CLINICAL STUDY PROTOCOL

Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Version and Date:	Nov. 5, 2018/Version 3.2
Product Name:	Recombinant anti-VEGF humanized monoclonal antibody injection (IBI305)
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	Zhou Hui (Senior Medical Director) Tel: (+86) 21-31652896 E-mail: hui.zhou@innoventbio.com
NCT Number	NCT02954172

SIGNATURE PAGE

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Protocol No.: CIBI305A301

Title	Name	Signature	Date
Senior Medical Director	Zhou Hui		11/5/2018
Senior Director of Biostatistics	Zhang Nan		11/05/2018

PROTOCOL SYNOPSIS

Sponsor/Company:	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug:	IBI305
Active Ingredient:	Recombinant anti-VEGF humanized monoclonal antibody
Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Coordinating Investigator:	Zhang Li
Coordinating Center:	Sun Yat-Sen University Cancer Center

Expected study duration: Each subject will receive treatment every 3-week until progressive disease (PD), unacceptable toxicity, withdrawal of informed consent, lost to follow-up or death (whichever comes first). The end of the study is defined as the 18th month after the randomization of the last subject.	**Phase:** III

Study Objectives:

Primary Objective:

- To compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC)

Secondary Objectives:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

Exploratory objectives:

	⁴⁄₃ To compare the population pharmacokinetics (PPK) of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC ⁴⁄₃ To compare the PD of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC
Study design: This is a randomized, double-blinded, multi-center phase III study. The study planned to enroll and randomize 436 subjects with non-squamous NSCLC in a 1:1 ratio to IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild type vs. unknown type). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first). Then subjects receive maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first). During the study, a CT or an MRI will be performed every 6 weeks (± 7 days) and be determined whether the study treatment will be continued by investigators at each site through tumor assessments until PD, withdrawal of informed consent, lost to follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for reasons other than PD, tumor assessments will be continued until PD, withdrawal of informed consent, loss of follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for PD, the investigators will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, lost to follow-up, death, or end of study.	
Number of Subjects:	436
Diagnosis and main inclusion criteria:	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be enrolled in the study: 1) Sign the formed consent form 2) Male or female ≥ 18 and ≤ 75 years old 3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIB), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types 4) Histologically or cytologically confirmed EGFR wild type or non-sensitive mutation type

	5) Must have at least one measurable target lesion (as per RECIST 1.1) 6) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1 7) Expected survival ≥ 6 months 8) Laboratory results during screening: a) Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ from urinalysis dipstick at baseline, a 24-h urine should be collected with total protein content < 1 g d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment 9) Able to comply with study protocol 10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug Exclusion Criteria: Subjects meeting any of the followings will not enrolled in the study: 1) Prior systemic chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIB not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible 2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component 3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18-point mutation (G719X), exon 19 deletion, and exon 21-point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll.

	4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time 5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava) 6) Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage; 7) Subjects who received radical thoracic radiotherapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug 8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study 9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (Outpatient/inpatient surgery requiring locoregional anesthetics, including central line insertion) 10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function for 10 consecutive days 11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents for 10 consecutive days. However, anticoagulants for prophylaxis are accepted 12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis 13) Uncontrolled hypertension after treatment (systolic greater than 140 mmHg and/or diastolic greater than 90 mmHg), history of hypertensive crisis or hypertensive encephalopathy 14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease

	15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess 16) Subjects with tracheoesophageal fistula 17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments) 18) Subjects with current interstitial lung disease or CT showing active pneumonia during screening 19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or papillary thyroid carcinoma 20) Subjects with active autoimmune disease 21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1 × 103 copies/L or ≥ 200 IU/mL; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1 × 103 copies/L or < 200 IU/mL might be eligible if the investigator determines that the subject's chronic hepatitis B infection is stable and participation in the study would add no further risks to the subject 22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis 23) Subjects with known history of allergic diseases or allergic physique 24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening 25) History of alcohol or drug abuse 26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study 27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents 28) Other conditions unsuitable for the inclusion as determined by the investigator
Investigational Drug, Dosage, and Route of Administration:	IBI305: 15 mg/kg in combination chemotherapy and 7.5 mg/kg **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)

Control Drug, Dosage, and Route of Administration:	Bevacizumab: 15 mg/kg in combination chemotherapy and 7.5 mg/kg maintenance monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)
Chemotherapy:	Paclitaxel: 175 mg/m² administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death. Carboplatin: Areas under the concentration-time curve (AUC) = 6.0 administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Evaluation criteria:

Efficacy endpoints:

Primary efficacy endpoint:

- Objective response rate (ORR)

Secondary efficacy endpoints:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Safety endpoints:

- Vital signs
- Physical examination
- Laboratory tests (routine blood test, blood chemistry, and urinalysis)
- 12-Lead ECG
- Adverse event (AE, including treatment-emergent AE (TEAE)), AE of special interest (AESI) (hypertension, proteinuria, gastrointestinal perforation, hemorrhage [cerebral hemorrhage, hematuria and upper gastrointestinal hemorrhage], cardiotoxicity, and thrombosis), and serious adverse event (SAE)
- Immunogenicity: Positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

PK/PD Endpoints:

- Population PK parameters, including steady-state trough concentrations after repeated doses

8/5 Changes of serum VEGF at different time points
Statistical methods: **Sample size calculation:** A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin. Estimation parameters for sample size: The significance level of the two-sided test is 0.05, the ORR of subjects in the IBI305 and bevacizumab groups is about 50.0%, and the equivalence margin for the ratio of ORR is taken as (0.75, 1/0.75). Based on the above hypothesis, each group requires 218 subjects (436 subjects in total). **Efficacy analysis:** Clinical equivalence will be determined by whether the 90% confidence interval (CI) of the ratio of ORR between the IBI305 and bevacizumab arms falls within the preset margin of (0.75, 1/0.75). The ORR and 95% CI of two groups, ORR difference and 90% CI, and ORR ratio and 90% CI will be estimated using the generalized linear model (GLM, including groups and stratification factors). Median survival (OS) and survival curves will be estimated using the Kaplan-Meier method. The hazard ratio (HR) and 95% CI of two groups will be estimated using the Cox model. DORs and PFSs will be analyzed by the same method as the median survivals. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted. **Safety analysis:** All adverse events (AE) will be coded using MedDRA and graded according to CTCAE v4.03. All treatment-emergent adverse events (TEAEs), Grade 3 or greater TEAEs, serious adverse events (SAEs), investigational drug-related TEAEs, investigational drug-related SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study termination, and adverse events of special interest (AESIs) will be listed based on system organ class, preferred terms, and groups and the numbers of corresponding subjects and percentages will be summarized. In addition, the severity of TEAEs and the correlation with the study drug will also be summarized by system organ class, preferred terms, and treatment groups. Measured values and changes from baseline for vital signs, physical examination, laboratory tests and 12-lead ECG will be analyzed using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation. The number and percentage of subjects who developed anti-drug antibodies and neutralizing antibodies during the study will be summarized by treatment group. **PK/PD exploratory analysis:** Mainly based on description, and inter-group comparison will be carried out if necessary

Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

a. After completing the on-site end-of-treatment visit 28 days after the last dose, subjects who discontinue the investigational drug treatment due to reasons other than PD should continue to undergo tumor assessments once every 6 weeks (±7 days) until PD (and begin post-PD follow-up thereafter), withdrawal of consent, start of another antineoplastic treatment, loss to follow-up, death, or study completion.

b. For subjects with PD, collect survival information once every 12 weeks (84 days, ±7 days) by phone until death, loss to follow-up, withdrawal of informed consent, or study completion. Subsequent antineoplastic treatments should be documented in the eCRF.

c. Only measure weight.

d. Clinical laboratory tests are carried out at the laboratory of each hospital. If screening laboratory tests (routine blood test, blood chemistry, and urinalysis) are performed within 7 days prior to the first dose, the screening results may be used as baseline data. For subsequent visits, all laboratory tests have to be completed within 3 days prior to the dose administration.

e. A urinalysis is required before each IBI305/bevacizumab infusion to test urine protein.

f. Women of childbearing age should undergo a serum/urine pregnancy test.

g. Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples will be tested at the designated central laboratory.

h. Image assessments (CT or MRI) of the brain, chest, abdomen, and pelvis should be completed at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

i. All subjects should undergo tumor tissue EGFR testing.

j. Each treatment cycle of the investigational product contains 3 weeks. The dose of IBI305 or bevacizumab is 15 mg/kg when used in combination with chemotherapeutic drugs and 7.5 mg/kg in the maintenance monotherapy, given on D1 of every treatment cycle until progressive disease (PD), unacceptable toxic reactions, withdrawal of informed consent, loss to follow-up, death, or end of study, whichever occurs first. After all assessments were completed, the study drug was administered followed by chemotherapy. The first dose of study drug was completed within 24 h after randomization.

k. Each treatment cycle is 3 weeks long. Chemotherapy (paclitaxel + carboplatin) is administered on D1 of each cycle for up to 6 cycles, or until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death. Paclitaxel is administered after the infusion of study drug is completed, followed by carboplatin.

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Abbreviations	Definitions
AE	Adverse event
AESI	Adverse event of special interest
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AUC	Area under the curve
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFDA	China Food and Drug Administration (now National Medical Products Administration)
CQA	Clinical quality assurance
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data collection
EGFR	Epithelial growth factor receptor
FAS	Full analysis set
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
ITT	Intention-to-treat

NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PTT	Partial thromboplastin time
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
SS	Safety set
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

1 INTRODUCTION

1.1 Study Background

1.1.1 Disease background

Lung cancer has the highest incidence and mortality globally among all cancers. According to the 2012 Global Cancer Statistics (GLOBOCAN 2012) published by International Agency for Research on Cancer, there were approximately 1.8 million new lung cancer cases worldwide, which accounted for 13% of the global newly-diagnosed cancers, and 58% of these cases occurred in underdeveloped areas[1]. According to the data released by the National Central Cancer Registry of China in 2015, lung cancer was the most prevalent malignancy in China in 2011, with about 650,000 new cases every year. Lung cancer was also the leading cause of death, with about 520,000 deaths per year[2]. The limited clinical treatment of lung cancer is the main reason for its poor prognosis. There is a huge demand for new types of lung cancer treatment drugs.

Approximately 85–90% of lung cancers are non-small cell lung cancer (NSCLC) and patients with NSCLC are usually in the advanced stages when diagnosed[3]. According to the Chinese guidelines for the diagnosis and treatment of primary lung cancer, anatomic pulmonary resection is the mainstay of treatment for early stage lung cancers[4]. However, despite surgery, some patients develop distance metastases that eventually lead to death[5]. Surgery is not possible for most patients with clearly diagnosed stage IIIB and IV as well as some patients with stage IIIA NSCLC[4]. Comprehensive treatment based on systemic therapy is used to maximize patient survival, control progressive disease, and improve the quality of life[6].

In recent years, anti-tumor therapies have entered a new era with the emergency of targeted drugs. Some of these targeted drugs have demonstrated satisfactory efficacy in the treatment of advanced NSCLC. These targeted drugs include monoclonal antibodies and tyrosine kinase inhibitors (TKIs), mostly targeting epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF), such as bevacizumab, cetuximab, gefitinib, erlotinib, and icotinib. Monoclonal antibodies have become the drugs of choice in various treatment guidelines due to the good targeting ability, low drug resistance, and good patient tolerability. Bevacizumab combination chemotherapy is a first-line therapy of NSCLC recommended by the National Comprehensive Cancer Network (NCCN)[7]. Additionally, bevacizumab in combination with paclitaxel/carboplatin has also been approved as the first-line therapy of unresectable advanced, metastatic, or relapsed non-squamous NSCLC by China Food and Drug Administration (CFDA) on Jul. 9, 2015[6].

Compared with traditional chemotherapy that directly inhibit or kill tumor cells, anti-angiogenic drugs have the following unique advantages[8]:

- The targets are genetically stable vascular endothelial cells (VECs) rather than highly heterogeneous tumor cells, thus leading to lower drug resistance;
- The number of tumor-induced VECs is far less than that of tumor cells, and the efficacy is preferable targeting on VECs and their cytokines;
- Normal VECs are quiescent, whereas tumor VECs are active in proliferation. Anti-angiogenic therapy targets activated cells and avoids damage to normal VECs, thus leading to better targeting ability;
- Anti-angiogenic therapy can normalize the tumor vessels and thereby reduce the pressure in tumor tissues. This enhances the delivery of chemotherapeutic agents into tumor tissues, thus increasing the efficacy of chemotherapy.

Angiogenesis is a basic biological characteristic of tumors. The growth of both solid and hematologic tumors are depended on angiogenesis regardless of the nature of tumor cells. Therefore, anti-angiogenic therapy is broad-spectrum and applicable to various tumors.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to human VEGF and blocks its biological activity. Bevacizumab consists of a framework region of a human antibody and a humanized murine antigen binding region that can inhibit the binding of VEGF to its receptors on epithelial cells, Flt-1 and KDR. By blocking the activity of VEGF and reducing tumor angiogenesis, tumor growth is inhibited[9].

In a study conducted by the Estern Cooperative Oncology Group (ECOG), compared with chemotherapy alone (paclitaxel/ carboplatin), bevacizumab in combination with paclitaxel/carboplatin significantly increased the overall survival (OS) (median: 12.3 vs. 10.3 months), progression-free survival (PFS) (median: 6.2 vs. 4.5 months), and overall response rate (ORR) (35% vs. 15%) in patients with advanced, metastatic, or relapsed non-squamous NSCLC[10]. In another foreign AVAiL study, different doses of bevacizumab (7 and 15 mg/kg) in combination with chemotherapy (cisplatin and gemcitabine) and placebo combine with chemotherapy were compared for the treatment of non-squamous NSCLC. The study found that the two bevacizumab groups had significantly increased the PFS (median: 6.7 months (7.5 mg/kg combination chemotherapy group) vs. 6.5 months (15 mg/kg combination chemotherapy group) vs. 6.1 months (placebo combination chemotherapy group)) and the ORR (37.8% (7.5 mg/kg combination chemotherapy group) vs. 34.6% (15 mg/kg combination chemotherapy group) vs. 21.6% (placebo combination chemotherapy group)) in patients with locally advanced, metastatic, or relapsed non-squamous NSCLC[11]. In a BEYOND study conducted in China, compared with

placebo in combination with paclitaxel/carboplatin, bevacizumab in combination with paclitaxel/carboplatin significantly increase the PFS (median: 9.2 vs. 6.5 months), OS (median: 24.3 vs. 17.7 months), and the ORR (54% vs. 26%) in patients with advanced or relapsed non-squamous NSCLC[12].

In China, the antibodies and fusion proteins targeting VEGF are research hotspots. However, since 2006, the clinical efficacies of various drugs have not been verified and no products have been marketed. Considering the complexity of macromolecular drugs and the limitations of drug development capability in China, advanced technologies in antibody development, production, and quality control is required to develop high-quality VEGF inhibitors that are safe and effective. IBI305 has showed high similarity to bevacizumab in various pharmaceutical and nonclinical studies (refer to Investigator's Brochure [IB]). Besides, the efficacy and safety of bevacizumab for treatment of locally advanced, metastatic or relapsed lung cancer have been verified. The relevant domestic and external pivotal clinical studies are referable for the protocol design of IBI305 clinical study. In summary, the clinical study of IBI305 for treatment of NSCLC has a solid foundation and relatively low risks. The successful development of IBI305 indicates an additional first-line targeted drug for lung cancer in China, providing doctors and patients with more therapeutic options.

1.1.2 Investigational drug

1.1.2.1 Description of investigational drug

IBI305 is a recombinant humanized anti-VEGF monoclonal antibody injection developed by Innovent Biologics (Suzhou) Co., Ltd. (hereafter as sponsor) that specifically binds human VEGF. The molecular weight of IBI305 is 149 KDa. IBI305 specifically binds to VEGF-A, inhibits the binding of VEGF-A to VEGF-R1 and VEGF-R2, blocks the signaling pathways such as PI3K/Akt/PKB and Ras-Raf-MEK-ERK. IBI305 also inhibits the growth, proliferation, and migration of VECs and angiogenesis, decreases the vascular permeability, blocks blood supply to tumor tissues, inhibits the proliferation and metastasis of tumor cells, and induces the apoptosis of tumor cells, thereby generates anti-tumor effects. The main active ingredient is recombinant humanized anti-VEGF monoclonal antibody and excipients include sodium acetate, sorbitol, and polysorbate 80[13]. Refer to the Investigator's Brochure for the detailed structure and physicochemical properties of IBI305.

1.1.2.2 Preclinical studies

Pharmaceutical studies

The pharmaceutical studies showed that stability, primary structure, higher-order structure, oligosaccharide distribution, charge variant, and product-related impurities of IBI305 are highly similar to those of bevacizumab, and the process-related impurities meet the proposed specification. Therefore, IBI305 is considered to have highly similar protein properties and product quality to bevacizumab[13].

Pharmacodynamic studies

In vitro and in vivo pharmacodynamic (PD) studies of IBI305 showed the following findings:

1) Target: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A with an affinity constant same as that of bevacizumab, indicating that IBI305, the same as bevacizumab, is a specific human VEGF blocker with a clear target.
2) Specificity: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A, medium-affinity binding to canine VEGF-A, but low-affinity binding to human VEGF-B, VEGF-C, VEGF-D, PlGF, suggesting that IBI305 recognizes specific targets and has low off-target toxicity risk; no obvious affinity to mouse VEGF-A_{164} and rat VEGF-A_{164}, suggesting that IBI305 has high species specificity.
3) Mechanism of action: IBI305 specifically binds to VEGF-A and inhibits the activation of VEGFR-2 and ERK1/2, blocks the proliferation and migration of HUVEC, and inhibits the sprouting from rat aortic ring, suggesting that IBI305 antagonizes VEGF-A-induced signaling pathway to block the proliferation and migration of VECs and inhibit angiogenesis, which leads to the reduction of nutritional supply and metastasis of tumor.
4) Anti-tumor effects: IBI305 significantly inhibits the growth of human colon cancer Ls174t and lung cancer NCI-H460 cells in xenografts in nude mice, indicating that IBI305 has significant anti-tumor effects.

Results from in vitro and in vivo studies of IBI305 showed highly similarity with that of bevacizumab designed simultaneously, demonstrating that the target, mechanism of action, and anti-tumor effects of IBI305 are highly similar to bevacizumab[13].

Pharmacokinetic studies

In vitro and in vivo pharmacokinetic (PK) studies of IBI305 showed the following findings:

1) IBI305 showed no significant cross-reactivity with normal human tissues and cynomolgus monkey tissues, and only cross-reacted with the positive-control. i.e. human angiosarcoma tissue, suggesting that IBI305 is highly specific to cancer tissues rather than normal human tissues and has very low on-target toxicity.
2) Linearity: With single dose or repeated doses of IBI305 (2-50 mg/kg) vis intravenous injection in cynomolgus monkeys, the test showed significant PK, thus reducing the suddenly rising toxicity risks with increased clinical doses.
3) Immunogenicity: With single dose or repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed abnormal changes of drug concentration-time curves in several animals. The anti-drug antibody (ADA) test results showed that IBI305 has a medium immunogenicity.
4) Accumulation: With repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed that drug exposure of the last dose was significantly higher than that of the first dose, and the steady-state drug concentration after repeated doses was higher than that after a single dose, suggesting that the drug may be accumulated in body.

The results of tissue cross-reactivity and PK/toxicokinetic studies in cynomolgus monkeys indicated that IBI305 and bevacizumab have similar characteristics in tissue cross-reactivity and PK/toxicokinetics[13].

Toxicological studies

Toxicological studies of IBI305 showed the following findings:

1) Single dose: With single dose of IBI305 (up to 300 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed good tolerability without any abnormal clinical symptoms and toxicity. The dose was about 48 times the proposed clinical dose for human based on body surface area. In the safety pharmacology test, with single dose of IBI305 (50 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed no significant effects on the central nervous system, respiratory system, and cardiovascular system, suggesting that the single dose of IBI305 via intravenous injection has a high safety.

2) Repeated doses: With repeated doses of IBI305 (up to 50 mg/kg) via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, equivalent to 20 times the proposed clinical dose for humans (based on the weight), the test showed extremely mild to mild linear growth arrest of metaphyseal lines at knee joint and disordered chondrocyte proliferation, extremely mild increases in macrophage count in white pulp of spleen, pulmonary (including bronchial) hemorrhage, and deposits of hemosiderin in lymphoid tissue of bronchial mucosa, indicating that the target organ toxicities are mainly in the bone, spleen, and lungs.

3) Immunotoxicity and immunogenicity: With repeated doses of IBI305 via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, the test showed medium immunotoxicity to the spleen. Different doses of IBI305 may result in the production of ADAs, a portion of which are neutralizing antibodies (NAbs), indicating that IBI305 has medium immunotoxicity and immunogenicity.

4) Local irritation test: With repeated dose of IBI305 via intravenous injection in cynomolgus monkeys, the test showed no irritation at the injection site, suggesting that administration of IBI305 via intravenous injection is safe and feasible.

5) In vitro hemolysis assay: With maximum proposed clinical concentration of IBI305 (9 mg/mL), the assay showed no hemolysis, suggesting that IBI305 is suitable for intravenous injection.

IBI305 has high similarity with bevacizumab in safety pharmacology, long-term toxicity, immunotoxicity, immunogenicity, local irritation, and hemolysis[13].

1.2 Study Principles and Risk/Benefit Assessment

1.2.1 Study principles and dose selection

A biosimilar drug refers to a therapeutic biological product that is similar in quality, safety and efficacy with an approved reference drug[14]. IBI305, developed and sold in the market by the sponsor, is a bevacizumab biosimilar, and has the same administration method and indications as bevacizumab.

This study is conducted in accordance with the "Guidelines on Development and Evaluation of Bosimilars (for Trial Version)" issued by the NMPA (formerly CFDA)[14]. The doses of IBI305 selected in this study are based on the preclinical studies that showed highly similarity between IBI305 and bevacizumab in pharmacology, PD, PK and toxicology (refer to the Investigator's Brochure for details). Besides, the efficacy and safety of bevacizumab for treatment of advanced, metastatic or relapsed non-squamous NSCLC have been verified, and the indications have also been approved in China. Therefore, the dose and administration of IBI305 is similar to bevacizumab in this study, that is, 15 mg/kg intravenously on D1 of every 3-week cycle when used in combination with chemotherapy (paclitaxel and carboplatin). In the subsequent maintenance monotherapy therapy, IBI305 will be given intravenously at a dose of 7.5 mg/kg on the first day of every 3-week cycle. This design of this study is to further demonstrate that IBI305 is similar to bevacizumab in clinical efficacy, safety, and immunogenicity in subjects with advanced, metastatic or relapsed non-squamous NSCLC.

1.2.2 Risk/benefit assessment

IBI305 is a bevacizumab biosimilar developed by the sponsor. Based on the clinical pharmacology and toxicology characteristics of IBI305, the risks and benefits of IBI305 are expected to be similar to bevacizumab.

The treatment-related risks of bevacizumab are detailed in its prescribing information. This study is the first human study of IBI305 so that unexpected adverse reactions will be possible. The design of this study ensures the minimized subject risks by close monitoring of the adverse events (AEs) before, during, and after the infusion of the investigational drugs. Once an adverse reaction occurs, the investigator will immediately take appropriate action for the subject safety.

The platinum-based therapy is the standard first-line regimen of advanced NSCLC[4]. This study uses the combination of paclitaxel/carboplatin, ensuring the basic anti-tumor therapy for subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC.

2.2 Secondary Objectives

Secondary objectives include:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) in subjects with advanced or relapsed non-squamous NSCLC treated by IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

2.3 Exploratory Objectives

- To compare the population pharmacokinetics (PPK) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC
- To compare the pharmacodynamics (PD) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC

3 STUDY PLAN

3.1 Overview of Study Design

This is a randomized, double-blind, active-controlled, and multi-center phase III study. A total of 436 subjects across 35 study sites with non-squamous NSCLC will be planned, randomized in a 1:1 ratio into the IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group, and stratified according to age (< 60 vs. ≥ 60 years old) and epidermal growth factor receptor (EGFR) status (wild type vs. unknown type). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first). Then subjects received maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing maintenance therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first).

After discontinuing the study drug, subjects will return to the study site 28 days (± 7 days) after the last dose for an end-of-treatment visit. If the subjects discontinue the study treatment for reasons other than PD, subsequent follow-up will be continued until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. If the subjects discontinue the study treatment for PD, the investigator will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival.

A CT or an MRI will be performed every 6 weeks (± 7 days) until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. The method for subsequent imaging examination should be consistent with that at baseline, and the chest, abdomen and pelvis of the subject must be scanned. Each assessment must be completed within 7 days from the most recent visit. The investigators then perform the evaluation based on the RECIST v1.1 criteria to determine whether the subject can continue receiving the next cycle of treatment. Furthermore, the independent tumor evaluation committee (Section 11.1.1) will also evaluate tumor response according to the RECIST v1.1. If the subjects discontinue the study treatment for reasons other than PD, subsequent tumor evaluation should be continued according to the study procedures until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death or, end of study.

The study design is shown in Figure 1.

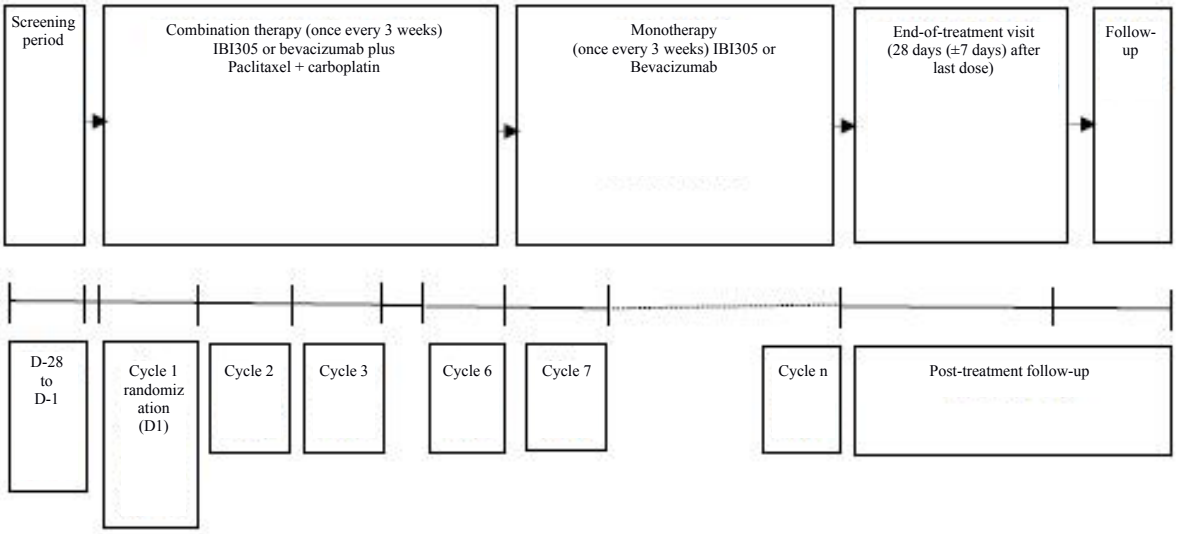

Figure 1. Study design schematic

3.2 Study Design Discussion

This is a randomized, double-blind study, and bias in treatment groups is avoided. Furthermore, the CT/MRI images of each subject will be evaluated by an independent tumor evaluation committee according to the RECIST v1.1 to ensure consistency in evaluation.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled in the study:

1) Sign the informed consent form
2) Male or female ≥ 18 and ≤ 75 years old
3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIB), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types
4) Histologically or cytologically confirmed EGFR wild type or non-sensitive mutation type
5) Must have at least one measurable target lesion (as per RECIST 1.1)
6) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1
7) Expected survival ≥ 6 months
8) Laboratory results during screening:
   a) Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L
   b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis
   c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline urinalysis must have undergone 24 h urine collection with total protein content < 1 g
   d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment
9) Able to comply with study protocol
10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug

4.2 Exclusion Criteria

Subjects meeting any of the followings are not enrolled in the study:

1) Prior systemic chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIB not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible
2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component
3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18 point mutation (G719X), exon 19 deletion, and exon 21 point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll.
4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time
5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava)
6) Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage;
7) Subjects who received radical thoracic radiation therapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug
8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study
9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (Outpatient/inpatient surgery requiring locoregional anesthetics, including central line insertion)

10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function for 10 consecutive days

11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents for 10 consecutive days. However, anticoagulants for prophylaxis are accepted

12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis

13) Uncontrolled hypertension (systolic greater than 140 mmHg and/or diastolic greater than 90 mmHg), history of hypertensive crisis or hypertensive encephalopathy

14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease

15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess

16) Subjects with tracheoesophageal fistula

17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments)

18) Subjects with current interstitial lung disease or CT showing active pneumonia during screening;

19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or papillary thyroid carcinoma

20) Subjects with active autoimmune disease

21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1 × 103 copies/L or ≥ 200 IU/mL; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1 × 103 copies/L or < 200 IU/mL might be eligible if the investigator determined that the subject's chronic hepatitis B infection was stable and participation in the study would add no further risks to the subject

22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis
23) Subjects with known history of allergic diseases or allergic physique
24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening
25) History of alcohol or drug abuse
26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study
27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents
28) Other conditions unsuitable for the inclusion as determined by the investigator

4.3 Screening Failure

Screening failure is that the subject who has signed the informed consent form fails to meet the inclusion criteria. Subjects with screening failure will not get a randomization number. The reasons of screening failure will be documented in the electronic case report forms (eCRFs).

4.4 Subject Restrictions

Female subjects of childbearing age must take effective contraceptive measures during the study and 6 months after the last dose.

Male subjects must take effective contraceptive measures during the study and 6 months after the last dose to avoid the pregnancy of their partners.

Restrictions on the use of medication during the study are shown in Section 5.9.

4.5 Subject Withdrawal and Replacement

All subjects may withdraw from this study at any time, with or without a reason. Subjects who withdraw from the study will not be subjected to discrimination or retaliation, and their medical treatment will not be affected.

Subjects may discontinue the study treatment or withdraw from the study under the following circumstances:

- $\frac{8}{5}$ Unacceptable toxicity
- $\frac{8}{5}$ Progressive disease

- Investigator believes that the subject should withdraw from the study. If an unacceptable adverse event (AE) occurs and the investigator believes that the subject should withdraw from the study, the study treatment should be discontinued and appropriate measures should be taken. In addition, the sponsor or personnel designated by the sponsor should be notified.
- Withdrawal of informed consent form by the subject
- Serious protocol deviation determined by the investigator and/or sponsor
- Poor protocol compliance
- Study termination by the investigator or sponsor for any reason
- Enrollment error* (enrollment of subjects who have violated the inclusion/exclusion criteria)
- Use of prohibited concomitant medications or other medications that the investigator believes that it may result in toxicities or may affect study results
- Subject lost to follow-up
- Death of subject

* If the subject is determined by the investigator and the sponsor's doctor to be medically suitable to continue with the study drugs without any risk or inconvenience, the mistakenly enrolled or randomized subject will continue with the study treatment and assessments.

In any cases, reasons for withdrawal must be documented in the eCRFs. If the subject withdraws from the study prematurely for any reason, the investigator should make every effort to persuade the subject to receive the corresponding assessment, and continue the follow-up of all unresolved AEs based on the AE reports and follow-up requirements (Table 2):

- If the subject withdraws during the study, the series of assessments listed under the End of Treatment Visit (Section 6.9) should be performed
- If the subject withdraws after the end of the treatment visit and has not experienced PD, the series of assessments listed under the Follow-Up for PD (Section 6.10) should be performed (tumor assessment is not required to be repeated if it has been performed within 6 weeks prior to this follow-up)
- If the subject withdraws during the follow-up for survival, the information of subsequent anti-tumor therapies and survival should be collected by telephone follow-up only

Subjects who withdraw their informed consent are not to be contacted again unless they clearly indicate the willingness to be contacted. The sponsor may use the clinical study data obtained before the withdrawal of informed consent.

Subjects who have been randomized will not be replaced.

5 STUDY TREATMENT

5.1 Therapies by Study Drugs

The study drugs of this study are IBI305 and bevacizumab.

In this study, the dose of IBI305 or bevacizumab during combination therapy with chemotherapy is 15 mg/kg, while the dose during maintenance monotherapy is 7.5 mg/kg. The study drugs are administered intravenously on D1 of each 3-week cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

The duration of the first dose of IBI305 or bevacizumab should be 90 min (± 15 min). If the first infusion is well-tolerated by the subject, then the duration of the second infusion can be shortened to 60 min (± 15 min). If the 60 min infusion is also well-tolerated by the subject, then the subsequent infusions can be completed within 30 min (± 15 min).

5.2 Chemotherapy

Paclitaxel will be administered after the IBI305 or bevacizumab infusion is completed, then followed by carboplatin:

Paclitaxel: 175 mg/m² administered via intravenous infusion for 3 h (may be adjusted according to clinical practice of each study site) on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Carboplatin: AUC 6.0, the infusion time is based on the standard practice of each study site, administered on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

The chemotherapeutic agents are supplied by the sponsor.

Formulas for calculating surface area, creatinine clearance and carboplatin dose are shown in Section 13.2.

5.3 Dose Adjustment of Each Study Drug

5.3.1 General principles

The reasons for dose adjustments or delayed administration, measures taken, and results should be documented in the medical records and eCRFs

If the concomitant symptoms exist at baseline, the investigator will determine whether the dose should be adjusted according to the change in severity of toxicity. For example, if the subject has Grade 1 "weakness" at baseline and Grade 2 "weakness" during the study treatment, the dose should be adjusted based on Grade 1 toxicity since the severity has increased by one grade

If several toxic reactions of different grades or severity occur simultaneously, the dose will be adjusted according to the highest observed grade/severity

If a dose adjustment is required solely due to abnormal lab test results, then the dose should be adjusted based on the measured values obtained prior to the start of the treatment cycle

If the investigator determines that the toxicity is unlikely to further develop into a serious or life-threatening event, the current dose will be continued without any adjustments or treatment interruptions. In addition, dose adjustments or treatment interruptions will not be performed for non-hemolytic anemia as the symptoms can be alleviated through blood transfusions.

If the investigator determines that a toxicity is caused by a specific therapeutic drug, then the dose adjustments of other drugs are not required

Discontinuation of one or two therapeutic drugs before PD will not affect the continued treatment with other drugs

Dose reductions or adjustments of IBI305 or bevacizumab are not permitted.

Subsequent therapeutic dose will not be adjusted according to weight change, unless the subject weight has changed by ≥ 10% from baseline

Once the dose of any chemotherapeutic agents is reduced, the original dose should no longer be adopted

If any but not all of the therapeutic drug (IBI305, bevacizumab or chemotherapeutic agents) treatments is interrupted due to toxicity, then this treatment will be considered as a treatment cycle

If the administration of any one of the chemotherapeutic agents is delayed for more than 3 weeks, the subject should permanently discontinue that chemotherapeutic agent

If IBI305/bevacizumab is continued/infused after a delay for more than 3 weeks, the investigator must discuss with the sponsor

5.3.2 Dose adjustments of study drugs

Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments (adjusted to 7.5 mg/kg for maintenance monotherapy) specified in the study protocol. The dose of IBI305 or bevacizumab is calculated according to the subject weight at baseline (prior to the first dose), and remains unchanged throughout the study, unless the subject weight has changed by ≥ 10% from baseline.

If an infusion reaction occurs during a 60-minute infusion, the infusion time should be extended to 90 minutes for all subsequent infusions. Likewise, if an infusion reaction occurs during a 30-minute infusion, the infusion time should be extended to 60 minutes for all subsequent infusions.

IBI305 or bevacizumab in combination with paclitaxel/carboplatin will be administered every 3-week treatment cycle for 6 cycles. If PD is not observed in subject during treatment, then the subject will continue to receive IBI305 or bevacizumab as maintenance monotherapy every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, death, or end of study (whichever comes first).

If IBI305 or bevacizumab is permanently discontinued due to unacceptable toxicity or subject refusal to continue the study drugs during the combination therapy, then the subject will continue to receive the chemotherapy (paclitaxel/carboplatin) until 6 treatment cycles are completed as determined by the investigator. If any one of the chemotherapeutic agents (paclitaxel or carboplatin) is prematurely discontinued due to unacceptable toxicity, the subject can continue to receive IBI305 or bevacizumab treatment until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first).

When a Grade 3 or 4 IBI305- or bevacizumab-related toxicity is observed, the investigators should determine whether to continue or terminate IBI305 or bevacizumab treatment according to the followings:

First occurrence:

IBI305 or bevacizumab administration should be interrupted until toxicity symptoms return to baseline level or are at least reduced to the Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or lower (except for the special circumstances listed below)

Note that when Grade 4 febrile neutropenia and/or thrombocytopenia occur(s), IBI305 or bevacizumab administration should be interrupted until the symptoms return to baseline levels or at least reduced to CTCAE Grade 1 or lower, since these events increase the risk of hemorrhage.

Re-occurrence in re-administration:

If Grade 3 IBI305- or bevacizumab-related toxicity occurs again, the investigator should assess the risk/benefit of study drug continuation for the subject. If such toxicity re-occurs again after re-administration, IBI305 or bevacizumab should be permanently discontinued

If Grade 4 IBI305- or bevacizumab-related toxicity occurs again, IBI305 or bevacizumab should be permanently discontinued

Measures should be taken in the following special circumstances (classified based on CTCAE version 4.03):

Hemorrhage

Subjects with Grade 3 or 4 hemorrhages should be treated accordingly and permanently discontinue the study treatment

Thrombosis/embolism

- Subjects with arterial thrombosis of any severity grades should permanently discontinue the study treatment
- Subjects with Grade 4 venous thrombosis should permanently discontinue the study treatment
- Subjects with Grade 3 venous thrombosis should interrupt the study treatment. If the anticoagulant therapy at the planned therapeutic dose is < 2 weeks, the study treatment should be interrupted until the anticoagulant therapy is completed. If the anticoagulant therapy at the planned therapeutic dose is > 2 weeks, IBI305 or bevacizumab administration should be interrupted for 2 weeks, and the study treatment can be restarted during the anticoagulant therapy if the following criteria are met:
  - INR is within the target range (usually 2-3) prior to restarting of study treatment
  - Subjects must not have experienced Grade 3 or 4 hemorrhage since enrollment
  - No signs of great vessel invasion or adjacency to great vessels from previous tumor assessments

  Note: Therapeutic dose of anticoagulant therapy is defined as the escalating dose of warfarin or other anticogulants until INR is maintained at no less than 1.5 (usually

2-3). The warfarin dose should be documented in the eCRFs, and the INR of subjects receiving anticoagulant therapy should be monitored during the treatment.

Hypertension

BP should be measured frequently to monitor the occurrence and exacerbation of hypertension. Subjects should remain at resting position for at least 5 min before BP measurement.

Definition of hypertension: pathologically increased BP with repeated measurements persistently over 140/90 mmHg

Table 2. Hypertension severity grades and interventions in CTCAE v4.03

CTCAE		Interventions
Grade 1	Pre-hypertension (systolic blood pressure of 120–139 mmHg, diastolic blood pressure of 80–89 mmHg)	Intervention not indicated
Grade 2	First-stage hypertension (systolic blood pressure of 140–159 mmHg, diastolic blood pressure of 90–99 mmHg; repeated or persistent hypertension of ≥ 24 h), a symptomatic increase of > 20 mmHg in systolic blood pressure, or an increase of > 140/90 mmHg from the previous normal range	Antihypertensive monotherapy. drug interruption. The treatment with the investigational product can be continued once the blood pressure is lower than 140/90 mmHg.
Grade 3	Second-stage hypertension (systolic blood pressure of ≥ 160 mmHg, diastolic blood pressure of ≥ 100 mmHg)	Multiple-agent antihypertensive therapy. Study treatment should be interrupted in case of persistent or symptomatic hypertension; study treatment should be permanently discontinued for uncontrollable hypertension.
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit, and hypertensive crisis)	Urgent intervention and permanent study treatment discontinuation indicated

The dose of antihypertensive agents used should be documented during each visit. If the subject remains hypertensive despite treatment discontinuation, BP and antihypertensive agents used should be monitored every 3 months until BP returns to normal or end of study.

Posterior reversible encephalopathy syndrome (PRES)

There have been a few reports of subjects with signs and symptoms consistent with PRES after study treatment. This is a rare neurological disease and its signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with PRES should permanently discontinue the study treatment.

Proteinuria

Urinalysis should be performed prior to each dose of IBI305/bevacizumab unless a 24-hour urinary protein test has already been done.

First occurrence of proteinuria:

After carrying out the urinalysis, if:

Urine protein is < 2+, continue study treatment as scheduled, no additional tests are required.

≥ 2+ (urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:

- 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled. and perform urinalysis dipstick test before each scheduled dose.
- 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g.

Second and subsequent occurrence of proteinuria:

< 3+ (urinalysis): continue study treatment as scheduled, no additional tests indicated.

≥ 3+ (urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:

- 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled.
- 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g.

Nephrotic syndrome (Grade 4): Study treatment is permanently discontinued

Gastrointestinal perforation

If gastrointestinal perforation occurs, appropriate measures should be taken and the study treatment should be permanently discontinued.

Wound healing complications

The study treatment should not begin within 28 d after a major surgery, or before the surgical wound is fully healed. If a complication of wound healing occurs during study treatment, the study treatment should be interrupted until the wound is fully healed. If an elective surgery is required, the study treatment should be interrupted.

Abdominal abscess or fistula

If abdominal abscess or fistula occurs, the study treatment should be discontinued. However, the investigator will determine whether study treatment will be continued if the above AE is resolved.

Infusion-related and allergic reactions:

Infusion-related reactions after first dose of the study drug is uncommon (< 3%), and the incidence of a severe reaction is only 0.2%.

If a mild (grade 1 or 2) reaction (such as fever, chills, headache, and nausea) occurs, pretreatment prior to subsequent administration should be performed and infusion time should not be reduced. If the subject is well-tolerated during infusion after pretreatment, the infusion time can be reduced by 30 minutes (+10 minutes) for subsequent administration with pretreatment. If an infusion-related AE occurs during a 60-minute infusion, the subsequent infusion should be completed within 90 minutes (+15 minutes) with pretreatment. Likewise, if an infusion-related AE occurs during a 30-minute infusion, the subsequent infusion should be completed in 60 minutes (+10 minutes) with pretreatment. If a subject has a grade 3 infusion-related reaction, the study treatment should be interrupted and not be restarted on the same day. However, since there lacks the dose adjustment method for grade 3 infusion-related reactions, the investigators may decide to either discontinue the study drug or perform pretreatment, and complete the infusion within 90 minutes (+15 minutes). If an adverse reaction still occurs during a 90-minute infusion, the infusion should be continued at a slower rate and then gradually returned to a 90-minute infusion. If the investigator is uncertain about the handling, the study treatment should be discontinued. When the study treatment is restarted, the subject should be closely monitored based on routine clinical practice until the possible time of adverse reaction has passed. If a subject has a grade 4 infusion-related reaction, the study treatment should be discontinued.

An allergic reaction is defined as the vascular collapse or shock (systolic BP < 90 mmHg, unresponsive to rehydration) that occurs within 30 minutes of a study drug infusion caused by an allergy, with or without respiratory distress. Skin reactions include pruritus, urticaria, and angioedema. Subjects with allergic reactions should discontinue the study treatment.

5.3.3 Dose adjustments of chemotherapy

Paclitaxel and carboplatin should be administered according to the study site guidelines and local prescribing information. For the specific information for use, preparation, and storage of paclitaxel and carboplatin, refer to the prescribing information and local dosing information. Carboplatin-based chemotherapies have a relatively high incidence of emesis. Therefore, antiemetics for prophylaxis can be used.

Hematological toxicity:

Absolute neutrophil count (ANC; dose can only be reduced when febrile neutropenia occurs. ANC must be ≥ 1.5 × 109/L and platelet count must be ≥ 100 × 109/L on D1 of each treatment cycle). Once the chemotherapeutic dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 × 109/L or ◡ 50 × 109/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.

Table 3. Dose adjustments of paclitaxel and carboplatin (febrile neutropenia and thrombocytopenia)

	Dose Adjustments of Paclitaxel/Carboplatin		
	First Occurrence	**Re-Occurrence After Dose Adjustment**	**Re-occurrence After Two Dose Adjustments**
Febrile neutropenia (regardless of duration)	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC *3*	Chemotherapy discontinuation
Lowest Level After Last Dose <25 × 10^9/L or <50 × 10^9/L with hemorrhage or requires blood transfusion	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC 3	Chemotherapy discontinuation

If the dose adjustment is required when ANC and thrombocytopenia occur concurrently, the low-dose chemotherapy should be adopted.

Chemotherapy may be delayed for up to 3 weeks. If after the chemotherapy has been delayed for 3 weeks, ANC does not reach ≥ 1.5×10^9/L and platelet count does not reach ≥ 100×10^9/L on D1 of the scheduled chemotherapy, the chemotherapy should be permanently discontinued. If the above values have been reached, the next course of chemotherapy should be continued.

The investigator should monitor the subject closely for toxicity with particular attention to early and evident signs of myelosuppression, infection, or febrile neutropenia to timely and appropriately treat the complications.

