CR, PR or SD)

5) Progression-free survival (PFS) and overall survival (OS) efficacy Evaluations

10.7 Population Analysis

10.7.1 Safety Population

The safety analyses population will include all subjects who receive at least one dose of the investigational drug. The safety analyses population will be the primary population for evaluating treatment administration, compliance and safety in the study.

10.7.2 Efficacy Population

The efficacy population will include all subjects who complete at least 1 cycle of treatment and have at least 1 post baseline tumor assessment of efficacy or discontinue study early due to progressive disease.

10.7.3 PK Population

The PK population will include all subjects who have at least one blood sample providing evaluable PK data.

10.8 Tabulation of Individual Participation Data

Data tabulations will summarize the following subject numbers:

- Enrolled
- Investigational drug treatment dose received
- Evaluable for safety and efficacy
- Protocol violations
- Protocol completions
- Withdraw from study due to:
  - Adverse event
  - Physician's recommendation
  - Withdrew consent
  - Lost to Follow-up

Other reasons as collected on the case report form.

11.STUDY MANAGEMENT

11.1 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented to assure that any missing data will be communicated with sites for clarification and resolution.

Standard Operating Procedures (SOPs) should be available to monitors. Monitors will verify that all the clinical trial procedures are conducted, documented and reported in compliance with the protocol, ICH, GCP, GLP, GMP and other applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.2 Clinical Monitoring Plan

Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirements.

A sponsor representative will meet with the investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording study data. After enrollment of the first subject, a sponsor representative will be assigned to periodically monitor each investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) and/or ICH guidelines were followed.

The investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed CRFs, signed consent forms and other study related documents are readily available for review.

As a sponsor for clinical trials, FDA regulations require the Investigators to facilitate monitoring process. Monitors will evaluate adherence to the protocol, regulations, SOPs, human subject protection, study data, specifically data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment
- Safety Monitor

11.3 Study Closure

The investigator may terminate the study at any time in the interest of subject welfare. The sponsor may terminate the study prematurely at any time. Reasons for the closure of an investigational site or termination of a study may include:

- The Investigator fails to comply with the protocol or ICH/GCP guidelines
- Safety concerns
- Inadequate recruitment of subjects by the investigator
- Completion of the study

If the clinical study is prematurely terminated or suspended, the sponsor or CRO representative will inform the investigator and the regulatory authorities of the termination/ suspension and the reasons for the termination/suspension as appropriate. The investigator should promptly notify the IEC/IRB of the termination or suspension and provide reasons. The sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause.

Premature termination of the study by either PI or sponsor will be governed under the terms of the contract between both parties.

12. REFERENCES

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13.GENERAL APPENDICES

13.1 Appendix 1 Eastern Cooperative Status Oncology Group Performance Status Score

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

13.2 Appendix 2 Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1	
Measurable Tumor Burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥10 mm in longest diameter (LD) and 2X the slice thickness for extranodal lesions. ≥15 mm in short axis diameter (SAD) for nodal lesions. ≥10 mm in LD for clinical lesions (must be measured using electronic calipers). ≥20 mm in LD for chest X-ray (if clearly defined and surrounded by aerated lung); CT is preferable. Ultrasound (US) cannot be used to measure lesions.
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SAD. To be measurable, nodal lesions must be ≥15 mm in SAD. Nodal lesions with SAD >10 mm and <15 mm are non- measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.
Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emission therapy (PET) or plain films are non-measurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Non-cystic lesions are preferable.
Lesions with Prior Local Treatment Too Small To Measure	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy. If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions That Split or Coalesce	If extranodal target lesions fragment, the LDs of the fragmented portions are added to calculate the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of Complete Response (CR)	CR requires the disappearance of all extranodal lesions, the regression of all nodal lesions to <10 mm SAD and the normalization of tumor marker level.
Definition of Progressive Disease (PD)	PD is assessed if the sum of the diameters has increased by ≥20% and ≥5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non- target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.
Assessment of New Lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (ie, 'new' bone lesions may be healing or flare of pre- existing lesions). If on is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET:(-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET

	at follow-up corresponding to pre-existing lesion on CT that is not progressing; not PD.
Recurrence of Lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall Response	One overall response table integrates target, non-target and new lesions and another table integrates non-target and new lesions for the assessment of subjects without measurable disease.
Confirmation of Response	Confirmation of PR/CR is ONLY required for non-randomized trials where response is the primary endpoint. In these trials, subsequent confirmation of PR with one interim timepoint of SD is acceptable.

Link:

https://www.sciencedirect.com/science/article/pii/S0959804908008733/pdfft?md5=14893671e2bb1311c1fe32 ab44638208&pid=1-s2.0-S0959804908008733-main.pdf

13.3 Appendix 3 modified RECIST 1.1 for immune based therapeutics (iRECIST)

iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD. iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in

short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD，iPR，iCR	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD；iCR	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or

				o size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				