Subjects should be informed to pay attention to these signs and receive treatment as soon as possible.

If the chemotherapy must be interrupted due to hematological toxicity, the complete blood count should be performed regularly (including WBC differentials) until all the counts reach the minimum requirements for treatment continuation. Thereafter the scheduled treatment plan will be performed.

Dose adjustments are not required for anemia. However, treatment based on guidelines of each clinic should be performed.

Gastrointestinal toxicity

Antiemetics will be used to control nausea and/or emesis. If grade 3 or 4 nausea and/or emesis occur(s) despite of antiemetics, the chemotherapeutic dose should be reduced by 20% for the next treatment cycle. The dose should be returned to the initial level as possible if the subject is tolerated.

If the subject experiences stomatitis on D1 of any treatment cycle, the chemotherapy should be interrupted until the symptoms resolve. If the stomatitis has not resolved after 3 weeks, the chemotherapy should be permanently discontinued (refer to CTCAE version 4.03). If an acute Grade 3 stomatitis occurs, the chemotherapeutic dose should be reduced to 75% of the proposed dose when symptoms resolve.

Hepatotoxicity (Paclitaxel)

The paclitaxel dose should be determined based on the lab values measured on D1 of each treatment cycle.

Table 4. Dose adjustment of paclitaxel (hepatotoxicity)

AST		Total bilirubin	Paclitaxel Dose
≤ 5 x UNL	and	WNL	175 mg/m^2
> 5 x UNL	or	> UNL ~ 1.5 x UN	150 mg/m
		> 1.5 x UN	0

If paclitaxel is interrupted due to hepatotoxicity, carboplatin should also be interrupted until paclitaxel is restarted. Paclitaxel will be interrupted for up to 3 weeks. If the subject's hepatic function does not return to the acceptable ranges in 3 weeks, paclitaxel should be permanently discontinued. The carboplatin dose will not be adjusted when hepatotoxicity occurs.

The investigators should avoid PD due to abnormal hepatic enzyme levels as possible. If PD occurs, all the study drugs should be permanently discontinued, including chemotherapy.

Cardiovascular toxicity (paclitaxel)

The arrhythmia in subjects was infrequent in previous clinical studies. However, most subjects were asymptomatic and electrocardiographic monitoring was not required. Asymptomatic transient bradycardia was observed in 29% of subjects, but significant atrioventricular block was rare. Cardiac events should be treated as follows:

Asymptomatic bradycardia: no intervention indicated

Symptomatic arrhythmia during infusion: Discontinue paclitaxel infusion and perform routine treatment of arrhythmia. Discontinue subsequent paclitaxel treatment. Document this AE in the AE Report Form of eCRF.

Chest pain and/or symptomatic hypotension (< 90/60 mmHg or rehydration therapy required): discontinue the paclitaxel infusion. Perform electrocardiography (ECG). If hypersensitivity reaction is suspected, administer diphenhydramine and dexamethasone via intravenous infusion. If the chest pain is not considered as cardiogenic, epinephrine or bronchodilators will be administered. Document this AE in the AE Report Form of eCRF. Discontinue subsequent paclitaxel treatment and provide symptomatic treatment. Consult a cardiologist if needed.

Neurotoxicity (paclitaxel)

The dose of paclitaxel should be adjusted according to Table when neuropathy occurs. The dose adjustment of carboplatin is not needed when neurotoxicity occurs.

Table 5. Dose adjustment of paclitaxel (neurotoxicity)

Toxicity Grade (CTCAE version 4.03)	Paclitaxel dose adjustment
Grade 1 or below	175 mg/m^2
2	Interrupt treatment until return to grade 1, then reduce dose to 140 mg/m^2 (20% of reduction) and restart infusion

Grade 3 or above	Interrupt treatment until return to grade 1, then reduce dose to 125 mg/m^2 (30% of reduction) and restart infusion.

Once the dose is reduced due to neurotoxicity, the original dose should no longer be adopted. If the neurotoxicity does not return to grade 1 after paclitaxel interruption for 3 weeks, paclitaxel should be permanently discontinued.

Allergic reactions/hypersensitivity reactions (paclitaxel)

Note: Prophylaxis for hypersensitivity reactions (see below) and close monitoring of vital signs are recommended for subjects with history of mild to moderate hypersensitivity reactions when hypersensitivity reactions reoccur.

Mild symptoms: complete paclitaxel infusion. Close monitoring; no treatment indicated.

Moderate symptoms: Interrupt paclitaxel infusion, administer diphenhydramine 25–50 mg and dexamethasone 10 mg via intravenous infusion. Once symptoms have resolved, resume paclitaxel infusion at a slower rate (20 mL/hour for 15 minutes, then at 40 mL/hour for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete). Document this AE in the AE Report Form of eCRF. If symptoms reoccur, interrupt the paclitaxel infusion and permanently discontinue subsequent paclitaxel infusion.

Severe and life-threatening symptoms: Interrupt paclitaxel infusion, administer diphenhydramine and dexamethasone via intravenous infusion (as above). Use epinephrine or bronchodilators if indicated. Document this AE in the AE Report Form of eCRF. Subsequent courses of paclitaxel infusion should be permanently discontinued.

Moderate or severe hypersensitivity reactions should be documented as AEs.

Other toxicities

If other unmentioned grade 3–4 toxicities occur, the chemotherapy should be interrupted until symptoms resolve or return to grade 1. Thereafter restart the infusion at 50% of the original dose (which should no longer be adopted). If the toxicity does not return to grade 1 after an interruption for 3 weeks, the chemotherapy should be permanently discontinued. Dose adjustments are not recommended for grade 1 and 2 toxicities.

5.4 Study Drug Properties

IBI305 is a bevacizumab biosimilar. The active ingredient of both drugs is recombinant humanized anti-VEGF monoclonal antibody; Bevacizumab is the standard commercially available drug, provided by the sponsor.

Detailed information on the study drugs is shown in Table .

Table 6. Study drugs

Study Drugs	Dosage Form and Strength	Excipient	Appearance	Manufacturer
IBI305	4 mL: 100 mg	Sodium acetate, sorbitol, and polysorbate 80	Sterile solution for intravenous injection pH 5.2 Clear, colorless liquid, no foreign matters, no floc or precipitation	Innovent Biologics (Suzhou) Co., Ltd.
Bevacizumab	4 mL: 100 mg	α,α-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, polysorbate 20, and sterile water for injection	Sterile solution for intravenous injection pH 5.9–6.3 Clear to slight opalescent, colorless to light brown	Roche Pharma (Schweiz) Ltd.

5.5 Preparation and Distribution

IBI305 or bevacizumab is diluted in 0.9% sodium chloride solution by the pharmacist or research nurse before infusion. Check the particles and discoloration prior to administration.

The investigator should ensure that the pharmacist or research nurse administers the study drugs according to study protocol.

5.6 Packaging, Labeling, and Storage

The sponsor should package and label the study drugs according to appropriate local regulations.

All study drugs (IBI305 and bevacizumab) must be stored at 2–8 °C away from light. The study drugs should be stored in a safe zone only accessible by authorized staff prior to dispensation to the subjects.

5.7 Subjects Allocation

After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in the Interactive Web Response System (IWRS) and enter the subject information into the IWRS. The IWRS will allocate a random number to the subject and provide a medication

number. Stratified randomization is used in this study. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild vs. unknown type).

5.8 Blinding

This is a randomized, double-blind, and active-controlled study, and only relevant study personnel had access to the randomization numbers. A non-blinded pharmacist or research nurse will prepare the medications since IBI305 and bevacizumab do not have an identical appearance. The pharmacist or research nurse who is responsible for preparing the study drugs is not allowed to disclose any information regarding treatment allocation to the subject, the subject's family members, or other personnel including the physician and the relevant study staff.

Unblinding: Subject unblinding should only be performed after database locking.

Emergency unblinding: In case of an emergency where the investigator must know the medication given to a particular subject, the investigator will unblind the subject via the IWRS and immediately inform the sponsor and CRO. The reasons for unblinding, date, and outcomes should be documented in the source document and eCRF of the subject.

5.9 Concomitant Medications and Treatments

All medications except for the study drugs, including other chemotherapies not specified in the study, Chinese herbal medicines, and other non-traditional therapies, are considered concomitant medications. All concomitant medications used within 30 days prior to screening should be documented in the eCRFs, including the information of generic name, route of administration, start date, end date, and indication.

5.9.1 Prohibited treatment

No other anti-tumor therapies or medications with anti-tumor indications, including Chinese herbal medicine, radiotherapy, or other investigational drugs, are allowed during this study other than IBI305, bevacizumab, paclitaxel, and carboplatin.

Severe myelosuppression is possible after chemotherapy. Granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are not allowed to be used prophylactically in the first treatment cycle.

5.9.2 Permitted treatment

Prophylactic use of anti-emetics, glucocorticoids, or other treatments targeting toxicities is permitted during the study. Unconventional treatments (such as acupuncture) and vitamins/microelements are permitted if their use does not affect the study endpoints as determined by the investigators.

Starting from the 2nd chemotherapy cycle, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are allowed to be used prophylactically to prevent severe myelosuppression.

Anti-viral therapy was permitted whenever necessary.

Stable doses of anti-epileptic drugs were permitted.

Radiotherapy for bone metastasis was permitted provided that the radiotherapy field did not include the target lesion

5.9.3 Treatment after study treatment

Subsequent therapy after the end of study treatment should be determined by the subject's attending doctor.

5.10 Treatment Compliance

Subjects should receive treatment at the study site. The dose and time of administration of IBI305 or bevacizumab and paclitaxel/carboplatin should be documented in the source records and eCRFs during each treatment cycle. Reasons for dose adjustments, therapy delay, and therapy discontinuation should be documented. Treatment compliance is monitored by medication dispensing and return records, medical records, and eCRFs.

5.11 Drug Return and Destruction

The containers, vials, infusion bags, and syringes of used and partially used drugs can be destroyed on-site according to the appropriate guidelines and operating procedures established by study sites and local agencies.

Unless the contents have significant safety issues requiring immediate destruction in accordance with local regulations, all the unused drugs should be returned and destroyed based on the requirements of sponsor.

5.12 Study Drug-Related Records

The designated personnel of the study sites should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines.

6 STUDY PROCEDURE

The detailed procedures of this study are shown in Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

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6.1 Screening Visits (D -28 to D -1)

Complete the screening visits within 28 days prior to study treatment commencement. The following procedures must be completed during screening to ensure that subject meets the requirements for participating in this study:

- Sign the ICF
- Record the demographics, including age, ethnicity, and gender
- Record the past medical history, including smoking history
- Record the history of anti-tumor therapies
- Record the concomitant medications (within 30 days prior to screening)
- Record the vital signs
- Measure the height and weight (including BMI)
- ECOG score
- Physical examination
- 12-Lead ECG
- Hepatitis B panel, anti-HCV, anti-HIV, and syphilis tests
- Clinical laboratory tests (routine blood test, coagulation test, blood chemistry, and urinalysis)

- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Imaging examinations (CT or MRI: Head, chest, abdomen, and pelvis cavity)*
- EGFR test#
- Review the inclusion/exclusion criteria
- Record the AEs and concomitant medications

* Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging results during screening will be used as the baseline data. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

If the subject has been tested for EGFR of tumor sample at the study site with documentation, the subject will not be required for retest.

6.2 Baseline Visits (D1 of cycle 1)

D1 refers to the day of receiving the first dose of the study drugs. Eligible subjects meeting the inclusion criteria will return to the study site and complete the following procedures:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests * (routine blood test, blood chemistry, and urinalysis)
- Confirm the inclusion/exclusion criteria

* If clinical laboratory screening tests (routine blood test, blood chemistry, urinalysis) are performed within 7 days prior to the first dose, then the results of the screening test can be used as baseline.

If the subject meets the inclusion criteria, the following procedures should be complete:

- Randomization and grouping
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Pharmacokinetic (PK) blood sampling (within 1 h prior to the study drug infusion,

immediately after the study drug infusion [+5 min])

- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Record the AEs and concomitant medications

6.3 Cycle 2 (week 4 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.4 Cycle 3 (week 7 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)

- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.5 Cycle 4 (week 10 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.6 Cycle 5 (week 13 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)

- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.7 Cycle 6 (week 16 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.8 Cycle 7 and Subsequent Treatment Cycles (±3 Days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Maintenance monotherapy will start from week 7 and the dose of study drug will be adjusted to 7.5 mg/kg. Subjects should complete the following procedures during each visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG

- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.9 End-Of-Treatment Visit

The end of treatment visit in study sites will be conducted in 28 days (±7 days) after the last dose of study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Immunogenicity test
- PD blood sampling
- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this visit)
- Subsequent anti-tumor therapy
- Record the AEs and concomitant medications

If the subject has not experienced PD, the subsequent follow-up for PD will be performed (Section 6.10). If the subject has experienced PD, the subsequent follow-up for survival will be performed (Section 6.11).

6.10 Disease Progression Visit

If the study drugs are discontinued for reasons other than PD, the end of treatment visit in study sites will be conducted in 28 days after the last dose of study drug, and tumor assessments should be conducted every 6 weeks (±7 days) until PD if possible (after which, follow-up for survival will be conducted [Section 6.11]), withdraw of informed consent, loss to follow-up, death,

start of other anti-tumor therapies, or end of study. During the visit, vital signs and weight measurements will be performed, and any subsequent anti-tumor therapies will be documented.

6.11 Survival Follow-Up

The investigator will make telephone follow-up every 12 weeks (±7 days) to collect the information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, loss to follow-up, death, or end of study.

6.12 Study Completion

The end of this study will be the18th month after randomization of the last subject. If the subjects continue to receive the study drug treatment before this cut-off time, the treatment should be discontinued and the end of treatment visit should be completed (Section 6.9).

6.13 Tumor Assessment

Imaging tests (CT or MRI) of the brain, chest, abdomen, and pelvis are required at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test was used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

The investigator should perform a tumor assessment based on RECIST v1.1 (Section 13.3) prior to each dose to determine whether the subject should continue with the next round of treatment. An independent review committee will also assess the tumor response (Section 11.1.1). Imaging tests will not be rescheduled if the study drugs or chemotherapeutic agents are interrupted due to toxicities. Every effort should be made to continue the schedule for imaging tests even for subjects who discontinue one or two study treatment(s) due to drug-related toxicities.

If subject experience PD according to the RECIST v1.1 criteria, the attending doctor should discuss with the subject regarding subsequent routine cancer therapies.

6.14 Clinical Laboratory Evaluations

Clinical laboratory tests will be conducted at the laboratories of each study site. Sample collection and analysis should be performed according to the requirements of each laboratory.

The following laboratory tests should be conducted according to the study procedures (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

):

Routine blood test: hemoglobin, hematocrit, WBC and differentials (including

absolute neutrophil and lymphocyte counts), platelets, and RBC

Routine coagulation test (baseline test): INR, aPTT, or PTT

➢ Blood chemistry: Creatinine, blood urea, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose, sodium, potassium, chloride, calcium, phosphorus, and magnesium

➢ Urinalysis: Specific gravity, pH, glucose, protein, occult blood, and leukocytes

➢ Pregnancy test: Serum/urine pregnancy tests are performed on women of childbearing age during screening and the end-of-treatment visit.

These tests are carried out at the laboratory of each trial site.

For subsequent visits, all laboratory tests need to be completed within 3 days prior to the administration. During the study, the frequency of these laboratory tests will be increased if safety is a concern. The investigator should review the laboratory test results throughout the study to determine whether the results are clinically significant. The investigator should assess the changes in laboratory test results. If the investigator considers a laboratory test result to be abnormal and of clinical significance, it is considered as an AE.

6.15 Vital Signs, Physical Examinations, and Other Safety Assessments

6.15.1 Vital signs

Vital signs include pulse, BP, temperature, and respiratory rate. The subject must rest for at least 5 minutes prior to each vital sign assessment.

Vital signs will be assessed according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

). During the study, the investigator may increase the frequency of vital sign measurement if

safety is a concern.

6.15.2 Height and weight

Height is only measured during screening. Weight is measure during each visit.

6.1.5.3 Physical examinations

The following organs/systems will be examined according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration		x	x	x	x	x	x	x			

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
(IBI305 or bevacizumab) [j]											
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

): general condition, head (eyes, ears, nose, and throat), neck and thyroid, respiratory system, cardiovascular system, abdomen, nervous system, skeletal muscles and limbs, as well as lymphatic system and skin.

6.15.4 12-Lead ECG

12-lead ECG will be performed during screening. During the study, each medication visit requires an ECG examination. The following ECG parameters should be documented: HR, PR-interval, QRS-complex, QT-interval, and QTc-interval. The subject must be in the supine position for at least 5 minutes prior to undergoing the 12-lead ECG. All ECG are evaluated by qualified physicians. All clinically significant abnormal findings should be reported as AEs.

6.15.5 Immunogenicity assessment

Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples were tested at the designated central laboratory.

6.15.6. Pharmacokinetics/pharmacodynamics

6.15.6.1 Pharmacokinetics

Study sites that are implementing version 2.0 and subsequent versions of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 hour prior to the dose in C4, within 1 h prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.

6.15.6.2 Pharmacodynamics

Study sites that are implementing version 2.0 and subsequent versions of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and during the end-of-treatment visit. Samples were tested at the designated central laboratory.

6.15.7 EGFR testing

EGFR mutation testing histologically or cytologically will be performed in all subjects (if the subject has been tested for EGFR at the study site histologically or cytologically with documentation, the subject will not be required to be retested). The testing will be conducted at the laboratory of each study site or a qualified third-party laboratory.

7 STUDY ASSESSMENTS

7.1 Efficacy Assessment

7.1.1 Primary efficacy endpoint

- Objective response rate (ORR)

ORR will be assessed using RECIST v1.1. ORR is defined as the proportion of subjects with tumor size reduction of a predefined amount and for a minimum time period, including patients who achieved complete response (CR) and partial response (PR). The cut-off date for data included in the primary efficacy evaluation is the 18th week after the last subject is randomized.

7.1.2 Secondary efficacy endpoints

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Each endpoint will be assessed using RECIST v1.1.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death before PD; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

PFS is defined as the time from the date of randomization to the date of PD or death; Subjects who do not progress or die will be censored on the date of the last tumor assessment.

DCR is defined as the proportion of patients whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved CR, PR, and SD.

OS is defined as the time from the date of randomization to the date of death of any cause. For subjects that are alive on the date of study completion or are lost to follow-up, their survival time will be censored at the date of last contact.

7.2 Safety Assessments

7.2.1 Adverse events

7.2.1.1 Definition

Adverse event

An AE refers to any untoward medical occurrence in a subject after signing the informed consent form, and does not necessarily have a causal relationship with the treatment. Thus, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether considered drug related.

Abnormalities resulting from PD are not considered as AEs.

Serious adverse event

A SAE refers to an AE meeting at least one of the followings:

(1) Lead to death, except for deaths caused by PD.

(2) Life-threatening (a "life-threatening event" is defined as an AE when the subject is at immediate risk of death at the time, but does not include the case that may lead to death only when the event worsens).

(3) Requires hospitalization or prolonged hospitalization, excluding an emergency or outpatient visit. Subjects with existing diseases or conditions prior to the enrollment that do not worsen during the study, and having hospitalization and/or surgery that was scheduled before the study or during the study do not meet the SAE criterion. Hospitalizations resulting from PD are not considered as SAEs.

(4) Results in permanent or severe disability/incapacity.

(5) Results in congenital anomalies/birth defects.

(6) Other important medical events: The event that does not result in death, is not life-threatening or does not require hospitalization, but may jeopardize the health of subjects and require medical intervention to prevent the SAEs above, is considered as an SAE

7.2.1.2 Severity of adverse events

The severity of AEs is evaluated using the 5-level criteria of NCI CTCAE v4.03.

For AEs not included in CTCAE v4.03, use the following CTCAE general guidelines:

$\frac{4}{3}$ Grade 1: Mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated.

- Grade 2: Moderate; minimal/local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life (such as cooking, shopping, using the phone, financial management, etc.).
- Grade 3: Severe or clinically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; limited ability of self-care (such as bathing, dressing, undressing, eating, using the toilet, taking medication), but not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

7.2.1.3 Relationship between adverse events and the investigational drug

The relationship between the study drugs and AEs can be determined using the followings:

Table 1. Correlation between AEs and investigational drugs

Correlation	CRITERIA
Related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can more reasonably explain the AE than the other causes (such as the pre-existing disease of the subject, environment, toxicity, or other treatment received); The AE resolves or is alleviated after treatment interruption or dose reduction; The AE is consistent with the known type of AEs of the suspicious drug or similar drugs; The AE occurs again after the drug administration is resumed.
Possibly related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can be used to explain the AE with the same level of rationality as other reasons (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE resolves or is alleviated after treatment interruption or dose reduction (if applicable).
Possibly not related	Other reasons can more reasonably explain the AE than the investigational drug (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear; The AE does not occur again or the situation of the AE is unknown after the drug administration is resumed.

Correlation	CRITERIA
Unrelated	The occurrence of the AE is not reasonably related to the time sequence of dosing, or The AE has other obvious causes (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject).
Cannot be determined	The above information is unclear and cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.

7.2.1.4 Serious adverse event reporting

SAEs that occur from the signing of informed consent form until 90 days (inclusive) after the last dose should be reported. The investigator must fill out the "CFDA SAE Report Form", regardless of whether it is the initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, CFDA, and ethics committee within 24 hours of noticing the event. The contact information for reporting is shown in the table below.

For SAEs occurring outside of the above-mentioned period, those considered related to the investigational drug shall also be reported to the sponsor.

The investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.

The investigator should also report the event to the CFDA, health administration departments, and ethics committees in accordance with the regulations.

When submitting the SAE report by email, it is recommended for the investigator to encrypt the report file and send the report file and password in separate emails.

Table. SAE report contacts

Unit	**Contact**	**Fax/Telephone/Address**
Hospital Name	**Ethics committee**	**Hospital Fax/Telephone**
Innovent Biologics (Suzhou) Co., Ltd.	Clinical Study Department PV	Fax: 021-31652800 Email: drugsafety@innoventbio.com

Office of Drug Research and Supervision, Department of Drug and Cosmetics Registration, China Food and Drug Administration		Address: Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing Post Code: 100053 Tel: 010-88330732 Fax: 010-88363228
Medical Administrative Department, Health Administration		Address: No. 38, Lishi Road, Xicheng District, Beijing Tel: 010- 68792001 Fax: 010-68792734
Province, Autonomous Region, Municipality Food and Drug Administration	Based on the requirements of the food and drug administration department of each province, autonomous region or municipality	

7.2.1.5 Management and follow-up of adverse events

The investigator is responsible for providing appropriate medical treatment for all AEs (Indicate the actions taken, such as suspension/termination of the investigational drug, dose modification, drug therapy, etc.). When an AE occurs, the investigator should actively take appropriate measures to ensure the safety of the subject. All AEs observed from the signing of the ICF to the time specified in the protocol (Table 2) must be followed.

The investigator should report any SAE that occurs after the time specified in the protocol (Table 2) and is suspected of being related to the investigational drug to the sponsor.

7.2.1.6 Adverse event of special interest and expedited reporting

The AESI for this study include:

- Gastrointestinal perforation
- Procedural and wound healing complications
- Hemorrhage
- Fistula
- Hypertension
- Thrombotic event
- Posterior reversible encephalopathy syndrome (PRES)

- Proteinuria
- Infusion-related reaction
- Ovarian failure
- Cardiac failure congestive

If the criteria for SAE is met, the SAE report should be submitted to the sponsor within the specified time limit (see 7.2.1.4 for details)

7.2.1.7 Pregnancy

Bevacizumab may be harmful to the fetus. Subjects or female partners of male subjects must use an effective form of contraception during the 6 months after the last dose.

During the study, if a female subject exposed to the study drug becomes pregnant, she must discontinue study treatment. The investigator must report to the sponsor within 24 hours of noticing the event and submit the "Innovent clinical Study Pregnancy Report/Follow-Up Form".

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

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

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

If the subject also experiences a SAE during the pregnancy, the CFDA SAE Report Form should also be filled out and reported according to SAE's procedures.

7.2.1.8 Time limits of documenting and reporting AEs

All AEs occurring from the time the subject signs the informed consent form to the time specified in the protocol (Table 2) (including SAEs and non-SAEs), regardless of their severity, must be collected and recorded on the AE page of the eCRF.

The investigator must fill out all the required information, including the description of the AE, start date, end date, severity, measures taken, outcome, seriousness, and causality with the investigational drug. Each AE should be documented separately.

Table 2. Reporting and follow-up of adverse events

	Reporting time limit	Visit time limit
AEs	From signing the informed consent form to *90 days* after the last dose (if the subject begins other anti-tumor therapies, only AEs related to the study drugs should be collected)	Until resolved or explainable stable determined by the investigator
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the outcome of the event is available, and the health conditions of the newborn should be followed up for at least 2 months according to the protocol

7.2.1.9 Precautions for AE documentation

Diagnosis, signs, and symptoms

If a diagnosis is already made, the eCRF should record the diagnosis instead of individual symptoms and signs (such as hepatic failure rather than jaundice, transaminase increased, and asterixis). However, if the signs and symptoms cannot be attributed to a definitive diagnosis, each independent event should be documented in the eCRFs as an AE or SAE. Update the report with visit information if a diagnosis is confirmed later.

AEs secondary to other events

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

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs. The initial severity should be documented, and the information should be updated if the event exacerbates.

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

Abnormalities in laboratory tests/vital signs

All clinically significant laboratory test abnormalities should be reported as AEs. It is the responsibility of the investigator to review all abnormal laboratory test results, and to make medical judgments as whether each abnormal laboratory test result should be reported as an AE.

Death

During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs, regardless of the causality with the investigational drug.

When recording a death event, if the cause of death is clear, the cause of death is recorded as an adverse event with the result of the adverse event being death, and the event is reported as an SAE; if the cause of the death is unknown at the time of reporting , "Death with Unknown Cause" should be recorded on the Adverse Event Form of the eCRF and the "Death with Unknown Cause" should be reported as an SAE first before further investigation is carried out to find the exact cause of death.

Pre-existing medical conditions

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

Hospitalization and prolonged hospitalization, or surgery

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

$\frac{4}{3}$ Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration, efficacy evaluation, etc.)

$\frac{4}{3}$ Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.

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

The investigator should fill in all required information, including AE terms

(diagnostic terms, or the record of symptoms and signs including laboratory test abnormalities if there is no diagnosis), start date, end date, severity level, whether it is an AESI, measures taken for the investigational product, treatment given for the AE, outcome, seriousness, and relationship with the investigational product. If the signs and symptoms cannot be attributed to a definitive diagnosis, each AE should be documented independently.

Progressive disease

A progressive disease is defined as the worsening of subject condition caused by the primary tumor that the investigational drug is targeting, the appearance of new lesions, or the progression of the primary lesion. Expected progressive disease should not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by progressive disease should not be reported as an SAE

8 STATISTICS

8.1 Sample Size Determination

A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin.

The sample size is estimated based on the following assumptions:

- The ORRs between IBI305 and bevacizumab group are equivalent
- The ORR of subjects in the bevacizumab groups is set to 50.0%
- The equivalence margin for the ratio of ORR is taken as (0.75, 1/0.75))
- The significance level of the two one-side test is 0.05
- 1:1 randomization

Based on the above hypotheses, a number of 218 subjects for each group is required (436 subjects in total). The sample size was estimated using PASS 2013.

8.2 Statistical Population

Intention-to-Treat (ITT): All randomized subjects.

Full Analysis Set (FAS): All randomized and evaluable subjects who received at least one dose of the study treatment. This dataset is used as the primary analysis set for efficacy assessment.

Per-Protocol (PP): Based on the FAS, subjects with the predetermined minimum drug exposure and without any predetermined major protocol deviations. This dataset is used as the secondary analysis set for efficacy assessment.

Safety set (SS): Includes all randomized subjects who received at least one dose of the study treatment and have safety evaluation data. This data set is used for the safety evaluation of this study.

PK analysis set (PKAS): Includes subjects in the FAS with at least one PPK measured value.

Pharmacodynamic analysis set (PDAS): Includes all subjects in the FAS set with at least one PD measured value.

8.3 General Principles for Statistical Analyses

For continuous variables, descriptive statistics should include the count, mean, standard deviation, median, maximum, and minimum. For categorical variables, descriptive statistics will include the number and percentage of each category. Statistical analyses will be carried out using SAS 9.4.

8.4 Statistical Methods

8.4.1 Adjustments for covariates

The stratification factors of randomization in this study include age and EGFR status, and the stratification factors will be considered in the model analysis (GLM or Cox) of primary and secondary efficacy parameters

8.4.2 Managing dropouts and missing data

The handling of dropout and missing data will be detailed in the statistical analysis plan

8.4.3 Multi-center study

Since this is a multicenter study, the primary endpoint (ORR) will be listed according to study sites and treatment groups. However, individual equivalence analysis will not be conducted. Trial sites with fewer than 5 ITT subjects per treatment group will need to be combined for analysis. Details will be discussed in the data review meeting.

8.4.4 Multiple comparisons and adjustments to multiplicity

The α adjustment for multiple comparisons is not considered.

8.5 Statistical Analyses

8.5.1 Subject distribution

Refer to Figure 1: Study design schematic for the schedule of activities. The number and percentage of patients who have completed or dropped out of the study (including the reason for dropouts such as loss to follow-up, AEs, and poor compliance) are summarized based on treatment groups.

The number and percentage of subjects in each analysis set are calculated based on treatment groups.

The number and percentage of protocol deviations are calculated based on treatment groups.

8.5.2 Demographics and other baseline characteristics

Demographic information such as age, height, sex, and weight, and other baseline characteristics such as disease history (including NSCLC diagnosis, staging, previous cancer treatment, and target and nontarget lesions) are summarized using descriptive statistics.

8.5.3 Compliance and drug exposure

The required dose and the actual dose must be documented in the eCRF. Subject compliance is calculated based on the ratio of the actual dose (number of doses) to the required dose (number of doses). Subject compliance is classified into the following categories: < 80%, 80–120%, and > 120%. The number and percentage of subjects in each category will be summarized.

8.5.4 Efficacy

The efficacy analysis will be based on the FAS. Results of the PP set will also be presented.

8.5.4.1 Primary efficacy endpoint

The primary objective of this study is to determine the clinical equivalence between IBI305 + paclitaxel/carboplatin and bevacizumab + paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC). The primary endpoint is objective response rate (ORR). ORR is defined as the incidence of confirmed complete response (CR) or partial response (PR), using a validated imaging method to evaluate target lesions and non-target lesions according to RECIST v1.1. Subjects without tumor assessments after baseline will be considered as not assessable. Subjects qualified for the evaluation of CR or PR must have at least one measurable lesion according to RECIST v1.1. The evaluation of clinical equivalence will be based on the ORR provided by the independent review committee (IRC). Results provided by the

investigator will be used for sensitivity analysis.

Clinical equivalence will be determined by whether the 90% CIs of ORR ratio for subjects in both IBI305 and bevacizumab groups falls within the equivalence margins of (0.75, 1/0.75).

The ORR and corresponding 95% confidence interval of the two treatment groups, the ORR difference and the 90% confidence interval, as well as the ORR ratio between the two groups and the 90% confidence interval will be estimated using the generalized linear model (GLM, which includes treatment groups and stratification factors).

8.5.4.2 Secondary efficacy endpoints

The secondary endpoints for this study include DOR, DCR, progress-free survival (PFS), and overall survival (OS).

DCR is defined as the incidence of patients with confirmed complete response (CR), partial response (PR), and stable disease (SD), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

OS refers to the time from the date of randomization to the date of death (of any cause). For subjects who are still alive at the time of the analysis, their survival time is censored on the last known alive date. PFS refers to the time from the date of randomization to the date of first documented PD or death, whichever occurs first. Subjects who do not progress or die will be censored on the date of the last tumor assessment. Subjects without tumor assessments after baseline are censored on their date of randomization.

Median OS and its 95% CI will be estimated using the Kaplan-Meier method. The survival curve will be plotted. The hazard ratio (HR) between the two groups and its 95% CI will be estimated using a Cox model. The Cox model includes treatment groups and stratification factors. DOR and PFS will be analyzed using the same method as for OS. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

8.5.4.3 Sensitivity analysis

The center effect (fixed or random) will be considered in the primary and secondary endpoints analysis models (GLM or Cox).

8.5.4.4 Antibody and efficacy analysis

Subjects who produce antibodies during the study will be listed. The difference in efficacy between subjects with and without antibodies will be compared if necessary.

Changes in PK parameters and steady-state trough concentrations of subjects with positive ADA are analyzed.

8.5.5 Exploratory analysis

Pharmacodynamic parameters: The changes in the serum VEGF level at different time points are described, and inter-group comparisons are carried out when necessary (based on the PD dataset)

Steady-state trough concentrations of the drug: The level of trough concentration is described and inter-group comparisons are carried out when necessary (based on the PPK dataset)

8.5.6 Interim analysis

No interim analysis is planned for this study.

8.5.7 Stratified analysis

Efficacy analysis of different levels of subjects is conducted based on the random stratification factors

8.5.8 Safety analysis

The safety analysis is based on the safety analysis set.

8.5.8.1 Adverse events

All adverse events (AE) will be coded using MedDRA and graded using CTCAE v4.03. All TEAEs, TEAEs ≥ grade 3, SAEs, drug-related TEAEs, drug-related SAEs, TEAEs resulting in the termination of study drugs, TEAEs resulting in the termination of study, and AESIs will be listed based on system organ class, preferred terms, and groups and the corresponding numbers and percentages of subjects will be summarized. In addition, the severity of TEAEs and relevance to the study drugs will also be summarized system organ class, preferred terms, and treatment groups.

8.5.8.2 Laboratory tests

All laboratory test results and changes relative to baseline will be summarized by scheduled time point and treatment group using descriptive statistics. Laboratory abnormalities will be listed.

8.5.8.3 ECG examinations

Results of ECG and changes relative to baseline will be summarized using descriptive statistics.

8.5.8.4 Vital signs, physical examinations, and other safety examinations

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

Results of physical examinations are listed by treatment groups.

8.5.8.5 Concomitant medications

Concomitant medications are non-study medications that meet one of the followings:

(1) Any drug therapy started during or after the first dose of the study treatment;

(2) Any drug therapy started before the first dose of the study treatment and continued after the first dose of the study treatment. Concomitant medications are listed by treatment groups.

9 QUALITY ASSURANCE AND QUALITY CONTROL

According to GCP principles, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems based on standard operating procedures (SOP), to ensure that the implementation of the clinical trial and the collection, documentation, and reporting of trial data is in accordance with the protocol, GCP, and applicable regulatory requirements.

To ensure that the data is reliable and processed correctly, there should be quality control for every step during the data processing.

In addition, the Clinical Quality Assurance (CQA) Department of the sponsor and/or CRO may conduct regular audits of the study process, including but not limited to auditing the study site, on-site visits, central laboratory, suppliers, clinical database, and the final clinical study report. Regulatory authorities may also conduct inspections during the trial or at any time after the trial is completed. The investigator and the research institution must allow the sponsor's representative and regulatory authorities to review source data.

9.1 Clinical Monitoring

The sponsor has authorized Wuxi Clinical Co., Ltd. to conduct clinical monitoring for this study. The clinical research associate (CRA) should follow the SOPs of Wuxi Clinical Co., Ltd. when carrying out monitoring, and has the same rights and responsibilities as the sponsor's monitor. The CRA should maintain regular communication with the investigator and the sponsor.

Before the start of the study, the associate monitor assess the qualifications of each study site, and report issues related to facilities, technical equipment, or medical staff to the sponsor. During

the study, the CRA will be responsible for confirming whether written informed consent is obtained from all subjects, and whether data documentation is accurate and complete. At the same time, the CRA will compare data entered in to the eCRF with source data, and notify the investigator of any errors or omissions. The CRA will also verify protocol compliance of the study site, as well as the dispensing and storage of investigational drugs to ensure protocol requirements are met.

The monitoring visit will be conducted in accordance with applicable statutes and regulations. Each site receives regular monitoring visits from the time the subjects are enrolled. The CRA should submit a written report to the sponsor after each monitoring visit to the study site.

9.2 Data Management/Coding

The Data Management and Biostatistics Department of Wuxi Clinical Co., Ltd will process data generated from this study in accordance with relevant SOPs.

This study will use an electronic data capture (EDC) system. Trial data will be entered into the eCRF by the investigator or authorized study personnel. Prior to launching of the study site or data entry, the investigator and authorized study personnel will receive appropriate training, and appropriate safety measures will be taken.

All data are input in Chinese. The eCRF should be completed during or soon after each visit, and should be constantly updated to ensure that it reflects the latest status of the subject. To avoid discrepancies in outcome assessments between different evaluators, ensure that baseline and all subsequent efficacy and safety assessments for the same subject are performed by the same person. The investigator must review trial data to ensure the accuracy and correctness of all data entered into the eCRF. During the study, the investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. The investigator needs to sign all verified data electronically.

The CRA will review the eCRF, and evaluate its completeness and consistency. The CRA will also compare the eCRF with the source documents to ensure the consistency of critical data. Data entry, corrections, or modifications are completed by the investigator or designated staff. The CRA do not have access to data entry. The data in eCRF is submitted to the data server, and any changes to the data will be documented in the audit trail, including the reason for the change, the name of the operator, as well as the time and date of the change. The roles and permissions of study personnel responsible for data entry will be predetermined. The CRA or data manager will submit data queries in the EDC system, and study personnel shall respond to the queries. The EDC system will record the audit trail of each query, including the name of the investigator, as well as the time and date.

Unless otherwise specified, the eCRF should be considered simply as a form for data collection and not a source document. A source file is used by the investigator or hospital, relevant to the subject, and can prove the existence of the subject, inclusion criteria, and all records of participation in the study, including laboratory records, ECG results, memorandum, pharmacy dispensing records, and subject folders.

The investigators are required to maintain all source documents and to offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each subject, regardless of the duration of the subject's participation in the study. The study number and subject number in all supporting documents (such as laboratory records or hospital records) submitted along with the eCRF should be carefully verified. All personal privacy information (including the name of the subject) should be deleted or be made indecipherable in order to protect subject privacy.

The investigator could be automatically added to the eCRF with his/her user ID. The investigators verify that the record have been reviewed and that the data are accurate with an electronic signature. The electronic signature is completed with the investigator's user ID and password. The system automatically attaches the date and time of the signature. The investigator could not share the user ID and password with other personnel. If data in the eCRF need to be modified, the procedures defined by the EDC system have to be followed. All modifications and reasons for the changes are recorded in the audit trail.

Training on the EDC system will be provided to study personnel at the study site.

Adverse events, and concurrent diseases/medical history will be coded. The medical dictionary used for coding will be described in the Clinical Study Report (CSR).

9.3 Audits and Inspections

The sponsor or its representative (WuXi Clinical Co., Ltd) may conduct quality assurance audits on the study site, database, and relevant study-related documents. Also, regulatory authorities may also decide to inspect the study site, database, and relevant study-related documents at its own discretion. The aim of audits and inspections is to systematically and independently check all study-related procedures and documents to ensure that the clinical study is being carried out in accordance with requirements of the trial protocol, GCP, Declaration of Helsinki, and applicable regulations. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

10 ETHICS

10.1 Independent Ethics Committee

The sponsor and its designated personnel will prepare all documents to be submitted to the independent ethics committee (IEC) of each study site. The trial protocol, informed consent form (ICF), investigators brochure, subject recruitment material or advertisements (if applicable), as well as other documents required by regulations must be submitted to the IEC for approval. Prior to the start of the study, written approval from the IEC must be obtained and provided to the sponsor. The IEC approval must clearly state the title, number, and version of the study protocol as well as the version of other documents (e.g. ICF) and the date of approval. The investigator must notify the sponsor of the IEC's written comments concerning delays, suspension and re-approval.

The study site must follow the requirements of the IEC. IEC requirements may include submitting the revised protocol, ICF, or subject recruitment material to the IEC for approval, local regulatory requirements for safety reports, and regular reports, updates, and submitting the final report as per IEC requirements. The above documents as well as the IEC approval must be provided to the sponsor or its designated personnel.

10.2 Implementation of Ethical Principles

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements (CPMP/ICH/135/95), and applicable statutes and regulations related to drugs and data protection in the country in which the study is conducted.

The GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. To protect the rights, safety, and healthy of subjects, this study will be carried out in accordance with GCP and applicable national regulations, as well as ethical principles outlined in the Declaration of Helsinki.

The investigator is required to follow the procedures specified in this protocol and must not change the procedures without the permission from the sponsor. Protocol deviations will be reported in accordance with the requirements of each ethics committee.

10.3 Subject Information and Informed Consent

Prior to undergoing any study procedure, the ICF should be used to explain to potential participants the potential risks and benefits of this study. The informed consent form should be in a language that is simple and be easy to understand. The ICF should state that informed consent is voluntary, emphasize the potential risks and benefits of participating in this study, and that the subject may withdraw from the study at any time. The investigator may only enroll a subject after fully explaining the details of the study, answering questions to the subject's satisfaction, giving the subject sufficient time for consideration, and obtaining written consent from the subject or his/her legal representative. All signed ICF must be retained in the investigator's documents or the subject's folder.

The investigator is responsible for explaining the contents of the ICF and obtaining the ICF signed and dated by the subject or his/her legal representative prior to starting the study. The investigator should provide the subject with a copy of the signed ICF. The investigator must document the informed consent process in the source document of the trial.

10.4 Protection of Subject Data

Information about data protection and privacy protection will be included in the ICF (or in some cases, in a separate document).

Study personnel must ensure that the privacy of clinical trial subjects are protected. In all documents submitted to the sponsor, the clinical trial subjects must only be identified with subject number and not with the full name.

Additional precautions should be taken to ensure the confidentiality of the documents and to prevent the identification of subjects based on genetic data. However, under special circumstances, some personnel may be permitted to see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, designated physician, or investigator will have access to the subject identification code and the subject's genetic data. In addition, regulatory agencies may request access to relevant documents.

11 STUDY MANAGEMENT

11.1 Organizational Structure

Refer to Table 3 for relevant collaborating parties.

Table 3. Organizational structure

Sponsor	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China Telephone: (+86) 0512-69566088
Contract research organization	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000
Data management and biostatistics	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000

11.1.1 Independent review committee

Central imaging evaluation will be performed by Parexel China Co., Ltd. The CT/MRI images of each subject will be evaluated using RECIST v1.1.

11.2 Archiving of Study Documents

Clinical trial documents (protocol and amendments, completed eCRFs, signed ICFs, etc.) must be retained and managed as per GCP requirements. The study site must retain these documents for 5 years after the completion of the study. The sponsor should retain clinical trial data for 5 years after the investigational drug is approved for marketing.

Study documents should be retained properly for future access or data traceability. Safety and environmental risks should be considered when retaining documents.

The documents associated with the study may only be destroyed with the written consent of the sponsor and the investigator. Study documents may be transferred to other parties that comply with or other locations that meet retention requirements only after the sponsor is notified and written consent thereof is obtained.

11.3 Access to Source Data/Documents

Source data refers to source records of subject data obtained from a clinical study. These source records are source documents, which include but are not limited to medical records (hospital records, nursing records, pharmacy dispensing records, etc.), electronic data, screening logs, laboratory test results, as well as medical device test results (ECG, CT/MRI, etc.). All source documents associated with the trial are retained by the study site and the investigator. The original ICFs will be retained according to standard practices developed by the clinical trial institution.

The investigator will prepare sufficient and accurate source documents for each randomized subject in order to document all examination results and other relevant data, and retain these documents properly.

During the study, the CRA will conduct on-site visits to verify protocol compliance, EDC data entry, documentation of subjects' medical history, drug inventory, and whether the study is carried out in accordance with applicable regulations. In addition, regulatory authorities, IRB, IEC, and/or the quality assurance department of the sponsor will verify source data and/or conduct on-site audits or inspections. The investigator should allow direct access to documents associated with the study, including medical records of subjects.

11.4 Protocol Revisions

The sponsor and the investigator must both agree on any appropriate protocol revisions during the course of the study. The sponsor shall ensure that the protocol revision is submitted to the regulatory authority in a timely manner.

All protocol revisions must be submitted to the IEC, and if needed, to regulatory authorities for approval. Revisions may only be implemented after approval from the IEC and regulatory authorities (if needed) is obtained (except for changes to eliminate immediate risks to subjects).

11.5 Investigator's Responsibilities

The investigator will conduct this study in accordance with the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP, and applicable regulations. Details of the investigator's responsibilities are list in Chapter 5 (Investigator's Responsibilities) of the Chinese GCP (NMPA order No. 3).

11.6 Study Termination

The study may be terminated after a discussion between relevant parties if the investigator or the sponsor becomes aware of circumstances or events that could jeopardize the subjects if the study is continued. The sponsor may also decide to terminate the study even without such findings.

Reasons for study termination include but are not limited to:

- Unexpected, serious, or unacceptable risks to enrolled subjects
- Slow recruitment
- The sponsor decides to suspend or discontinue the development of the drug

11.7 Publishing Policies

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish study results. The investigator shall not publish any data relevant to this study (posters, abstracts, papers, etc.) without prior communication with the sponsor. Information on the publishing policies of the sponsor and investigator will be described in the clinical trial agreement.

11.8 Finance and Insurance

The sponsor will purchase insurance for subjects participating in the study in accordance with local regulations, and bear the cost of treatment and corresponding financial compensation for the subjects who suffer injury during the study due to the investigational drug or the study process. Insurance related terms shall be saved in the study folder.

12 REFERENCES

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13 APPENDIX

13.1 Appendix I

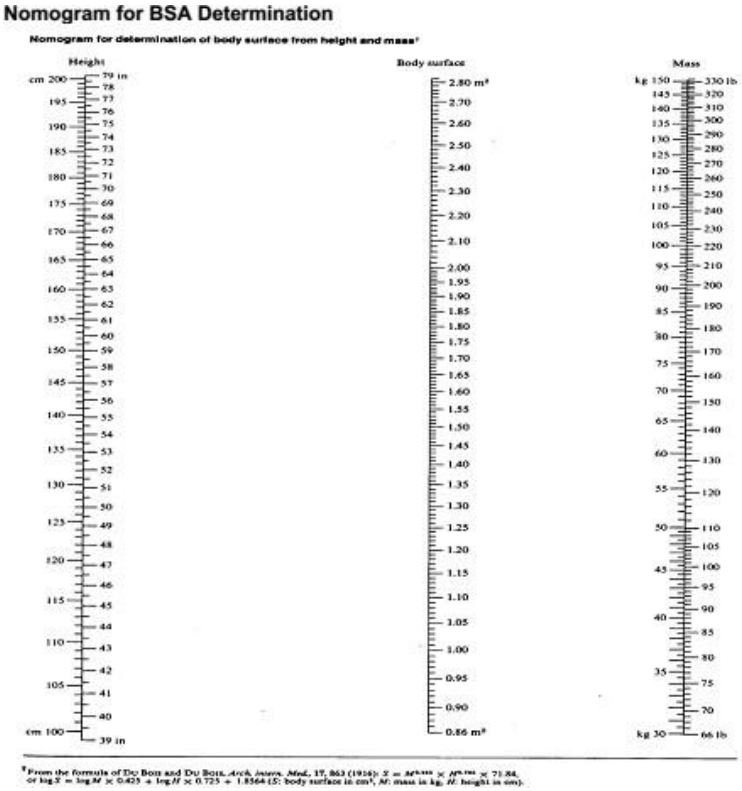
Eastern Cooperative Oncology Group (ECOG) Performance Status Score

Score	Performance Status
0	Fully active, and able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activities but able to move around easily and carry out work of a light or sedentary nature, e.g. light house work or office work
2	Capable of moving around easily and self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or wheelchair more than 50% of waking hours
4	Bedridden and incapable of self-care
5	Death

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

13.2 Appendix II

Calculation of body surface area



Body surface are (m2) = 0.00616 height (cm) + 0.01286 weight (kg) - 0.1529

Creatinine Clearance (Cockroft-Gault Equation)

Ccr (mL/min) = [(140 - age) x weight (kg)]/[72 x Scr (mg/dL)]

Female subjects: results × 0.85

1 mg/dL = 88.41 μmol/L

Carboplatin Dose (Calvert Equation)

Carboplatin dose (mg) = target AUC (mg/mL/min) × [creatinine clearance rate (mL/min) + 25]

Note: During the study, if the carboplatin dose calculated using the Calvert equation excessively exceeds the usual clinical dose, choose one of the following two methods to ensure the patient

safety:

1. Retest the serum creatinine and re-calculate the dose (preferred option).

2. Based on clinical experience, the investigator may choose the highest dose tolerated by the subject. The dose should remain unchanged for the subsequent cycles.

13.3 APPENDIX 3

RECIST v1.1

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or not measurable as follows:

1.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be documented as not measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Not measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with a short axis ≥10 and <15 mm) as well as truly not measurable lesions. Lesions considered truly not measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis involving the skin or lungs, abdominal masses/ abdominal organomegaly identified by physical exam but not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding measurable bone lesions, cystic lesions, and lesions with prior locoregional treatment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (such as CT or MRI) can be considered as measurable lesions if the soft tissue components meet the definition of measurability described above.
- Blastic bone lesions are not measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor not measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these noncystic lesions are preferred for selection as target lesions.

Lesions with prior locoregional treatment:

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

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be documented with metric symbols. Calipers should be used if clinical assessments are required. All baseline evaluations should be performed as close as possible to the beginning of the treatment but never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and its diameter is ≥10 mm as assessed using calipers (e.g. skin nodules). For skin lesions, documentation by color photography including a plotting scale to estimate the size of the lesion is recommended. As noted above, when lesions can be evaluated by both clinical examination and imaging evaluation, the latter should be undertaken since it is more objective and may also

be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they have clear boundaries and are surrounded by aerated lung tissues.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound should not be used for measuring lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is recommended. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy: The utilization of these techniques is not recommended for objective tumor evaluation. However, they can be used to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper limit of normal, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into the protocol on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases if required by the protocol (for example, residual lesions in tumor types such as seminoma, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), cytological confirmation of the neoplastic origin of any effusion that appears or worsens during

treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

2.2 Baseline Documentation of "Target" and "Non-Target" Lesions

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those with reproducible repeated measurements. It may be the case that, the largest lesion does not have reproducible measurements, in which circumstance the next largest lesion with reproducible measurements should be selected.

Lymph nodes merit special mention since their normal anatomical structures may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must have a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is invaded by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant measurable node. In this example, 20 mm should be reported as the node measurement. All other pathological nodes (those with a short axis ≥ 10 mm but < 15 mm) should be considered non-

target lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions; short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". In addition, it is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response Criteria

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduced short axis of <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions vs. the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions vs. the smallest sum during the study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also have an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum of diameters during the study as reference.

2.3.2 Special notes on the assessment of lymph nodes which are target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as during the baseline examination), even if the nodes regress to below 10 mm at the time of the study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must have a

short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that are "too small to measure". During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurements of these lesions are potentially non-reproducible, therefore providing this default value will prevent false responses or progressions caused by measurement errors. To reiterate, however, if the radiologist is able to provide an actual measurement, that value should be recorded, even if it is below 5 mm.

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

2.3.3 Evaluation of non-target lesions

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

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

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

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

2.3.4 Special notes on the assessment of progression of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: *When the patient also has measurable lesions*. In this setting, to achieve 'unequivocal progression' on the basis of the non-target lesion, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR of the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A minimal increase in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only lesions that are not measurable. This circumstance arises in some phase III trials when the presence of measurable lesions is not a criterion for study enrollment. The same general concepts apply here as well. However, in this instance there are no measurable lesions to factor into the interpretation of an increase in non-measurable lesion burden. Because worsening in non-target lesion cannot be easily quantified (by definition: if all lesions are truly not measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall lesion burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase of diameter in a measurable lesion). Examples include an increase in pleural effusion from "trace" to "large amount", an increase in lymphangitic lesion from localized to widespread, or a description in the protocol such as "sufficient to require a change in therapy". If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to diseases that are not measurable, the very nature of these diseases makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on the detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumors (for example, some new bone lesions which may be simply healed or flare of pre-existing lesions). This is particularly

important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported by a CT scan as a "new" cystic lesion, while it is actually not.

A lesion identified during a follow-up in an anatomical location that is not discovered during the baseline scan is considered a new lesion and will indicate disease progression. For example, a patient with a visceral disease at baseline has a brain CT or MRI which reveals metastases. The patient's brain metastases are considered evidence of PD even if he/she does not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new lesion. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" lesions). New lesions on the basis of FDG-PET imaging can be identified as follows:

a. A negative FDG-PET at baseline and a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
If the positive FDG-PET at follow-up corresponds to a new lesion site confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new lesion site on CT, additional follow-up CT scans are needed to determine if there is truly progression at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing lesion site on CT that is not progressing according to the anatomic images, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy, so the study protocol should clearly state if post-treatment assessments are to be considered when determining best overall response. The study protocol must specify how any new therapy introduced before progression will affect best response designation. Assignment of best overall response for the patient will depend on the findings of both target and non-target lesions and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the

protocol requirements, confirmatory measurement may also be required. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine which one is the "best overall response".

2.4.1 Time point response

It is assumed that at each time point specified by the study protocol, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2 Missing assessments and non-evaluable targets

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

2.4.3 Best overall response: all time points

The best response is determined once all the data for the patient is obtained.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, the best overall response of a patient who has SD at the first assessment, PR at the second, and PD at the last is PR). When SD is believed to be best response, it must also meet the minimum time from baseline specified by the protocol. If the minimum time is not met, otherwise SD is the best time point response, the patient's best response depends on subsequent assessments. For example, if a patient has SD at the first assessment, PD at the second and does not meet the minimum duration for SD, his/her best response is PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

2.4.4 Special notes on response assessment

When nodal lesions are included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even if the nodes are normal in size in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the case report form (CRF).

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must explain how missing data/assessments will be addressed in the determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response. Instead, it is a reason for stopping the study treatment. The objective response status of this type of patients is to be determined by evaluation of target and non-target lesions as shown in Table 1–3.

Conditions that define "early progression, early death, and non-evaluability" are study specific and should be clearly described in each study protocol (depending on treatment duration and treatment periodicity).

In some circumstances it may be difficult to distinguish a residual lesion from normal tissues. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (by fine needle aspirate/biopsy) before assigning a status of complete response.

Like a biopsy, FDG-PET may also be used to upgrade a response to a CR in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be pre-defined in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Table 1. Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not all were evaluated	No	PR
SD	Non-PD or Not all were evaluated	No	SD
Not all were evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

Table 2. Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all were evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = not evaluable.

a "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since SD is increasingly used as an endpoint for assessment of efficacy in some trials, thus assigning this category in the absence of measurable lesions is not advised.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression is suspected.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided that the minimum duration for SD is met, otherwise PD
CR	PD	SD provided that the minimum duration for SD is met, otherwise PD
CR	NE	SD provided that the minimum duration for SD is met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided that the minimum duration for SD is met, otherwise PD
PR	NE	SD provided that the minimum duration for SD is met, otherwise NE
NE	NE	NE

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

a If CR is truly achieved at the first time point, then any lesions seen at a subsequent time point, even those meeting PR criteria relative to baseline, make the disease PD at that time point (since lesions must have reappeared after CR). Best response would depend on whether the minimum duration for SD is met. However, sometimes CR may be claimed and subsequent scans suggest small lesions are likely still present, while in fact the patient have PR instead of CR at the first time point. Under these circumstances, CR should be changed to PR and the best response is PR.

2.5 Frequency of Tumor Re-Evaluation

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

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

2.6 Confirmation of Measurements/Duration of Response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement errors. This will also permit appropriate interpretation of results in the context of historical data. Response confirmation has been traditionally required in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements after study entry must have met the minimum interval for SD (generally not shorter than 6–8 weeks) defined in the study protocol at least once.

2.6.2 Duration of overall response

The duration of overall response is measured from the time CR/PR measurement criteria are first met CR/PR (whichever is first documented) until the date when recurrent or progressive disease is objectively documented for the first time (using the shortest time to progressive disease documented during the study as reference).

The duration of overall complete response is measured from the time CR measurement criteria are first met until the date when recurrent disease is objectively documented for the first time.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from the date of randomization) until the criteria for progression are met, using the smallest sum during the study as reference (if the baseline sum is the smallest, then it is used as the reference for the calculation of PD).

The clinical relevance of the duration of stable disease varies with different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for the determination of stable disease.

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

14 INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized, double-blind, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin vs. bevacizumab plus paclitaxel/carboplatin in treatment-naive patients with advanced or relapsed non-squamous NSCLC.

Protocol No.: CIBI305A301

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

Instructions for the Investigator: Please sign and date this signature page, type the investigator's name and job title, as well as the name of the study site, and return this document to Innovent Biologics (Suzhou) Co., Ltd.

I have read the entire contents of this study protocol and shall perform the study as required:

Investigator's signature: _____ Date: _____

Name (in Print): _____

Job Title: _____

Name and Address of Study Site: _____

_____

_____

Amendment History for the Study Protocol of a Randomized, Double-Blinded, Multi-Center Phase III Study Comparing the Efficacy and Safety of IBI305 in Combination with Paclitaxel/Carboplatin vs. Bevacizumab in Combination with Paclitaxel/Carboplatin in Treatment-Naive Subjects with Advanced or Relapsed Non-Squamous Non-Small Cell Lung Cancer

Protocol no.: CIBI305A301

Document Amendment History

Old Version/Date: Version 3.1/Aug. 27, 2018

New Version/Date: Version 3.2/Nov. 5, 2018

1	**Subject**	Version No. and Version Date
	Section/Page	Cover/Page 1; Footer/Pages 1–79
	Old text	Aug. 27, 2018/Version 3.1
	New text	Nov. 5, 2018/Version 3.2
	Reason for change	Version Revision.
2	**Subject**	Definition of efficacy endpoint
	Section/Page	Section 7.1.1/Page 50
	Old text	It is defined as the proportion of subjects with tumor size reduction of a predefined amount
	New text	It is defined as the proportion of subjects with tumor size reduction of a predefined amount and for a minimum time period
	Reason for change	Consistent with the content in version 3.0.
3	**Subject**	Primary efficacy analysis
	Section/Page	Section 8.5.4.1/Page 58
	Old text	ORR is defined as the incidence of complete response (CR) or partial response (PR), and a radiological method is used to evaluate target and non-target lesions according to RECIST v1.1.
	New text	ORR is defined as the incidence of confirmed complete response (CR) or partial response (PR), using a validated imaging method to evaluate target lesions and non-target lesions according to RECIST v1.1.
	Reason for change	Consistent with the content in version 3.0.
4	**Subject**	Secondary efficacy analysis
	Section/Page	Section 8.5.4.2/Page 58
	Old text	DCR is defined as the incidence of complete response (CR), partial response (PR) and stable disease (SD), and a radiological method is used to evaluate target and non-target lesions according to RECIST v1.1.

	New text	DCR is defined as the incidence of patients with confirmed complete response (CR), partial response (PR), and stable disease (SD), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions.
	Reason for change	Consistent with the content in version 3.0.

CLINICAL STUDY PROTOCOL

Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Version and Date:	Aug. 27, 2018/Version 3.1
Product Name:	Recombinant anti-VEGF humanized monoclonal antibody injection (IBI305)
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	Zhou Hui (Senior Medical Director) Tel: (+86) 21-31652896 E-mail: hui.zhou@innoventbio.com

SIGNATURE PAGE

Protocol Title: A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer

Protocol No.: CIBI305A301

Title	Name	Signature	Date
Senior Medical Director	Zhou Hui		2018.8.27
Senior Director of Biostatistics	Zhang Nan		

PROTOCOL SYNOPSIS

Sponsor/Company:	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug:	IBI305
Active Ingredient:	Recombinant anti-VEGF humanized monoclonal antibody
Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Coordinating Investigator:	Zhang Li
Coordinating Center:	Sun Yat-Sen University Cancer Center

Expected study duration: Each subject will receive treatment every 3-week until progressive disease (PD), unacceptable toxicity, withdrawal of informed consent, lost to follow-up or death (whichever comes first). The end of the study is defined as the 18th month after the randomization of the last subject.	**Phase:** III

Study Objectives:

Primary Objective:

- To compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC)

Secondary Objectives:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

Exploratory objectives:

- To compare the population pharmacokinetics (PPK) of IBI305 and bevacizumab in subjects with

	advanced or recurrent non-squamous NSCLC 4/3 To compare the PD of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC
Study design: This is a randomized, double-blinded, multi-center phase III study. The study planned to enroll and randomize 436 subjects with non-squamous NSCLC in a 1:1 ratio to IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild type vs. unknown type). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first). Then subjects receive maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first). During the study, a CT or an MRI will be performed every 6 weeks (± 7 days) and be determined whether the study treatment will be continued by investigators at each site through tumor assessments until PD, withdrawal of informed consent, lost to follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for reasons other than PD, tumor assessments will be continued until PD, withdrawal of informed consent, loss of follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for PD, the investigators will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, lost to follow-up, death, or end of study.	
Number of Subjects:	436
Diagnosis and main inclusion criteria:	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be enrolled in the study: 1) Sign the formed consent form 2) Male or female ≥ 18 and ≤ 75 years old 3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIB), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types 4) Histologically or cytologically confirmed EGFR wild type or non-sensitive mutation type 5) Must have at least one measurable target lesion (as per RECIST 1.1) 6) Eastern Cooperative Oncology Group Performance Status (ECOG PS)

	score of 0–1 7) Expected survival ≥ 6 months 8) Laboratory results during screening: a) Routine blood test: WBC ≥ 3.0 × 10^9/L, ANC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and hemoglobin ≥ 90 g/L b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ from urinalysis dipstick at baseline, a 24-h urine should be collected with total protein content < 1 g d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment 9) Able to comply with study protocol 10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug Exclusion Criteria: Subjects meeting any of the followings will not enrolled in the study: 1) Prior systemic chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIB not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible 2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component 3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18-point mutation (G719X), exon 19 deletion, and exon 21-point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll. 4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time

	5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava) 6) Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage; 7) Subjects who received radical thoracic radiotherapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug 8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study 9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (Outpatient/inpatient surgery requiring locoregional anesthetics, including central line insertion) 10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function for 10 consecutive days 11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents for 10 consecutive days. However, anticoagulants for prophylaxis are accepted 12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis 13) Uncontrolled hypertension after treatment (systolic greater than 140 mmHg and/or diastolic greater than 90 mmHg), history of hypertensive crisis or hypertensive encephalopathy 14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease 15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal

	fistula, or intra-abdominal abscess 16) Subjects with tracheoesophageal fistula 17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments) 18) Subjects with current interstitial lung disease or CT showing active pneumonia during screening 19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or papillary thyroid carcinoma 20) Subjects with active autoimmune disease 21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1 × 103 copies/L or ≥ 200 IU/mL; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1 × 103 copies/L or < 200 IU/mL might be eligible if the investigator determines that the subject's chronic hepatitis B infection is stable and participation in the study would add no further risks to the subject 22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis 23) Subjects with known history of allergic diseases or allergic physique 24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening 25) History of alcohol or drug abuse 26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study 27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents 28) Other conditions unsuitable for the inclusion as determined by the investigator
Investigational Drug, Dosage, and Route of Administration:	IBI305: 15 mg/kg in combination chemotherapy and 7.5 mg/kg **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)
Control Drug, Dosage, and Route of Administration:	Bevacizumab: 15 mg/kg in combination chemotherapy and 7.5 mg/kg **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of

	informed consent, lost to follow-up, death, or end of study (whichever comes first)
Chemotherapy:	Paclitaxel: 175 mg/m² administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death. Carboplatin: Areas under the concentration-time curve (AUC) = 6.0 administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Evaluation criteria:

Efficacy endpoints:

Primary efficacy endpoint:

- Objective response rate (ORR)

Secondary efficacy endpoints:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Safety endpoints:

- Vital signs
- Physical examination
- Laboratory tests (routine blood test, blood chemistry, and urinalysis)
- 12-Lead ECG
- Adverse event (AE, including treatment-emergent AE (TEAE)), AE of special interest (AESI) (hypertension, proteinuria, gastrointestinal perforation, hemorrhage [cerebral hemorrhage, hematuria and upper gastrointestinal hemorrhage], cardiotoxicity, and thrombosis), and serious adverse event (SAE)
- Immunogenicity: Positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

PK/PD Endpoints:

- Population PK parameters, including steady-state trough concentrations after repeated doses
- Changes of serum VEGF at different time points

Statistical methods:

Sample size calculation:

A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin. Estimation parameters for sample size: The significance level of the two-sided test is 0.05, the ORR of subjects in the IBI305 and bevacizumab groups is about 50.0%, and the equivalence margin for the ratio of ORR is taken as (0.75, 1/0.75). Based on the above hypothesis, each group requires 218 subjects (436 subjects in total).

Efficacy analysis:

Clinical equivalence will be determined by whether the 90% confidence interval (CI) of the ratio of ORR between the IBI305 and bevacizumab arms falls within the preset margin of (0.75, 1/0.75). The ORR and 95% CI of two groups, ORR difference and 90% CI, and ORR ratio and 90% CI will be estimated using the generalized linear model (GLM, including groups and stratification factors).

Median survival (OS) and survival curves will be estimated using the Kaplan-Meier method. The hazard ratio (HR) and 95% CI of two groups will be estimated using the Cox model. DORs and PFSs will be analyzed by the same method as the median survivals. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

Safety analysis:

All adverse events (AE) will be coded using MedDRA and graded according to CTCAE v4.03. All treatment-emergent adverse events (TEAEs), Grade 3 or greater TEAEs, serious adverse events (SAEs), investigational drug-related TEAEs, investigational drug-related SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study termination, and adverse events of special interest (AESIs) will be listed based on system organ class, preferred terms, and groups and the numbers of corresponding subjects and percentages will be summarized. In addition, the severity of TEAEs and the correlation with the study drug will also be summarized by system organ class, preferred terms, and treatment groups.

Measured values and changes from baseline for vital signs, physical examination, laboratory tests and 12-lead ECG will be analyzed using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation.

The number and percentage of subjects who developed anti-drug antibodies and neutralizing antibodies during the study will be summarized by treatment group.

PK/PD exploratory analysis:

Mainly based on description, and inter-group comparison will be carried out if necessary

Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
AEs	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

a. After completing the on-site end-of-treatment visit 28 days after the last dose, subjects who discontinue the investigational drug treatment due to reasons other than PD should continue to undergo tumor assessments once every 6 weeks (±7 days) until PD (and begin post-PD follow-up thereafter), withdrawal of consent, start of another antineoplastic treatment, loss to follow-up, death, or study completion.

b. For subjects with PD, collect survival information once every 12 weeks (84 days, ±7 days) by phone until death, loss to follow-up, withdrawal of informed consent, or study completion. Subsequent antineoplastic treatments should be documented in the eCRF.

c. Only measure weight.

d. Clinical laboratory tests are carried out at the laboratory of each hospital. If screening laboratory tests (routine blood test, blood chemistry, and urinalysis) are performed within 7 days prior to the first dose, the screening results may be used as baseline data. For subsequent visits, all laboratory tests have to be completed within 3 days prior to the dose administration.

e. A urinalysis is required before each IBI305/bevacizumab infusion to test urine protein.

f. Women of childbearing age should undergo a serum/urine pregnancy test.

g. Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples will be tested at the designated central laboratory.

h. Image assessments (CT or MRI) of the brain, chest, abdomen, and pelvis should be completed at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

i. All subjects should undergo tumor tissue EGFR testing.

j. Each treatment cycle of the investigational product contains 3 weeks. The dose of IBI305 or bevacizumab is 15 mg/kg when used in combination with chemotherapeutic drugs and 7.5 mg/kg in the maintenance monotherapy, given on D1 of every treatment cycle until progressive disease (PD), unacceptable toxic reactions, withdrawal of informed consent, loss to follow-up, death, or end of study, whichever occurs first. After all assessments were completed, the study drug was administered followed by chemotherapy. The first dose of study drug was completed within 24 h after randomization.

k. Each treatment cycle is 3 weeks long. Chemotherapy (paclitaxel + carboplatin) is administered on D1 of each cycle for up to 6 cycles, or until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death. Paclitaxel is administered after the infusion of study drug is completed, followed by carboplatin.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definitions
AE	Adverse event
AESI	Adverse event of special interest
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AUC	Area under the curve
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFDA	China Food and Drug Administration (now National Medical Products Administration)
CQA	Clinical quality assurance
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data collection
EGFR	Epithelial growth factor receptor
FAS	Full analysis set
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
ITT	Intention-to-treat

NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PTT	Partial thromboplastin time
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
SS	Safety set
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

1 INTRODUCTION

1.1 Study Background

1.1.1 Disease background

Lung cancer has the highest incidence and mortality globally among all cancers. According to the 2012 Global Cancer Statistics (GLOBOCAN 2012) published by International Agency for Research on Cancer, there were approximately 1.8 million new lung cancer cases worldwide, which accounted for 13% of the global newly-diagnosed cancers, and 58% of these cases occurred in underdeveloped areas[1]. According to the data released by the National Central Cancer Registry of China in 2015, lung cancer was the most prevalent malignancy in China in 2011, with about 650,000 new cases every year. Lung cancer was also the leading cause of death, with about 520,000 deaths per year[2]. The limited clinical treatment of lung cancer is the main reason for its poor prognosis. There is a huge demand for new types of lung cancer treatment drugs.

Approximately 85–90% of lung cancers are non-small cell lung cancer (NSCLC) and patients with NSCLC are usually in the advanced stages when diagnosed[3]. According to the Chinese guidelines for the diagnosis and treatment of primary lung cancer, anatomic pulmonary resection is the mainstay of treatment for early stage lung cancers[4]. However, despite surgery, some patients develop distance metastases that eventually lead to death[5]. Surgery is not possible for most patients with clearly diagnosed stage IIIB and IV as well as some patients with stage IIIA NSCLC[4]. Comprehensive treatment based on systemic therapy is used to maximize patient survival, control progressive disease, and improve the quality of life[6].

In recent years, anti-tumor therapies have entered a new era with the emergency of targeted drugs. Some of these targeted drugs have demonstrated satisfactory efficacy in the treatment of advanced NSCLC. These targeted drugs include monoclonal antibodies and tyrosine kinase inhibitors (TKIs), mostly targeting epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF), such as bevacizumab, cetuximab, gefitinib, erlotinib, and icotinib. Monoclonal antibodies have become the drugs of choice in various treatment guidelines due to the good targeting ability, low drug resistance, and good patient tolerability. Bevacizumab combination chemotherapy is a first-line therapy of NSCLC recommended by the National Comprehensive Cancer Network (NCCN)[7]. Additionally, bevacizumab in combination with paclitaxel/carboplatin has also been approved as the first-line therapy of unresectable advanced, metastatic, or relapsed non-squamous NSCLC by China Food and Drug Administration (CFDA) on Jul. 9, 2015[6].

Compared with traditional chemotherapy that directly inhibit or kill tumor cells, anti-angiogenic drugs have the following unique advantages[8]:

- The targets are genetically stable vascular endothelial cells (VECs) rather than highly heterogeneous tumor cells, thus leading to lower drug resistance;
- The number of tumor-induced VECs is far less than that of tumor cells, and the efficacy is preferable targeting on VECs and their cytokines;
- Normal VECs are quiescent, whereas tumor VECs are active in proliferation. Anti-angiogenic therapy targets activated cells and avoids damage to normal VECs, thus leading to better targeting ability;
- Anti-angiogenic therapy can normalize the tumor vessels and thereby reduce the pressure in tumor tissues. This enhances the delivery of chemotherapeutic agents into tumor tissues, thus increasing the efficacy of chemotherapy.

Angiogenesis is a basic biological characteristic of tumors. The growth of both solid and hematologic tumors are depended on angiogenesis regardless of the nature of tumor cells. Therefore, anti-angiogenic therapy is broad-spectrum and applicable to various tumors.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to human VEGF and blocks its biological activity. Bevacizumab consists of a framework region of a human antibody and a humanized murine antigen binding region that can inhibit the binding of VEGF to its receptors on epithelial cells, Flt-1 and KDR. By blocking the activity of VEGF and reducing tumor angiogenesis, tumor growth is inhibited[9].

In a study conducted by the Estern Cooperative Oncology Group (ECOG), compared with chemotherapy alone (paclitaxel/ carboplatin), bevacizumab in combination with paclitaxel/carboplatin significantly increased the overall survival (OS) (median: 12.3 vs. 10.3 months), progression-free survival (PFS) (median: 6.2 vs. 4.5 months), and overall response rate (ORR) (35% vs. 15%) in patients with advanced, metastatic, or relapsed non-squamous NSCLC[10]. In another foreign AVAiL study, different doses of bevacizumab (7 and 15 mg/kg) in combination with chemotherapy (cisplatin and gemcitabine) and placebo combine with chemotherapy were compared for the treatment of non-squamous NSCLC. The study found that the two bevacizumab groups had significantly increased the PFS (median: 6.7 months (7.5 mg/kg combination chemotherapy group) vs. 6.5 months (15 mg/kg combination chemotherapy group) vs. 6.1 months (placebo combination chemotherapy group)) and the ORR (37.8% (7.5 mg/kg combination chemotherapy group) vs. 34.6% (15 mg/kg combination chemotherapy group) vs. 21.6% (placebo combination chemotherapy group)) in patients with locally advanced, metastatic, or relapsed non-squamous NSCLC[11]. In a BEYOND study conducted in China, compared with

placebo in combination with paclitaxel/carboplatin, bevacizumab in combination with paclitaxel/carboplatin significantly increase the PFS (median: 9.2 vs. 6.5 months), OS (median: 24.3 vs. 17.7 months), and the ORR (54% vs. 26%) in patients with advanced or relapsed non-squamous NSCLC[12].

In China, the antibodies and fusion proteins targeting VEGF are research hotspots. However, since 2006, the clinical efficacies of various drugs have not been verified and no products have been marketed. Considering the complexity of macromolecular drugs and the limitations of drug development capability in China, advanced technologies in antibody development, production, and quality control is required to develop high-quality VEGF inhibitors that are safe and effective. IBI305 has showed high similarity to bevacizumab in various pharmaceutical and nonclinical studies (refer to Investigator's Brochure [IB]). Besides, the efficacy and safety of bevacizumab for treatment of locally advanced, metastatic or relapsed lung cancer have been verified. The relevant domestic and external pivotal clinical studies are referable for the protocol design of IBI305 clinical study. In summary, the clinical study of IBI305 for treatment of NSCLC has a solid foundation and relatively low risks. The successful development of IBI305 indicates an additional first-line targeted drug for lung cancer in China, providing doctors and patients with more therapeutic options.

1.1.2 Investigational drug

1.1.2.1 Description of investigational drug

IBI305 is a recombinant humanized anti-VEGF monoclonal antibody injection developed by Innovent Biologics (Suzhou) Co., Ltd. (hereafter as sponsor) that specifically binds human VEGF. The molecular weight of IBI305 is 149 KDa. IBI305 specifically binds to VEGF-A, inhibits the binding of VEGF-A to VEGF-R1 and VEGF-R2, blocks the signaling pathways such as PI3K/Akt/PKB and Ras-Raf-MEK-ERK. IBI305 also inhibits the growth, proliferation, and migration of VECs and angiogenesis, decreases the vascular permeability, blocks blood supply to tumor tissues, inhibits the proliferation and metastasis of tumor cells, and induces the apoptosis of tumor cells, thereby generates anti-tumor effects. The main active ingredient is recombinant humanized anti-VEGF monoclonal antibody and excipients include sodium acetate, sorbitol, and polysorbate 80[13]. Refer to the Investigator's Brochure for the detailed structure and physicochemical properties of IBI305.

1.1.2.2 Preclinical studies

Pharmaceutical studies

The pharmaceutical studies showed that stability, primary structure, higher-order structure, oligosaccharide distribution, charge variant, and product-related impurities of IBI305 are highly similar to those of bevacizumab, and the process-related impurities meet the proposed specification. Therefore, IBI305 is considered to have highly similar protein properties and product quality to bevacizumab[13].

Pharmacodynamic studies

In vitro and in vivo pharmacodynamic (PD) studies of IBI305 showed the following findings:

1) Target: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A with an affinity constant same as that of bevacizumab, indicating that IBI305, the same as bevacizumab, is a specific human VEGF blocker with a clear target.
2) Specificity: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A, medium-affinity binding to canine VEGF-A, but low-affinity binding to human VEGF-B, VEGF-C, VEGF-D, PlGF, suggesting that IBI305 recognizes specific targets and has low off-target toxicity risk; no obvious affinity to mouse VEGF-A_{164} and rat VEGF-A_{164}, suggesting that IBI305 has high species specificity.
3) Mechanism of action: IBI305 specifically binds to VEGF-A and inhibits the activation of VEGFR-2 and ERK1/2, blocks the proliferation and migration of HUVEC, and inhibits the sprouting from rat aortic ring, suggesting that IBI305 antagonizes VEGF-A-induced signaling pathway to block the proliferation and migration of VECs and inhibit angiogenesis, which leads to the reduction of nutritional supply and metastasis of tumor.
4) Anti-tumor effects: IBI305 significantly inhibits the growth of human colon cancer Ls174t and lung cancer NCI-H460 cells in xenografts in nude mice, indicating that IBI305 has significant anti-tumor effects.

Results from in vitro and in vivo studies of IBI305 showed highly similarity with that of bevacizumab designed simultaneously, demonstrating that the target, mechanism of action, and anti-tumor effects of IBI305 are highly similar to bevacizumab[13].

Pharmacokinetic studies

In vitro and in vivo pharmacokinetic (PK) studies of IBI305 showed the following findings:

1) IBI305 showed no significant cross-reactivity with normal human tissues and cynomolgus monkey tissues, and only cross-reacted with the positive-control. i.e. human angiosarcoma tissue, suggesting that IBI305 is highly specific to cancer tissues rather than normal human tissues and has very low on-target toxicity.
2) Linearity: With single dose or repeated doses of IBI305 (2-50 mg/kg) vis intravenous injection in cynomolgus monkeys, the test showed significant PK, thus reducing the suddenly rising toxicity risks with increased clinical doses.
3) Immunogenicity: With single dose or repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed abnormal changes of drug concentration-time curves in several animals. The anti-drug antibody (ADA) test results showed that IBI305 has a medium immunogenicity.
4) Accumulation: With repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed that drug exposure of the last dose was significantly higher than that of the first dose, and the steady-state drug concentration after repeated doses was higher than that after a single dose, suggesting that the drug may be accumulated in body.

The results of tissue cross-reactivity and PK/toxicokinetic studies in cynomolgus monkeys indicated that IBI305 and bevacizumab have similar characteristics in tissue cross-reactivity and PK/toxicokinetics[13].

Toxicological studies

Toxicological studies of IBI305 showed the following findings:

1) Single dose: With single dose of IBI305 (up to 300 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed good tolerability without any abnormal clinical symptoms and toxicity. The dose was about 48 times the proposed clinical dose for human based on body surface area. In the safety pharmacology test, with single dose of IBI305 (50 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed no significant effects on the central nervous system, respiratory system, and cardiovascular system, suggesting that the single dose of IBI305 via intravenous injection has a high safety.

2) Repeated doses: With repeated doses of IBI305 (up to 50 mg/kg) via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, equivalent to 20 times the proposed clinical dose for humans (based on the weight), the test showed extremely mild to mild linear growth arrest of metaphyseal lines at knee joint and disordered chondrocyte proliferation, extremely mild increases in macrophage count in white pulp of spleen, pulmonary (including bronchial) hemorrhage, and deposits of hemosiderin in lymphoid tissue of bronchial mucosa, indicating that the target organ toxicities are mainly in the bone, spleen, and lungs.

3) Immunotoxicity and immunogenicity: With repeated doses of IBI305 via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, the test showed medium immunotoxicity to the spleen. Different doses of IBI305 may result in the production of ADAs, a portion of which are neutralizing antibodies (NAbs), indicating that IBI305 has medium immunotoxicity and immunogenicity.

4) Local irritation test: With repeated dose of IBI305 via intravenous injection in cynomolgus monkeys, the test showed no irritation at the injection site, suggesting that administration of IBI305 via intravenous injection is safe and feasible.

5) In vitro hemolysis assay: With maximum proposed clinical concentration of IBI305 (9 mg/mL), the assay showed no hemolysis, suggesting that IBI305 is suitable for intravenous injection.

IBI305 has high similarity with bevacizumab in safety pharmacology, long-term toxicity, immunotoxicity, immunogenicity, local irritation, and hemolysis[13].

1.2 Study Principles and Risk/Benefit Assessment

1.2.1 Study principles and dose selection

A biosimilar drug refers to a therapeutic biological product that is similar in quality, safety and efficacy with an approved reference drug[14]. IBI305, developed and sold in the market by the sponsor, is a bevacizumab biosimilar, and has the same administration method and indications as bevacizumab.

This study is conducted in accordance with the "Guidelines on Development and Evaluation of Bosimilars (for Trial Version)" issued by the NMPA (formerly CFDA)[14]. The doses of IBI305 selected in this study are based on the preclinical studies that showed highly similarity between IBI305 and bevacizumab in pharmacology, PD, PK and toxicology (refer to the Investigator's Brochure for details). Besides, the efficacy and safety of bevacizumab for treatment of advanced, metastatic or relapsed non-squamous NSCLC have been verified, and the indications have also been approved in China. Therefore, the dose and administration of IBI305 is similar to bevacizumab in this study, that is, 15 mg/kg intravenously on D1 of every 3-week cycle when used in combination with chemotherapy (paclitaxel and carboplatin). In the subsequent maintenance monotherapy therapy, IBI305 will be given intravenously at a dose of 7.5 mg/kg on the first day of every 3-week cycle. This design of this study is to further demonstrate that IBI305 is similar to bevacizumab in clinical efficacy, safety, and immunogenicity in subjects with advanced, metastatic or relapsed non-squamous NSCLC.

1.2.2 Risk/benefit assessment

IBI305 is a bevacizumab biosimilar developed by the sponsor. Based on the clinical pharmacology and toxicology characteristics of IBI305, the risks and benefits of IBI305 are expected to be similar to bevacizumab.

The treatment-related risks of bevacizumab are detailed in its prescribing information. This study is the first human study of IBI305 so that unexpected adverse reactions will be possible. The design of this study ensures the minimized subject risks by close monitoring of the adverse events (AEs) before, during, and after the infusion of the investigational drugs. Once an adverse reaction occurs, the investigator will immediately take appropriate action for the subject safety.

The platinum-based therapy is the standard first-line regimen of advanced NSCLC[4]. This study uses the combination of paclitaxel/carboplatin, ensuring the basic anti-tumor therapy for subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC.

2.2 Secondary Objectives

Secondary objectives include:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) in subjects with advanced or relapsed non-squamous NSCLC treated by IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

2.3 Exploratory Objectives

- To compare the population pharmacokinetics (PPK) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC
- To compare the pharmacodynamics (PD) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC

3 STUDY PLAN

3.1 Overview of Study Design

This is a randomized, double-blind, active-controlled, and multi-center phase III study. A total of 436 subjects across 35 study sites with non-squamous NSCLC will be planned, randomized in a 1:1 ratio into the IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group, and stratified according to age (< 60 vs. ≥ 60 years old) and epidermal growth factor receptor (EGFR) status (wild type vs. unknown type). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first). Then subjects received maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing maintenance therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first).

After discontinuing the study drug, subjects will return to the study site 28 days (± 7 days) after the last dose for an end-of-treatment visit. If the subjects discontinue the study treatment for reasons other than PD, subsequent follow-up will be continued until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. If the subjects discontinue the study treatment for PD, the investigator will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival.

A CT or an MRI will be performed every 6 weeks (± 7 days) until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. The method for subsequent imaging examination should be consistent with that at baseline, and the chest, abdomen and pelvis of the subject must be scanned. Each assessment must be completed within 7 days from the most recent visit. The investigators then perform the evaluation based on the RECIST v1.1 criteria to determine whether the subject can continue receiving the next cycle of treatment. Furthermore, the independent tumor evaluation committee (Section 11.1.1) will also evaluate tumor response according to the RECIST v1.1. If the subjects discontinue the study treatment for reasons other than PD, subsequent tumor evaluation should be continued according to the study procedures until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death or, end of study.

The study design is shown in Figure 1.

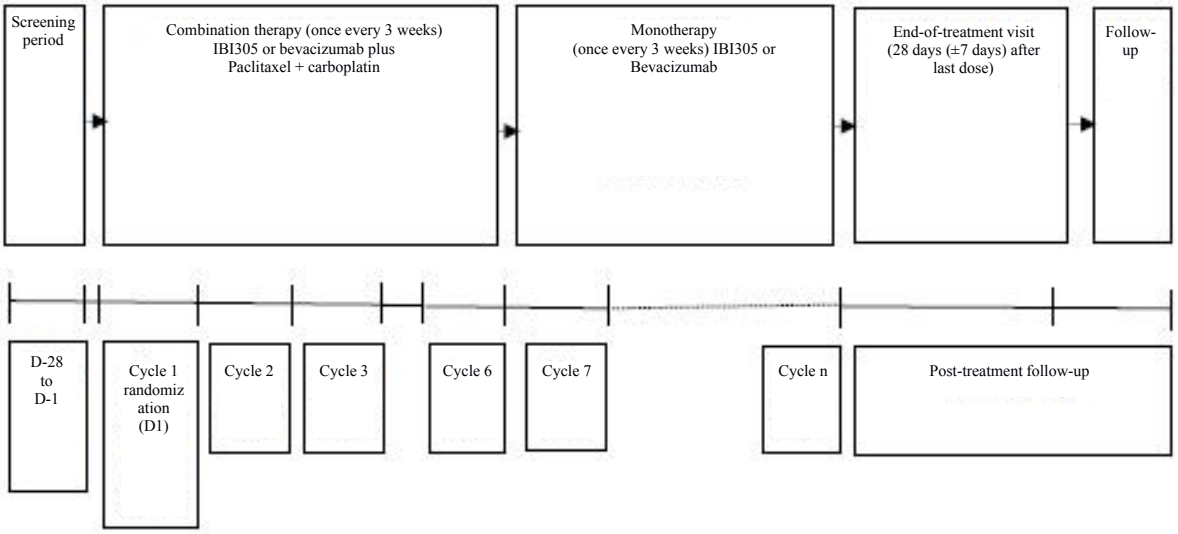

Figure 1. Study design schematic

3.2 Study Design Discussion

This is a randomized, double-blind study, and bias in treatment groups is avoided. Furthermore, the CT/MRI images of each subject will be evaluated by an independent tumor evaluation committee according to the RECIST v1.1 to ensure consistency in evaluation.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled in the study:

1) Sign the informed consent form
2) Male or female ≥ 18 and ≤ 75 years old
3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIB), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types
4) Histologically or cytologically confirmed EGFR wild type or non-sensitive mutation type
5) Must have at least one measurable target lesion (as per RECIST 1.1)
6) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1
7) Expected survival ≥ 6 months
8) Laboratory results during screening:
   a) Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L
   b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis
   c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline urinalysis must have undergone 24 h urine collection with total protein content < 1 g
   d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment
9) Able to comply with study protocol
10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug

4.2 Exclusion Criteria

Subjects meeting any of the followings are not enrolled in the study:

1) Prior systemic chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIB not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible
2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component
3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18 point mutation (G719X), exon 19 deletion, and exon 21 point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll.
4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time
5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava)
6) Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage;
7) Subjects who received radical thoracic radiation therapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug
8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study
9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (Outpatient/inpatient surgery requiring locoregional anesthetics, including central line insertion)

10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function for 10 consecutive days

11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents for 10 consecutive days. However, anticoagulants for prophylaxis are accepted

12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis

13) Uncontrolled hypertension (systolic greater than 140 mmHg and/or diastolic greater than 90 mmHg), history of hypertensive crisis or hypertensive encephalopathy

14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease

15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess

16) Subjects with tracheoesophageal fistula

17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments)

18) Subjects with current interstitial lung disease or CT showing active pneumonia during screening;

19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or papillary thyroid carcinoma

20) Subjects with active autoimmune disease

21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1 × 103 copies/L or ≥ 200 IU/mL; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1 × 103 copies/L or < 200 IU/mL might be eligible if the investigator determined that the subject's chronic hepatitis B infection was stable and participation in the study would add no further risks to the subject

22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis
23) Subjects with known history of allergic diseases or allergic physique
24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening
25) History of alcohol or drug abuse
26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study
27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents
28) Other conditions unsuitable for the inclusion as determined by the investigator

4.3 Screening Failure

Screening failure is that the subject who has signed the informed consent form fails to meet the inclusion criteria. Subjects with screening failure will not get a randomization number. The reasons of screening failure will be documented in the electronic case report forms (eCRFs).

4.4 Subject Restrictions

Female subjects of childbearing age must take effective contraceptive measures during the study and 6 months after the last dose.

Male subjects must take effective contraceptive measures during the study and 6 months after the last dose to avoid the pregnancy of their partners.

Restrictions on the use of medication during the study are shown in Section 5.9.

4.5 Subject Withdrawal and Replacement

All subjects may withdraw from this study at any time, with or without a reason. Subjects who withdraw from the study will not be subjected to discrimination or retaliation, and their medical treatment will not be affected.

Subjects may discontinue the study treatment or withdraw from the study under the following circumstances:

- $\frac{8}{5}$ Unacceptable toxicity
- $\frac{8}{5}$ Progressive disease

- Investigator believes that the subject should withdraw from the study. If an unacceptable adverse event (AE) occurs and the investigator believes that the subject should withdraw from the study, the study treatment should be discontinued and appropriate measures should be taken. In addition, the sponsor or personnel designated by the sponsor should be notified.
- Withdrawal of informed consent form by the subject
- Serious protocol deviation determined by the investigator and/or sponsor
- Poor protocol compliance
- Study termination by the investigator or sponsor for any reason
- Enrollment error* (enrollment of subjects who have violated the inclusion/exclusion criteria)
- Use of prohibited concomitant medications or other medications that the investigator believes that it may result in toxicities or may affect study results
- Subject lost to follow-up
- Death of subject

* If the subject is determined by the investigator and the sponsor's doctor to be medically suitable to continue with the study drugs without any risk or inconvenience, the mistakenly enrolled or randomized subject will continue with the study treatment and assessments.

In any cases, reasons for withdrawal must be documented in the eCRFs. If the subject withdraws from the study prematurely for any reason, the investigator should make every effort to persuade the subject to receive the corresponding assessment, and continue the follow-up of all unresolved AEs based on the AE reports and follow-up requirements (Table 2):

- If the subject withdraws during the study, the series of assessments listed under the End of Treatment Visit (Section 6.9) should be performed
- If the subject withdraws after the end of the treatment visit and has not experienced PD, the series of assessments listed under the Follow-Up for PD (Section 6.10) should be performed (tumor assessment is not required to be repeated if it has been performed within 6 weeks prior to this follow-up)
- If the subject withdraws during the follow-up for survival, the information of subsequent anti-tumor therapies and survival should be collected by telephone follow-up only

Subjects who withdraw their informed consent are not to be contacted again unless they clearly indicate the willingness to be contacted. The sponsor may use the clinical study data obtained before the withdrawal of informed consent.

Subjects who have been randomized will not be replaced.

5 STUDY TREATMENT

5.1 Therapies by Study Drugs

The study drugs of this study are IBI305 and bevacizumab.

In this study, the dose of IBI305 or bevacizumab during combination therapy with chemotherapy is 15 mg/kg, while the dose during maintenance monotherapy is 7.5 mg/kg. The study drugs are administered intravenously on D1 of each 3-week cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

The duration of the first dose of IBI305 or bevacizumab should be 90 min (± 15 min). If the first infusion is well-tolerated by the subject, then the duration of the second infusion can be shortened to 60 min (± 15 min). If the 60 min infusion is also well-tolerated by the subject, then the subsequent infusions can be completed within 30 min (± 15 min).

5.2 Chemotherapy

Paclitaxel will be administered after the IBI305 or bevacizumab infusion is completed, then followed by carboplatin:

Paclitaxel: 175 mg/m² administered via intravenous infusion for 3 h (may be adjusted according to clinical practice of each study site) on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Carboplatin: AUC 6.0, the infusion time is based on the standard practice of each study site, administered on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

The chemotherapeutic agents are supplied by the sponsor.

Formulas for calculating surface area, creatinine clearance and carboplatin dose are shown in Section 13.2.

5.3 Dose Adjustment of Each Study Drug

5.3.1 General principles

The reasons for dose adjustments or delayed administration, measures taken, and results should be documented in the medical records and eCRFs

If the concomitant symptoms exist at baseline, the investigator will determine whether the dose should be adjusted according to the change in severity of toxicity. For example, if the subject has Grade 1 "weakness" at baseline and Grade 2 "weakness" during the study treatment, the dose should be adjusted based on Grade 1 toxicity since the severity has increased by one grade

If several toxic reactions of different grades or severity occur simultaneously, the dose will be adjusted according to the highest observed grade/severity

If a dose adjustment is required solely due to abnormal lab test results, then the dose should be adjusted based on the measured values obtained prior to the start of the treatment cycle

If the investigator determines that the toxicity is unlikely to further develop into a serious or life-threatening event, the current dose will be continued without any adjustments or treatment interruptions. In addition, dose adjustments or treatment interruptions will not be performed for non-hemolytic anemia as the symptoms can be alleviated through blood transfusions.

If the investigator determines that a toxicity is caused by a specific therapeutic drug, then the dose adjustments of other drugs are not required

Discontinuation of one or two therapeutic drugs before PD will not affect the continued treatment with other drugs

Dose reductions or adjustments of IBI305 or bevacizumab are not permitted.

Subsequent therapeutic dose will not be adjusted according to weight change, unless the subject weight has changed by ≥ 10% from baseline

Once the dose of any chemotherapeutic agents is reduced, the original dose should no longer be adopted

If any but not all of the therapeutic drug (IBI305, bevacizumab or chemotherapeutic agents) treatments is interrupted due to toxicity, then this treatment will be considered as a treatment cycle

If the administration of any one of the chemotherapeutic agents is delayed for more than 3 weeks, the subject should permanently discontinue that chemotherapeutic agent

If IBI305/bevacizumab is continued/infused after a delay for more than 3 weeks, the investigator must discuss with the sponsor

5.3.2 Dose adjustments of study drugs

Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments (adjusted to 7.5 mg/kg for maintenance monotherapy) specified in the study protocol. The dose of IBI305 or bevacizumab is calculated according to the subject weight at baseline (prior to the first dose), and remains unchanged throughout the study, unless the subject weight has changed by ≥ 10% from baseline.

If an infusion reaction occurs during a 60-minute infusion, the infusion time should be extended to 90 minutes for all subsequent infusions. Likewise, if an infusion reaction occurs during a 30-minute infusion, the infusion time should be extended to 60 minutes for all subsequent infusions.

IBI305 or bevacizumab in combination with paclitaxel/carboplatin will be administered every 3-week treatment cycle for 6 cycles. If PD is not observed in subject during treatment, then the subject will continue to receive IBI305 or bevacizumab as maintenance monotherapy every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, death, or end of study (whichever comes first).

If IBI305 or bevacizumab is permanently discontinued due to unacceptable toxicity or subject refusal to continue the study drugs during the combination therapy, then the subject will continue to receive the chemotherapy (paclitaxel/carboplatin) until 6 treatment cycles are completed as determined by the investigator. If any one of the chemotherapeutic agents (paclitaxel or carboplatin) is prematurely discontinued due to unacceptable toxicity, the subject can continue to receive IBI305 or bevacizumab treatment until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first).

When a Grade 3 or 4 IBI305- or bevacizumab-related toxicity is observed, the investigators should determine whether to continue or terminate IBI305 or bevacizumab treatment according to the followings:

First occurrence:

IBI305 or bevacizumab administration should be interrupted until toxicity symptoms return to baseline level or are at least reduced to the Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or lower (except for the special circumstances listed below)

Note that when Grade 4 febrile neutropenia and/or thrombocytopenia occur(s), IBI305 or bevacizumab administration should be interrupted until the symptoms return to baseline levels or at least reduced to CTCAE Grade 1 or lower, since these events increase the risk of hemorrhage.

Re-occurrence in re-administration:

If Grade 3 IBI305- or bevacizumab-related toxicity occurs again, the investigator should assess the risk/benefit of study drug continuation for the subject. If such toxicity re-occurs again after re-administration, IBI305 or bevacizumab should be permanently discontinued

If Grade 4 IBI305- or bevacizumab-related toxicity occurs again, IBI305 or bevacizumab should be permanently discontinued

Measures should be taken in the following special circumstances (classified based on CTCAE version 4.03):

Hemorrhage

Subjects with Grade 3 or 4 hemorrhages should be treated accordingly and permanently discontinue the study treatment

Thrombosis/embolism

- Subjects with arterial thrombosis of any severity grades should permanently discontinue the study treatment
- Subjects with Grade 4 venous thrombosis should permanently discontinue the study treatment
- Subjects with Grade 3 venous thrombosis should interrupt the study treatment. If the anticoagulant therapy at the planned therapeutic dose is < 2 weeks, the study treatment should be interrupted until the anticoagulant therapy is completed. If the anticoagulant therapy at the planned therapeutic dose is > 2 weeks, IBI305 or bevacizumab administration should be interrupted for 2 weeks, and the study treatment can be restarted during the anticoagulant therapy if the following criteria are met:
  - INR is within the target range (usually 2-3) prior to restarting of study treatment
  - Subjects must not have experienced Grade 3 or 4 hemorrhage since enrollment
  - No signs of great vessel invasion or adjacency to great vessels from previous tumor assessments

  Note: Therapeutic dose of anticoagulant therapy is defined as the escalating dose of warfarin or other anticogulants until INR is maintained at no less than 1.5 (usually

2-3). The warfarin dose should be documented in the eCRFs, and the INR of subjects receiving anticoagulant therapy should be monitored during the treatment.

Hypertension

BP should be measured frequently to monitor the occurrence and exacerbation of hypertension. Subjects should remain at resting position for at least 5 min before BP measurement.

Definition of hypertension: pathologically increased BP with repeated measurements persistently over 140/90 mmHg

Table 2. Hypertension severity grades and interventions in CTCAE v4.03

CTCAE		Interventions
Grade 1	Pre-hypertension (systolic blood pressure of 120–139 mmHg, diastolic blood pressure of 80–89 mmHg)	Intervention not indicated
Grade 2	First-stage hypertension (systolic blood pressure of 140–159 mmHg, diastolic blood pressure of 90–99 mmHg; repeated or persistent hypertension of ≥ 24 h), a symptomatic increase of > 20 mmHg in systolic blood pressure, or an increase of > 140/90 mmHg from the previous normal range	Antihypertensive monotherapy. drug interruption. The treatment with the investigational product can be continued once the blood pressure is lower than 140/90 mmHg.
Grade 3	Second-stage hypertension (systolic blood pressure of ≥ 160 mmHg, diastolic blood pressure of ≥ 100 mmHg)	Multiple-agent antihypertensive therapy. Study treatment should be interrupted in case of persistent or symptomatic hypertension; study treatment should be permanently discontinued for uncontrollable hypertension.
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit, and hypertensive crisis)	Urgent intervention and permanent study treatment discontinuation indicated

The dose of antihypertensive agents used should be documented during each visit. If the subject remains hypertensive despite treatment discontinuation, BP and antihypertensive agents used should be monitored every 3 months until BP returns to normal or end of study.

Posterior reversible encephalopathy syndrome (PRES)

There have been a few reports of subjects with signs and symptoms consistent with PRES after study treatment. This is a rare neurological disease and its signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with PRES should permanently discontinue the study treatment.

Proteinuria

Urinalysis should be performed prior to each dose of IBI305/bevacizumab unless a 24-hour urinary protein test has already been done.

First occurrence of proteinuria:

After carrying out the urinalysis, if:

Urine protein is < 2+, continue study treatment as scheduled, no additional tests are required.

≥ 2+ (urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:

- 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled. and perform urinalysis dipstick test before each scheduled dose.
- 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g.

Second and subsequent occurrence of proteinuria:

< 3+ (urinalysis): continue study treatment as scheduled, no additional tests indicated.

≥ 3+ (urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:

- 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled.
- 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g.

Nephrotic syndrome (Grade 4): Study treatment is permanently discontinued

Gastrointestinal perforation

If gastrointestinal perforation occurs, appropriate measures should be taken and the study treatment should be permanently discontinued.

Wound healing complications

The study treatment should not begin within 28 d after a major surgery, or before the surgical wound is fully healed. If a complication of wound healing occurs during study treatment, the study treatment should be interrupted until the wound is fully healed. If an elective surgery is required, the study treatment should be interrupted.

Abdominal abscess or fistula

If abdominal abscess or fistula occurs, the study treatment should be discontinued. However, the investigator will determine whether study treatment will be continued if the above AE is resolved.

Infusion-related and allergic reactions:

Infusion-related reactions after first dose of the study drug is uncommon (< 3%), and the incidence of a severe reaction is only 0.2%.

If a mild (grade 1 or 2) reaction (such as fever, chills, headache, and nausea) occurs, pretreatment prior to subsequent administration should be performed and infusion time should not be reduced. If the subject is well-tolerated during infusion after pretreatment, the infusion time can be reduced by 30 minutes (+10 minutes) for subsequent administration with pretreatment. If an infusion-related AE occurs during a 60-minute infusion, the subsequent infusion should be completed within 90 minutes (+15 minutes) with pretreatment. Likewise, if an infusion-related AE occurs during a 30-minute infusion, the subsequent infusion should be completed in 60 minutes (+10 minutes) with pretreatment. If a subject has a grade 3 infusion-related reaction, the study treatment should be interrupted and not be restarted on the same day. However, since there lacks the dose adjustment method for grade 3 infusion-related reactions, the investigators may decide to either discontinue the study drug or perform pretreatment, and complete the infusion within 90 minutes (+15 minutes). If an adverse reaction still occurs during a 90-minute infusion, the infusion should be continued at a slower rate and then gradually returned to a 90-minute infusion. If the investigator is uncertain about the handling, the study treatment should be discontinued. When the study treatment is restarted, the subject should be closely monitored based on routine clinical practice until the possible time of adverse reaction has passed. If a subject has a grade 4 infusion-related reaction, the study treatment should be discontinued.

An allergic reaction is defined as the vascular collapse or shock (systolic BP < 90 mmHg, unresponsive to rehydration) that occurs within 30 minutes of a study drug infusion caused by

an allergy, with or without respiratory distress. Skin reactions include pruritus, urticaria, and angioedema. Subjects with allergic reactions should discontinue the study treatment.

5.3.3 Dose adjustments of chemotherapy

Paclitaxel and carboplatin should be administered according to the study site guidelines and local prescribing information. For the specific information for use, preparation, and storage of paclitaxel and carboplatin, refer to the prescribing information and local dosing information. Carboplatin-based chemotherapies have a relatively high incidence of emesis. Therefore, antiemetics for prophylaxis can be used.

Hematological toxicity:

Absolute neutrophil count (ANC; dose can only be reduced when febrile neutropenia occurs. ANC must be ≥ 1.5 × 109/L and platelet count must be ≥ 100 × 109/L on D1 of each treatment cycle). Once the chemotherapeutic dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 × 109/L or 50 × 109/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.

Table 3. Dose adjustments of paclitaxel and carboplatin (febrile neutropenia and thrombocytopenia)

	Dose Adjustments of Paclitaxel/Carboplatin		
	First Occurrence	**Re-Occurrence After Dose Adjustment**	**Re-occurrence After Two Dose Adjustments**
Febrile neutropenia (regardless of duration)	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC *3*	Chemotherapy discontinuation
Lowest Level After Last Dose <25 × 10^9/L or <50 × 10^9/L with hemorrhage or requires blood transfusion	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC 3	Chemotherapy discontinuation

If the dose adjustment is required when ANC and thrombocytopenia occur concurrently, the low-dose chemotherapy should be adopted.

Chemotherapy may be delayed for up to 3 weeks. If after the chemotherapy has been delayed for 3 weeks, ANC does not reach ≥ 1.5×10^9/L and platelet count does not reach ≥ 100×10^9/L on D1 of the scheduled chemotherapy, the chemotherapy should be permanently discontinued. If the above values have been reached, the next course of chemotherapy should be continued.

The investigator should monitor the subject closely for toxicity with particular attention to early and evident signs of myelosuppression, infection, or febrile neutropenia to timely and appropriately treat the complications.

Subjects should be informed to pay attention to these signs and receive treatment as soon as possible.

If the chemotherapy must be interrupted due to hematological toxicity, the complete blood count should be performed regularly (including WBC differentials) until all the counts reach the minimum requirements for treatment continuation. Thereafter the scheduled treatment plan will be performed.

Dose adjustments are not required for anemia. However, treatment based on guidelines of each clinic should be performed.

Gastrointestinal toxicity

Antiemetics will be used to control nausea and/or emesis. If grade 3 or 4 nausea and/or emesis occur(s) despite of antiemetics, the chemotherapeutic dose should be reduced by 20% for the next treatment cycle. The dose should be returned to the initial level as possible if the subject is tolerated.

If the subject experiences stomatitis on D1 of any treatment cycle, the chemotherapy should be interrupted until the symptoms resolve. If the stomatitis has not resolved after 3 weeks, the chemotherapy should be permanently discontinued (refer to CTCAE version 4.03). If an acute Grade 3 stomatitis occurs, the chemotherapeutic dose should be reduced to 75% of the proposed dose when symptoms resolve.

Hepatotoxicity (Paclitaxel)

The paclitaxel dose should be determined based on the lab values measured on D1 of each treatment cycle.

Table 4. Dose adjustment of paclitaxel (hepatotoxicity)

AST		Total bilirubin	Paclitaxel Dose
≤ 5 x UNL	and	WNL	175 mg/m^2
> 5 x UNL	or	> UNL ~ 1.5 x UN	150 mg/m
		> 1.5 x UN	0

If paclitaxel is interrupted due to hepatotoxicity, carboplatin should also be interrupted until paclitaxel is restarted. Paclitaxel will be interrupted for up to 3 weeks. If the subject's hepatic function does not return to the acceptable ranges in 3 weeks, paclitaxel should be permanently discontinued. The carboplatin dose will not be adjusted when hepatotoxicity occurs.

The investigators should avoid PD due to abnormal hepatic enzyme levels as possible. If PD occurs, all the study drugs should be permanently discontinued, including chemotherapy.

Cardiovascular toxicity (paclitaxel)

The arrhythmia in subjects was infrequent in previous clinical studies. However, most subjects were asymptomatic and electrocardiographic monitoring was not required. Asymptomatic transient bradycardia was observed in 29% of subjects, but significant atrioventricular block was rare. Cardiac events should be treated as follows:

Asymptomatic bradycardia: no intervention indicated

Symptomatic arrhythmia during infusion: Discontinue paclitaxel infusion and perform routine treatment of arrhythmia. Discontinue subsequent paclitaxel treatment. Document this AE in the AE Report Form of eCRF.

Chest pain and/or symptomatic hypotension (< 90/60 mmHg or rehydration therapy required): discontinue the paclitaxel infusion. Perform electrocardiography (ECG). If hypersensitivity reaction is suspected, administer diphenhydramine and dexamethasone via intravenous infusion. If the chest pain is not considered as cardiogenic, epinephrine or bronchodilators will be administered. Document this AE in the AE Report Form of eCRF. Discontinue subsequent paclitaxel treatment and provide symptomatic treatment. Consult a cardiologist if needed.

Neurotoxicity (paclitaxel)

The dose of paclitaxel should be adjusted according to Table when neuropathy occurs. The dose adjustment of carboplatin is not needed when neurotoxicity occurs.

Table 5. Dose adjustment of paclitaxel (neurotoxicity)

Toxicity Grade (CTCAE version 4.03)	Paclitaxel dose adjustment
Grade 1 or below	175 mg/m^2
2	Interrupt treatment until return to grade 1, then reduce dose to 140 mg/m^2 (20% of reduction) and restart infusion

Grade 3 or above	Interrupt treatment until return to grade 1, then reduce dose to 125 mg/m^2 (30% of reduction) and restart infusion.

Once the dose is reduced due to neurotoxicity, the original dose should no longer be adopted. If the neurotoxicity does not return to grade 1 after paclitaxel interruption for 3 weeks, paclitaxel should be permanently discontinued.

Allergic reactions/hypersensitivity reactions (paclitaxel)

Note: Prophylaxis for hypersensitivity reactions (see below) and close monitoring of vital signs are recommended for subjects with history of mild to moderate hypersensitivity reactions when hypersensitivity reactions reoccur.

Mild symptoms: complete paclitaxel infusion. Close monitoring; no treatment indicated.

Moderate symptoms: Interrupt paclitaxel infusion, administer diphenhydramine 25–50 mg and dexamethasone 10 mg via intravenous infusion. Once symptoms have resolved, resume paclitaxel infusion at a slower rate (20 mL/hour for 15 minutes, then at 40 mL/hour for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete). Document this AE in the AE Report Form of eCRF. If symptoms reoccur, interrupt the paclitaxel infusion and permanently discontinue subsequent paclitaxel infusion.

Severe and life-threatening symptoms: Interrupt paclitaxel infusion, administer diphenhydramine and dexamethasone via intravenous infusion (as above). Use epinephrine or bronchodilators if indicated. Document this AE in the AE Report Form of eCRF. Subsequent courses of paclitaxel infusion should be permanently discontinued.

Moderate or severe hypersensitivity reactions should be documented as AEs.

Other toxicities

If other unmentioned grade 3–4 toxicities occur, the chemotherapy should be interrupted until symptoms resolve or return to grade 1. Thereafter restart the infusion at 50% of the original dose (which should no longer be adopted). If the toxicity does not return to grade 1 after an interruption for 3 weeks, the chemotherapy should be permanently discontinued. Dose adjustments are not recommended for grade 1 and 2 toxicities.

5.4 Study Drug Properties

IBI305 is a bevacizumab biosimilar. The active ingredient of both drugs is recombinant humanized anti-VEGF monoclonal antibody; Bevacizumab is the standard commercially available drug, provided by the sponsor.

Detailed information on the study drugs is shown in Table .

Table 6. Study drugs

Study Drugs	Dosage Form and Strength	Excipient	Appearance	Manufacturer
IBI305	4 mL: 100 mg	Sodium acetate, sorbitol, and polysorbate 80	Sterile solution for intravenous injection pH 5.2 Clear, colorless liquid, no foreign matters, no floc or precipitation	Innovent Biologics (Suzhou) Co., Ltd.
Bevacizumab	4 mL: 100 mg	α,α-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, polysorbate 20, and sterile water for injection	Sterile solution for intravenous injection pH 5.9–6.3 Clear to slight opalescent, colorless to light brown	Roche Pharma (Schweiz) Ltd.

5.5 Preparation and Distribution

IBI305 or bevacizumab is diluted in 0.9% sodium chloride solution by the pharmacist or research nurse before infusion. Check the particles and discoloration prior to administration.

The investigator should ensure that the pharmacist or research nurse administers the study drugs according to study protocol.

5.6 Packaging, Labeling, and Storage

The sponsor should package and label the study drugs according to appropriate local regulations.

All study drugs (IBI305 and bevacizumab) must be stored at 2–8 °C away from light. The study drugs should be stored in a safe zone only accessible by authorized staff prior to dispensation to the subjects.

5.7 Subjects Allocation

After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in the Interactive Web Response System (IWRS) and enter the subject information into the IWRS. The IWRS will allocate a random number to the subject and provide a medication

number. Stratified randomization is used in this study. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild vs. unknown type).

5.8 Blinding

This is a randomized, double-blind, and active-controlled study, and only relevant study personnel had access to the randomization numbers. A non-blinded pharmacist or research nurse will prepare the medications since IBI305 and bevacizumab do not have an identical appearance. The pharmacist or research nurse who is responsible for preparing the study drugs is not allowed to disclose any information regarding treatment allocation to the subject, the subject's family members, or other personnel including the physician and the relevant study staff.

Unblinding: Subject unblinding should only be performed after database locking.

Emergency unblinding: In case of an emergency where the investigator must know the medication given to a particular subject, the investigator will unblind the subject via the IWRS and immediately inform the sponsor and CRO. The reasons for unblinding, date, and outcomes should be documented in the source document and eCRF of the subject.

5.9 Concomitant Medications and Treatments

All medications except for the study drugs, including other chemotherapies not specified in the study, Chinese herbal medicines, and other non-traditional therapies, are considered concomitant medications. All concomitant medications used within 30 days prior to screening should be documented in the eCRFs, including the information of generic name, route of administration, start date, end date, and indication.

5.9.1 Prohibited treatment

No other anti-tumor therapies or medications with anti-tumor indications, including Chinese herbal medicine, radiotherapy, or other investigational drugs, are allowed during this study other than IBI305, bevacizumab, paclitaxel, and carboplatin.

Severe myelosuppression is possible after chemotherapy. Granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are not allowed to be used prophylactically in the first treatment cycle.

5.9.2 Permitted treatment

Prophylactic use of anti-emetics, glucocorticoids, or other treatments targeting toxicities is permitted during the study. Unconventional treatments (such as acupuncture) and vitamins/microelements are permitted if their use does not affect the study endpoints as determined by the investigators.

Starting from the 2nd chemotherapy cycle, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are allowed to be used prophylactically to prevent severe myelosuppression.

Anti-viral therapy was permitted whenever necessary.

Stable doses of anti-epileptic drugs were permitted.

Radiotherapy for bone metastasis was permitted provided that the radiotherapy field did not include the target lesion

5.9.3 Treatment after study treatment

Subsequent therapy after the end of study treatment should be determined by the subject's attending doctor.

5.10 Treatment Compliance

Subjects should receive treatment at the study site. The dose and time of administration of IBI305 or bevacizumab and paclitaxel/carboplatin should be documented in the source records and eCRFs during each treatment cycle. Reasons for dose adjustments, therapy delay, and therapy discontinuation should be documented. Treatment compliance is monitored by medication dispensing and return records, medical records, and eCRFs.

5.11 Drug Return and Destruction

The containers, vials, infusion bags, and syringes of used and partially used drugs can be destroyed on-site according to the appropriate guidelines and operating procedures established by study sites and local agencies.

Unless the contents have significant safety issues requiring immediate destruction in accordance with local regulations, all the unused drugs should be returned and destroyed based on the requirements of sponsor.

5.12 Study Drug-Related Records

The designated personnel of the study sites should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines.

6 STUDY PROCEDURE

The detailed procedures of this study are shown in Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

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6.1 Screening Visits (D -28 to D -1)

Complete the screening visits within 28 days prior to study treatment commencement. The following procedures must be completed during screening to ensure that subject meets the requirements for participating in this study:

- Sign the ICF
- Record the demographics, including age, ethnicity, and gender
- Record the past medical history, including smoking history
- Record the history of anti-tumor therapies
- Record the concomitant medications (within 30 days prior to screening)
- Record the vital signs
- Measure the height and weight (including BMI)
- ECOG score
- Physical examination
- 12-Lead ECG
- Hepatitis B panel, anti-HCV, anti-HIV, and syphilis tests
- Clinical laboratory tests (routine blood test, coagulation test, blood chemistry, and urinalysis)

- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Imaging examinations (CT or MRI: Head, chest, abdomen, and pelvis cavity)*
- EGFR test#
- Review the inclusion/exclusion criteria
- Record the AEs and concomitant medications

* Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging results during screening will be used as the baseline data. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

If the subject has been tested for EGFR of tumor sample at the study site with documentation, the subject will not be required for retest.

6.2 Baseline Visits (D1 of cycle 1)

D1 refers to the day of receiving the first dose of the study drugs. Eligible subjects meeting the inclusion criteria will return to the study site and complete the following procedures:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests * (routine blood test, blood chemistry, and urinalysis)
- Confirm the inclusion/exclusion criteria

* If clinical laboratory screening tests (routine blood test, blood chemistry, urinalysis) are performed within 7 days prior to the first dose, then the results of the screening test can be used as baseline.

If the subject meets the inclusion criteria, the following procedures should be complete:

- Randomization and grouping
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Pharmacokinetic (PK) blood sampling (within 1 h prior to the study drug infusion,

immediately after the study drug infusion [+5 min])

- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Record the AEs and concomitant medications

6.3 Cycle 2 (week 4 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.4 Cycle 3 (week 7 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)

- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.5 Cycle 4 (week 10 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.6 Cycle 5 (week 13 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)

- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.7 Cycle 6 (week 16 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.8 Cycle 7 and Subsequent Treatment Cycles (±3 Days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Maintenance monotherapy will start from week 7 and the dose of study drug will be adjusted to 7.5 mg/kg. Subjects should complete the following procedures during each visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG

- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.9 End-Of-Treatment Visit

The end of treatment visit in study sites will be conducted in 28 days (±7 days) after the last dose of study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Immunogenicity test
- PD blood sampling
- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this visit)
- Subsequent anti-tumor therapy
- Record the AEs and concomitant medications

If the subject has not experienced PD, the subsequent follow-up for PD will be performed (Section 6.10). If the subject has experienced PD, the subsequent follow-up for survival will be performed (Section 6.11).

6.10 Disease Progression Visit

If the study drugs are discontinued for reasons other than PD, the end of treatment visit in study sites will be conducted in 28 days after the last dose of study drug, and tumor assessments should be conducted every 6 weeks (±7 days) until PD if possible (after which, follow-up for survival will be conducted [Section 6.11]), withdraw of informed consent, loss to follow-up, death,

start of other anti-tumor therapies, or end of study. During the visit, vital signs and weight measurements will be performed, and any subsequent anti-tumor therapies will be documented.

6.11 Survival Follow-Up

The investigator will make telephone follow-up every 12 weeks (±7 days) to collect the information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, loss to follow-up, death, or end of study.

6.12 Study Completion

The end of this study will be the18th month after randomization of the last subject. If the subjects continue to receive the study drug treatment before this cut-off time, the treatment should be discontinued and the end of treatment visit should be completed (Section 6.9).

6.13 Tumor Assessment

Imaging tests (CT or MRI) of the brain, chest, abdomen, and pelvis are required at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test was used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

The investigator should perform a tumor assessment based on RECIST v1.1 (Section 13.3) prior to each dose to determine whether the subject should continue with the next round of treatment. An independent review committee will also assess the tumor response (Section 11.1.1). Imaging tests will not be rescheduled if the study drugs or chemotherapeutic agents are interrupted due to toxicities. Every effort should be made to continue the schedule for imaging tests even for subjects who discontinue one or two study treatment(s) due to drug-related toxicities.

If subject experience PD according to the RECIST v1.1 criteria, the attending doctor should discuss with the subject regarding subsequent routine cancer therapies.

6.14 Clinical Laboratory Evaluations

Clinical laboratory tests will be conducted at the laboratories of each study site. Sample collection and analysis should be performed according to the requirements of each laboratory.

The following laboratory tests should be conducted according to the study procedures (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

):

Routine blood test: hemoglobin, hematocrit, WBC and differentials (including

absolute neutrophil and lymphocyte counts), platelets, and RBC

Routine coagulation test (baseline test): INR, aPTT, or PTT

➢ Blood chemistry: Creatinine, blood urea, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose, sodium, potassium, chloride, calcium, phosphorus, and magnesium

➢ Urinalysis: Specific gravity, pH, glucose, protein, occult blood, and leukocytes

➢ Pregnancy test: Serum/urine pregnancy tests are performed on women of childbearing age during screening and the end-of-treatment visit.

These tests are carried out at the laboratory of each trial site.

For subsequent visits, all laboratory tests need to be completed within 3 days prior to the administration. During the study, the frequency of these laboratory tests will be increased if safety is a concern. The investigator should review the laboratory test results throughout the study to determine whether the results are clinically significant. The investigator should assess the changes in laboratory test results. If the investigator considers a laboratory test result to be abnormal and of clinical significance, it is considered as an AE.

6.15 Vital Signs, Physical Examinations, and Other Safety Assessments

6.15.1 Vital signs

Vital signs include pulse, BP, temperature, and respiratory rate. The subject must rest for at least 5 minutes prior to each vital sign assessment.

Vital signs will be assessed according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

). During the study, the investigator may increase the frequency of vital sign measurement if

safety is a concern.

6.15.2 Height and weight

Height is only measured during screening. Weight is measure during each visit.

6.1.5.3 Physical examinations

The following organs/systems will be examined according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration		x	x	x	x	x	x	x			

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
(IBI305 or bevacizumab) [j]											
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

): general condition, head (eyes, ears, nose, and throat), neck and thyroid, respiratory system, cardiovascular system, abdomen, nervous system, skeletal muscles and limbs, as well as lymphatic system and skin.

6.15.4 12-Lead ECG

12-lead ECG will be performed during screening. During the study, each medication visit requires an ECG examination. The following ECG parameters should be documented: HR, PR-interval, QRS-complex, QT-interval, and QTc-interval. The subject must be in the supine position for at least 5 minutes prior to undergoing the 12-lead ECG. All ECG are evaluated by qualified physicians. All clinically significant abnormal findings should be reported as AEs.

6.15.5 Immunogenicity assessment

Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples were tested at the designated central laboratory.

6.15.6. Pharmacokinetics/pharmacodynamics

6.15.6.1 Pharmacokinetics

Study sites that are implementing version 3.1 of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 hour prior to the dose in C4, within 1 h prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.

6.15.6.2 Pharmacodynamics

Study sites that are implementing version 2.0 and subsequent versions of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and during the end-of-treatment visit. Samples were tested at the designated central laboratory.

6.15.7 EGFR testing

EGFR mutation testing histologically or cytologically will be performed in all subjects (if the subject has been tested for EGFR at the study site histologically or cytologically with documentation, the subject will not be required to be retested). The testing will be conducted at the laboratory of each study site or a qualified third-party laboratory.

7 STUDY ASSESSMENTS

7.1 Efficacy Assessment

7.1.1 Primary efficacy endpoint

- Objective response rate (ORR)

ORR will be assessed using RECIST v1.1. ORR is defined as the proportion of subjects whose tumor volume has reduced to a predetermined value, including patients who achieved complete response (CR) and partial response (PR). The cut-off date for data included in the primary efficacy evaluation is the 18th week after the last subject is randomized.

7.1.2 Secondary efficacy endpoints

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Each endpoint will be assessed using RECIST v1.1.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death before PD; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

PFS is defined as the time from the date of randomization to the date of PD or death; Subjects who do not progress or die will be censored on the date of the last tumor assessment.

DCR is defined as the proportion of patients whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved CR, PR, and SD.

OS is defined as the time from the date of randomization to the date of death of any cause. For subjects that are alive on the date of study completion or are lost to follow-up, their survival time will be censored at the date of last contact.

7.2 Safety Assessments

7.2.1 Adverse events

7.2.1.1 Definition

Adverse event

An AE refers to any untoward medical occurrence in a subject after signing the informed consent form, and does not necessarily have a causal relationship with the treatment. Thus, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether considered drug related.

Abnormalities resulting from PD are not considered as AEs.

Serious adverse event

A SAE refers to an AE meeting at least one of the followings:

(1) Lead to death, except for deaths caused by PD.

(2) Life-threatening (a "life-threatening event" is defined as an AE when the subject is at immediate risk of death at the time, but does not include the case that may lead to death only when the event worsens).

(3) Requires hospitalization or prolonged hospitalization, excluding an emergency or outpatient visit. Subjects with existing diseases or conditions prior to the enrollment that do not worsen during the study, and having hospitalization and/or surgery that was scheduled before the study or during the study do not meet the SAE criterion. Hospitalizations resulting from PD are not considered as SAEs.

(4) Results in permanent or severe disability/incapacity.

(5) Results in congenital anomalies/birth defects.

(6) Other important medical events: The event that does not result in death, is not life-threatening or does not require hospitalization, but may jeopardize the health of subjects and require medical intervention to prevent the SAEs above, is considered as an SAE

7.2.1.2 Severity of adverse events

The severity of AEs is evaluated using the 5-level criteria of NCI CTCAE v4.03.

For AEs not included in CTCAE v4.03, use the following CTCAE general guidelines:

- Grade 1: Mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated.
- Grade 2: Moderate; minimal/local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life (such as cooking, shopping, using the phone, financial management, etc.).
- Grade 3: Severe or clinically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; limited ability of self-care (such as bathing, dressing, undressing, eating, using the toilet, taking medication), but not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

7.2.1.3 Relationship between adverse events and the investigational drug

The relationship between the study drugs and AEs can be determined using the followings:

Table 4. Correlation between AEs and investigational drugs

Correlation	CRITERIA
Related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can more reasonably explain the AE than the other causes (such as the pre-existing disease of the subject, environment, toxicity, or other treatment received); The AE resolves or is alleviated after treatment interruption or dose reduction; The AE is consistent with the known type of AEs of the suspicious drug or similar drugs; The AE occurs again after the drug administration is resumed.
Possibly related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can be used to explain the AE with the same level of rationality as other reasons (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE resolves or is alleviated after treatment interruption or dose reduction (if applicable).
Possibly not related	Other reasons can more reasonably explain the AE than the investigational drug (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear; The AE does not occur again or the situation of the AE is unknown after

	the drug administration is resumed.
Unrelated	¾ The occurrence of the AE is not reasonably related to the time sequence of dosing, or ¾ The AE has other obvious causes (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject).
Cannot be determined	¾ The above information is unclear and cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.

7.2.1.4 Serious adverse event reporting

SAEs that occur from the signing of informed consent form until 90 days (inclusive) after the last dose should be reported. The investigator must fill out the "CFDA SAE Report Form", regardless of whether it is the initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, CFDA, and ethics committee within 24 hours of noticing the event. The contact information for reporting is shown in the table below.

For SAEs occurring outside of the above-mentioned period, those considered related to the investigational drug shall also be reported to the sponsor.

The investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.

The investigator should also report the event to the CFDA, health administration departments, and ethics committees in accordance with the regulations.

When submitting the SAE report by email, it is recommended for the investigator to encrypt the report file and send the report file and password in separate emails.

Table. SAE report contacts

Unit	**Contact**	**Fax/Telephone/Address**
Hospital Name	**Ethics committee**	**Hospital Fax/Telephone**
Innovent Biologics (Suzhou) Co., Ltd.	Clinical Study Department PV	Fax: 021-31652800 Email: drugsafety@innoventbio.com

Office of Drug Research and Supervision, Department of Drug and Cosmetics Registration, China Food and Drug Administration		Address: Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing Post Code: 100053 Tel: 010-88330732 Fax: 010-88363228
Medical Administrative Department, Health Administration		Address: No. 38, Lishi Road, Xicheng District, Beijing Tel: 010- 68792001 Fax: 010-68792734
Province, Autonomous Region, Municipality Food and Drug Administration	Based on the requirements of the food and drug administration department of each province, autonomous region or municipality	

7.2.1.5 Management and follow-up of adverse events

The investigator is responsible for providing appropriate medical treatment for all AEs (Indicate the actions taken, such as suspension/termination of the investigational drug, dose modification, drug therapy, etc.). When an AE occurs, the investigator should actively take appropriate measures to ensure the safety of the subject. All AEs observed from the signing of the ICF to the time specified in the protocol (Table 2) must be followed.

The investigator should report any SAE that occurs after the time specified in the protocol (Table 2) and is suspected of being related to the investigational drug to the sponsor.

7.2.1.6 Adverse event of special interest and expedited reporting

The AESI for this study include:

- Gastrointestinal perforation
- Procedural and wound healing complications
- Hemorrhage
- Fistula
- Hypertension
- Thrombotic event
- Posterior reversible encephalopathy syndrome (PRES)

- Proteinuria
- Infusion-related reaction
- Ovarian failure
- Cardiac failure congestive

If the criteria for SAE is met, the SAE report should be submitted to the sponsor within the specified time limit (see 7.2.1.4 for details)

7.2.1.7 Pregnancy

Bevacizumab may be harmful to the fetus. Subjects or female partners of male subjects must use an effective form of contraception during the 6 months after the last dose.

During the study, if a female subject exposed to the study drug becomes pregnant, she must discontinue study treatment. The investigator must report to the sponsor within 24 hours of noticing the event and submit the "Innovent clinical Study Pregnancy Report/Follow-Up Form".

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

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

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

If the subject also experiences a SAE during the pregnancy, the CFDA SAE Report Form should also be filled out and reported according to SAE's procedures.

7.2.1.8 Time limits of documenting and reporting AEs

All AEs occurring from the time the subject signs the informed consent form to the time specified in the protocol (Table 2) (including SAEs and non-SAEs), regardless of their severity, must be collected and recorded on the AE page of the eCRF.

The investigator must fill out all the required information, including the description of the AE, start date, end date, severity, measures taken, outcome, seriousness, and causality with the investigational drug. Each AE should be documented separately.

Table 5. Reporting and follow-up of adverse events

	Reporting time limit	Visit time limit
AEs	From signing the informed consent form to *90 days* after the last dose (if the subject begins other anti-tumor therapies, only AEs related to the study drugs should be collected)	Until resolved or explainable stable determined by the investigator
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the outcome of the event is available, and the health conditions of the newborn should be followed up for at least 2 months according to the protocol

7.2.1.9 Precautions for AE documentation

Diagnosis, signs, and symptoms

If a diagnosis is already made, the eCRF should record the diagnosis instead of individual symptoms and signs (such as hepatic failure rather than jaundice, transaminase increased, and asterixis). However, if the signs and symptoms cannot be attributed to a definitive diagnosis, each independent event should be documented in the eCRFs as an AE or SAE. Update the report with visit information if a diagnosis is confirmed later.

AEs secondary to other events

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

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs. The initial severity should be documented, and the information should be updated if the event exacerbates.

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

Abnormalities in laboratory tests/vital signs

All clinically significant laboratory test abnormalities should be reported as AEs. It is the responsibility of the investigator to review all abnormal laboratory test results, and to make medical judgments as whether each abnormal laboratory test result should be reported as an AE.

Death

During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs, regardless of the causality with the investigational drug.

When recording a death event, if the cause of death is clear, the cause of death is recorded as an adverse event with the result of the adverse event being death, and the event is reported as an SAE; if the cause of the death is unknown at the time of reporting , "Death with Unknown Cause" should be recorded on the Adverse Event Form of the eCRF and the "Death with Unknown Cause" should be reported as an SAE first before further investigation is carried out to find the exact cause of death.

Pre-existing medical conditions

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

Hospitalization and prolonged hospitalization, or surgery

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

$\frac{4}{3}$ Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration, efficacy evaluation, etc.)

$\frac{4}{3}$ Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.

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

The investigator should fill in all required information, including AE terms

(diagnostic terms, or the record of symptoms and signs including laboratory test abnormalities if there is no diagnosis), start date, end date, severity level, whether it is an AESI, measures taken for the investigational product, treatment given for the AE, outcome, seriousness, and relationship with the investigational product. If the signs and symptoms cannot be attributed to a definitive diagnosis, each AE should be documented independently.

Progressive disease

A progressive disease is defined as the worsening of subject condition caused by the primary tumor that the investigational drug is targeting, the appearance of new lesions, or the progression of the primary lesion. Expected progressive disease should not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by progressive disease should not be reported as an SAE

8 STATISTICS

8.1 Sample Size Determination

A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin.

The sample size is estimated based on the following assumptions:

- The ORRs between IBI305 and bevacizumab group are equivalent
- The ORR of subjects in the bevacizumab groups is set to 50.0%
- The equivalence margin for the ratio of ORR is taken as (0.75, 1/0.75))
- The significance level of the two one-side test is 0.05
- 1:1 randomization

Based on the above hypotheses, a number of 218 subjects for each group is required (436 subjects in total). The sample size was estimated using PASS 2013.

8.2 Statistical Population

Intention-to-Treat (ITT): All randomized subjects.

Full Analysis Set (FAS): All randomized and evaluable subjects who received at least one dose of the study treatment. This dataset is used as the primary analysis set for efficacy assessment.

Per-Protocol (PP): Based on the FAS, subjects with the predetermined minimum drug exposure and without any predetermined major protocol deviations. This dataset is used as the secondary analysis set for efficacy assessment.

Safety set (SS): Includes all randomized subjects who received at least one dose of the study treatment and have safety evaluation data. This data set is used for the safety evaluation of this study.

PK analysis set (PKAS): Includes subjects in the FAS with at least one PPK measured value.

Pharmacodynamic analysis set (PDAS): Includes all subjects in the FAS set with at least one PD measured value.

8.3 General Principles for Statistical Analyses

For continuous variables, descriptive statistics should include the count, mean, standard deviation, median, maximum, and minimum. For categorical variables, descriptive statistics will include the number and percentage of each category. Statistical analyses will be carried out using SAS 9.4.

8.4 Statistical Methods

8.4.1 Adjustments for covariates

The stratification factors of randomization in this study include age and EGFR status, and the stratification factors will be considered in the model analysis (GLM or Cox) of primary and secondary efficacy parameters

8.4.2 Managing dropouts and missing data

The handling of dropout and missing data will be detailed in the statistical analysis plan

8.4.3 Multi-center study

Since this is a multicenter study, the primary endpoint (ORR) will be listed according to study sites and treatment groups. However, individual equivalence analysis will not be conducted. Trial sites with fewer than 5 ITT subjects per treatment group will need to be combined for analysis. Details will be discussed in the data review meeting.

8.4.4 Multiple comparisons and adjustments to multiplicity

The α adjustment for multiple comparisons is not considered.

8.5 Statistical Analyses

8.5.1 Subject distribution

Refer to Figure 1: Study design schematic for the schedule of activities. The number and percentage of patients who have completed or dropped out of the study (including the reason for dropouts such as loss to follow-up, AEs, and poor compliance) are summarized based on treatment groups.

The number and percentage of subjects in each analysis set are calculated based on treatment groups.

The number and percentage of protocol deviations are calculated based on treatment groups.

8.5.2 Demographics and other baseline characteristics

Demographic information such as age, height, sex, and weight, and other baseline characteristics such as disease history (including NSCLC diagnosis, staging, previous cancer treatment, and target and nontarget lesions) are summarized using descriptive statistics.

8.5.3 Compliance and drug exposure

The required dose and the actual dose must be documented in the eCRF. Subject compliance is calculated based on the ratio of the actual dose (number of doses) to the required dose (number of doses). Subject compliance is classified into the following categories: < 80%, 80–120%, and > 120%. The number and percentage of subjects in each category will be summarized.

8.5.4 Efficacy

The efficacy analysis will be based on the FAS. Results of the PP set will also be presented.

8.5.4.1 Primary efficacy endpoint

The primary objective of this study is to determine the clinical equivalence between IBI305 + paclitaxel/carboplatin and bevacizumab + paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC). The primary endpoint is objective response rate (ORR). ORR is defined as the incidence of complete response (CR) or partial response (PR), and a radiological method is used to evaluate target and non-target lesions according to RECIST v1.1. Subjects without tumor assessments after baseline will be considered as not assessable. Subjects qualified for the evaluation of CR or PR must have at least one measurable lesion according to RECIST v1.1. The evaluation of clinical equivalence will be based on the ORR provided by the independent review committee (IRC). Results provided by the investigator will be used for sensitivity analysis.

Clinical equivalence will be determined by whether the 90% CIs of ORR ratio for subjects in both IBI305 and bevacizumab groups falls within the equivalence margins of (0.75, 1/0.75).

The ORR and corresponding 95% confidence interval of the two treatment groups, the ORR difference and the 90% confidence interval, as well as the ORR ratio between the two groups and the 90% confidence interval will be estimated using the generalized linear model (GLM, which includes treatment groups and stratification factors).

8.5.4.2 Secondary efficacy endpoints

The secondary endpoints for this study include DOR, DCR, progress-free survival (PFS), and overall survival (OS).

DCR is defined as the incidence of complete response (CR), partial response (PR) and stable disease (SD), and a radiological method is used to evaluate target and non-target lesions according to RECIST v1.1.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

OS refers to the time from the date of randomization to the date of death (of any cause). For subjects who are still alive at the time of the analysis, their survival time is censored on the last known alive date. PFS refers to the time from the date of randomization to the date of first documented PD or death, whichever occurs first. Subjects who do not progress or die will be censored on the date of the last tumor assessment. Subjects without tumor assessments after baseline are censored on their date of randomization.

Median OS and its 95% CI will be estimated using the Kaplan-Meier method. The survival curve will be plotted. The hazard ratio (HR) between the two groups and its 95% CI will be estimated using a Cox model. The Cox model includes treatment groups and stratification factors. DOR and PFS will be analyzed using the same method as for OS. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

8.5.4.3 Sensitivity analysis

The center effect (fixed or random) will be considered in the primary and secondary endpoints analysis models (GLM or Cox).

8.5.4.4 Antibody and efficacy analysis

Subjects who produce antibodies during the study will be listed. The difference in efficacy between subjects with and without antibodies will be compared if necessary.

Changes in PK parameters and steady-state trough concentrations of subjects with positive ADA are analyzed.

8.5.5 Exploratory analysis

Pharmacodynamic parameters: The changes in the serum VEGF level at different time points are described, and inter-group comparisons are carried out when necessary (based on the PD dataset)

Steady-state trough concentrations of the drug: The level of trough concentration is described and inter-group comparisons are carried out when necessary (based on the PPK dataset)

8.5.6 Interim analysis

No interim analysis is planned for this study.

8.5.7 Stratified analysis

Efficacy analysis of different levels of subjects is conducted based on the random stratification factors

8.5.8 Safety analysis

The safety analysis is based on the safety analysis set.

8.5.8.1 Adverse events

All adverse events (AE) will be coded using MedDRA and graded using CTCAE v4.03. All TEAEs, TEAEs ≥ grade 3, SAEs, drug-related TEAEs, drug-related SAEs, TEAEs resulting in the termination of study drugs, TEAEs resulting in the termination of study, and AESIs will be listed based on system organ class, preferred terms, and groups and the corresponding numbers and percentages of subjects will be summarized. In addition, the severity of TEAEs and relevance to the study drugs will also be summarized system organ class, preferred terms, and treatment groups.

8.5.8.2 Laboratory tests

All laboratory test results and changes relative to baseline will be summarized by scheduled time point and treatment group using descriptive statistics. Laboratory abnormalities will be listed.

8.5.8.3 ECG examinations

Results of ECG and changes relative to baseline will be summarized using descriptive statistics.

8.5.8.4 Vital signs, physical examinations, and other safety examinations

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

Results of physical examinations are listed by treatment groups.

8.5.8.5 Concomitant medications

Concomitant medications are non-study medications that meet one of the followings:

(1) Any drug therapy started during or after the first dose of the study treatment;

(2) Any drug therapy started before the first dose of the study treatment and continued after the first dose of the study treatment. Concomitant medications are listed by treatment groups.

9 QUALITY ASSURANCE AND QUALITY CONTROL

According to GCP principles, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems based on standard operating procedures (SOP), to ensure that the implementation of the clinical trial and the collection, documentation, and reporting of trial data is in accordance with the protocol, GCP, and applicable regulatory requirements.

To ensure that the data is reliable and processed correctly, there should be quality control for every step during the data processing.

In addition, the Clinical Quality Assurance (CQA) Department of the sponsor and/or CRO may conduct regular audits of the study process, including but not limited to auditing the study site, on-site visits, central laboratory, suppliers, clinical database, and the final clinical study report. Regulatory authorities may also conduct inspections during the trial or at any time after the trial is completed. The investigator and the research institution must allow the sponsor's representative and regulatory authorities to review source data.

9.1 Clinical Monitoring

The sponsor has authorized Wuxi Clinical Co., Ltd. to conduct clinical monitoring for this study. The clinical research associate (CRA) should follow the SOPs of Wuxi Clinical Co., Ltd. when carrying out monitoring, and has the same rights and responsibilities as the sponsor's monitor. The CRA should maintain regular communication with the investigator and the sponsor.

Before the start of the study, the associate monitor assess the qualifications of each study site, and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the study, the CRA will be responsible for confirming whether written informed consent is obtained from all subjects, and whether data documentation is accurate and complete. At the same time, the CRA will compare data entered in to the eCRF with source data, and notify the investigator of any errors or omissions. The CRA will also verify protocol compliance of the study site, as well as the dispensing and storage of investigational drugs to ensure protocol requirements are met.

The monitoring visit will be conducted in accordance with applicable statutes and regulations. Each site receives regular monitoring visits from the time the subjects are enrolled. The CRA should submit a written report to the sponsor after each monitoring visit to the study site.

9.2 Data Management/Coding

The Data Management and Biostatistics Department of Wuxi Clinical Co., Ltd will process data generated from this study in accordance with relevant SOPs.

This study will use an electronic data capture (EDC) system. Trial data will be entered into the eCRF by the investigator or authorized study personnel. Prior to launching of the study site or data entry, the investigator and authorized study personnel will receive appropriate training, and appropriate safety measures will be taken.

All data are input in Chinese. The eCRF should be completed during or soon after each visit, and should be constantly updated to ensure that it reflects the latest status of the subject. To avoid discrepancies in outcome assessments between different evaluators, ensure that baseline and all subsequent efficacy and safety assessments for the same subject are performed by the same person. The investigator must review trial data to ensure the accuracy and correctness of all data entered into the eCRF. During the study, the investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. The investigator needs to sign all verified data electronically.

The CRA will review the eCRF, and evaluate its completeness and consistency. The CRA will also compare the eCRF with the source documents to ensure the consistency of critical data. Data entry, corrections, or modifications are completed by the investigator or designated staff. The CRA do not have access to data entry. The data in eCRF is submitted to the data server, and any changes to the data will be documented in the audit trail, including the reason for the change, the name of the operator, as well as the time and date of the change. The roles and permissions of study personnel responsible for data entry will be predetermined. The CRA or data manager will submit data queries in the EDC system, and study personnel shall respond to the queries. The EDC system will record the audit trail of each query, including the name of the investigator, as well as the time and date.

Unless otherwise specified, the eCRF should be considered simply as a form for data collection and not a source document. A source file is used by the investigator or hospital, relevant to the subject, and can prove the existence of the subject, inclusion criteria, and all records of participation in the study, including laboratory records, ECG results, memorandum, pharmacy dispensing records, and subject folders.

The investigators are required to maintain all source documents and to offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each subject, regardless of the duration of the subject's participation in the study. The study number and subject number in all supporting documents (such as laboratory records or hospital records) submitted along with the eCRF should be carefully verified. All personal privacy information (including the name of the subject) should be deleted or be made indecipherable in order to protect subject privacy.

The investigator could be automatically added to the eCRF with his/her user ID. The investigators verify that the record have been reviewed and that the data are accurate with an electronic signature. The electronic signature is completed with the investigator's user ID and password. The system automatically attaches the date and time of the signature. The investigator could not share the user ID and password with other personnel. If data in the eCRF need to be modified, the procedures defined by the EDC system have to be followed. All modifications and reasons for the changes are recorded in the audit trail.

Training on the EDC system will be provided to study personnel at the study site.

Adverse events, and concurrent diseases/medical history will be coded. The medical dictionary used for coding will be described in the Clinical Study Report (CSR).

9.3 Audits and Inspections

The sponsor or its representative (WuXi Clinical Co., Ltd) may conduct quality assurance audits on the study site, database, and relevant study-related documents. Also, regulatory authorities may also decide to inspect the study site, database, and relevant study-related documents at its own discretion. The aim of audits and inspections is to systematically and independently check all study-related procedures and documents to ensure that the clinical study is being carried out in accordance with requirements of the trial protocol, GCP, Declaration of Helsinki, and applicable regulations. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

10 ETHICS

10.1 Independent Ethics Committee

The sponsor and its designated personnel will prepare all documents to be submitted to the independent ethics committee (IEC) of each study site. The trial protocol, informed consent form (ICF), investigators brochure, subject recruitment material or advertisements (if applicable), as well as other documents required by regulations must be submitted to the IEC for approval. Prior to the start of the study, written approval from the IEC must be obtained and provided to the sponsor. The IEC approval must clearly state the title, number, and version of the study protocol as well as the version of other documents (e.g. ICF) and the date of approval. The investigator must notify the sponsor of the IEC's written comments concerning delays, suspension and re-approval.

The study site must follow the requirements of the IEC. IEC requirements may include submitting the revised protocol, ICF, or subject recruitment material to the IEC for approval, local regulatory requirements for safety reports, and regular reports, updates, and submitting the final report as per IEC requirements. The above documents as well as the IEC approval must be provided to the sponsor or its designated personnel.

10.2 Implementation of Ethical Principles

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements (CPMP/ICH/135/95), and applicable statutes and regulations related to drugs and data protection in the country in which the study is conducted.

The GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. To protect the rights, safety, and healthy of subjects, this study will be carried out in accordance with GCP and applicable national regulations, as well as ethical principles outlined in the Declaration of Helsinki.

The investigator is required to follow the procedures specified in this protocol and must not change the procedures without the permission from the sponsor. Protocol deviations will be reported in accordance with the requirements of each ethics committee.

10.3 Subject Information and Informed Consent

Prior to undergoing any study procedure, the ICF should be used to explain to potential participants the potential risks and benefits of this study. The informed consent form should be in a language that is simple and be easy to understand. The ICF should state that informed consent is voluntary, emphasize the potential risks and benefits of participating in this study, and that the subject may withdraw from the study at any time. The investigator may only enroll a subject after fully explaining the details of the study, answering questions to the subject's satisfaction, giving the subject sufficient time for consideration, and obtaining written consent from the subject or his/her legal representative. All signed ICF must be retained in the investigator's documents or the subject's folder.

The investigator is responsible for explaining the contents of the ICF and obtaining the ICF signed and dated by the subject or his/her legal representative prior to starting the study. The investigator should provide the subject with a copy of the signed ICF. The investigator must document the informed consent process in the source document of the trial.

10.4 Protection of Subject Data

Information about data protection and privacy protection will be included in the ICF (or in some cases, in a separate document).

Study personnel must ensure that the privacy of clinical trial subjects are protected. In all documents submitted to the sponsor, the clinical trial subjects must only be identified with subject number and not with the full name.

Additional precautions should be taken to ensure the confidentiality of the documents and to prevent the identification of subjects based on genetic data. However, under special circumstances, some personnel may be permitted to see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, designated physician, or investigator will have access to the subject identification code and the subject's genetic data. In addition, regulatory agencies may request access to relevant documents.

11 STUDY MANAGEMENT

11.1 Organizational Structure

Refer to Table 3 for relevant collaborating parties.

Table 6. Organizational structure

Sponsor	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China Telephone: (+86) 0512-69566088
Contract research organization	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000
Data management and biostatistics	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000

11.1.1 Independent review committee

Central imaging evaluation will be performed by Parexel China Co., Ltd. The CT/MRI images of each subject will be evaluated using RECIST v1.1.

11.2 Archiving of Study Documents

Clinical trial documents (protocol and amendments, completed eCRFs, signed ICFs, etc.) must be retained and managed as per GCP requirements. The study site must retain these documents for 5 years after the completion of the study. The sponsor should retain clinical trial data for 5 years after the investigational drug is approved for marketing.

Study documents should be retained properly for future access or data traceability. Safety and environmental risks should be considered when retaining documents.

The documents associated with the study may only be destroyed with the written consent of the sponsor and the investigator. Study documents may be transferred to other parties that comply with or other locations that meet retention requirements only after the sponsor is notified and written consent thereof is obtained.

11.3 Access to Source Data/Documents

Source data refers to source records of subject data obtained from a clinical study. These source records are source documents, which include but are not limited to medical records (hospital records, nursing records, pharmacy dispensing records, etc.), electronic data, screening logs, laboratory test results, as well as medical device test results (ECG, CT/MRI, etc.). All source documents associated with the trial are retained by the study site and the investigator. The original ICFs will be retained according to standard practices developed by the clinical trial institution.

The investigator will prepare sufficient and accurate source documents for each randomized subject in order to document all examination results and other relevant data, and retain these documents properly.

During the study, the CRA will conduct on-site visits to verify protocol compliance, EDC data entry, documentation of subjects' medical history, drug inventory, and whether the study is carried out in accordance with applicable regulations. In addition, regulatory authorities, IRB, IEC, and/or the quality assurance department of the sponsor will verify source data and/or conduct on-site audits or inspections. The investigator should allow direct access to documents associated with the study, including medical records of subjects.

11.4 Protocol Revisions

The sponsor and the investigator must both agree on any appropriate protocol revisions during the course of the study. The sponsor shall ensure that the protocol revision is submitted to the regulatory authority in a timely manner.

All protocol revisions must be submitted to the IEC, and if needed, to regulatory authorities for approval. Revisions may only be implemented after approval from the IEC and regulatory authorities (if needed) is obtained (except for changes to eliminate immediate risks to subjects).

11.5 Investigator's Responsibilities

The investigator will conduct this study in accordance with the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP, and applicable regulations. Details of the investigator's responsibilities are list in Chapter 5 (Investigator's Responsibilities) of the Chinese GCP (NMPA order No. 3).

11.6 Study Termination

The study may be terminated after a discussion between relevant parties if the investigator or the sponsor becomes aware of circumstances or events that could jeopardize the subjects if the study is continued. The sponsor may also decide to terminate the study even without such findings.

Reasons for study termination include but are not limited to:

- Unexpected, serious, or unacceptable risks to enrolled subjects
- Slow recruitment
- The sponsor decides to suspend or discontinue the development of the drug

11.7 Publishing Policies

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish study results. The investigator shall not publish any data relevant to this study (posters, abstracts, papers, etc.) without prior communication with the sponsor. Information on the publishing policies of the sponsor and investigator will be described in the clinical trial agreement.

11.8 Finance and Insurance

The sponsor will purchase insurance for subjects participating in the study in accordance with local regulations, and bear the cost of treatment and corresponding financial compensation for the subjects who suffer injury during the study due to the investigational drug or the study process. Insurance related terms shall be saved in the study folder.

12 REFERENCES

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13 APPENDIX

13.1 Appendix I

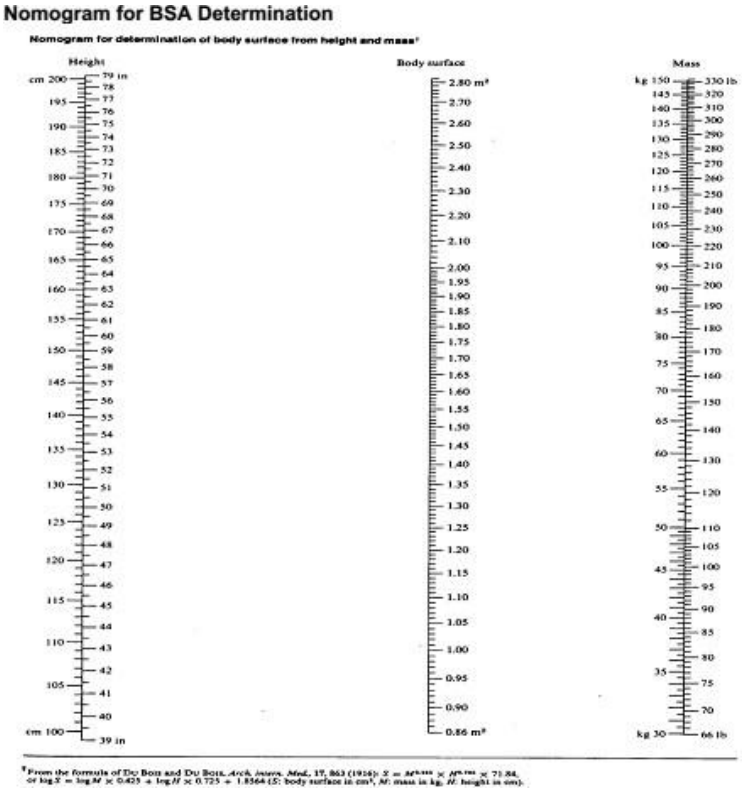
Eastern Cooperative Oncology Group (ECOG) Performance Status Score

Score	Performance Status
0	Fully active, and able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activities but able to move around easily and carry out work of a light or sedentary nature, e.g. light house work or office work
2	Capable of moving around easily and self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or wheelchair more than 50% of waking hours
4	Bedridden and incapable of self-care
5	Death

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

13.2 Appendix II

Calculation of body surface area



Body surface are (m2) = 0.00616 height (cm) + 0.01286 weight (kg) - 0.1529

Creatinine Clearance (Cockroft-Gault Equation)

Ccr (mL/min) = [(140 - age) x weight (kg)]/[72 x Scr (mg/dL)]

Female subjects: results × 0.85

1 mg/dL = 88.41 μmol/L

Carboplatin Dose (Calvert Equation)

Carboplatin dose (mg) = target AUC (mg/mL/min) × [creatinine clearance rate (mL/min) + 25]

Note: During the study, if the carboplatin dose calculated using the Calvert equation excessively exceeds the usual clinical dose, choose one of the following two methods to ensure the patient safety:

1. Retest the serum creatinine and re-calculate the dose (preferred option).

2. Based on clinical experience, the investigator may choose the highest dose tolerated by the subject. The dose should remain unchanged for the subsequent cycles.

13.3 APPENDIX 3

RECIST v1.1

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or not measurable as follows:

1.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be documented as not measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Not measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with a short axis ≥10 and <15 mm) as well as truly not measurable lesions. Lesions considered truly not measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis involving the skin or lungs, abdominal masses/ abdominal organomegaly identified by physical exam but not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding measurable bone lesions, cystic lesions, and lesions with prior locoregional treatment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (such as CT or MRI) can be considered as measurable lesions if the soft tissue components meet the definition of measurability described above.
- Blastic bone lesions are not measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor not measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these noncystic lesions are preferred for selection as target lesions.

Lesions with prior locoregional treatment:

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

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be documented with metric symbols. Calipers should be used if clinical assessments are required. All baseline evaluations should be performed as close as possible to the beginning of the treatment but never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and its diameter is ≥10 mm as assessed using calipers (e.g. skin nodules). For skin lesions, documentation by color photography including a plotting scale to estimate the size of the lesion is recommended. As noted above, when lesions can be evaluated by both clinical examination and imaging evaluation, the latter should be undertaken since it is more objective and may also

be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they have clear boundaries and are surrounded by aerated lung tissues.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound should not be used for measuring lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is recommended. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy: The utilization of these techniques is not recommended for objective tumor evaluation. However, they can be used to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper limit of normal, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into the protocol on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases if required by the protocol (for example, residual lesions in tumor types such as seminoma, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), cytological confirmation of the neoplastic origin of any effusion that appears or worsens during

treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

2.2 Baseline Documentation of "Target" and "Non-Target" Lesions

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those with reproducible repeated measurements. It may be the case that, the largest lesion does not have reproducible measurements, in which circumstance the next largest lesion with reproducible measurements should be selected.

Lymph nodes merit special mention since their normal anatomical structures may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must have a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is invaded by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant measurable node. In this example, 20 mm should be reported as the node measurement. All other pathological nodes (those with a short axis ≥ 10 mm but < 15 mm) should be considered non-

target lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions; short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". In addition, it is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response Criteria

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduced short axis of <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions vs. the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions vs. the smallest sum during the study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also have an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum of diameters during the study as reference.

2.3.2 Special notes on the assessment of lymph nodes which are target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as during the baseline examination), even if the nodes regress to below 10 mm at the time of the study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must have a

short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that are "too small to measure". During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurements of these lesions are potentially non-reproducible, therefore providing this default value will prevent false responses or progressions caused by measurement errors. To reiterate, however, if the radiologist is able to provide an actual measurement, that value should be recorded, even if it is below 5 mm.

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

2.3.3 Evaluation of non-target lesions

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

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

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

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

2.3.4 Special notes on the assessment of progression of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: *When the patient also has measurable lesions*. In this setting, to achieve 'unequivocal progression' on the basis of the non-target lesion, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR of the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A minimal increase in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only lesions that are not measurable. This circumstance arises in some phase III trials when the presence of measurable lesions is not a criterion for study enrollment. The same general concepts apply here as well. However, in this instance there are no measurable lesions to factor into the interpretation of an increase in non-measurable lesion burden. Because worsening in non-target lesion cannot be easily quantified (by definition: if all lesions are truly not measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall lesion burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase of diameter in a measurable lesion). Examples include an increase in pleural effusion from "trace" to "large amount", an increase in lymphangitic lesion from localized to widespread, or a description in the protocol such as "sufficient to require a change in therapy". If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to diseases that are not measurable, the very nature of these diseases makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on the detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumors (for example, some new bone lesions which may be simply healed or flare of pre-existing lesions). This is particularly

important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported by a CT scan as a "new" cystic lesion, while it is actually not.

A lesion identified during a follow-up in an anatomical location that is not discovered during the baseline scan is considered a new lesion and will indicate disease progression. For example, a patient with a visceral disease at baseline has a brain CT or MRI which reveals metastases. The patient's brain metastases are considered evidence of PD even if he/she does not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new lesion. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" lesions). New lesions on the basis of FDG-PET imaging can be identified as follows:

a. A negative FDG-PET at baseline and a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
If the positive FDG-PET at follow-up corresponds to a new lesion site confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new lesion site on CT, additional follow-up CT scans are needed to determine if there is truly progression at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing lesion site on CT that is not progressing according to the anatomic images, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy, so the study protocol should clearly state if post-treatment assessments are to be considered when determining best overall response. The study protocol must specify how any new therapy introduced before progression will affect best response designation. Assignment of best overall response for the patient will depend on the findings of both target and non-target lesions and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the

protocol requirements, confirmatory measurement may also be required. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine which one is the "best overall response".

2.4.1 Time point response

It is assumed that at each time point specified by the study protocol, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2 Missing assessments and non-evaluable targets

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

2.4.3 Best overall response: all time points

The best response is determined once all the data for the patient is obtained.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, the best overall response of a patient who has SD at the first assessment, PR at the second, and PD at the last is PR). When SD is believed to be best response, it must also meet the minimum time from baseline specified by the protocol. If the minimum time is not met, otherwise SD is the best time point response, the patient's best response depends on subsequent assessments. For example, if a patient has SD at the first assessment, PD at the second and does not meet the minimum duration for SD, his/her best response is PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

2.4.4 Special notes on response assessment

When nodal lesions are included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even if the nodes are normal in size in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the case report form (CRF).

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must explain how missing data/assessments will be addressed in the determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response. Instead, it is a reason for stopping the study treatment. The objective response status of this type of patients is to be determined by evaluation of target and non-target lesions as shown in Table 1–3.

Conditions that define "early progression, early death, and non-evaluability" are study specific and should be clearly described in each study protocol (depending on treatment duration and treatment periodicity).

In some circumstances it may be difficult to distinguish a residual lesion from normal tissues. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (by fine needle aspirate/biopsy) before assigning a status of complete response.

Like a biopsy, FDG-PET may also be used to upgrade a response to a CR in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be pre-defined in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Table 1. Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not all were evaluated	No	PR
SD	Non-PD or Not all were evaluated	No	SD
Not all were evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

Table 2. Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all were evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = not evaluable.

a "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since SD is increasingly used as an endpoint for assessment of efficacy in some trials, thus assigning this category in the absence of measurable lesions is not advised.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression is suspected.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided that the minimum duration for SD is met, otherwise PD
CR	PD	SD provided that the minimum duration for SD is met, otherwise PD
CR	NE	SD provided that the minimum duration for SD is met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided that the minimum duration for SD is met, otherwise PD
PR	NE	SD provided that the minimum duration for SD is met, otherwise NE
NE	NE	NE

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

a If CR is truly achieved at the first time point, then any lesions seen at a subsequent time point, even those meeting PR criteria relative to baseline, make the disease PD at that time point (since lesions must have reappeared after CR). Best response would depend on whether the minimum duration for SD is met. However, sometimes CR may be claimed and subsequent scans suggest small lesions are likely still present, while in fact the patient have PR instead of CR at the first time point. Under these circumstances, CR should be changed to PR and the best response is PR.

2.5 Frequency of Tumor Re-Evaluation

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

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

2.6 Confirmation of Measurements/Duration of Response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement errors. This will also permit appropriate interpretation of results in the context of historical data. Response confirmation has been traditionally required in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements after study entry must have met the minimum interval for SD (generally not shorter than 6–8 weeks) defined in the study protocol at least once.

2.6.2 Duration of overall response

The duration of overall response is measured from the time CR/PR measurement criteria are first met CR/PR (whichever is first documented) until the date when recurrent or progressive disease is objectively documented for the first time (using the shortest time to progressive disease documented during the study as reference).

The duration of overall complete response is measured from the time CR measurement criteria are first met until the date when recurrent disease is objectively documented for the first time.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from the date of randomization) until the criteria for progression are met, using the smallest sum during the study as reference (if the baseline sum is the smallest, then it is used as the reference for the calculation of PD).

The clinical relevance of the duration of stable disease varies with different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for the determination of stable disease.

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

14 INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized, double-blind, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin vs. bevacizumab plus paclitaxel/carboplatin in treatment-naive patients with advanced or relapsed non-squamous NSCLC.

Protocol No.: CIBI305A301

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

Instructions for the Investigator: Please sign and date this signature page, type the investigator's name and job title, as well as the name of the study site, and return this document to Innovent Biologics (Suzhou) Co., Ltd.

I have read the entire contents of this study protocol and shall perform the study as required:

Investigator's signature: _____ Date: _____

Name (in Print): _____

Job Title: _____

Name and Address of Study Site: _____

_____

_____

A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer

Protocol no.: CIBI305A301

Document Amendment History

Old Version/Date: V3.0/Sep. 25, 2017

New Version/Date: V3.1/Aug. 27, 2018

1	**Subject**	Version No. and Version Date
	Section/Page	Cover/Page 1; Footer/Pages 1–79
	Old text	Sep. 25, 2017/Version 3.0
	New text	Aug. 27, 2018/Version 3.1
	Reason for change	Version Revision.
2	**Subject**	Contact
	Section/Page	Cover/Page 1
	Old text	Tel: (+86) 021-31652896
	New text	Tel: (+86) 21-31652896
	Reason for change	Clerical errors are corrected.
3	**Subject**	Statistician
	Section/Page	Signature Page/Page 2
	Old text	Wei Zhaohui, Director of Biostatistics
	New text	Zhang Nan, Senior Director of Biostatistics
	Reason for change	Statistician is updated
4	**Subject**	The criteria for the equivalence evaluation are changed from the difference of ORR between the equivalence margin of (-12.5%, 16.7%) to the ratio of ORR between the equivalence margin of (0.75, 1/0.75)
	Section/Page	Protocol Synopsis/Page 8; Section 8.1/Page 56
	Old text	The equivalence margin is taken as (-12.5%, 16.7%)
	New text	The equivalence margin for the ratio of ORR is taken as (0.75, 1/0.75)
	Reason for change	In the "Considerations for the design and review of clinical studies on biosimilars of bevacizumab injection" published by the CDE in Nov. 2017, the use of ratio (RR) is recommended to calculate the equivalence margin.
5	**Subject**	Version number is updated
	Section/Page	Section 6.15.6/Pages 48 and 49
		Study centers that officially implement the 2.0 version of the protocol

	Old text	
	New text	Study centers that officially implement the 2.0 and subsequent versions of the protocol
	Reason for change	Version Revision.
6	**Subject**	Definition of efficacy endpoint
	Section/Page	Section 7.1.1/Page 50
	Old text	It is defined as the proportion of subjects with tumor size reduction of a predefined amount and for a minimum time period
	New text	It is defined as the proportion of subjects with tumor size reduction of a predefined amount
	Reason for change	According to RECIST 1.1, the efficacy evaluation in randomized double-blind controlled studies does not require to verify the response
7	**Subject**	Definition of efficacy endpoint
	Section/Page	Section 7.1.1/Page 50
	Old text	The cut-off date for the analysis of primary efficacy endpoint in this study is 18 weeks after subject randomization.
	New text	The cut-off date for data included in the primary efficacy evaluation is the 18th week after the last subject is randomized.
	Reason for change	This point is clarified here
8	**Subject**	Statistical Population
	Section/Page	Section 8.2/Page 56
	Old text	Full Analysis Set (FAS): All randomized subjects who received at least one dose of the study treatment.
	New text	Full analysis set (FAS): includes all randomized and evaluable subjects who have received at least one dose of the study drugs.
	Reason for change	The sensitivity in detecting the equivalence at the endpoint can be improved by rejecting subjects from the analysis set who cannot be evaluated due to the lack of measurable lesions at baseline
9	**Subject**	Descriptive statistics of categorical variables
	Section/Page	Section 8.3/Page 57
	Old text	For categorical variables, descriptive statistics will include frequency as well as the absolute or relative percentage
	New text	For categorical variables, descriptive statistics will include the number and percentage of each category
	Reason for change	In general, the statistical description of categorical variables uses the number of cases and percentage rather than the absolute or relative rate
10	**Subject**	Covariate adjustment
	Section/Page	Section 8.4.1/Page 57
	Old text	Not applicable
	New text	The stratification factors of randomization in this study include age and EGFR status, and the stratification factors will be considered in the model analysis (GLM or Cox) of

		primary and secondary efficacy parameters
	Reason for change	In the protocol description of the generalized linear model (GLM) and Cox model, the following stratification factors are also included in addition to the group: Age (< 60 years vs. ≥ 60 years) and EGFR status (wild type vs. unknown type), so corresponding changes are made here.
11	**Subject**	Handling of dropouts or missing data
	Section/Page	Section 8.4.2/Page 57
	Old text	The analyses of primary and secondary endpoints will include data from dropouts. The handling of missing data will be detailed in the statistical analysis plan
	New text	The handling of dropout and missing data will be detailed in the statistical analysis plan
	Reason for change	A detailed description of the methods used for handling dropout and missing data will be provided in the statistical analysis plan (SAP), including which methods are used for the primary analysis and which method is used for the sensitive analysis
12	**Subject**	Primary efficacy analysis
	Section/Page	Section 8.5.4.1/Page 58
	Old text	ORR is defined as the incidence of confirmed complete response (CR) or partial response (PR), using a validated imaging method to evaluate target lesions and non-target lesions according to RECIST v1.1.
	New text	ORR is defined as the incidence of complete response (CR) or partial response (PR), and a radiological method is used to evaluate target and non-target lesions according to RECIST v1.1.
	Reason for change	According to RECIST 1.1, the efficacy evaluation in randomized double-blind controlled studies does not require to verify the response.
13	**Subject**	The criteria for the equivalence evaluation are changed from the difference of ORR between the equivalence margin of (-12.5%, 16.7%) to the ratio of ORR between the equivalence margin of (0.75, 1/0.75)
	Section/Page	Section 8.5.4.1/Page 58
	Old text	Clinical equivalence will be determined by whether the 90% confidence interval (CI) of the difference in ORR between the IBI305 and bevacizumab arms falls within the preset margin of (12.5% to 16.7%).
	New text	Clinical equivalence will be determined by whether the 90% CIs of ORR ratio for subjects in both IBI305 and bevacizumab groups falls within the equivalence margins of (0.75, 1/0.75).
	Reason for change	In the "Considerations for the design and review of clinical studies on biosimilars of bevacizumab injection" published by the CDE in Nov. 2017, the use of ratio (RR) is recommended to calculate the equivalence margin.
14	**Subject**	Handling of the missing data
	Section/Page	Section 8.5.4.1/Page 58
	Old text	Subjects without tumor assessments beyond baseline will be considered unresponsive to treatment
	New text	Subjects without tumor assessments after baseline will be considered as not assessable
	Reason for change	A detailed description of the treatment methods will be provided in the SAP, including

		which methods are used for the primary analysis and which method is used for the sensitive analysis, rather than directly defining these subjects here as no response.
15	**Subject**	Secondary efficacy analysis
	Section/Page	Section 8.5.4.2/Page 58
	Old text	DCR is defined as the incidence of patients with confirmed complete response (CR), partial response (PR), and stable disease (SD), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions.
	New text	DCR is defined as the incidence of complete response (CR), partial response (PR) and stable disease (SD), and a radiological method is used to evaluate target and non-target lesions according to RECIST v1.1
	Reason for change	According to RECIST 1.1, the efficacy evaluation in randomized double-blind controlled studies does not require to verify the response.
16	**Subject**	Secondary efficacy analysis
	Section/Page	Section 8.5.4.2/Page 58
	Old text	PFS refers to the time from the date of randomization to the date of first documented PD or death, whichever occurs first. The investigator will assess PD using RECIST v1.1
	New text	PFS refers to the time from the date of randomization to the date of first documented PD or death, whichever occurs first.
	Reason for change	Both analyses will be performed
17	**Subject**	Antibody and efficacy analysis
	Section/Page	Section 8.5.4.4/Page 59
	Old text	Subjects who develop antibodies during the clinical study will be summarized in detail
	New text	Subjects who produce antibodies during the study will be listed.
	Reason for change	It is clarified that the method used in case-by-case description is through a list.

CLINICAL STUDY PROTOCOL

Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Version and Date:	Sep. 25, 2017/Version 3.0
Product Name:	Recombinant anti-VEGF humanized monoclonal antibody injection (IBI305)
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	Zhou Hui (Senior Medical Director) Tel: (+86) 021-31652896 E-mail: hui.zhou@innoventbio.com

SIGNATURE PAGE

Protocol Title: A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer

Protocol No.: CIBI305A301

Title	Name	Signature	Da
Senior Medical Director	Zhou Hui	周辉	2017.9.25
Director of Biostatistics	Wei Zhaohui	魏朝辉	2017.9.25

PROTOCOL SYNOPSIS

Sponsor/Company:	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug:	IBI305
Active Ingredient:	Recombinant anti-VEGF humanized monoclonal antibody
Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Coordinating Investigator:	Zhang Li
Coordinating Center:	Sun Yat-Sen University Cancer Center
Expected study duration: Each subject will receive treatment every 3-week until progressive disease (PD), unacceptable toxicity, withdrawal of informed consent, lost to follow-up or death (whichever comes first). The end of the study is defined as the 18th month after the randomization of the last subject.	**Phase:** III

Study Objectives:

Primary Objective:

- To compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC)

Secondary Objectives:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

Exploratory objectives:

- To compare the population pharmacokinetics (PPK) of IBI305 and bevacizumab in subjects with

	advanced or recurrent non-squamous NSCLC $\frac{4}{3}$ To compare the PD of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC
Study design: This is a randomized, double-blinded, multi-center phase III study. The study planned to enroll and randomize 436 subjects with non-squamous NSCLC in a 1:1 ratio to IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild type vs. unknown type). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first). Then subjects receive maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first). During the study, a CT or an MRI will be performed every 6 weeks (± 7 days) and be determined whether the study treatment will be continued by investigators at each site through tumor assessments until PD, withdrawal of informed consent, lost to follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for reasons other than PD, tumor assessments will be continued until PD, withdrawal of informed consent, loss of follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for PD, the investigators will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, lost to follow-up, death, or end of study.	
Number of Subjects:	436
Diagnosis and main inclusion criteria:	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be enrolled in the study: 1) Sign the formed consent form 2) Male or female ≥ 18 and ≤ 75 years old 3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIB), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types 4) Histologically or cytologically confirmed EGFR wild type or non-sensitive mutation type 5) Must have at least one measurable target lesion (as per RECIST 1.1) 6) Eastern Cooperative Oncology Group Performance Status (ECOG PS)

	score of 0–1 7) Expected survival ≥ 6 months 8) Laboratory results during screening: a) Routine blood test: WBC ≥ 3.0 × 10^9/L, ANC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and hemoglobin ≥ 90 g/L b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ from urinalysis dipstick at baseline, a 24-h urine should be collected with total protein content < 1 g d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment 9) Able to comply with study protocol 10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug Exclusion Criteria: Subjects meeting any of the followings will not enrolled in the study: 1) Prior systemic chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIB not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible 2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component 3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18-point mutation (G719X), exon 19 deletion, and exon 21-point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll. 4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time

	5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava) 6) Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage; 7) Subjects who received radical thoracic radiotherapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug 8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study 9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (Outpatient/inpatient surgery requiring locoregional anesthetics, including central line insertion) 10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function for 10 consecutive days 11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents for 10 consecutive days. However, anticoagulants for prophylaxis are accepted 12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis 13) Uncontrolled hypertension after treatment (systolic greater than 140 mmHg and/or diastolic greater than 90 mmHg), history of hypertensive crisis or hypertensive encephalopathy 14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease 15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal

	fistula, or intra-abdominal abscess 16) Subjects with tracheoesophageal fistula 17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments) 18) Subjects with current interstitial lung disease or CT showing active pneumonia during screening 19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or papillary thyroid carcinoma 20) Subjects with active autoimmune disease 21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1 × 103 copies/L or ≥ 200 IU/mL; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1 × 103 copies/L or < 200 IU/mL might be eligible if the investigator determines that the subject's chronic hepatitis B infection is stable and participation in the study would add no further risks to the subject 22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis 23) Subjects with known history of allergic diseases or allergic physique 24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening 25) History of alcohol or drug abuse 26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study 27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents 28) Other conditions unsuitable for the inclusion as determined by the investigator
Investigational Drug, Dosage, and Route of Administration:	IBI305: 15 mg/kg in combination chemotherapy and 7.5 mg/kg **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)
Control Drug, Dosage, and Route of Administration:	Bevacizumab: 15 mg/kg in combination chemotherapy and 7.5 mg/kg **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed

	consent, lost to follow-up, death, or end of study (whichever comes first)
Chemotherapy:	Paclitaxel: 175 mg/m² administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death. Carboplatin: Areas under the concentration-time curve (AUC) = 6.0 administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Evaluation criteria:

Efficacy endpoints:

Primary efficacy endpoint:

- Objective response rate (ORR)

Secondary efficacy endpoints:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Safety endpoints:

- Vital signs
- Physical examination
- Laboratory tests (routine blood test, blood chemistry, and urinalysis)
- 12-Lead ECG
- Adverse event (AE, including treatment-emergent AE (TEAE)), AE of special interest (AESI) (hypertension, proteinuria, gastrointestinal perforation, hemorrhage [cerebral hemorrhage, hematuria and upper gastrointestinal hemorrhage], cardiotoxicity, and thrombosis), and serious adverse event (SAE)
- Immunogenicity: Positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

PK/PD Endpoints:

- Population PK parameters, including steady-state trough concentrations after repeated doses
- Changes of serum VEGF at different time points

Statistical methods:

Sample size calculation:

A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin. Estimation parameters for sample size: The significance level of the two-sided test is 0.05, the ORR of subjects in the IBI305 and bevacizumab groups is about 50.0%, and the equivalence margin is taken as (-12.5%, 16.7%). Based on the above hypothesis, each group requires 218 subjects (436 subjects in total).

Efficacy analysis:

Clinical equivalence will be determined by whether the 90% confidence interval (CI) of the difference in ORR between the IBI305 and bevacizumab arms falls within the preset margin of (-12.5%, 16.7%). The ORR and 95% CI of two groups, ORR difference and 90% CI, and ORR ratio and 90% CI will be estimated using the generalized linear model (GLM, including groups and stratification factors).

Median survival (OS) and survival curves will be estimated using the Kaplan-Meier method. The hazard ratio (HR) and 95% CI of two groups will be estimated using the Cox model. DORs and PFSs will be analyzed by the same method as the median survivals. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

Safety analysis:

All adverse events (AE) will be coded using MedDRA and graded according to CTCAE v4.03. All treatment-emergent adverse events (TEAEs), Grade 3 or greater TEAEs, serious adverse events (SAEs), investigational drug-related TEAEs, investigational drug-related SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study termination, and adverse events of special interest (AESIs) will be listed based on system organ class, preferred terms, and groups and the numbers of corresponding subjects and percentages will be summarized. In addition, the severity of TEAEs and the correlation with the study drug will also be summarized by system organ class, preferred terms, and treatment groups.

Measured values and changes from baseline for vital signs, physical examination, laboratory tests and 12-lead ECG will be analyzed using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation.

The number and percentage of subjects who developed anti-drug antibodies and neutralizing antibodies during the study will be summarized by treatment group.

PK/PD exploratory analysis:

Mainly based on description, and inter-group comparison will be carried out if necessary

Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
AEs	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

a. After completing the on-site end-of-treatment visit 28 days after the last dose, subjects who discontinue the investigational drug treatment due to reasons other than PD should continue to undergo tumor assessments once every 6 weeks (±7 days) until PD (and begin post-PD follow-up thereafter), withdrawal of consent, start of another antineoplastic treatment, loss to follow-up, death, or study completion.

b. For subjects with PD, collect survival information once every 12 weeks (84 days, ±7 days) by phone until death, loss to follow-up, withdrawal of informed consent, or study completion. Subsequent antineoplastic treatments should be documented in the eCRF.

c. Only measure weight.

d. Clinical laboratory tests are carried out at the laboratory of each hospital. If screening laboratory tests (routine blood test, blood chemistry, and urinalysis) are performed within 7 days prior to the first dose, the screening results may be used as baseline data. For subsequent visits, all laboratory tests have to be completed within 3 days prior to the dose administration.

e. A urinalysis is required before each IBI305/bevacizumab infusion to test urine protein.

f. Women of childbearing age should undergo a serum/urine pregnancy test.

g. Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples will be tested at the designated central laboratory.

h. Image assessments (CT or MRI) of the brain, chest, abdomen, and pelvis should be completed at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

i. All subjects should undergo tumor tissue EGFR testing.

j. Each treatment cycle of the investigational product contains 3 weeks. The dose of IBI305 or bevacizumab is 15 mg/kg when used in combination with chemotherapeutic drugs and 7.5 mg/kg in the maintenance monotherapy, given on D1 of every treatment cycle until progressive disease (PD), unacceptable toxic reactions, withdrawal of informed consent, loss to follow-up, death, or end of study, whichever occurs first. After all assessments were completed, the study drug was administered followed by chemotherapy. The first dose of study drug was completed within 24 h after randomization.

k. Each treatment cycle is 3 weeks long. Chemotherapy (paclitaxel + carboplatin) is administered on D1 of each cycle for up to 6 cycles, or until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death. Paclitaxel is administered after the infusion of study drug is completed, followed by carboplatin.

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Abbreviations	Definitions
AE	Adverse event
AESI	Adverse event of special interest
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AUC	Area under the curve
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFDA	China Food and Drug Administration (now National Medical Products Administration)
CQA	Clinical quality assurance
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data collection
EGFR	Epithelial growth factor receptor
FAS	Full analysis set
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
ITT	Intention-to-treat

NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PTT	Partial thromboplastin time
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
SS	Safety set
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

1 INTRODUCTION

1.1 Study Background

1.1.1 Disease background

Lung cancer has the highest incidence and mortality globally among all cancers. According to the 2012 Global Cancer Statistics (GLOBOCAN 2012) published by International Agency for Research on Cancer, there were approximately 1.8 million new lung cancer cases worldwide, which accounted for 13% of the global newly-diagnosed cancers, and 58% of these cases occurred in underdeveloped areas[1]. According to the data released by the National Central Cancer Registry of China in 2015, lung cancer was the most prevalent malignancy in China in 2011, with about 650,000 new cases every year. Lung cancer was also the leading cause of death, with about 520,000 deaths per year[2]. The limited clinical treatment of lung cancer is the main reason for its poor prognosis. There is a huge demand for new types of lung cancer treatment drugs.

Approximately 85–90% of lung cancers are non-small cell lung cancer (NSCLC) and patients with NSCLC are usually in the advanced stages when diagnosed[3]. According to the Chinese guidelines for the diagnosis and treatment of primary lung cancer, anatomic pulmonary resection is the mainstay of treatment for early stage lung cancers[4]. However, despite surgery, some patients develop distance metastases that eventually lead to death[5]. Surgery is not possible for most patients with clearly diagnosed stage IIIB and IV as well as some patients with stage IIIA NSCLC[4]. Comprehensive treatment based on systemic therapy is used to maximize patient survival, control progressive disease, and improve the quality of life[6].

In recent years, anti-tumor therapies have entered a new era with the emergency of targeted drugs. Some of these targeted drugs have demonstrated satisfactory efficacy in the treatment of advanced NSCLC. These targeted drugs include monoclonal antibodies and tyrosine kinase inhibitors (TKIs), mostly targeting epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF), such as bevacizumab, cetuximab, gefitinib, erlotinib, and icotinib. Monoclonal antibodies have become the drugs of choice in various treatment guidelines due to the good targeting ability, low drug resistance, and good patient tolerability. Bevacizumab combination chemotherapy is a first-line therapy of NSCLC recommended by the National Comprehensive Cancer Network (NCCN)[7]. Additionally, bevacizumab in combination with paclitaxel/carboplatin has also been approved as the first-line therapy of unresectable advanced, metastatic, or relapsed non-squamous NSCLC by China Food and Drug Administration (CFDA) on Jul. 9, 2015[6].

Compared with traditional chemotherapy that directly inhibit or kill tumor cells, anti-angiogenic drugs have the following unique advantages[8]:

- The targets are genetically stable vascular endothelial cells (VECs) rather than highly heterogeneous tumor cells, thus leading to lower drug resistance;
- The number of tumor-induced VECs is far less than that of tumor cells, and the efficacy is preferable targeting on VECs and their cytokines;
- Normal VECs are quiescent, whereas tumor VECs are active in proliferation. Anti-angiogenic therapy targets activated cells and avoids damage to normal VECs, thus leading to better targeting ability;
- Anti-angiogenic therapy can normalize the tumor vessels and thereby reduce the pressure in tumor tissues. This enhances the delivery of chemotherapeutic agents into tumor tissues, thus increasing the efficacy of chemotherapy.

Angiogenesis is a basic biological characteristic of tumors. The growth of both solid and hematologic tumors are depended on angiogenesis regardless of the nature of tumor cells. Therefore, anti-angiogenic therapy is broad-spectrum and applicable to various tumors.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to human VEGF and blocks its biological activity. Bevacizumab consists of a framework region of a human antibody and a humanized murine antigen binding region that can inhibit the binding of VEGF to its receptors on epithelial cells, Flt-1 and KDR. By blocking the activity of VEGF and reducing tumor angiogenesis, tumor growth is inhibited[9].

In a study conducted by the Estern Cooperative Oncology Group (ECOG), compared with chemotherapy alone (paclitaxel/ carboplatin), bevacizumab in combination with paclitaxel/carboplatin significantly increased the overall survival (OS) (median: 12.3 vs. 10.3 months), progression-free survival (PFS) (median: 6.2 vs. 4.5 months), and overall response rate (ORR) (35% vs. 15%) in patients with advanced, metastatic, or relapsed non-squamous NSCLC[10]. In another foreign AVAiL study, different doses of bevacizumab (7 and 15 mg/kg) in combination with chemotherapy (cisplatin and gemcitabine) and placebo combine with chemotherapy were compared for the treatment of non-squamous NSCLC. The study found that the two bevacizumab groups had significantly increased the PFS (median: 6.7 months (7.5 mg/kg combination chemotherapy group) vs. 6.5 months (15 mg/kg combination chemotherapy group) vs. 6.1 months (placebo combination chemotherapy group)) and the ORR (37.8% (7.5 mg/kg combination chemotherapy group) vs. 34.6% (15 mg/kg combination chemotherapy group) vs. 21.6% (placebo combination chemotherapy group)) in patients with locally advanced, metastatic, or relapsed non-squamous NSCLC[11]. In a BEYOND study conducted in China, compared with

placebo in combination with paclitaxel/carboplatin, bevacizumab in combination with paclitaxel/carboplatin significantly increase the PFS (median: 9.2 vs. 6.5 months), OS (median: 24.3 vs. 17.7 months), and the ORR (54% vs. 26%) in patients with advanced or relapsed non-squamous NSCLC[12].

In China, the antibodies and fusion proteins targeting VEGF are research hotspots. However, since 2006, the clinical efficacies of various drugs have not been verified and no products have been marketed. Considering the complexity of macromolecular drugs and the limitations of drug development capability in China, advanced technologies in antibody development, production, and quality control is required to develop high-quality VEGF inhibitors that are safe and effective. IBI305 has showed high similarity to bevacizumab in various pharmaceutical and nonclinical studies (refer to Investigator's Brochure [IB]). Besides, the efficacy and safety of bevacizumab for treatment of locally advanced, metastatic or relapsed lung cancer have been verified. The relevant domestic and external pivotal clinical studies are referable for the protocol design of IBI305 clinical study. In summary, the clinical study of IBI305 for treatment of NSCLC has a solid foundation and relatively low risks. The successful development of IBI305 indicates an additional first-line targeted drug for lung cancer in China, providing doctors and patients with more therapeutic options.

1.1.2 Investigational drug

1.1.2.1 Description of investigational drug

IBI305 is a recombinant humanized anti-VEGF monoclonal antibody injection developed by Innovent Biologics (Suzhou) Co., Ltd. (hereafter as sponsor) that specifically binds human VEGF. The molecular weight of IBI305 is 149 KDa. IBI305 specifically binds to VEGF-A, inhibits the binding of VEGF-A to VEGF-R1 and VEGF-R2, blocks the signaling pathways such as PI3K/Akt/PKB and Ras-Raf-MEK-ERK. IBI305 also inhibits the growth, proliferation, and migration of VECs and angiogenesis, decreases the vascular permeability, blocks blood supply to tumor tissues, inhibits the proliferation and metastasis of tumor cells, and induces the apoptosis of tumor cells, thereby generates anti-tumor effects. The main active ingredient is recombinant humanized anti-VEGF monoclonal antibody and excipients include sodium acetate, sorbitol, and polysorbate 80[13]. Refer to the Investigator's Brochure for the detailed structure and physicochemical properties of IBI305.

1.1.2.2 Preclinical studies

Pharmaceutical studies

The pharmaceutical studies showed that stability, primary structure, higher-order structure, oligosaccharide distribution, charge variant, and product-related impurities of IBI305 are highly similar to those of bevacizumab, and the process-related impurities meet the proposed specification. Therefore, IBI305 is considered to have highly similar protein properties and product quality to bevacizumab[13].

Pharmacodynamic studies

In vitro and in vivo pharmacodynamic (PD) studies of IBI305 showed the following findings:

1) Target: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A with an affinity constant same as that of bevacizumab, indicating that IBI305, the same as bevacizumab, is a specific human VEGF blocker with a clear target.
2) Specificity: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A, medium-affinity binding to canine VEGF-A, but low-affinity binding to human VEGF-B, VEGF-C, VEGF-D, PlGF, suggesting that IBI305 recognizes specific targets and has low off-target toxicity risk; no obvious affinity to mouse VEGF-A_{164} and rat VEGF-A_{164}, suggesting that IBI305 has high species specificity.
3) Mechanism of action: IBI305 specifically binds to VEGF-A and inhibits the activation of VEGFR-2 and ERK1/2, blocks the proliferation and migration of HUVEC, and inhibits the sprouting from rat aortic ring, suggesting that IBI305 antagonizes VEGF-A-induced signaling pathway to block the proliferation and migration of VECs and inhibit angiogenesis, which leads to the reduction of nutritional supply and metastasis of tumor.
4) Anti-tumor effects: IBI305 significantly inhibits the growth of human colon cancer Ls174t and lung cancer NCI-H460 cells in xenografts in nude mice, indicating that IBI305 has significant anti-tumor effects.

Results from in vitro and in vivo studies of IBI305 showed highly similarity with that of bevacizumab designed simultaneously, demonstrating that the target, mechanism of action, and anti-tumor effects of IBI305 are highly similar to bevacizumab[13].

Pharmacokinetic studies

In vitro and in vivo pharmacokinetic (PK) studies of IBI305 showed the following findings:

1) IBI305 showed no significant cross-reactivity with normal human tissues and cynomolgus monkey tissues, and only cross-reacted with the positive-control. i.e. human angiosarcoma tissue, suggesting that IBI305 is highly specific to cancer tissues rather than normal human tissues and has very low on-target toxicity.
2) Linearity: With single dose or repeated doses of IBI305 (2-50 mg/kg) vis intravenous injection in cynomolgus monkeys, the test showed significant PK, thus reducing the suddenly rising toxicity risks with increased clinical doses.
3) Immunogenicity: With single dose or repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed abnormal changes of drug concentration-time curves in several animals. The anti-drug antibody (ADA) test results showed that IBI305 has a medium immunogenicity.
4) Accumulation: With repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed that drug exposure of the last dose was significantly higher than that of the first dose, and the steady-state drug concentration after repeated doses was higher than that after a single dose, suggesting that the drug may be accumulated in body.

The results of tissue cross-reactivity and PK/toxicokinetic studies in cynomolgus monkeys indicated that IBI305 and bevacizumab have similar characteristics in tissue cross-reactivity and PK/toxicokinetics[13].

Toxicological studies

Toxicological studies of IBI305 showed the following findings:

1) Single dose: With single dose of IBI305 (up to 300 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed good tolerability without any abnormal clinical symptoms and toxicity. The dose was about 48 times the proposed clinical dose for human based on body surface area. In the safety pharmacology test, with single dose of IBI305 (50 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed no significant effects on the central nervous system, respiratory system, and cardiovascular system, suggesting that the single dose of IBI305 via intravenous injection has a high safety.

2) Repeated doses: With repeated doses of IBI305 (up to 50 mg/kg) via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, equivalent to 20 times the proposed clinical dose for humans (based on the weight), the test showed extremely mild to mild linear growth arrest of metaphyseal lines at knee joint and disordered chondrocyte proliferation, extremely mild increases in macrophage count in white pulp of spleen, pulmonary (including bronchial) hemorrhage, and deposits of hemosiderin in lymphoid tissue of bronchial mucosa, indicating that the target organ toxicities are mainly in the bone, spleen, and lungs.

3) Immunotoxicity and immunogenicity: With repeated doses of IBI305 via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, the test showed medium immunotoxicity to the spleen. Different doses of IBI305 may result in the production of ADAs, a portion of which are neutralizing antibodies (NAbs), indicating that IBI305 has medium immunotoxicity and immunogenicity.

4) Local irritation test: With repeated dose of IBI305 via intravenous injection in cynomolgus monkeys, the test showed no irritation at the injection site, suggesting that administration of IBI305 via intravenous injection is safe and feasible.

5) In vitro hemolysis assay: With maximum proposed clinical concentration of IBI305 (9 mg/mL), the assay showed no hemolysis, suggesting that IBI305 is suitable for intravenous injection.

IBI305 has high similarity with bevacizumab in safety pharmacology, long-term toxicity, immunotoxicity, immunogenicity, local irritation, and hemolysis[13].

1.2 Study Principles and Risk/Benefit Assessment

1.2.1 Study principles and dose selection

A biosimilar drug refers to a therapeutic biological product that is similar in quality, safety and efficacy with an approved reference drug[14]. IBI305, developed and sold in the market by the sponsor, is a bevacizumab biosimilar, and has the same administration method and indications as bevacizumab.

This study is conducted in accordance with the "Guidelines on Development and Evaluation of Bosimilars (for Trial Version)" issued by the NMPA (formerly CFDA)[14]. The doses of IBI305 selected in this study are based on the preclinical studies that showed highly similarity between IBI305 and bevacizumab in pharmacology, PD, PK and toxicology (refer to the Investigator's Brochure for details). Besides, the efficacy and safety of bevacizumab for treatment of advanced, metastatic or relapsed non-squamous NSCLC have been verified, and the indications have also been approved in China. Therefore, the dose and administration of IBI305 is similar to bevacizumab in this study, that is, 15 mg/kg intravenously on D1 of every 3-week cycle when used in combination with chemotherapy (paclitaxel and carboplatin). In the subsequent maintenance monotherapy therapy, IBI305 will be given intravenously at a dose of 7.5 mg/kg on the first day of every 3-week cycle. This design of this study is to further demonstrate that IBI305 is similar to bevacizumab in clinical efficacy, safety, and immunogenicity in subjects with advanced, metastatic or relapsed non-squamous NSCLC.

1.2.2 Risk/benefit assessment

IBI305 is a bevacizumab biosimilar developed by the sponsor. Based on the clinical pharmacology and toxicology characteristics of IBI305, the risks and benefits of IBI305 are expected to be similar to bevacizumab.

The treatment-related risks of bevacizumab are detailed in its prescribing information. This study is the first human study of IBI305 so that unexpected adverse reactions will be possible. The design of this study ensures the minimized subject risks by close monitoring of the adverse events (AEs) before, during, and after the infusion of the investigational drugs. Once an adverse reaction occurs, the investigator will immediately take appropriate action for the subject safety.

The platinum-based therapy is the standard first-line regimen of advanced NSCLC[4]. This study uses the combination of paclitaxel/carboplatin, ensuring the basic anti-tumor therapy for subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC.

2.2 Secondary Objectives

Secondary objectives include:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) in subjects with advanced or relapsed non-squamous NSCLC treated by IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

2.3 Exploratory Objectives

- To compare the population pharmacokinetics (PPK) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC
- To compare the pharmacodynamics (PD) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC

3 STUDY PLAN

3.1 Overview of Study Design

This is a randomized, double-blind, active-controlled, and multi-center phase III study. A total of 436 subjects across 35 study sites with non-squamous NSCLC will be planned, randomized in a 1:1 ratio into the IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group, and stratified according to age (< 60 vs. ≥ 60 years old) and epidermal growth factor receptor (EGFR) status (wild type vs. unknown type). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first). Then subjects received maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing maintenance therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first).

After discontinuing the study drug, subjects will return to the study site 28 days (± 7 days) after the last dose for an end-of-treatment visit. If the subjects discontinue the study treatment for reasons other than PD, subsequent follow-up will be continued until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. If the subjects discontinue the study treatment for PD, the investigator will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival.

A CT or an MRI will be performed every 6 weeks (± 7 days) until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. The method for subsequent imaging examination should be consistent with that at baseline, and the chest, abdomen and pelvis of the subject must be scanned. Each assessment must be completed within 7 days from the most recent visit. The investigators then perform the evaluation based on the RECIST v1.1 criteria to determine whether the subject can continue receiving the next cycle of treatment. Furthermore, the independent tumor evaluation committee (Section 11.1.1) will also evaluate tumor response according to the RECIST v1.1. If the subjects discontinue the study treatment for reasons other than PD, subsequent tumor evaluation should be continued according to the study procedures until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death or, end of study.

The study design is shown in Figure 1.

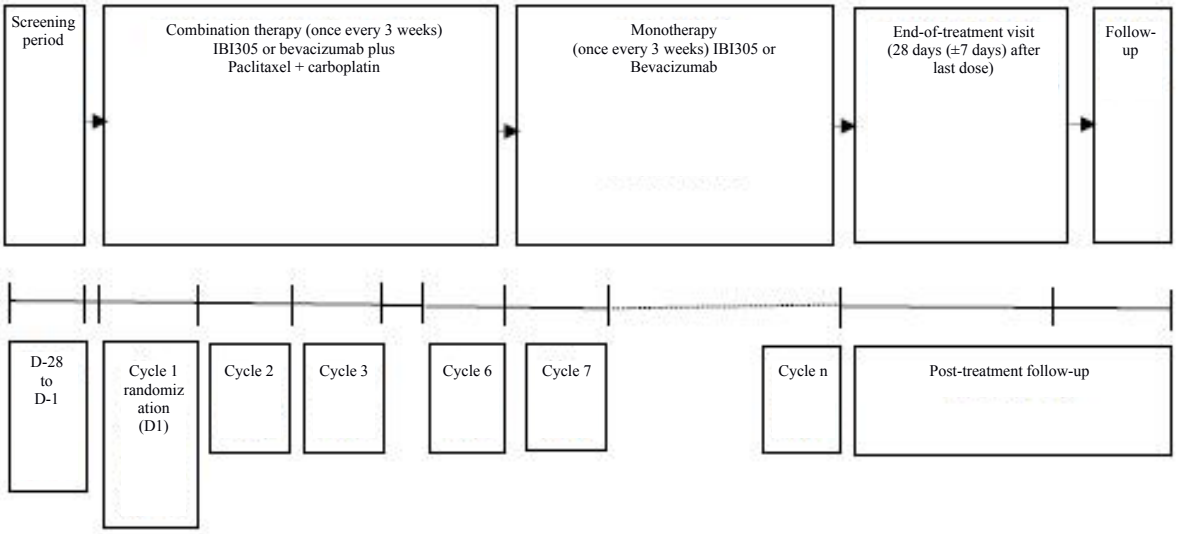

Figure 1. Study design schematic

3.2 Study Design Discussion

This is a randomized, double-blind study, and bias in treatment groups is avoided. Furthermore, the CT/MRI images of each subject will be evaluated by an independent tumor evaluation committee according to the RECIST v1.1 to ensure consistency in evaluation.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled in the study:

1) Sign the informed consent form
2) Male or female ≥ 18 and ≤ 75 years old
3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIB), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types
4) Histologically or cytologically confirmed EGFR wild type or non-sensitive mutation type
5) Must have at least one measurable target lesion (as per RECIST 1.1)
6) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1
7) Expected survival ≥ 6 months
8) Laboratory results during screening:
   a) Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L
   b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis
   c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline urinalysis must have undergone 24 h urine collection with total protein content < 1 g
   d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment
9) Able to comply with study protocol
10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug

4.2 Exclusion Criteria

Subjects meeting any of the followings are not enrolled in the study:

1) Prior systemic chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIB not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible
2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component
3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18 point mutation (G719X), exon 19 deletion, and exon 21 point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll.
4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time
5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava)
6) Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage;
7) Subjects who received radical thoracic radiation therapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug
8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study
9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (Outpatient/inpatient surgery requiring locoregional anesthetics, including central line insertion)

10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function for 10 consecutive days

11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents for 10 consecutive days. However, anticoagulants for prophylaxis are accepted

12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis

13) Uncontrolled hypertension (systolic greater than 140 mmHg and/or diastolic greater than 90 mmHg), history of hypertensive crisis or hypertensive encephalopathy

14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease

15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess

16) Subjects with tracheoesophageal fistula

17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments)

18) Subjects with current interstitial lung disease or CT showing active pneumonia during screening;

19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or papillary thyroid carcinoma

20) Subjects with active autoimmune disease

21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1 × 103 copies/L or ≥ 200 IU/mL; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1 × 103 copies/L or < 200 IU/mL might be eligible if the investigator determined that the subject's chronic hepatitis B infection was stable and participation in the study would add no further risks to the subject

22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis
23) Subjects with known history of allergic diseases or allergic physique
24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening
25) History of alcohol or drug abuse
26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study
27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents
28) Other conditions unsuitable for the inclusion as determined by the investigator

4.3 Screening Failure

Screening failure is that the subject who has signed the informed consent form fails to meet the inclusion criteria. Subjects with screening failure will not get a randomization number. The reasons of screening failure will be documented in the electronic case report forms (eCRFs).

4.4 Subject Restrictions

Female subjects of childbearing age must take effective contraceptive measures during the study and 6 months after the last dose.

Male subjects must take effective contraceptive measures during the study and 6 months after the last dose to avoid the pregnancy of their partners.

Restrictions on the use of medication during the study are shown in Section 5.9.

4.5 Subject Withdrawal and Replacement

All subjects may withdraw from this study at any time, with or without a reason. Subjects who withdraw from the study will not be subjected to discrimination or retaliation, and their medical treatment will not be affected.

Subjects may discontinue the study treatment or withdraw from the study under the following circumstances:

- $\frac{8}{5}$ Unacceptable toxicity
- $\frac{8}{5}$ Progressive disease

- Investigator believes that the subject should withdraw from the study. If an unacceptable adverse event (AE) occurs and the investigator believes that the subject should withdraw from the study, the study treatment should be discontinued and appropriate measures should be taken. In addition, the sponsor or personnel designated by the sponsor should be notified.
- Withdrawal of informed consent form by the subject
- Serious protocol deviation determined by the investigator and/or sponsor
- Poor protocol compliance
- Study termination by the investigator or sponsor for any reason
- Enrollment error* (enrollment of subjects who have violated the inclusion/exclusion criteria)
- Use of prohibited concomitant medications or other medications that the investigator believes that it may result in toxicities or may affect study results
- Subject lost to follow-up
- Death of subject

* If the subject is determined by the investigator and the sponsor's doctor to be medically suitable to continue with the study drugs without any risk or inconvenience, the mistakenly enrolled or randomized subject will continue with the study treatment and assessments.

In any cases, reasons for withdrawal must be documented in the eCRFs. If the subject withdraws from the study prematurely for any reason, the investigator should make every effort to persuade the subject to receive the corresponding assessment, and continue the follow-up of all unresolved AEs based on the AE reports and follow-up requirements (Table 2):

- If the subject withdraws during the study, the series of assessments listed under the End of Treatment Visit (Section 6.9) should be performed
- If the subject withdraws after the end of the treatment visit and has not experienced PD, the series of assessments listed under the Follow-Up for PD (Section 6.10) should be performed (tumor assessment is not required to be repeated if it has been performed within 6 weeks prior to this follow-up)
- If the subject withdraws during the follow-up for survival, the information of subsequent anti-tumor therapies and survival should be collected by telephone follow-up only

Subjects who withdraw their informed consent are not to be contacted again unless they clearly indicate the willingness to be contacted. The sponsor may use the clinical study data obtained before the withdrawal of informed consent.

Subjects who have been randomized will not be replaced.

5 STUDY TREATMENT

5.1 Therapies by Study Drugs

The study drugs of this study are IBI305 and bevacizumab.

In this study, the dose of IBI305 or bevacizumab during combination therapy with chemotherapy is 15 mg/kg, while the dose during maintenance monotherapy is 7.5 mg/kg. The study drugs are administered intravenously on D1 of each 3-week cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

The duration of the first dose of IBI305 or bevacizumab should be 90 min (± 15 min). If the first infusion is well-tolerated by the subject, then the duration of the second infusion can be shortened to 60 min (± 15 min). If the 60 min infusion is also well-tolerated by the subject, then the subsequent infusions can be completed within 30 min (± 15 min).

5.2 Chemotherapy

Paclitaxel will be administered after the IBI305 or bevacizumab infusion is completed, then followed by carboplatin:

Paclitaxel: 175 mg/m² administered via intravenous infusion for 3 h (may be adjusted according to clinical practice of each study site) on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Carboplatin: AUC 6.0, the infusion time is based on the standard practice of each study site, administered on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

The chemotherapeutic agents are supplied by the sponsor.

Formulas for calculating surface area, creatinine clearance and carboplatin dose are shown in Section 13.2.

5.3 Dose Adjustment of Each Study Drug

5.3.1 General principles

The reasons for dose adjustments or delayed administration, measures taken, and results should be documented in the medical records and eCRFs

If the concomitant symptoms exist at baseline, the investigator will determine whether the dose should be adjusted according to the change in severity of toxicity. For example, if the subject has Grade 1 "weakness" at baseline and Grade 2 "weakness" during the study treatment, the dose should be adjusted based on Grade 1 toxicity since the severity has increased by one grade

If several toxic reactions of different grades or severity occur simultaneously, the dose will be adjusted according to the highest observed grade/severity

If a dose adjustment is required solely due to abnormal lab test results, then the dose should be adjusted based on the measured values obtained prior to the start of the treatment cycle

If the investigator determines that the toxicity is unlikely to further develop into a serious or life-threatening event, the current dose will be continued without any adjustments or treatment interruptions. In addition, dose adjustments or treatment interruptions will not be performed for non-hemolytic anemia as the symptoms can be alleviated through blood transfusions.

If the investigator determines that a toxicity is caused by a specific therapeutic drug, then the dose adjustments of other drugs are not required

Discontinuation of one or two therapeutic drugs before PD will not affect the continued treatment with other drugs

Dose reductions or adjustments of IBI305 or bevacizumab are not permitted.

Subsequent therapeutic dose will not be adjusted according to weight change, unless the subject weight has changed by ≥ 10% from baseline

Once the dose of any chemotherapeutic agents is reduced, the original dose should no longer be adopted

If any but not all of the therapeutic drug (IBI305, bevacizumab or chemotherapeutic agents) treatments is interrupted due to toxicity, then this treatment will be considered as a treatment cycle

If the administration of any one of the chemotherapeutic agents is delayed for more than 3 weeks, the subject should permanently discontinue that chemotherapeutic agent

If IBI305/bevacizumab is continued/infused after a delay for more than 3 weeks, the investigator must discuss with the sponsor

5.3.2 Dose adjustments of study drugs

Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments (adjusted to 7.5 mg/kg for maintenance monotherapy) specified in the study protocol. The dose of IBI305 or bevacizumab is calculated according to the subject weight at baseline (prior to the first dose), and remains unchanged throughout the study, unless the subject weight has changed by ≥ 10% from baseline.

If an infusion reaction occurs during a 60-minute infusion, the infusion time should be extended to 90 minutes for all subsequent infusions. Likewise, if an infusion reaction occurs during a 30-minute infusion, the infusion time should be extended to 60 minutes for all subsequent infusions.

IBI305 or bevacizumab in combination with paclitaxel/carboplatin will be administered every 3-week treatment cycle for 6 cycles. If PD is not observed in subject during treatment, then the subject will continue to receive IBI305 or bevacizumab as maintenance monotherapy every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, death, or end of study (whichever comes first).

If IBI305 or bevacizumab is permanently discontinued due to unacceptable toxicity or subject refusal to continue the study drugs during the combination therapy, then the subject will continue to receive the chemotherapy (paclitaxel/carboplatin) until 6 treatment cycles are completed as determined by the investigator. If any one of the chemotherapeutic agents (paclitaxel or carboplatin) is prematurely discontinued due to unacceptable toxicity, the subject can continue to receive IBI305 or bevacizumab treatment until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first).

When a Grade 3 or 4 IBI305- or bevacizumab-related toxicity is observed, the investigators should determine whether to continue or terminate IBI305 or bevacizumab treatment according to the followings:

First occurrence:

IBI305 or bevacizumab administration should be interrupted until toxicity symptoms return to baseline level or are at least reduced to the Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or lower (except for the special circumstances listed below)

Note that when Grade 4 febrile neutropenia and/or thrombocytopenia occur(s), IBI305 or bevacizumab administration should be interrupted until the symptoms return to baseline levels or at least reduced to CTCAE Grade 1 or lower, since these events increase the risk of hemorrhage.

Re-occurrence in re-administration:

If Grade 3 IBI305- or bevacizumab-related toxicity occurs again, the investigator should assess the risk/benefit of study drug continuation for the subject. If such toxicity re-occurs again after re-administration, IBI305 or bevacizumab should be permanently discontinued

If Grade 4 IBI305- or bevacizumab-related toxicity occurs again, IBI305 or bevacizumab should be permanently discontinued

Measures should be taken in the following special circumstances (classified based on CTCAE version 4.03):

Hemorrhage

Subjects with Grade 3 or 4 hemorrhages should be treated accordingly and permanently discontinue the study treatment

Thrombosis/embolism

- Subjects with arterial thrombosis of any severity grades should permanently discontinue the study treatment
- Subjects with Grade 4 venous thrombosis should permanently discontinue the study treatment
- Subjects with Grade 3 venous thrombosis should interrupt the study treatment. If the anticoagulant therapy at the planned therapeutic dose is < 2 weeks, the study treatment should be interrupted until the anticoagulant therapy is completed. If the anticoagulant therapy at the planned therapeutic dose is > 2 weeks, IBI305 or bevacizumab administration should be interrupted for 2 weeks, and the study treatment can be restarted during the anticoagulant therapy if the following criteria are met:
  - INR is within the target range (usually 2-3) prior to restarting of study treatment
  - Subjects must not have experienced Grade 3 or 4 hemorrhage since enrollment
  - No signs of great vessel invasion or adjacency to great vessels from previous tumor assessments

  Note: Therapeutic dose of anticoagulant therapy is defined as the escalating dose of warfarin or other anticogulants until INR is maintained at no less than 1.5 (usually

2-3). The warfarin dose should be documented in the eCRFs, and the INR of subjects receiving anticoagulant therapy should be monitored during the treatment.

Hypertension

BP should be measured frequently to monitor the occurrence and exacerbation of hypertension. Subjects should remain at resting position for at least 5 min before BP measurement.

Definition of hypertension: pathologically increased BP with repeated measurements persistently over 140/90 mmHg

Table 2. Hypertension severity grades and interventions in CTCAE v4.03

CTCAE		Interventions
Grade 1	Pre-hypertension (systolic blood pressure of 120–139 mmHg, diastolic blood pressure of 80–89 mmHg)	Intervention not indicated
Grade 2	First-stage hypertension (systolic blood pressure of 140–159 mmHg, diastolic blood pressure of 90–99 mmHg; repeated or persistent hypertension of ≥ 24 h), a symptomatic increase of > 20 mmHg in systolic blood pressure, or an increase of > 140/90 mmHg from the previous normal range	Antihypertensive monotherapy. drug interruption. The treatment with the investigational product can be continued once the blood pressure is lower than 140/90 mmHg.
Grade 3	Second-stage hypertension (systolic blood pressure of ≥ 160 mmHg, diastolic blood pressure of ≥ 100 mmHg)	Multiple-agent antihypertensive therapy. Study treatment should be interrupted in case of persistent or symptomatic hypertension; study treatment should be permanently discontinued for uncontrollable hypertension.
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit, and hypertensive crisis)	Urgent intervention and permanent study treatment discontinuation indicated

The dose of antihypertensive agents used should be documented during each visit. If the subject remains hypertensive despite treatment discontinuation, BP and antihypertensive agents used should be monitored every 3 months until BP returns to normal or end of study.

Posterior reversible encephalopathy syndrome (PRES)

There have been a few reports of subjects with signs and symptoms consistent with PRES after study treatment. This is a rare neurological disease and its signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with PRES should permanently discontinue the study treatment.

Proteinuria

Urinalysis should be performed prior to each dose of IBI305/bevacizumab unless a 24-hour urinary protein test has already been done.

First occurrence of proteinuria:

After carrying out the urinalysis, if:

Urine protein is < 2+, continue study treatment as scheduled, no additional tests are required.

≥ 2+ (urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:

- 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled. and perform urinalysis dipstick test before each scheduled dose.
- 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g.

Second and subsequent occurrence of proteinuria:

< 3+ (urinalysis): continue study treatment as scheduled, no additional tests indicated.

≥ 3+ (urinalysis): perform 24-hour urinary protein test within 3 days prior to administration:

- 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled.
- 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g.

Nephrotic syndrome (Grade 4): Study treatment is permanently discontinued

Gastrointestinal perforation

If gastrointestinal perforation occurs, appropriate measures should be taken and the study treatment should be permanently discontinued.

Wound healing complications

The study treatment should not begin within 28 d after a major surgery, or before the surgical wound is fully healed. If a complication of wound healing occurs during study treatment, the study treatment should be interrupted until the wound is fully healed. If an elective surgery is required, the study treatment should be interrupted.

Abdominal abscess or fistula

If abdominal abscess or fistula occurs, the study treatment should be discontinued. However, the investigator will determine whether study treatment will be continued if the above AE is resolved.

Infusion-related and allergic reactions:

Infusion-related reactions after first dose of the study drug is uncommon (< 3%), and the incidence of a severe reaction is only 0.2%.

If a mild (grade 1 or 2) reaction (such as fever, chills, headache, and nausea) occurs, pretreatment prior to subsequent administration should be performed and infusion time should not be reduced. If the subject is well-tolerated during infusion after pretreatment, the infusion time can be reduced by 30 minutes (+10 minutes) for subsequent administration with pretreatment. If an infusion-related AE occurs during a 60-minute infusion, the subsequent infusion should be completed within 90 minutes (+15 minutes) with pretreatment. Likewise, if an infusion-related AE occurs during a 30-minute infusion, the subsequent infusion should be completed in 60 minutes (+10 minutes) with pretreatment. If a subject has a grade 3 infusion-related reaction, the study treatment should be interrupted and not be restarted on the same day. However, since there lacks the dose adjustment method for grade 3 infusion-related reactions, the investigators may decide to either discontinue the study drug or perform pretreatment, and complete the infusion within 90 minutes (+15 minutes). If an adverse reaction still occurs during a 90-minute infusion, the infusion should be continued at a slower rate and then gradually returned to a 90-minute infusion. If the investigator is uncertain about the handling, the study treatment should be discontinued. When the study treatment is restarted, the subject should be closely monitored based on routine clinical practice until the possible time of adverse reaction has passed. If a subject has a grade 4 infusion-related reaction, the study treatment should be discontinued.

An allergic reaction is defined as the vascular collapse or shock (systolic BP < 90 mmHg, unresponsive to rehydration) that occurs within 30 minutes of a study drug infusion caused by an allergy, with or without respiratory distress. Skin reactions include pruritus, urticaria, and angioedema. Subjects with allergic reactions should discontinue the study treatment.

5.3.3 Dose adjustments of chemotherapy

Paclitaxel and carboplatin should be administered according to the study site guidelines and local prescribing information. For the specific information for use, preparation, and storage of paclitaxel and carboplatin, refer to the prescribing information and local dosing information. Carboplatin-based chemotherapies have a relatively high incidence of emesis. Therefore, antiemetics for prophylaxis can be used.

Hematological toxicity:

Absolute neutrophil count (ANC; dose can only be reduced when febrile neutropenia occurs. ANC must be ≥ 1.5 × 109/L and platelet count must be ≥ 100 × 109/L on D1 of each treatment cycle). Once the chemotherapeutic dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 × 10^9/L or ◡50 × 10^9/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.

Table 3. Dose adjustments of paclitaxel and carboplatin (febrile neutropenia and thrombocytopenia)

	Dose Adjustments of Paclitaxel/Carboplatin		
	First Occurrence	**Re-Occurrence After Dose Adjustment**	**Re-occurrence After Two Dose Adjustments**
Febrile neutropenia (regardless of duration)	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC *3*	Chemotherapy discontinuation
Lowest Level After Last Dose <25 × 10^9/L or <50 × 10^9/L with hemorrhage or requires blood transfusion	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5	Paclitaxel = 100 mg/m^2 Carboplatin = AUC 3	Chemotherapy discontinuation

If the dose adjustment is required when ANC and thrombocytopenia occur concurrently, the low-dose chemotherapy should be adopted.

Chemotherapy may be delayed for up to 3 weeks. If after the chemotherapy has been delayed for 3 weeks, ANC does not reach ≥ 1.5 × 10^9/L and platelet count does not reach ≥ 100 × 10^9/L on D1 of the scheduled chemotherapy, the chemotherapy should be permanently discontinued. If the above values have been reached, the next course of chemotherapy should be continued.

The investigator should monitor the subject closely for toxicity with particular attention to early and evident signs of myelosuppression, infection, or febrile neutropenia to timely and appropriately treat the complications.

Subjects should be informed to pay attention to these signs and receive treatment as soon as possible.

If the chemotherapy must be interrupted due to hematological toxicity, the complete blood count should be performed regularly (including WBC differentials) until all the counts reach the minimum requirements for treatment continuation. Thereafter the scheduled treatment plan will be performed.

Dose adjustments are not required for anemia. However, treatment based on guidelines of each clinic should be performed.

Gastrointestinal toxicity

Antiemetics will be used to control nausea and/or emesis. If grade 3 or 4 nausea and/or emesis occur(s) despite of antiemetics, the chemotherapeutic dose should be reduced by 20% for the next treatment cycle. The dose should be returned to the initial level as possible if the subject is tolerated.

If the subject experiences stomatitis on D1 of any treatment cycle, the chemotherapy should be interrupted until the symptoms resolve. If the stomatitis has not resolved after 3 weeks, the chemotherapy should be permanently discontinued (refer to CTCAE version 4.03). If an acute Grade 3 stomatitis occurs, the chemotherapeutic dose should be reduced to 75% of the proposed dose when symptoms resolve.

Hepatotoxicity (Paclitaxel)

The paclitaxel dose should be determined based on the lab values measured on D1 of each treatment cycle.

Table 4. Dose adjustment of paclitaxel (hepatotoxicity)

AST		**Total bilirubin**	**Paclitaxel Dose**
≤ 5 x UNL	and	WNL	175 mg/m^2
> 5 x UNL	or	> UNL ~ 1.5 x UN	150 mg/m
		> 1.5 x UN	0

If paclitaxel is interrupted due to hepatotoxicity, carboplatin should also be interrupted until paclitaxel is restarted. Paclitaxel will be interrupted for up to 3 weeks. If the subject's hepatic function does not return to the acceptable ranges in 3 weeks, paclitaxel should be permanently discontinued. The carboplatin dose will not be adjusted when hepatotoxicity occurs.

The investigators should avoid PD due to abnormal hepatic enzyme levels as possible. If PD occurs, all the study drugs should be permanently discontinued, including chemotherapy.

Cardiovascular toxicity (paclitaxel)

The arrhythmia in subjects was infrequent in previous clinical studies. However, most subjects were asymptomatic and electrocardiographic monitoring was not required. Asymptomatic transient bradycardia was observed in 29% of subjects, but significant atrioventricular block was rare. Cardiac events should be treated as follows:

Asymptomatic bradycardia: no intervention indicated

Symptomatic arrhythmia during infusion: Discontinue paclitaxel infusion and perform routine treatment of arrhythmia. Discontinue subsequent paclitaxel treatment. Document this AE in the AE Report Form of eCRF.

Chest pain and/or symptomatic hypotension (< 90/60 mmHg or rehydration therapy required): discontinue the paclitaxel infusion. Perform electrocardiography (ECG). If hypersensitivity reaction is suspected, administer diphenhydramine and dexamethasone via intravenous infusion. If the chest pain is not considered as cardiogenic, epinephrine or bronchodilators will be administered. Document this AE in the AE Report Form of eCRF. Discontinue subsequent paclitaxel treatment and provide symptomatic treatment. Consult a cardiologist if needed.

Neurotoxicity (paclitaxel)

The dose of paclitaxel should be adjusted according to Table when neuropathy occurs. The dose adjustment of carboplatin is not needed when neurotoxicity occurs.

Table 5. Dose adjustment of paclitaxel (neurotoxicity)

Toxicity Grade (CTCAE version 4.03)	Paclitaxel dose adjustment
Grade 1 or below	175 mg/m^2
2	Interrupt treatment until return to grade 1, then reduce dose to 140 mg/m^2 (20% of reduction) and restart infusion

Grade 3 or above	Interrupt treatment until return to grade 1, then reduce dose to 125 mg/m^2 (30% of reduction) and restart infusion.

Once the dose is reduced due to neurotoxicity, the original dose should no longer be adopted. If the neurotoxicity does not return to grade 1 after paclitaxel interruption for 3 weeks, paclitaxel should be permanently discontinued.

Allergic reactions/hypersensitivity reactions (paclitaxel)

Note: Prophylaxis for hypersensitivity reactions (see below) and close monitoring of vital signs are recommended for subjects with history of mild to moderate hypersensitivity reactions when hypersensitivity reactions reoccur.

Mild symptoms: complete paclitaxel infusion. Close monitoring; no treatment indicated.

Moderate symptoms: Interrupt paclitaxel infusion, administer diphenhydramine 25–50 mg and dexamethasone 10 mg via intravenous infusion. Once symptoms have resolved, resume paclitaxel infusion at a slower rate (20 mL/hour for 15 minutes, then at 40 mL/hour for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete). Document this AE in the AE Report Form of eCRF. If symptoms reoccur, interrupt the paclitaxel infusion and permanently discontinue subsequent paclitaxel infusion.

Severe and life-threatening symptoms: Interrupt paclitaxel infusion, administer diphenhydramine and dexamethasone via intravenous infusion (as above). Use epinephrine or bronchodilators if indicated. Document this AE in the AE Report Form of eCRF. Subsequent courses of paclitaxel infusion should be permanently discontinued.

Moderate or severe hypersensitivity reactions should be documented as AEs.

Other toxicities

If other unmentioned grade 3–4 toxicities occur, the chemotherapy should be interrupted until symptoms resolve or return to grade 1. Thereafter restart the infusion at 50% of the original dose (which should no longer be adopted). If the toxicity does not return to grade 1 after an interruption for 3 weeks, the chemotherapy should be permanently discontinued. Dose adjustments are not recommended for grade 1 and 2 toxicities.

5.4 Study Drug Properties

IBI305 is a bevacizumab biosimilar. The active ingredient of both drugs is recombinant humanized anti-VEGF monoclonal antibody; Bevacizumab is the standard commercially available drug, provided by the sponsor.

Detailed information on the study drugs is shown in Table .

Table 6. Study drugs

Study Drugs	Dosage Form and Strength	Excipient	Appearance	Manufacturer
IBI305	4 mL: 100 mg	Sodium acetate, sorbitol, and polysorbate 80	Sterile solution for intravenous injection pH 5.2 Clear, colorless liquid, no foreign matters, no floc or precipitation	Innovent Biologics (Suzhou) Co., Ltd.
Bevacizumab	4 mL: 100 mg	α,α-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, polysorbate 20, and sterile water for injection	Sterile solution for intravenous injection pH 5.9–6.3 Clear to slight opalescent, colorless to light brown	Roche Pharma (Schweiz) Ltd.

5.5 Preparation and Distribution

IBI305 or bevacizumab is diluted in 0.9% sodium chloride solution by the pharmacist or research nurse before infusion. Check the particles and discoloration prior to administration.

The investigator should ensure that the pharmacist or research nurse administers the study drugs according to study protocol.

5.6 Packaging, Labeling, and Storage

The sponsor should package and label the study drugs according to appropriate local regulations.

All study drugs (IBI305 and bevacizumab) must be stored at 2–8 °C away from light. The study drugs should be stored in a safe zone only accessible by authorized staff prior to dispensation to the subjects.

5.7 Subjects Allocation

After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in the Interactive Web Response System (IWRS) and enter the subject information into the IWRS. The IWRS will allocate a random number to the subject and provide a medication

number. Stratified randomization is used in this study. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild vs. unknown type).

5.8 Blinding

This is a randomized, double-blind, and active-controlled study, and only relevant study personnel had access to the randomization numbers. A non-blinded pharmacist or research nurse will prepare the medications since IBI305 and bevacizumab do not have an identical appearance. The pharmacist or research nurse who is responsible for preparing the study drugs is not allowed to disclose any information regarding treatment allocation to the subject, the subject's family members, or other personnel including the physician and the relevant study staff.

Unblinding: Subject unblinding should only be performed after database locking.

Emergency unblinding: In case of an emergency where the investigator must know the medication given to a particular subject, the investigator will unblind the subject via the IWRS and immediately inform the sponsor and CRO. The reasons for unblinding, date, and outcomes should be documented in the source document and eCRF of the subject.

5.9 Concomitant Medications and Treatments

All medications except for the study drugs, including other chemotherapies not specified in the study, Chinese herbal medicines, and other non-traditional therapies, are considered concomitant medications. All concomitant medications used within 30 days prior to screening should be documented in the eCRFs, including the information of generic name, route of administration, start date, end date, and indication.

5.9.1 Prohibited treatment

No other anti-tumor therapies or medications with anti-tumor indications, including Chinese herbal medicine, radiotherapy, or other investigational drugs, are allowed during this study other than IBI305, bevacizumab, paclitaxel, and carboplatin.

Severe myelosuppression is possible after chemotherapy. Granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are not allowed to be used prophylactically in the first treatment cycle.

5.9.2 Permitted treatment

Prophylactic use of anti-emetics, glucocorticoids, or other treatments targeting toxicities is permitted during the study. Unconventional treatments (such as acupuncture) and vitamins/microelements are permitted if their use does not affect the study endpoints as determined by the investigators.

Starting from the 2nd chemotherapy cycle, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are allowed to be used prophylactically to prevent severe myelosuppression.

Anti-viral therapy was permitted whenever necessary.

Stable doses of anti-epileptic drugs were permitted.

Radiotherapy for bone metastasis was permitted provided that the radiotherapy field did not include the target lesion

5.9.3 Treatment after study treatment

Subsequent therapy after the end of study treatment should be determined by the subject's attending doctor.

5.10 Treatment Compliance

Subjects should receive treatment at the study site. The dose and time of administration of IBI305 or bevacizumab and paclitaxel/carboplatin should be documented in the source records and eCRFs during each treatment cycle. Reasons for dose adjustments, therapy delay, and therapy discontinuation should be documented. Treatment compliance is monitored by medication dispensing and return records, medical records, and eCRFs.

5.11 Drug Return and Destruction

The containers, vials, infusion bags, and syringes of used and partially used drugs can be destroyed on-site according to the appropriate guidelines and operating procedures established by study sites and local agencies.

Unless the contents have significant safety issues requiring immediate destruction in accordance with local regulations, all the unused drugs should be returned and destroyed based on the requirements of sponsor.

5.12 Study Drug-Related Records

The designated personnel of the study sites should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines.

6 STUDY PROCEDURE

The detailed procedures of this study are shown in Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

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6.1 Screening Visits (D -28 to D -1)

Complete the screening visits within 28 days prior to study treatment commencement. The following procedures must be completed during screening to ensure that subject meets the requirements for participating in this study:

- Sign the ICF
- Record the demographics, including age, ethnicity, and gender
- Record the past medical history, including smoking history
- Record the history of anti-tumor therapies
- Record the concomitant medications (within 30 days prior to screening)
- Record the vital signs
- Measure the height and weight (including BMI)
- ECOG score
- Physical examination
- 12-Lead ECG
- Hepatitis B panel, anti-HCV, anti-HIV, and syphilis tests
- Clinical laboratory tests (routine blood test, coagulation test, blood chemistry, and urinalysis)

- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Imaging examinations (CT or MRI: Head, chest, abdomen, and pelvis cavity)*
- EGFR test#
- Review the inclusion/exclusion criteria
- Record the AEs and concomitant medications

* Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging results during screening will be used as the baseline data. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

If the subject has been tested for EGFR of tumor sample at the study site with documentation, the subject will not be required for retest.

6.2 Baseline Visits (D1 of cycle 1)

D1 refers to the day of receiving the first dose of the study drugs. Eligible subjects meeting the inclusion criteria will return to the study site and complete the following procedures:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests * (routine blood test, blood chemistry, and urinalysis)
- Confirm the inclusion/exclusion criteria

* If clinical laboratory screening tests (routine blood test, blood chemistry, urinalysis) are performed within 7 days prior to the first dose, then the results of the screening test can be used as baseline.

If the subject meets the inclusion criteria, the following procedures should be complete:

- Randomization and grouping
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Pharmacokinetic (PK) blood sampling (within 1 h prior to the study drug infusion,

immediately after the study drug infusion [+5 min])

- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Record the AEs and concomitant medications

6.3 Cycle 2 (week 4 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.4 Cycle 3 (week 7 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)

- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.5 Cycle 4 (week 10 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.6 Cycle 5 (week 13 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)

- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.7 Cycle 6 (week 16 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.8 Cycle 7 and Subsequent Treatment Cycles (±3 Days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Maintenance monotherapy will start from week 7 and the dose of study drug will be adjusted to 7.5 mg/kg. Subjects should complete the following procedures during each visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG

- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.9 End-Of-Treatment Visit

The end of treatment visit in study sites will be conducted in 28 days (±7 days) after the last dose of study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Immunogenicity test
- PD blood sampling
- Blood/urine pregnancy test (for female subjects of childbearing age only)
- Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this visit)
- Subsequent anti-tumor therapy
- Record the AEs and concomitant medications

If the subject has not experienced PD, the subsequent follow-up for PD will be performed (Section 6.10). If the subject has experienced PD, the subsequent follow-up for survival will be performed (Section 6.11).

6.10 Disease Progression Visit

If the study drugs are discontinued for reasons other than PD, the end of treatment visit in study sites will be conducted in 28 days after the last dose of study drug, and tumor assessments should be conducted every 6 weeks (±7 days) until PD if possible (after which, follow-up for survival will be conducted [Section 6.11]), withdraw of informed consent, loss to follow-up, death,

start of other anti-tumor therapies, or end of study. During the visit, vital signs and weight measurements will be performed, and any subsequent anti-tumor therapies will be documented.

6.11 Survival Follow-Up

The investigator will make telephone follow-up every 12 weeks (±7 days) to collect the information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, loss to follow-up, death, or end of study.

6.12 Study Completion

The end of this study will be the18th month after randomization of the last subject. If the subjects continue to receive the study drug treatment before this cut-off time, the treatment should be discontinued and the end of treatment visit should be completed (Section 6.9).

6.13 Tumor Assessment

Imaging tests (CT or MRI) of the brain, chest, abdomen, and pelvis are required at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test was used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

The investigator should perform a tumor assessment based on RECIST v1.1 (Section 13.3) prior to each dose to determine whether the subject should continue with the next round of treatment. An independent review committee will also assess the tumor response (Section 11.1.1). Imaging tests will not be rescheduled if the study drugs or chemotherapeutic agents are interrupted due to toxicities. Every effort should be made to continue the schedule for imaging tests even for subjects who discontinue one or two study treatment(s) due to drug-related toxicities.

If subject experience PD according to the RECIST v1.1 criteria, the attending doctor should discuss with the subject regarding subsequent routine cancer therapies.

6.14 Clinical Laboratory Evaluations

Clinical laboratory tests will be conducted at the laboratories of each study site. Sample collection and analysis should be performed according to the requirements of each laboratory.

The following laboratory tests should be conducted according to the study procedures (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

):

Routine blood test: hemoglobin, hematocrit, WBC and differentials (including

absolute neutrophil and lymphocyte counts), platelets, and RBC

Routine coagulation test (baseline test): INR, aPTT, or PTT

➢ Blood chemistry: Creatinine, blood urea, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose, sodium, potassium, chloride, calcium, phosphorus, and magnesium

➢ Urinalysis: Specific gravity, pH, glucose, protein, occult blood, and leukocytes

➢ Pregnancy test: Serum/urine pregnancy tests are performed on women of childbearing age during screening and the end-of-treatment visit.

These tests are carried out at the laboratory of each trial site.

For subsequent visits, all laboratory tests need to be completed within 3 days prior to the administration. During the study, the frequency of these laboratory tests will be increased if safety is a concern. The investigator should review the laboratory test results throughout the study to determine whether the results are clinically significant. The investigator should assess the changes in laboratory test results. If the investigator considers a laboratory test result to be abnormal and of clinical significance, it is considered as an AE.

6.15 Vital Signs, Physical Examinations, and Other Safety Assessments

6.15.1 Vital signs

Vital signs include pulse, BP, temperature, and respiratory rate. The subject must rest for at least 5 minutes prior to each vital sign assessment.

Vital signs will be assessed according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

). During the study, the investigator may increase the frequency of vital sign measurement if

safety is a concern.

6.15.2 Height and weight

Height is only measured during screening. Weight is measure during each visit.

6.1.5.3 Physical examinations

The following organs/systems will be examined according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration		x	x	x	x	x	x	x			

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
(IBI305 or bevacizumab) [j]											
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

): general condition, head (eyes, ears, nose, and throat), neck and thyroid, respiratory system, cardiovascular system, abdomen, nervous system, skeletal muscles and limbs, as well as lymphatic system and skin.

6.15.4 12-Lead ECG

12-lead ECG will be performed during screening. During the study, each medication visit requires an ECG examination. The following ECG parameters should be documented: HR, PR-interval, QRS-complex, QT-interval, and QTc-interval. The subject must be in the supine position for at least 5 minutes prior to undergoing the 12-lead ECG. All ECG are evaluated by qualified physicians. All clinically significant abnormal findings should be reported as AEs.

6.15.5 Immunogenicity assessment

Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples were tested at the designated central laboratory.

6.15.6. Pharmacokinetics/pharmacodynamics

6.15.6.1 Pharmacokinetics

Study sites that are implementing version 2.0 of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 hour prior to the dose in C4, within 1 h prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.

6.15.6.2 Pharmacodynamics

Study sites that are implementing version 2.0 of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and during the end-of-treatment visit. Samples were tested at the designated central laboratory.

6.15.7 EGFR testing

EGFR mutation testing histologically or cytologically will be performed in all subjects (if the subject has been tested for EGFR at the study site histologically or cytologically with documentation, the subject will not be required to be retested). The testing will be conducted at the laboratory of each study site or a qualified third-party laboratory.

7 STUDY ASSESSMENTS

7.1 Efficacy Assessment

7.1.1 Primary efficacy endpoint

- Objective response rate (ORR)

ORR will be assessed using RECIST v1.1. ORR is defined as the proportion of subjects whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved complete response (CR) and partial response (PR). The cut-off date for the analysis of primary efficacy endpoint in this study is 18 weeks after subject randomization.

7.1.2 Secondary efficacy endpoints

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Each endpoint will be assessed using RECIST v1.1.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death before PD; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

PFS is defined as the time from the date of randomization to the date of PD or death; Subjects who do not progress or die will be censored on the date of the last tumor assessment.

DCR is defined as the proportion of patients whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved CR, PR, and SD.

OS is defined as the time from the date of randomization to the date of death of any cause. For subjects that are alive on the date of study completion or are lost to follow-up, their survival time will be censored at the date of last contact.

7.2 Safety Assessments

7.2.1 Adverse events

7.2.1.1 Definition

Adverse event

An AE refers to any untoward medical occurrence in a subject after signing the informed consent form, and does not necessarily have a causal relationship with the treatment. Thus, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether considered drug related.

Abnormalities resulting from PD are not considered as AEs.

Serious adverse event

A SAE refers to an AE meeting at least one of the followings:

(1) Lead to death, except for deaths caused by PD.

(2) Life-threatening (a "life-threatening event" is defined as an AE when the subject is at immediate risk of death at the time, but does not include the case that may lead to death only when the event worsens).

(3) Requires hospitalization or prolonged hospitalization, excluding an emergency or outpatient visit. Subjects with existing diseases or conditions prior to the enrollment that do not worsen during the study, and having hospitalization and/or surgery that was scheduled before the study or during the study do not meet the SAE criterion. Hospitalizations resulting from PD are not considered as SAEs.

(4) Results in permanent or severe disability/incapacity.

(5) Results in congenital anomalies/birth defects.

(6) Other important medical events: The event that does not result in death, is not life-threatening or does not require hospitalization, but may jeopardize the health of subjects and require medical intervention to prevent the SAEs above, is considered as an SAE

7.2.1.2 Severity of adverse events

The severity of AEs is evaluated using the 5-level criteria of NCI CTCAE v4.03.

For AEs not included in CTCAE v4.03, use the following CTCAE general guidelines:

- Grade 1: Mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated.
- Grade 2: Moderate; minimal/local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life (such as cooking, shopping, using the phone, financial management, etc.).
- Grade 3: Severe or clinically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; limited ability of self-care (such as bathing, dressing, undressing, eating, using the toilet, taking medication), but not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

7.2.1.3 Relationship between adverse events and the investigational drug

The relationship between the study drugs and AEs can be determined using the followings:

Table 7. Correlation between AEs and investigational drugs

Correlation	CRITERIA
Related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can more reasonably explain the AE than the other causes (such as the pre-existing disease of the subject, environment, toxicity, or other treatment received); The AE resolves or is alleviated after treatment interruption or dose reduction; The AE is consistent with the known type of AEs of the suspicious drug or similar drugs; The AE occurs again after the drug administration is resumed.
Possibly related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can be used to explain the AE with the same level of rationality as other reasons (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE resolves or is alleviated after treatment interruption or dose reduction (if applicable).
Possibly not related	Other reasons can more reasonably explain the AE than the investigational drug (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear; The AE does not occur again or the situation of the AE is unknown after the drug administration is resumed.

Unrelated	4/3	The occurrence of the AE is not reasonably related to the time sequence of dosing, or
	4/3	The AE has other obvious causes (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject).
Cannot be determined	4/3	The above information is unclear and cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.

7.2.1.4 Serious adverse event reporting

SAEs that occur from the signing of informed consent form until 90 days (inclusive) after the last dose should be reported. The investigator must fill out the "CFDA SAE Report Form", regardless of whether it is the initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, CFDA, and ethics committee within 24 hours of noticing the event. The contact information for reporting is shown in the table below.

For SAEs occurring outside of the above-mentioned period, those considered related to the investigational drug shall also be reported to the sponsor.

The investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.

The investigator should also report the event to the CFDA, health administration departments, and ethics committees in accordance with the regulations.

When submitting the SAE report by email, it is recommended for the investigator to encrypt the report file and send the report file and password in separate emails.

Table. SAE report contacts

Unit	**Contact**	**Fax/Telephone/Address**
Hospital Name	**Ethics committee**	**Hospital Fax/Telephone**
Innovent Biologics (Suzhou) Co., Ltd.	Clinical Study Department PV	Fax: 021-31652800 Email: drugsafety@innoventbio.com

Office of Drug Research and Supervision, Department of Drug and Cosmetics Registration, China Food and Drug Administration		Address: Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing Post Code: 100053 Tel: 010-88330732 Fax: 010-88363228
Medical Administrative Department, Health Administration		Address: No. 38, Lishi Road, Xicheng District, Beijing Tel: 010- 68792001 Fax: 010-68792734
Province, Autonomous Region, Municipality Food and Drug Administration	Based on the requirements of the food and drug administration department of each province, autonomous region or municipality	

7.2.1.5 Management and follow-up of adverse events

The investigator is responsible for providing appropriate medical treatment for all AEs (Indicate the actions taken, such as suspension/termination of the investigational drug, dose modification, drug therapy, etc.). When an AE occurs, the investigator should actively take appropriate measures to ensure the safety of the subject. All AEs observed from the signing of the ICF to the time specified in the protocol (Table 2) must be followed.

The investigator should report any SAE that occurs after the time specified in the protocol (Table 2) and is suspected of being related to the investigational drug to the sponsor.

7.2.1.6 Adverse event of special interest and expedited reporting

The AESI for this study include:

- Gastrointestinal perforation
- Procedural and wound healing complications
- Hemorrhage
- Fistula
- Hypertension
- Thrombotic event
- Posterior reversible encephalopathy syndrome (PRES)

- Proteinuria
- Infusion-related reaction
- Ovarian failure
- Cardiac failure congestive

If the criteria for SAE is met, the SAE report should be submitted to the sponsor within the specified time limit (see 7.2.1.4 for details)

7.2.1.7 Pregnancy

Bevacizumab may be harmful to the fetus. Subjects or female partners of male subjects must use an effective form of contraception during the 6 months after the last dose.

During the study, if a female subject exposed to the study drug becomes pregnant, she must discontinue study treatment. The investigator must report to the sponsor within 24 hours of noticing the event and submit the "Innovent clinical Study Pregnancy Report/Follow-Up Form".

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

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

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

If the subject also experiences a SAE during the pregnancy, the CFDA SAE Report Form should also be filled out and reported according to SAE's procedures.

7.2.1.8 Time limits of documenting and reporting AEs

All AEs occurring from the time the subject signs the informed consent form to the time specified in the protocol (Table 2) (including SAEs and non-SAEs), regardless of their severity, must be collected and recorded on the AE page of the eCRF.

The investigator must fill out all the required information, including the description of the AE, start date, end date, severity, measures taken, outcome, seriousness, and causality with the investigational drug. Each AE should be documented separately.

Table 8. Reporting and follow-up of adverse events

	Reporting time limit	Visit time limit
AEs	From signing the informed consent form to *90 days* after the last dose (if the subject begins other anti-tumor therapies, only AEs related to the study drugs should be collected)	Until resolved or explainable stable determined by the investigator
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the outcome of the event is available, and the health conditions of the newborn should be followed up for at least 2 months according to the protocol

7.2.1.9 Precautions for AE documentation

Diagnosis, signs, and symptoms

If a diagnosis is already made, the eCRF should record the diagnosis instead of individual symptoms and signs (such as hepatic failure rather than jaundice, transaminase increased, and asterixis). However, if the signs and symptoms cannot be attributed to a definitive diagnosis, each independent event should be documented in the eCRFs as an AE or SAE. Update the report with visit information if a diagnosis is confirmed later.

AEs secondary to other events

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

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs. The initial severity should be documented, and the information should be updated if the event exacerbates.

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

Abnormalities in laboratory tests/vital signs

All clinically significant laboratory test abnormalities should be reported as AEs. It is the responsibility of the investigator to review all abnormal laboratory test results, and to make medical judgments as whether each abnormal laboratory test result should be reported as an AE.

Death

During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs, regardless of the causality with the investigational drug.

When recording a death event, if the cause of death is clear, the cause of death is recorded as an adverse event with the result of the adverse event being death, and the event is reported as an SAE; if the cause of the death is unknown at the time of reporting , "Death with Unknown Cause" should be recorded on the Adverse Event Form of the eCRF and the "Death with Unknown Cause" should be reported as an SAE first before further investigation is carried out to find the exact cause of death.

Pre-existing medical conditions

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

Hospitalization and prolonged hospitalization, or surgery

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

$\frac{4}{3}$ Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration, efficacy evaluation, etc.)

$\frac{4}{3}$ Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.

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

The investigator should fill in all required information, including AE terms

(diagnostic terms, or the record of symptoms and signs including laboratory test abnormalities if there is no diagnosis), start date, end date, severity level, whether it is an AESI, measures taken for the investigational product, treatment given for the AE, outcome, seriousness, and relationship with the investigational product. If the signs and symptoms cannot be attributed to a definitive diagnosis, each AE should be documented independently.

Progressive disease

A progressive disease is defined as the worsening of subject condition caused by the primary tumor that the investigational drug is targeting, the appearance of new lesions, or the progression of the primary lesion. Expected progressive disease should not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by progressive disease should not be reported as an SAE

8 STATISTICS

8.1 Sample Size Determination

A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin.

The sample size is estimated based on the following assumptions:

- The ORRs between IBI305 and bevacizumab group are equivalent
- The ORR of subjects in the bevacizumab groups is set to 50.0%
- The equivalence margin is taken as (-12.5%, 16.7%)
- The significance level of the two one-side test is 0.05
- 1:1 randomization

Based on the above hypotheses, a number of 218 subjects for each group is required (436 subjects in total). The sample size was estimated using PASS 2013.

8.2 Statistical Population

Intention-to-Treat (ITT): All randomized subjects.

Full Analysis Set (FAS): All randomized subjects who received at least one dose of the study treatment. This dataset is used as the primary analysis set for efficacy assessment.

Per-Protocol (PP): Based on the FAS, subjects with the predetermined minimum drug exposure and without any predetermined major protocol deviations. This dataset is used as the secondary analysis set for efficacy assessment.

Safety set (SS): Includes all randomized subjects who received at least one dose of the study treatment and have safety evaluation data. This data set is used for the safety evaluation of this study.

PK analysis set (PKAS): Includes subjects in the FAS with at least one PPK measured value.

Pharmacodynamic analysis set (PDAS): Includes all subjects in the FAS set with at least one PD measured value.

8.3 General Principles for Statistical Analyses

For continuous variables, descriptive statistics should include the count, mean, standard deviation, median, maximum, and minimum. For categorical variables, descriptive statistics will include the frequency as well as the absolute or relative percentage. Statistical analyses will be carried out using SAS 9.4.

8.4 Statistical Methods

8.4.1 Adjustments for covariates

Not applicable.

8.4.2 Managing dropouts and missing data

The analyses of primary and secondary endpoints will include data from dropouts. The management of missing data is described in the Statistical Analysis Plan.

8.4.3 Multi-center study

Since this is a multicenter study, the primary endpoint (ORR) will be listed according to study sites and treatment groups. However, individual equivalence analysis will not be conducted. Trial sites with fewer than 5 ITT subjects per treatment group will need to be combined for analysis. Details will be discussed in the data review meeting.

8.4.4 Multiple comparisons and adjustments to multiplicity

The α adjustment for multiple comparisons is not considered.

8.5 Statistical Analyses

8.5.1 Subject distribution

Refer to Figure 1: Study design schematic for the schedule of activities. The number and percentage of patients who have completed or dropped out of the study (including the reason for dropouts such as loss to follow-up, AEs, and poor compliance) are summarized based on treatment groups.

The number and percentage of subjects in each analysis set are calculated based on treatment groups.

The number and percentage of protocol deviations are calculated based on treatment groups.

8.5.2 Demographics and other baseline characteristics

Demographic information such as age, height, sex, and weight, and other baseline characteristics such as disease history (including NSCLC diagnosis, staging, previous cancer treatment, and target and nontarget lesions) are summarized using descriptive statistics.

8.5.3 Compliance and drug exposure

The required dose and the actual dose must be documented in the eCRF. Subject compliance is calculated based on the ratio of the actual dose (number of doses) to the required dose (number of doses). Subject compliance is classified into the following categories: < 80%, 80–120%, and > 120%. The number and percentage of subjects in each category will be summarized.

8.5.4 Efficacy

The efficacy analysis will be based on the FAS. Results of the PP set will also be presented.

8.5.4.1 Primary efficacy endpoint

The primary objective of this study is to determine the clinical equivalence between IBI305 + paclitaxel/carboplatin and bevacizumab + paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC). The primary endpoint is objective response rate (ORR). ORR is defined as the incidence of patients with confirmed complete response (CR) or partial response (PR), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions. Subjects without tumor assessments beyond baseline will be considered unresponsive to treatment. Subjects qualified for the evaluation of CR or PR must have at least one measurable lesion according to RECIST v1.1. The evaluation of clinical equivalence will be based on the ORR provided by the independent review committee (IRC). Results provided by the investigator will be used for sensitivity analysis.

Clinical equivalence will be declared if the 90% confidence interval of the difference in ORR between IBI305 and bevacizumab groups falls within the preset margin of (-12.5%, 16.7%). The ORR and corresponding 95% confidence interval of the two treatment groups, the ORR difference and the 90% confidence interval, as well as the ORR ratio between the two groups and the 90% confidence interval will be estimated using the generalized linear model (GLM, which includes treatment groups and stratification factors).

8.5.4.2 Secondary efficacy endpoints

The secondary endpoints for this study include DOR, DCR, progress-free survival (PFS), and overall survival (OS).

DCR is defined as the incidence of patients with confirmed complete response (CR), partial response (PR), and stable disease (SD), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

OS refers to the time from the date of randomization to the date of death (of any cause). For subjects who are still alive at the time of the analysis, their survival time is censored on the last known alive date. PFS refers to the time from the date of randomization to the date of first documented PD or death, whichever occurs first. The investigator will assess PD using RECIST v1.1. Subjects who do not progress or die will be censored on the date of the last tumor assessment. Subjects without tumor assessments after baseline are censored on their date of randomization.

Median OS and its 95% CI will be estimated using the Kaplan-Meier method. The survival curve will be plotted. The hazard ratio (HR) between the two groups and its 95% CI will be estimated using a Cox model. The Cox model includes treatment groups and stratification factors. DOR and PFS will be analyzed using the same method as for OS. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

8.5.4.3 Sensitivity analysis

The center effect (fixed or random) will be considered in the primary and secondary endpoints analysis models (GLM or Cox).

8.5.4.4 Antibody and efficacy analysis

Subjects who develop antibodies during the clinical study will be summarized in detail. The difference in efficacy between subjects with and without antibodies will be compared if necessary.

Changes in PK parameters and steady-state trough concentrations of subjects with positive ADA are analyzed.

8.5.5 Exploratory analysis

Pharmacodynamic parameters: The changes in the serum VEGF level at different time points are described, and inter-group comparisons are carried out when necessary (based on the PD dataset)

Steady-state trough concentrations of the drug: The level of trough concentration is described and inter-group comparisons are carried out when necessary (based on the PPK dataset)

8.5.6 Interim analysis

No interim analysis is planned for this study.

8.5.7 Stratified analysis

Efficacy analysis of different levels of subjects is conducted based on the random stratification factors

8.5.8 Safety analysis

The safety analysis is based on the safety analysis set.

8.5.8.1 Adverse events

All adverse events (AE) will be coded using MedDRA and graded using CTCAE v4.03. All TEAEs, TEAEs ≥ grade 3, SAEs, drug-related TEAEs, drug-related SAEs, TEAEs resulting in the termination of study drugs, TEAEs resulting in the termination of study, and AESIs will be listed based on system organ class, preferred terms, and groups and the corresponding numbers and percentages of subjects will be summarized. In addition, the severity of TEAEs and relevance to the study drugs will also be summarized system organ class, preferred terms, and treatment groups.

8.5.8.2 Laboratory tests

All laboratory test results and changes relative to baseline will be summarized by scheduled time point and treatment group using descriptive statistics. Laboratory abnormalities will be listed.

8.5.8.3 ECG examinations

Results of ECG and changes relative to baseline will be summarized using descriptive statistics.

8.5.8.4 Vital signs, physical examinations, and other safety examinations

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

Results of physical examinations are listed by treatment groups.

8.5.8.5 Concomitant medications

Concomitant medications are non-study medications that meet one of the followings:

(1) Any drug therapy started during or after the first dose of the study treatment;

(2) Any drug therapy started before the first dose of the study treatment and continued after the first dose of the study treatment. Concomitant medications are listed by treatment groups.

9 QUALITY ASSURANCE AND QUALITY CONTROL

According to GCP principles, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems based on standard operating procedures (SOP), to ensure that the implementation of the clinical trial and the collection, documentation, and reporting of trial data is in accordance with the protocol, GCP, and applicable regulatory requirements.

To ensure that the data is reliable and processed correctly, there should be quality control for every step during the data processing.

In addition, the Clinical Quality Assurance (CQA) Department of the sponsor and/or CRO may conduct regular audits of the study process, including but not limited to auditing the study site, on-site visits, central laboratory, suppliers, clinical database, and the final clinical study report. Regulatory authorities may also conduct inspections during the trial or at any time after the trial is completed. The investigator and the research institution must allow the sponsor's representative and regulatory authorities to review source data.

9.1 Clinical Monitoring

The sponsor has authorized Wuxi Clinical Co., Ltd. to conduct clinical monitoring for this study. The clinical research associate (CRA) should follow the SOPs of Wuxi Clinical Co., Ltd. when carrying out monitoring, and has the same rights and responsibilities as the sponsor's monitor. The CRA should maintain regular communication with the investigator and the sponsor.

Before the start of the study, the associate monitor assess the qualifications of each study site, and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the study, the CRA will be responsible for confirming whether written informed consent is obtained from all subjects, and whether data documentation is accurate and complete. At the same time, the CRA will compare data entered in to the eCRF with source data, and notify the investigator of any errors or omissions. The CRA will also verify protocol compliance of the study site, as well as the dispensing and storage of investigational drugs to ensure protocol requirements are met.

The monitoring visit will be conducted in accordance with applicable statutes and regulations. Each site receives regular monitoring visits from the time the subjects are enrolled. The CRA should submit a written report to the sponsor after each monitoring visit to the study site.

9.2 Data Management/Coding

The Data Management and Biostatistics Department of Wuxi Clinical Co., Ltd will process data generated from this study in accordance with relevant SOPs.

This study will use an electronic data capture (EDC) system. Trial data will be entered into the eCRF by the investigator or authorized study personnel. Prior to launching of the study site or data entry, the investigator and authorized study personnel will receive appropriate training, and appropriate safety measures will be taken.

All data are input in Chinese. The eCRF should be completed during or soon after each visit, and should be constantly updated to ensure that it reflects the latest status of the subject. To avoid discrepancies in outcome assessments between different evaluators, ensure that baseline and all subsequent efficacy and safety assessments for the same subject are performed by the same person. The investigator must review trial data to ensure the accuracy and correctness of all data entered into the eCRF. During the study, the investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. The investigator needs to sign all verified data electronically.

The CRA will review the eCRF, and evaluate its completeness and consistency. The CRA will also compare the eCRF with the source documents to ensure the consistency of critical data. Data entry, corrections, or modifications are completed by the investigator or designated staff. The CRA do not have access to data entry. The data in eCRF is submitted to the data server, and any changes to the data will be documented in the audit trail, including the reason for the change, the name of the operator, as well as the time and date of the change. The roles and permissions of study personnel responsible for data entry will be predetermined. The CRA or data manager will submit data queries in the EDC system, and study personnel shall respond to the queries. The EDC system will record the audit trail of each query, including the name of the investigator, as well as the time and date.

Unless otherwise specified, the eCRF should be considered simply as a form for data collection and not a source document. A source file is used by the investigator or hospital, relevant to the subject, and can prove the existence of the subject, inclusion criteria, and all records of participation in the study, including laboratory records, ECG results, memorandum, pharmacy dispensing records, and subject folders.

The investigators are required to maintain all source documents and to offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each subject, regardless of the duration of the subject's participation in the study. The study number and subject number in all supporting documents (such as laboratory records or hospital records) submitted along with the eCRF should be carefully verified. All personal privacy information (including the name of the subject) should be deleted or be made indecipherable in order to protect subject privacy.

The investigator could be automatically added to the eCRF with his/her user ID. The investigators verify that the record have been reviewed and that the data are accurate with an electronic signature. The electronic signature is completed with the investigator's user ID and password. The system automatically attaches the date and time of the signature. The investigator could not share the user ID and password with other personnel. If data in the eCRF need to be modified, the procedures defined by the EDC system have to be followed. All modifications and reasons for the changes are recorded in the audit trail.

Training on the EDC system will be provided to study personnel at the study site.

Adverse events, and concurrent diseases/medical history will be coded. The medical dictionary used for coding will be described in the Clinical Study Report (CSR).

9.3 Audits and Inspections

The sponsor or its representative (WuXi Clinical Co., Ltd) may conduct quality assurance audits on the study site, database, and relevant study-related documents. Also, regulatory authorities may also decide to inspect the study site, database, and relevant study-related documents at its own discretion. The aim of audits and inspections is to systematically and independently check all study-related procedures and documents to ensure that the clinical study is being carried out in accordance with requirements of the trial protocol, GCP, Declaration of Helsinki, and applicable regulations. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

10 ETHICS

10.1 Independent Ethics Committee

The sponsor and its designated personnel will prepare all documents to be submitted to the independent ethics committee (IEC) of each study site. The trial protocol, informed consent form (ICF), investigators brochure, subject recruitment material or advertisements (if applicable), as well as other documents required by regulations must be submitted to the IEC for approval. Prior to the start of the study, written approval from the IEC must be obtained and provided to the sponsor. The IEC approval must clearly state the title, number, and version of the study protocol as well as the version of other documents (e.g. ICF) and the date of approval. The investigator must notify the sponsor of the IEC's written comments concerning delays, suspension and re-approval.

The study site must follow the requirements of the IEC. IEC requirements may include submitting the revised protocol, ICF, or subject recruitment material to the IEC for approval, local regulatory requirements for safety reports, and regular reports, updates, and submitting the final report as per IEC requirements. The above documents as well as the IEC approval must be provided to the sponsor or its designated personnel.

10.2 Implementation of Ethical Principles

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements (CPMP/ICH/135/95), and applicable statutes and regulations related to drugs and data protection in the country in which the study is conducted.

The GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. To protect the rights, safety, and healthy of subjects, this study will be carried out in accordance with GCP and applicable national regulations, as well as ethical principles outlined in the Declaration of Helsinki.

The investigator is required to follow the procedures specified in this protocol and must not change the procedures without the permission from the sponsor. Protocol deviations will be reported in accordance with the requirements of each ethics committee.

10.3 Subject Information and Informed Consent

Prior to undergoing any study procedure, the ICF should be used to explain to potential participants the potential risks and benefits of this study. The informed consent form should be in a language that is simple and be easy to understand. The ICF should state that informed consent is voluntary, emphasize the potential risks and benefits of participating in this study, and that the subject may withdraw from the study at any time. The investigator may only enroll a subject after fully explaining the details of the study, answering questions to the subject's satisfaction, giving the subject sufficient time for consideration, and obtaining written consent from the subject or his/her legal representative. All signed ICF must be retained in the investigator's documents or the subject's folder.

The investigator is responsible for explaining the contents of the ICF and obtaining the ICF signed and dated by the subject or his/her legal representative prior to starting the study. The investigator should provide the subject with a copy of the signed ICF. The investigator must document the informed consent process in the source document of the trial.

10.4 Protection of Subject Data

Information about data protection and privacy protection will be included in the ICF (or in some cases, in a separate document).

Study personnel must ensure that the privacy of clinical trial subjects is protected. In all documents submitted to the sponsor, the clinical trial subjects must only be identified with subject number and not with the full name.

Additional precautions should be taken to ensure the confidentiality of the documents and to prevent the identification of subjects based on genetic data. However, under special circumstances, some personnel may be permitted to see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, designated physician, or investigator will have access to the subject identification code and the subject's genetic data. In addition, regulatory agencies may request access to relevant documents.

11 STUDY MANAGEMENT

11.1 Organizational Structure

Refer to Table 3 for relevant collaborating parties.

Table 9. Organizational structure

Sponsor	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China Telephone: (+86) 0512-69566088
Contract research organization	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000
Data management and biostatistics	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000

11.1.1 Independent review committee

Central imaging evaluation will be performed by Parexel China Co., Ltd. The CT/MRI images of each subject will be evaluated using RECIST v1.1.

11.2 Archiving of Study Documents

Clinical trial documents (protocol and amendments, completed eCRFs, signed ICFs, etc.) must be retained and managed as per GCP requirements. The study site must retain these documents for 5 years after the completion of the study. The sponsor should retain clinical trial data for 5 years after the investigational drug is approved for marketing.

Study documents should be retained properly for future access or data traceability. Safety and environmental risks should be considered when retaining documents.

The documents associated with the study may only be destroyed with the written consent of the sponsor and the investigator. Study documents may be transferred to other parties that comply with or other locations that meet retention requirements only after the sponsor is notified and written consent thereof is obtained.

11.3 Access to Source Data/Documents

Source data refers to source records of subject data obtained from a clinical study. These source records are source documents, which include but are not limited to medical records (hospital records, nursing records, pharmacy dispensing records, etc.), electronic data, screening logs, laboratory test results, as well as medical device test results (ECG, CT/MRI, etc.). All source documents associated with the trial are retained by the study site and the investigator. The original ICFs will be retained according to standard practices developed by the clinical trial institution.

The investigator will prepare sufficient and accurate source documents for each randomized subject in order to document all examination results and other relevant data, and retain these documents properly.

During the study, the CRA will conduct on-site visits to verify protocol compliance, EDC data entry, documentation of subjects' medical history, drug inventory, and whether the study is carried out in accordance with applicable regulations. In addition, regulatory authorities, IRB, IEC, and/or the quality assurance department of the sponsor will verify source data and/or conduct on-site audits or inspections. The investigator should allow direct access to documents associated with the study, including medical records of subjects.

11.4 Protocol Revisions

The sponsor and the investigator must both agree on any appropriate protocol revisions during the course of the study. The sponsor shall ensure that the protocol revision is submitted to the regulatory authority in a timely manner.

All protocol revisions must be submitted to the IEC, and if needed, to regulatory authorities for approval. Revisions may only be implemented after approval from the IEC and regulatory authorities (if needed) is obtained (except for changes to eliminate immediate risks to subjects).

11.5 Investigator's Responsibilities

The investigator will conduct this study in accordance with the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP, and applicable regulations. Details of the investigator's responsibilities are list in Chapter 5 (Investigator's Responsibilities) of the Chinese GCP (NMPA order No. 3).

11.6 Study Termination

The study may be terminated after a discussion between relevant parties if the investigator or the sponsor becomes aware of circumstances or events that could jeopardize the subjects if the study is continued. The sponsor may also decide to terminate the study even without such findings.

Reasons for study termination include but are not limited to:

- Unexpected, serious, or unacceptable risks to enrolled subjects
- Slow recruitment
- The sponsor decides to suspend or discontinue the development of the drug

11.7 Publishing Policies

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish study results. The investigator shall not publish any data relevant to this study (posters, abstracts, papers, etc.) without prior communication with the sponsor. Information on the publishing policies of the sponsor and investigator will be described in the clinical trial agreement.

11.8 Finance and Insurance

The sponsor will purchase insurance for subjects participating in the study in accordance with local regulations, and bear the cost of treatment and corresponding financial compensation for the subjects who suffer injury during the study due to the investigational drug or the study process. Insurance related terms shall be saved in the study folder.

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13 APPENDIX

13.1 Appendix I

Eastern Cooperative Oncology Group (ECOG) Performance Status Score

Score	Performance Status
0	Fully active, and able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activities but able to move around easily and carry out work of a light or sedentary nature, e.g. light house work or office work
2	Capable of moving around easily and self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or wheelchair more than 50% of waking hours
4	Bedridden and incapable of self-care
5	Death

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

13.2 Appendix II

Calculation of body surface area

Body surface are (m2) = 0.00616 height (cm) + 0.01286 weight (kg) - 0.1529

Creatinine Clearance (Cockroft-Gault Equation)

Ccr (mL/min) = [(140 - age) x weight (kg)]/[72 x Scr (mg/dL)]

Female subjects: results × 0.85

1 mg/dL = 88.41 μmol/L

Carboplatin Dose (Calvert Equation)

Carboplatin dose (mg) = target AUC (mg/mL/min) × [creatinine clearance rate (mL/min) + 25]

Note: During the study, if the carboplatin dose calculated using the Calvert equation excessively exceeds the usual clinical dose, choose one of the following two methods to ensure the patient safety:

1. Retest the serum creatinine and re-calculate the dose (preferred option).

2. Based on clinical experience, the investigator may choose the highest dose tolerated by the subject. The dose should remain unchanged for the subsequent cycles.

13.3 APPENDIX 3

RECIST v1.1

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or not measurable as follows:

1.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be documented as not measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Not measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with a short axis ≥10 and <15 mm) as well as truly not measurable lesions. Lesions considered truly not measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis involving the skin or lungs, abdominal masses/ abdominal organomegaly identified by physical exam but not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding measurable bone lesions, cystic lesions, and lesions with prior locoregional treatment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (such as CT or MRI) can be considered as measurable lesions if the soft tissue components meet the definition of measurability described above.
- Blastic bone lesions are not measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor not measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these noncystic lesions are preferred for selection as target lesions.

Lesions with prior locoregional treatment:

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

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be documented with metric symbols. Calipers should be used if clinical assessments are required. All baseline evaluations should be performed as close as possible to the beginning of the treatment but never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and its diameter is ≥10 mm as assessed using calipers (e.g. skin nodules). For skin lesions, documentation by color photography including a plotting scale to estimate the size of the lesion is recommended. As noted above, when lesions can be evaluated by both clinical examination and imaging evaluation, the latter should be undertaken since it is more objective and may also

be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they have clear boundaries and are surrounded by aerated lung tissues.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound should not be used for measuring lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is recommended. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy: The utilization of these techniques is not recommended for objective tumor evaluation. However, they can be used to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper limit of normal, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into the protocol on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases if required by the protocol (for example, residual lesions in tumor types such as seminoma, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), cytological confirmation of the neoplastic origin of any effusion that appears or worsens during

treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

2.2 Baseline Documentation of "Target" and "Non-Target" Lesions

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those with reproducible repeated measurements. It may be the case that, the largest lesion does not have reproducible measurements, in which circumstance the next largest lesion with reproducible measurements should be selected.

Lymph nodes merit special mention since their normal anatomical structures may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must have a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is invaded by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant measurable node. In this example, 20 mm should be reported as the node measurement. All other pathological nodes (those with a short axis ≥ 10 mm but < 15 mm) should be considered non-

target lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions; short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". In addition, it is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response Criteria

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduced short axis of <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions vs. the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions vs. the smallest sum during the study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also have an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum of diameters during the study as reference.

2.3.2 Special notes on the assessment of lymph nodes which are target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as during the baseline examination), even if the nodes regress to below 10 mm at the time of the study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must have a

short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that are "too small to measure". During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurements of these lesions are potentially non-reproducible, therefore providing this default value will prevent false responses or progressions caused by measurement errors. To reiterate, however, if the radiologist is able to provide an actual measurement, that value should be recorded, even if it is below 5 mm.

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

2.3.3 Evaluation of non-target lesions

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

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

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

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

2.3.4 Special notes on the assessment of progression of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: *When the patient also has measurable lesions*. In this setting, to achieve 'unequivocal progression' on the basis of the non-target lesion, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR of the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A minimal increase in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only lesions that are not measurable. This circumstance arises in some phase III trials when the presence of measurable lesions is not a criterion for study enrollment. The same general concepts apply here as well. However, in this instance there are no measurable lesions to factor into the interpretation of an increase in non-measurable lesion burden. Because worsening in non-target lesion cannot be easily quantified (by definition: if all lesions are truly not measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall lesion burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase of diameter in a measurable lesion). Examples include an increase in pleural effusion from "trace" to "large amount", an increase in lymphangitic lesion from localized to widespread, or a description in the protocol such as "sufficient to require a change in therapy". If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to diseases that are not measurable, the very nature of these diseases makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on the detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumors (for example, some new bone lesions which may be simply healed or flare of pre-existing lesions). This is particularly

important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported by a CT scan as a "new" cystic lesion, while it is actually not.

A lesion identified during a follow-up in an anatomical location that is not discovered during the baseline scan is considered a new lesion and will indicate disease progression. For example, a patient with a visceral disease at baseline has a brain CT or MRI which reveals metastases. The patient's brain metastases are considered evidence of PD even if he/she does not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new lesion. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" lesions). New lesions on the basis of FDG-PET imaging can be identified as follows:

a. A negative FDG-PET at baseline and a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
If the positive FDG-PET at follow-up corresponds to a new lesion site confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new lesion site on CT, additional follow-up CT scans are needed to determine if there is truly progression at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing lesion site on CT that is not progressing according to the anatomic images, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy, so the study protocol should clearly state if post-treatment assessments are to be considered when determining best overall response. The study protocol must specify how any new therapy introduced before progression will affect best response designation. Assignment of best overall response for the patient will depend on the findings of both target and non-target lesions and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the

protocol requirements, confirmatory measurement may also be required. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine which one is the "best overall response".

2.4.1 Time point response

It is assumed that at each time point specified by the study protocol, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2 Missing assessments and non-evaluable targets

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

2.4.3 Best overall response: all time points

The best response is determined once all the data for the patient is obtained.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, the best overall response of a patient who has SD at the first assessment, PR at the second, and PD at the last is PR). When SD is believed to be best response, it must also meet the minimum time from baseline specified by the protocol. If the minimum time is not met, otherwise SD is the best time point response, the patient's best response depends on subsequent assessments. For example, if a patient has SD at the first assessment, PD at the second and does not meet the minimum duration for SD, his/her best response is PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

2.4.4 Special notes on response assessment

When nodal lesions are included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even if the nodes are normal in size in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the case report form (CRF).

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must explain how missing data/assessments will be addressed in the determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response. Instead, it is a reason for stopping the study treatment. The objective response status of this type of patients is to be determined by evaluation of target and non-target lesions as shown in Table 1–3.

Conditions that define "early progression, early death, and non-evaluability" are study specific and should be clearly described in each study protocol (depending on treatment duration and treatment periodicity).

In some circumstances it may be difficult to distinguish a residual lesion from normal tissues. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (by fine needle aspirate/biopsy) before assigning a status of complete response.

Like a biopsy, FDG-PET may also be used to upgrade a response to a CR in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be pre-defined in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Table 1. Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not all were evaluated	No	PR
SD	Non-PD or Not all were evaluated	No	SD
Not all were evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

Table 2. Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all were evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = not evaluable.

a "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since SD is increasingly used as an endpoint for assessment of efficacy in some trials, thus assigning this category in the absence of measurable lesions is not advised.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression is suspected.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided that the minimum duration for SD is met, otherwise PD
CR	PD	SD provided that the minimum duration for SD is met, otherwise PD
CR	NE	SD provided that the minimum duration for SD is met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided that the minimum duration for SD is met, otherwise PD
PR	NE	SD provided that the minimum duration for SD is met, otherwise NE
NE	NE	NE

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

a If CR is truly achieved at the first time point, then any lesions seen at a subsequent time point, even those meeting PR criteria relative to baseline, make the disease PD at that time point (since lesions must have reappeared after CR). Best response would depend on whether the minimum duration for SD is met. However, sometimes CR may be claimed and subsequent scans suggest small lesions are likely still present, while in fact the patient have PR instead of CR at the first time point. Under these circumstances, CR should be changed to PR and the best response is PR.

2.5 Frequency of Tumor Re-Evaluation

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

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

2.6 Confirmation of Measurements/Duration of Response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement errors. This will also permit appropriate interpretation of results in the context of historical data. Response confirmation has been traditionally required in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements after study entry must have met the minimum interval for SD (generally not shorter than 6–8 weeks) defined in the study protocol at least once.

2.6.2 Duration of overall response

The duration of overall response is measured from the time CR/PR measurement criteria are first met CR/PR (whichever is first documented) until the date when recurrent or progressive disease is objectively documented for the first time (using the shortest time to progressive disease documented during the study as reference).

The duration of overall complete response is measured from the time CR measurement criteria are first met until the date when recurrent disease is objectively documented for the first time.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from the date of randomization) until the criteria for progression are met, using the smallest sum during the study as reference (if the baseline sum is the smallest, then it is used as the reference for the calculation of PD).

The clinical relevance of the duration of stable disease varies with different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for the determination of stable disease.

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

14 INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized, double-blind, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin vs. bevacizumab plus paclitaxel/carboplatin in treatment-naive patients with advanced or relapsed non-squamous NSCLC.

Protocol No.: CIBI305A301

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

Instructions for the Investigator: Please sign and date this signature page, type the investigator's name and job title, as well as the name of the study site, and return this document to Innovent Biologics (Suzhou) Co., Ltd.

I have read the entire contents of this study protocol and shall perform the study as required:

Investigator's signature: _____ Date: _____

Name (in Print): _____

Job Title: _____

Name and Address of Study Site: _____

_____

_____

CIBI305A301 STUDY PROTOCOL V3.0 REVISION OVERVIEW

Protocol Version: v3.0
Version Date: Sep. 25, 2017

原文	After revision	Reason for amendment
P1: Cover **Version and Date:** Sep. 26, 2016/Version 2.0	Version Date/No.: Sep. 25, *2017/Version 3.0*	● Protocol version number and version date are updated
P1: Cover **Sponsor Contact:** Zhou Hui (Medical Director) Tel: (+86) 021-31652896 E-mail: hui.zhou@innoventbio.com	**Sponsor Contact:** Zhou Hui, *Senior Medical Director* Tel: (+86) 021-31652896 E-mail: hui.zhou@innoventbio.com	● The contact of sponsor is updated
P2: SIGNATURE PAGE Title Medical Director	Title *Senior Medical Director*	● The contact of sponsor is updated
P4: Diagnosis and main inclusion criteria: **Inclusion Criteria:** 2) Male or female ≥ 18 and ≤ 70 years old	2) Male or female ≥ 18 and ≤ *75* years old	● The upper age limit is modified

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P4: Diagnosis and main inclusion criteria: **Inclusion Criteria:** 3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIb), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types	3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage **IIIB**), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types	• The medical term is modified
P4: Diagnosis and main inclusion criteria: **Inclusion Criteria:** 4) Histologically or cytologically confirmed EGFR wild type	4) Histologically or cytologically confirmed EGFR wild type **or non-sensitive mutation type**	• The enrollment of patients carrying the non-sensitive mutant type of EGFR is added
P4: Diagnosis and main inclusion criteria: **Inclusion Criteria:** 8) Laboratory results during screening: 9) Routine blood test: WBC ≥ 3.0 × 10^9/L, ANC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and hemoglobin ≥ 90 g/L	8) Laboratory results during screening: a) Routine blood test: WBC ≥ 3.0 × 10^9/L, ANC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and hemoglobin ≥ 90 g/L	• The laboratory test results are unified,

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10) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis 11) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ from urinalysis dipstick at baseline, a 24-h urine should be collected with total protein content < 1 g 12) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment	b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for patients without liver metastasis, or ALT and AST < 5 × ULN for patients with liver metastasis c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline *urinalysis* must have undergone 24 h urine collection with total protein content < 1 g d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment	
P4: Diagnosis and main inclusion criteria: **Inclusion Criteria:** 13) Able to comply with study protocol	9) Able to comply with study protocol	• The No. of inclusion criteria is changed
P4: Diagnosis and main inclusion criteria: **Inclusion Criteria:** 14) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or	10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants)	• The No. of inclusion criteria is changed

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contraceptive implants) during the study and for 6 months after the infusion of the study drug	during the study and for 6 months after the infusion of the study drug	
P5: Exclusion Criteria: 1) Prior chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIb not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible	1) Prior **systemic** chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage *IIIB* not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible	• Patients who clearly underwent systemic chemotherapy or targeted therapy need to be excluded
P5: Exclusion Criteria: 3) Histologically or cytologically confirmed EGFR mutation type. Subjects with unknown EGFR status for various reasons could be enrolled	3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18-point mutation (G719X), exon 19 deletion, and exon 21-point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll.	• The definition of EGRF sensitive mutations are clarified
P5: Exclusion Criteria:		• The amount of blood coughed up

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4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL	4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL **each** time	each time is specified
P5: Exclusion Criteria: 6) History of brain metastasis, spinal cord compression, or carcinomatous meningitis, or brain metastasis confirmed by CT or MRI during screening	*6) **Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage;***	• The description of brain metastasis is clarified
P6: Exclusion Criteria: 9) Subject who received minor surgery (including catheterization) within 48 h prior to the first dose of the study drug	9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (**Outpatient/inpatient surgery requiring locoregional anesthetics**, including *central line insertion*)	• The definition of minor surgery is clarified
P6: Exclusion Criteria: 10) Currently or recently (within 10 days prior to the first dose of study drug) used aspirin (> 325 mg/day) or other nonsteroidal anti-inflammatory drugs known to inhibit platelet function	10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function **for 10 consecutive days**	• The unacceptable number of days of use is clarified

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P6: Exclusion Criteria: 11) Currently or recently (within 10 days prior to the first dose of study drug) received treatment with full dose oral or parenteral anticoagulants or thrombolytic agents. However, anticoagulants for prophylaxis are accepted.	11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents **for 10 consecutive days**. However, anticoagulants for prophylaxis are accepted	• The unacceptable number of days of use is clarified
P6: Exclusion Criteria: 13) Uncontrolled hypertension (systolic greater than 150 mmHg and/or diastolic greater than 100 mmHg), history of hypertensive crisis or hypertensive encephalopathy	13) Uncontrolled hypertension **after treatment** (systolic greater than *140* mmHg and/or diastolic greater than *90* mmHg), history of hypertensive crisis or hypertensive encephalopathy	• Correction
P6: Exclusion Criteria: 18) Subjects with pulmonary fibrosis history or active pneumonia shown on CT during screening	18) *Subjects with current interstitial lung disease* or CT showing active pneumonia during screening	• The exclusion of patients with interstitial lung disease is clarified
P6: Exclusion Criteria: 19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery,	19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal	• Thyroid papillary carcinoma is excluded

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ductal carcinoma in situ after radical surgery	carcinoma in situ after radical surgery, or **papillary thyroid carcinoma**	
P6: Exclusion Criteria: 20) Subjects with autoimmune disease	20) Subjects with **active** autoimmune disease	• The exclusion of active autoimmune diseases is clarified
P6: Exclusion Criteria: 21) Subjects with positive test result of HBsAg, and peripheral blood HBV DNA titer ≥ 1×10^3 copies/L; subjects with positive test result of HBsAg and peripheral blood HBV DNA titer < 1×10^3 copies/L are eligible if the investigator determine that the subject's chronic hepatitis B is stable and participation in the study would add no further risks to the subject	21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1×10^3 copies/L **or ≥ 200 IU/mL**; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1×10^3 copies/L **or < 200 IU/mL** might be eligible if the investigator determines that the subject's chronic hepatitis B infection is stable and participation in the study would add no further risks to the subject	• Correction
P10: **Table 1. Schedule of follow-up visits** Cycle (C) and day (D) | C4D1 Vital signs | *X*	Cycle (C) and day (D) | C4D1 Vital signs | *X*	• Format adjustment

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Physical examination	*X*	Physical examination	*X*	
12-Lead ECG	*X*	12-Lead ECG	*X*	
Routine blood test [d]	*X*	Routine blood test [d]	*X*	
Blood chemistry [d]	*X*	Blood chemistry [d]	*X*	
Immunogenicity [g]	*X*	Immunogenicity [g]	*X*	
Study drug (IBI305 or bevacizumab) [j]	*X*	Study drug (IBI305 or bevacizumab) [j]	*X*	
Chemotherapy (paclitaxel + carboplatin) [k]	*X*	Chemotherapy (paclitaxel + carboplatin) [k]	*X*	
Concomitant medications	*X*	Concomitant medications	*X*	
AEs	*X*	AEs	*X*	
Pharmacokinetics (PK)	*X*	Pharmacokinetics (PK)	*X*	
P11:				• The requirement for urinalysis is

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e) Prior to each IBI305/bevacizumab infusion, test paper should be used to examine urinary protein.	e) A *urinalysis* is required before each IBI305/bevacizumab infusion to test urine protein.	clarified
P11: f) Women of childbearing age should undergo serum pregnancy tests.	f) Women of childbearing age should undergo a *serum/urine pregnancy test*.	• It is clarified that the urine pregnancy test can be performed
P12: i) All subjects should undergo tumor tissue EGFR testing, but the test does not need to be repeated if it can be confirmed with relevant reports that the test has already been completed at the trial site. EGFR testing will be carried out at the laboratory of each trial site.	i) All subjects should undergo tumor tissue EGFR testing.	• Correction
P12: j) Each treatment cycle for the investigational drug is 3 weeks long. IBI305 or bevacizumab is administered on D1 of each cycle, at 15 mg/kg during combination treatment with chemotherapy and 7.5 mg/kg during monotherapy, until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or study completion, whichever occurs first. After all assessments are	j) Each treatment cycle of the investigational product contains 3 weeks. The dose of IBI305 or bevacizumab is 15 mg/kg when used in combination with chemotherapeutic drugs and 7.5 mg/kg in the maintenance monotherapy, given on D1 of every treatment cycle until progressive disease (PD), unacceptable toxic reactions, withdrawal of informed consent, loss to follow-up, death, or end of study, whichever occurs first. After	• The time window for the administration of the first dose was clarified

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completed, the study drug is administered followed by chemotherapy. After all assessments are completed, the study drug is administered followed by chemotherapy.	all assessments were completed, the study drug was administered followed by chemotherapy. **The first dose of study drug was completed within 24 h after randomization.**	
P12: l) Study sites that are implementing version 2.0 of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h before the first dose of the study drug (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 h prior to the dose in C4, within 1 hour prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.	~~Deleted from the original text~~	• Deletion
m) Study sites that are implementing version 2.0 of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: Within 1 h prior to the first dose of the study	~~Deleted from the original text~~	• Deletion

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drug (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and at the end of treatment visit. Samples were tested at the designated central laboratory.		
P18: Study Background However, despite surgery, some patients develop distance metastases that eventually lead to death[5]. Surgery is not possible for most patients with clearly diagnosed stage IIIb and IV as well as some patients with stage IIIa NSCLC[4]. Comprehensive treatment based on systemic therapy is used to maximize patient survival, control progressive disease, and improve the quality of life[6]	However, surgical operations cannot be carried out for almost all stage IV patients with a clear diagnosis, most stage *IIIB* patients, and some stage *IIIA* patients of NSCLC [4]. These patients are mostly given a comprehensive treatment based on systemic therapy to maximize their survival and control the degree of disease progression while improving their quality of life [6].	• The medical term is modified
P26: 4.1 Inclusion Criteria 2) Male or female ≥ 18 and ≤ 70 years old	2) Male or female ≥ 18 and ≤ *75* years old	• The upper age limit is modified
P26: 4.1 Inclusion Criteria 3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIb), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be	3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage *IIIB*), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be	• The medical term is modified

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categorized according to the main cell types	categorized according to the main cell types	
P**26: 4.1 Inclusion Criteria** 4) Histologically or cytologically confirmed EGFR wild type	4) Histologically or cytologically confirmed EGFR wild type **or non-sensitive mutation type**	• The enrollment of patients carrying the non-sensitive mutant type of EGFR is added
P**26: 4.1 Inclusion Criteria** 8) Laboratory results during screening: 9) Routine blood test: WBC ≥ 3.0 × 109/L, ANC ≥ 1.5 × 109/L, platelets ≥ 100 × 109/L, and hemoglobin ≥ 90 g/L 10) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis 11) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2 + in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline must have undergone 24 h urine collection with total protein content <1 g 12) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days	8) Laboratory results during screening: a) Routine blood test: WBC ≥ 3.0 × 10^9/L, ANC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and hemoglobin ≥ 90 g/L b) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for patients without liver metastasis, or ALT and AST < 5 × ULN for patients with liver metastasis c) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline *urinalysis* must have undergone 24 h urine collection with total protein content < 1 g d) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment	• The laboratory test results are unified

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prior to the study treatment		

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P26: 4.2 Exclusion Criteria 1) Prior chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIb not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible	1) Prior **systemic** chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage **IIIB** not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible	• Patients who clearly underwent systemic chemotherapy or targeted therapy need to be excluded
P27: 3) Histologically or cytologically confirmed EGFR mutation type. Subjects with unknown EGFR status for various reasons could be enrolled.	3) Histologically or cytologically confirmed EGFR-sensitive mutation type (including exon 18 point mutation (G719X), exon 19 deletion, and exon 21 point mutations (L858R and L861Q)). Subjects with unknown EGFR status for various reasons might enroll.	• The definition of EGRF sensitive mutations are clarified
P27: 4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL	4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL **each** time	• The amount of blood coughed up each time is

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each time		specified
P27： 6) History of brain metastasis, spinal cord compression, or carcinomatous meningitis, or brain metastasis confirmed by CT or MRI during screening	*6) **Symptomatic CNS metastasis; subjects with asymptomatic brain metastasis or subjects who are symptomatically stable after treatment for brain metastasis might enroll if the following criteria are met: measurable lesions outside the CNS; no midbrain, pons, cerebellum, medulla or spinal cord metastasis; no history of intracranial hemorrhage;***	• The description of brain metastasis is clarified
P27： 9) Subject who received minor surgery (including catheterization) within 48 h prior to the first dose of the study drug	9) Subjects who received minor surgery within 48 hours prior to the first dose of the study treatment (**Outpatient/inpatient surgery requiring locoregional anesthetics**, including *central line insertion*)	• The definition of minor surgery is clarified
P27： 10) Currently or recently (within 10 days prior to the first dose of study drug) used aspirin (> 325 mg/day) or other nonsteroidal anti-inflammatory drugs known to inhibit platelet function	10) Currently or recently (within 10 days prior to the first dose of the study treatment) used aspirin (> 325 mg/day) or other known NSAIDs to inhibit platelet function **for 10 consecutive days**	• The unacceptable number of days of use is clarified

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P27： 11) Currently or recently (within 10 days prior to the first dose of study drug) received treatment with full dose oral or parenteral anticoagulants or thrombolytic agents. However, anticoagulants for prophylaxis are accepted.	11) Currently or recently (within 10 days prior to the first dose of the study treatment) received treatment with full dose oral or parenteral anticoagulant or thrombolytic agents **for 10 consecutive days**. However, anticoagulants for prophylaxis are accepted	• The unacceptable number of days of use is clarified
P27： 13) Uncontrolled hypertension (systolic greater than 150 mmHg and/or diastolic greater than 100 mmHg), history of hypertensive crisis or hypertensive encephalopathy	13) Uncontrolled hypertension (systolic greater than *140* mmHg and/or diastolic greater than *90* mmHg), history of hypertensive crisis or hypertensive encephalopathy	• Correction
P27： 18) Subjects with pulmonary fibrosis history or active pneumonia shown on CT during screening	18) *Subjects with current interstitial lung disease* or CT showing active pneumonia during screening;	
19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after	19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical	• Thyroid papillary carcinoma is excluded

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radical surgery, ductal carcinoma in situ after radical surgery	carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or **papillary thyroid carcinoma**	
P28： 20) Subjects with autoimmune disease	20) Subjects with **active** autoimmune disease	• The exclusion of active autoimmune diseases is clarified
P28： 21) Subjects with positive test result of HBsAg, and peripheral blood HBV DNA titer ≥ 1 × 10^3 copies/L; subjects with positive test result of HBsAg and peripheral blood HBV DNA titer < 1 × 10^3 copies/L are eligible if the investigator determined that the subject's chronic hepatitis B is table and participation in the study would add no further risks to the subject	21) Subjects who were HBsAg-positive, and peripheral blood HBV DNA titer ≥ 1 × 10^3 copies/L **or ≥ 200 IU/mL**; subjects who were HBsAg-positive and peripheral blood HBV DNA titer < 1 × 10^3 copies/L **or < 200 IU/mL** might be eligible if the investigator determined that the subject's chronic hepatitis B infection was stable and participation in the study would add no further risks to the subject	• Correction
P32：Hypertension Subjects should remain at resting position for at least 5 min before BP measurement.	**Definition of hypertension: pathologically increased BP with repeated measurements persistently over 140/90 mmHg** **Table 2. Hypertension severity grades and interventions in**	• The description of hypertension is updated according to the definition in

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Grade 1 hypertension: Asymptomatic transient (< 24 h) increase in BP (> 20 mmHg diastolic blood pressure), or > 150/100 mmHg in this measurement, but previous BP was within normal range. No interventions are required. Grade 2 hypertension: Repeated or sustained (> 24 h) or symptomatic BP increase (> 20 mmHg diastolic blood pressure), or > 150/100 mmHg in this measurement, but previous BP was within normal range. One antihypertensive drug can be used. Once BP is lowered to < 150/100 mmHg, the subject may continue the study treatment. Grade 3 hypertension: Requires more than one antihypertensive drugs or more potent treatment. Study treatment should be interrupted in case of persistent or symptomatic hypertension; study treatment should be permanently discontinued for uncontrollable hypertension. Grade 4 hypertension: Life-threatening (i.e. hypertensive crisis). The study treatment should be permanently discontinued in case of Grade 4	**CTCAE v4.03**		CTCAE4.03
	CTCAE		**Interventions**
	Grade 1	**Pre-hypertension (systolic blood pressure of 120–139 mmHg, diastolic blood pressure of 80–89 mmHg)**	**Intervention not indicated**
	Grade 2	**First-stage hypertension (systolic blood pressure of 140–159 mmHg, diastolic blood pressure of 90–99 mmHg; repeated or persistent hypertension of ≥ 24 h), a symptomatic increase of > 20 mmHg in systolic blood pressure, or an increase of > 140/90 mmHg from the previous normal range**	**Antihypertensive monotherapy. drug interruption. The treatment with the investigational product can be continued once the blood pressure is lower than 140/90 mmHg.**

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hypertension. The dose of all antihypertensive agents used should be documented during each visit.	**Grade 3**	**Second-stage hypertension (systolic blood pressure of ≥ 160 mmHg, diastolic blood pressure of ≥ 100 mmHg)**	**Multiple-agent antihypertensive therapy. Study treatment should be interrupted in case of persistent or symptomatic hypertension; study treatment should be permanently discontinued for uncontrollable hypertension.**	
	Grade 4	**Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurological deficit, and hypertensive crisis)**	**Urgent intervention and permanent study treatment discontinuation indicated**	
P33： Proteinuria Urinalysis dipstick test should be performed prior to each IBI305		*Urinalysis* should be performed prior to each dose of	• The requirement for urinalysis is

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or bevacizumab infusion unless 24-h proteinuria test has already been performed. ***First occurrence of proteinuria:*** The urinalysis dipstick test should be performed if: Urine protein is < 2+, continue study treatment as scheduled, no additional tests are required. Urine protein is ≥ 2+ (strip test), continue study treatment as scheduled, and a 24-h urine protein test should be performed within 3 days prior to the next treatment cycle: - If 24-h urine protein is < 2 g, continue study treatment as scheduled, and perform urinalysis dipstick test before each scheduled dose. - If 24-h urine protein is > 2 g, the current study treatment is interrupted, and a 24-h urine protein test should be performed within 3 days prior to the next planned dose. Study treatment is delayed until 24-h urine protein is ≤ 2 g, and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24-h urine	IBI305/bevacizumab unless a 24-hour urinary protein test has already been done. First occurrence of proteinuria: After carrying out the *urinalysis*, if: Urine protein is < 2+, continue study treatment as scheduled, no additional tests are required. ≥ 2+ (*urinalysis*): perform 24-hour urinary protein test within 3 days *prior to administration*: • 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled. and perform *urinalysis* dipstick test before each scheduled dose. • 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g. Second and subsequent occurrence of proteinuria: < 3+ (*urinalysis*): continue study treatment as scheduled, no additional tests indicated.	clarified

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protein is > 2 g. ***Second and subsequent occurrence of proteinuria:*** < 3+ (strip test): continue study treatment as scheduled, no additional tests are required. Urine protein is ≥ 3+ (strip test), continue study treatment as scheduled, and a 24-h urine protein test should be performed within 3 days prior to the next treatment cycle: - If 24-h urine protein ≤ 2 g, continue study treatment as scheduled. - If 24-h urine protein is > 2 g, the current study treatment is interrupted, and a 24-h urine protein test should be performed within 3 days prior to the next planned dose. Study treatment is delayed until 24-h urine protein is ≤ 2 g, and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24-h urine protein is > 2 g. Nephrotic syndrome (Grade 4): Study treatment is permanently discontinued	≥ 3+ (*urinalysis*): perform 24-hour urinary protein test within 3 days *prior to administration*: • 24-hour urinary protein ≤ 2 g: continue study treatment as scheduled. • 24-hour urinary protein > 2 g: delay study treatment until 24-hour urinary protein ≤ 2 g. and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24 h urine protein is > 2 g. Nephrotic syndrome (Grade 4): Study treatment is permanently discontinued	

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<table>
<tr>
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<tr>
<td>P35： Absolute neutrophil count (ANC; dose can only be reduced when febrile neutropenia occurs. ANC must be ≥ 1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L on D1 of each treatment cycle)
Table 2. Dose adjustments of paclitaxel and carboplatin (febrile neutropenia)
<table>
<tr><td></td><td colspan="2">Dose Adjustments of Paclitaxel/Carboplatin ANC (D1 of ea h treatment cycle)</td></tr>
<tr><td></td><td>< 1.5 x 10^9/L</td><td>≥ 1.5 x 10^9/L</td></tr>
<tr><td>Febrile neutropenia
(regardless of duration)</td><td>0</td><td>Paclitaxel = 150 mg/m^2
Carboplatin = AUC 4.5</td></tr>
</table>
Platelet count:
Table 3. Dose adjustments of paclitaxel and carboplatin (thrombocytopenia)
<table>
<tr><td colspan="3">Dose Adjustments of</td></tr>
</table>
</td>
<td>Absolute neutrophil count (ANC; dose can only be reduced when febrile neutropenia occurs. ANC must be ≥ 1.5 × 10^9/L and platelet count must be ≥ 100 × 10^9/L on D1 of each treatment cycle). Once the chemotherapeutic dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 × 10^9/L or ◡ 50 × 10^9/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.
Table 3. Dose adjustments of paclitaxel and carboplatin (febrile neutropenia and thrombocytopenia)
<table>
<tr><td colspan="4">Dose Adjustments of Paclitaxel/Carboplatin</td></tr>
<tr><td colspan="2">First Occurrence</td><td>Re-Occurrence After Dose Adjustment</td><td>Re-occurrence After Two Dose Adjustments</td></tr>
<tr><td>Febrile neutropenia</td><td>Paclitaxel = 150 mg/m^2</td><td>Paclitaxel = 100 mg/m^2</td><td>Chemotherapy discontinuation</td></tr>
</table>
</td>
<td>• The principles of dose adjustment due to hematological toxicity are clarified</td>
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<table>
<tr>
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<table>
<tr><td>Lowest Level After L st Dose</td><td colspan="2">Paclitaxel/Carboplatin Platelet count (D1 of each treatment cycle)</td></tr>
<tr><td></td><td>< 100 x 10^9/L</td><td>≥ 100 x 10^9/L</td></tr>
<tr><td>< 25 × 10^9/L or
< 50 × 10^9/L with hemorrhage or requires blood transfusion</td><td>0</td><td>Paclitaxel = 150 mg/m^2
Carboplatin = AUC 4.5</td></tr>
</table>

Once the chemotherapeutic dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 × 10^9/L or < 50 × 10^9/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If dose reduction is required due to another incident of febrile neutropenia or thrombocytopenia, the dose of paclitaxel and carboplatin will be reduced to 100 mg/m^2 and AUC 3.0, respectively. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.
</td>
<td>
<table>
<tr><td>(regardless of duration)</td><td>Carboplatin = AUC 4.5</td><td>Carboplatin = AUC 3</td><td></td></tr>
<tr><td>Lowest Level After Last Dose
<25 × 10^9/L or
<50 × 10^9/L with hemorrhage or requires blood transfusion</td><td>Paclitaxel = 150 mg/m^2
Carboplatin = AUC 4.5</td><td>Paclitaxel = 100 mg/m^2
Carboplatin = AUC 3</td><td>Chemotherapy discontinuation</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>P39：Concomitant Medications and Treatments</td>
<td>5.9.1 Prohibited treatment</td>
<td>• Correction</td>
</tr>
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5.9.1 Prohibited medications 5.9.2 Medications allowed	*5.9.2* Permitted *treatment*	
P39： Medications allowed None	**Anti-viral therapy was permitted whenever necessary.** **Stable doses of anti-epileptic drugs were permitted.** **Radiotherapy for bone metastasis was permitted provided that the radiotherapy field did not include the target lesion.**	• Addition
P40：Screening Visits (D -28 to D -1) • Blood pregnancy test (for female subjects of childbearing age only)	• Blood/**urine** pregnancy test (for women of childbearing age only)	• Urine pregnancy test is added
P44：**End-Of-Treatment Visit** • Blood pregnancy test (for female subjects of childbearing age only)	• Blood/**urine** pregnancy test (for women of childbearing age only)	• Urine pregnancy test is added

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P45：Clinical Laboratory Evaluations Blood chemistry: blood urea nitrogen	Blood chemistry: *Blood urea*	• The name of urea test item is clarified
P45：Clinical Laboratory Evaluations ➢ Pregnancy test: Serum pregnancy tests are performed on women of childbearing age during screening and the end-of-treatment visit.	Pregnancy test: Blood/**urine** pregnancy test will be carried out for all women of childbearing age during the screening period and in the end-of-treatment visit	• Urine pregnancy test is added
P48：Primary efficacy endpoint The cutoff date for the primary efficacy endpoint analysis of this study is 6 months after subject randomization.	The cut-off date for the analysis of primary efficacy endpoint in this study is **18 weeks** after subject randomization.	• The evaluation of primary efficacy endpoint is adjusted to after the completion of the combined treatment
P50: Serious adverse event reporting The investigator should immediately take appropriate medical measures to treat any SAE that occurs during the trial. And the SAE should be recorded in the tables of adverse events and serious adverse events in the eCRF and source documents;	*SAEs that occur from the signing of informed consent form until 90 days (inclusive) after the last dose should be reported. The investigator must fill out the "CFDA SAE Report Form", regardless of whether it is the initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, CFDA, and ethics committee within 24 hours of noticing the event.*	• The contact information for serious adverse events is added

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<td>regardless of whether the SAE is related to the treatment, the investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.

Contact information for the reporting of SAE/pregnancy to the sponsor:

Fax: 021-31652800

SAE reporting email: drugsafety@innoventbio.com

When submitting the SAE report by email, it is recommended for the investigator to encrypt the report file and send the report file and password in separate emails.

At the same time, the investigator should follow the SAE reporting procedures issued by relevant regulatory authorities or the independent ethics committee.

The investigator should follow up the SAE until it disappears or recovers to a result that the investigator believes it can be explained without further follow-ups, such as clinical stability or improvement. The time limit for the follow-up report and the report of answered queries is the same as that for the initial report.</td>
<td>The contact information for reporting is shown in the table below.

For SAEs occurring outside of the above-mentioned period, those considered related to the investigational drug shall also be reported to the sponsor.

The investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.

The investigator should also report the event to the CFDA, health administration departments, and ethics committees in accordance with the regulations.

When submitting the SAE report by email, it is recommended for the investigator to encrypt the report file and send the report file and password in separate emails.

Table. SAE report contacts
<table>
<tr><td>Unit</td><td>Contact</td><td>Fax/Telephone/Address</td></tr>
<tr><td>Hospital Name</td><td>Ethics committee</td><td>Hospital</td></tr>
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			Fax/Telephone		
	Innovent Biologics (Suzhou) Co., Ltd.	**Clinical Study Department PV**	**Fax: 021-31652800** **Email: drugsafety@innoventbio.com**		
	Office of Drug Research and Supervision, Department of Drug and Cosmetics Registration, China Food and Drug Administration		**Address: Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing** **Post Code: 100053** **Tel: 010-88330732** **Fax: 010-88363228**		
	Medical Administrative Department, Health Administration		**Address: No. 38, Lishi Road, Xicheng District, Beijing** **Tel: 010-**		

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	68792001 **Fax: 010-68792734** **Province, Autonomous Region, Municipality Food and Drug Administration**: **Based on the requirements of the food and drug administration department of each province, autonomous region or municipality**	
P51： Among them, Grade 2 gastrointestinal perforation, procedural and wound healing complications, hemorrhage, fistula, arterial thrombotic events and proteinuria, and all above adverse events of special interest (AESIs) of Grade 3 and above should be reported as AESIs to the sponsor in accordance with the SAE reporting time limit and procedures (see 7.2.1.4 for details) even if they do not meet the SAE definition.	*If the criteria for SAE is met, the SAE report should be submitted to the sponsor within the specified time limit (see 7.2.1.4 for details).*	• It is clarified that all events meeting the SAE criteria should be reported
P51：pregnancy Bevacizumab may be harmful to the fetus. Subjects or female	Bevacizumab may be harmful to the fetus. Subjects or female	• The management of pregnancy

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partners of male subjects must use an effective form of contraception during the 6 months after the last dose. If any female subject or the female partner of any male subject becomes pregnant during the study, the drug should be discontinued immediately and the investigator should be notified. The investigator should report the pregnancy to the sponsor within 24 h of knowing the event by filling out the pregnancy form. The Investigator should also discuss with the subject (and the female partner of the male subject) regarding the risk of continuing pregnancy and its possible impact on the fetus. The investigator should follow up the pregnancy to determine its outcome (including abortion) and the status of the mother and the baby for not less than 8 weeks after delivery, and report the follow-up results as the pregnancy follow-up report to the sponsor according to the procedure and time limit the same as those for the first report. Complications and termination of pregnancy due to medical reasons should be reported as AE or SAE. A spontaneous abortion should be reported as an SAE. For any congenital abnormalities/birth defects or SAEs of the mother and child during the perinatal period, they should be recorded and reported in accordance with the procedure and time limit for reporting SAEs.	partners of male subjects must use an effective form of contraception during the 6 months after the last dose. **During the study, if a female subject exposed to the study drug becomes pregnant, she must discontinue study treatment. The investigator must report to the sponsor within 24 hours of noticing the event and submit the "Innovent clinical Study Pregnancy Report/Follow-Up Form".** **During the study, if a female partner of a male subject exposed to the study drugs becomes pregnant, the subject will continue in the study. The investigator must report to the sponsor within 24 hours of noticing the event and submit the "Innovent Clinical Study Pregnancy Report/Follow-Up Form".** **The investigator must continuously monitor and visit on the outcome of the pregnancy until 8 weeks after the subject gives birth. The outcome should be reported to the sponsor.** **If the outcome of the pregnancy is stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defect), or medical abortion, it should be considered as an SAE and the event is required to be reported in accordance with SAE procedures and time limits.** **If the subject also experiences a SAE during the pregnancy, the CFDA SAE Report Form should also be filled out and reported according to SAE's procedures.**	events is clarified

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P51：

Table 10. Reporting and follow-up of adverse events

	Reporting time limit	**Visit time limit**
AEs	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or explainable stable determined by the investigator
Adverse events of special interest (AESIs)	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or explainable stable determined by the investigator
Serious adverse event	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or explainable stable determined by the investigator
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the outcome of the event is available, and the health conditions of the newborn should

Table 8. Report and follow-up of adverse events

	Reporting Time Limit	Visit Time Limit	
AEs	From signing the informed consent form to *90 days* after the last dose **(if the subject begins other anti-tumor therapies, only AEs related to the study drugs should be collected)**	Until resolved or stable determined by the investigator	• The time limit for the reporting and follow-up of adverse events is modified
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the end of the pregnancy, and visit according to the protocol on the health status of the newborn for at least 2 months	

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		be followed up for at least 2 months according to the protocol		
P52：Abnormalities in laboratory tests/vital signs Not all abnormalities in laboratory tests/vital signs should be reported as AEs. Only the abnormalities in laboratory tests/vital signs that meet the following criteria are reported as AEs: ⅔ Accompanied with clinical symptoms ⅔ Lead to changes in the dose of the study treatment (such as dose adjustment, dose interruption, or permanent drug withdrawal) ⅔ Require medical intervention or changes in concomitant therapy ⅔ Judged by the investigator as clinically significant It is the responsibility of the investigator to review all abnormal laboratory test results and vital signs, and to determine whether each abnormal laboratory test result or vital signs should be reported as AEs. If clinically significant laboratory abnormalities or abnormal vital signs are characteristic of a disease or syndrome (such as increased levels of alkaline phosphatase and total bilirubin caused by cholecystitis that are higher than 5 times the upper limit of normal),			*All clinically significant laboratory test abnormalities should be reported as AEs. It is the responsibility of the investigator to review all abnormal laboratory test results, and to make medical judgments as whether each abnormal laboratory test result should be reported as an AE.*	• The recording criteria of AEs are clarified

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only the diagnosis is recorded on the AE report of the eCRF (i.e., cholecystitis). Conversely, the laboratory abnormalities or abnormal vital signs are recorded on the AE report of the eCRF, and it should be indicated that whether the test value is above or below the normal range (for example, it should be recorded as "blood potassium increased" instead of "blood potassium abnormal"). If there is a standard clinical term corresponding to the laboratory abnormalities or abnormal vital signs, the clinical term should be recorded on the eCRF (such as "anemia", instead of "hemoglobin decreased"). The same clinically significant laboratory abnormalities or abnormal vital signs found during multiple follow-ups should not be repeatedly recorded as AEs or SAEs in the eCRF unless there is a change in its severity or etiology.		
P53：Death During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs and reported to the sponsor timely, regardless of the causality with the investigational drug. When recording a death event, if there is an AE leading to the death, a single medical concept should be used on the AE report of the eCRF to record the event leading to the death, and the event should be reported as an SAE in an expedited manner; if the cause of the death is unknown at the time of reporting , "Death with Unknown	During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs, regardless of the causality with the investigational drug. When recording a death event, *if the cause of death is clear, the cause of death is recorded as an adverse event with the result of the adverse event being death, and the event is reported as an SAE;* if the cause of the death is unknown at the time of reporting , "Death with Unknown Cause" should be recorded on the Adverse Event Form of	• The treatment procedure of death events is clarified

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Cause" should be recorded on the AE report of the eCRF. The "Death with Unknown Cause" should be reported as an SAE in an expedited manner before further investigation is carried out to find the exact cause of death. If the cause of death is confirmed to be PD, then the event should not be documented and reported as an AE/SAE. However, the event should be documented in the Mortality Report Form of the eCRF and reported to the sponsor timely.	the eCRF and the "Death with Unknown Cause" should be reported as an SAE first before further investigation is carried out to find the exact cause of death.	
P54： **Progressive disease** For any event, if it can be clearly determined that the event is caused by progressive disease, the event is not reported as an AE. Hospitalization or death caused by progressive disease does not need to be reported in an expedited fashion.	**Progressive disease** *A progressive disease is defined as the worsening of subject condition caused by the primary tumor that the investigational drug is targeting, the appearance of new lesions, or the progression of the primary lesion. Expected progressive disease should not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by progressive disease should not be reported as an SAE.*	• The definition of progressive disease is clarified
P54： **Lack of efficacy** When the disease treated by the study treatment deteriorates, it may	~~Deleted from the original text~~	• Deletion

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not be possible to determine whether it is due to the lack of efficacy or the occurrence of an adverse event. In this case, unless the investigator believes that the deterioration of the condition is related to the study treatment, such changes are all regarded as the lack of efficacy rather than adverse events.		
P54: Overdose When there is an accompanying AE, the AE should be recorded; when there is not accompanying AE, the overdose should be recorded on the eCRF.	~~Deleted from the original text~~	• Deletion
P67: Appendix II **Carboplatin Dose (Calvert Equation)** Carboplatin dose (mg) = target AUC (mg/mL/min) × [creatinine clearance rate (mL/min) + 25]	**Carboplatin Dose (Calvert Equation)** Carboplatin dose (mg) = target AUC (mg/mL/min) × [creatinine clearance rate (mL/min) + 25] **Note: During the study, if the carboplatin dose calculated using the Calvert equation** excessively exceeds the usual clinical dose, choose one of the following two methods to ensure the patient safety: 1. Retest the serum creatinine and re-calculate the dose (preferred option). 2. Based on clinical experience, the investigator may choose the highest dose tolerated by the subject. The dose should remain	• The calculation method for the dose of carboplatin when it exceeds the clinical dose is added

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	unchanged for the subsequent cycles.	

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CLINICAL STUDY PROTOCOL

Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Version and Date:	Sep. 26, 2016/Version 2.0 Jun. 02, 2016/Version 1.0
Product Name:	Recombinant anti-VEGF humanized monoclonal antibody injection (IBI305)
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	Zhou Hui (Medical Director) Tel: (+86) 021-31652896 E-mail: hui.zhou@innoventbio.com

SIGNATURE PAGE

Protocol Title: A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer

Protocol No.: CIBI305A301

Title	Name	Signature	Date
Medical Director	Zhou Hui		2016.9.26
Director of Biostatistics	Wei Zhaohui		2016.9.26

PROTOCOL SYNOPSIS

Sponsor/Company:	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug:	IBI305
Active Ingredient:	Recombinant anti-VEGF humanized monoclonal antibody
Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Coordinating Investigator:	Zhang Li
Coordinating Center:	Sun Yat-Sen University Cancer Center

Expected study duration: Each subject will receive treatment every 3-week until progressive disease (PD), unacceptable toxicity, withdrawal of informed consent, lost to follow-up or death (whichever comes first). The end of the study is defined as the 18th month after the randomization of the last subject.	**Phase:** III

Study Objectives:

Primary Objective:

- To compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC)

Secondary Objectives:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

Exploratory objectives:

- To compare the population pharmacokinetics (PPK) of IBI305 and bevacizumab in subjects with

	advanced or recurrent non-squamous NSCLC $\frac{4}{3}$ To compare the PD of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC

Study design:

This is a randomized, double-blinded, multi-center phase III study. The study planned to enroll and randomize 436 subjects with non-squamous NSCLC in a 1:1 ratio to IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild type vs. unknown type).

Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first). Then subjects receive maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

During the study, a CT or an MRI will be performed every 6 weeks (± 7 days) and be determined whether the study treatment will be continued by investigators at each site through tumor assessments until PD, withdrawal of informed consent, lost to follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for reasons other than PD, tumor assessments will be continued until PD, withdrawal of informed consent, loss of follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for PD, the investigators will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, lost to follow-up, death, or end of study.

Number of Subjects:	436
Diagnosis and main inclusion criteria:	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be enrolled in the study: 1) Sign the formed consent form 2) Male or female ≥ 18 and ≤ 70 years old 3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIb), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types 4) Histologically or cytologically confirmed EGFR wild type 5) Must have at least one measurable target lesion (as per RECIST 1.1) 6) Eastern Cooperative Oncology Group Performance Status (ECOG PS)

	score of 0–1 7) Expected survival ≥ 6 months 8) Laboratory results during screening: 9) Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L 10) Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis 11) Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ from urinalysis dipstick at baseline, a 24-h urine should be collected with total protein content < 1 g 12) INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment 13) Able to comply with study protocol 14) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug Exclusion Criteria: Subjects meeting any of the followings will not enrolled in the study: 1) Prior chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIb not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible 2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component 3) Histologically or cytologically confirmed EGFR mutation type. Subjects with unknown EGFR status for various reasons could be enrolled 4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL 5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great

	vessel (such as pulmonary artery or superior vena cava) 6) History of brain metastasis, spinal cord compression, or carcinomatous meningitis, or brain metastasis confirmed by CT or MRI during screening 7) Subjects who received radical thoracic radiotherapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug 8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study 9) Subject who received minor surgery (including catheterization) within 48 h prior to the first dose of the study drug 10) Currently or recently (within 10 days prior to the first dose of study drug) used aspirin (> 325 mg/day) or other nonsteroidal anti-inflammatory drugs known to inhibit platelet function 11) Currently or recently (within 10 days prior to the first dose of study drug) received treatment with full dose oral or parenteral anticoagulants or thrombolytic agents. However, anticoagulants for prophylaxis are accepted. 12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis 13) Uncontrolled hypertension (systolic greater than 150 mmHg and/or diastolic greater than 100 mmHg), history of hypertensive crisis or hypertensive encephalopathy 14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease 15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess 16) Subjects with tracheoesophageal fistula 17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments) 18) Subjects with pulmonary fibrosis history or active pneumonia shown on CT during screening

	19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery 20) Subjects with autoimmune disease 21) Subjects with positive test result of HBsAg, and peripheral blood HBV DNA titer $\geq 1 \times 10^3$ copies/L; subjects with positive test result of HBsAg and peripheral blood HBV DNA titer $< 1 \times 10^3$ copies/L are eligible if the investigator determine that the subject's chronic hepatitis B is stable and participation in the study would add no further risks to the subject 22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis 23) Subjects with known history of allergic diseases or allergic physique 24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening 25) History of alcohol or drug abuse 26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study 27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents 28) Other conditions unsuitable for the inclusion as determined by the investigator
Investigational Drug, Dosage, and Route of Administration:	IBI305: 15 mg/kg in combination chemotherapy and 7.5 mg/kg maintenance monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)
Control Drug, Dosage, and Route of Administration:	Bevacizumab: 15 mg/kg in combination chemotherapy and 7.5 mg/kg **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)
Chemotherapy:	Paclitaxel: 175 mg/m² administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death. Carboplatin: Areas under the concentration-time curve (AUC) = 6.0 administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles

	until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Evaluation criteria:

Efficacy endpoints:

Primary efficacy endpoint:

- Objective response rate (ORR)

Secondary efficacy endpoints:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Safety endpoints:

- Vital signs
- Physical examination
- Laboratory tests (routine blood test, blood chemistry, and urinalysis)
- 12-Lead ECG
- Adverse event (AE, including treatment-emergent AE (TEAE)), AE of special interest (AESI) (hypertension, proteinuria, gastrointestinal perforation, hemorrhage [cerebral hemorrhage, hematuria and upper gastrointestinal hemorrhage], cardiotoxicity, and thrombosis), and serious adverse event (SAE)
- Immunogenicity: Positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

PK/PD Endpoints:

- Population PK parameters, including steady-state trough concentrations after repeated doses
- Changes of serum VEGF at different time points

Statistical methods:

Sample size calculation:

A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin. Estimation parameters for sample size: The significance level of the two-sided test is 0.05, the ORR of subjects in the IBI305 and bevacizumab groups is about 50.0%, and the equivalence margin is taken as (-12.5%, 16.7%). Based on the above hypothesis, each group requires 218 subjects (436 subjects in total).

Efficacy analysis:

Clinical equivalence will be determined by whether the 90% confidence interval (CI) of the difference in ORR between the IBI305 and bevacizumab arms falls within the preset margin of (-12.5%, 16.7%). The ORR and 95% CI of two groups, ORR difference and 90% CI, and ORR ratio and 90% CI will be estimated using the generalized

linear model (GLM, including groups and stratification factors).

Median survival (OS) and survival curves will be estimated using the Kaplan-Meier method. The hazard ratio (HR) and 95% CI of two groups will be estimated using the Cox model. DORs and PFSs will be analyzed by the same method as the median survivals. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

Safety analysis:

All adverse events (AE) will be coded using MedDRA and graded according to CTCAE v4.03. All treatment-emergent adverse events (TEAEs), Grade 3 or greater TEAEs, serious adverse events (SAEs), investigational drug-related TEAEs, investigational drug-related SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study termination, and adverse events of special interest (AESIs) will be listed based on system organ class, preferred terms, and groups and the numbers of corresponding subjects and percentages will be summarized. In addition, the severity of TEAEs and the correlation with the study drug will also be summarized by system organ class, preferred terms, and treatment groups.

Measured values and changes from baseline for vital signs, physical examination, laboratory tests and 12-lead ECG will be analyzed using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation.

The number and percentage of subjects who developed anti-drug antibodies and neutralizing antibodies during the study will be summarized by treatment group.

PK/PD exploratory analysis:

Mainly based on description, and inter-group comparison will be carried out if necessary

Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Survival follow-up									x	x	x
Pharmacokinetic (PK)[l]		x	x		x	x	x				
VEGF testing[m]		x	x				x		x		

a. After completing the on-site end-of-treatment visit 28 days after the last dose, subjects who discontinue the investigational drug treatment due to reasons other than PD should continue to undergo tumor assessments once every 6 weeks (±7 days) until PD (and begin post-PD follow-up thereafter), withdrawal of consent, start of another antineoplastic treatment, loss to follow-up, death, or study completion.

b. For subjects with PD, collect survival information once every 12 weeks (84 days, ±7 days) by phone until death, loss to follow-up, withdrawal of informed consent, or study completion. Subsequent antineoplastic treatments should be documented in the eCRF.

c. Only measure weight.

d. Clinical laboratory tests are carried out at the laboratory of each hospital. If screening laboratory tests (routine blood test, blood chemistry, and urinalysis) are performed within 7 days prior to the first dose, the screening results may be used as baseline data. For subsequent visits, all laboratory tests have to be completed within 3 days prior to the dose administration.

e. Prior to each IBI305/bevacizumab infusion, test paper should be used to examine urinary protein.

f. Women of childbearing age should undergo serum pregnancy tests.

g. Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples will be tested at the designated central laboratory.

h. Image assessments (CT or MRI) of the brain, chest, abdomen, and pelvis should be completed at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

i. All subjects should undergo tumor tissue EGFR testing, but the test does not need to be repeated if it can be confirmed with relevant reports that the test has already been completed at the trial site. EGFR testing will be carried out at the laboratory of each trial site.

j. Each treatment cycle for the investigational drug is 3 weeks long. IBI305 or bevacizumab is administered on D1 of each cycle, at 15 mg/kg during combination treatment with chemotherapy and 7.5 mg/kg during monotherapy, until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or study completion, whichever occurs first. After all assessments are completed, the study drug is administered followed by chemotherapy. After all assessments are completed, the study drug is administered followed by chemotherapy.

k. Each treatment cycle is 3 weeks long. Chemotherapy (paclitaxel + carboplatin) is administered on D1 of each cycle for up to 6 cycles, or until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death. Paclitaxel is administered after the infusion of study drug is completed, followed by carboplatin.

l. Study sites that are implementing version 2.0 of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h before the first dose of the study drug (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 h prior to the dose in C4, within 1 hour prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.

m. Study sites that are implementing version 2.0 of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: Within 1 h prior to the first dose of the study drug (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and at the end of treatment visit. Samples were tested at the designated central laboratory.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definitions
AE	Adverse event
AESI	Adverse event of special interest
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AUC	Area under the curve
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFDA	China Food and Drug Administration (now National Medical Products Administration)
CQA	Clinical quality assurance
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data collection
EGFR	Epithelial growth factor receptor
FAS	Full analysis set
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
ITT	Intention-to-treat

NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PTT	Partial thromboplastin time
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
SS	Safety set
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

1 INTRODUCTION

1.1 Study Background

1.1.1 Disease background

Lung cancer has the highest incidence and mortality globally among all cancers. According to the 2012 Global Cancer Statistics (GLOBOCAN 2012) published by International Agency for Research on Cancer, there were approximately 1.8 million new lung cancer cases worldwide, which accounted for 13% of the global newly-diagnosed cancers, and 58% of these cases occurred in underdeveloped areas[1]. According to the data released by the National Central Cancer Registry of China in 2015, lung cancer was the most prevalent malignancy in China in 2011, with about 650,000 new cases every year. Lung cancer was also the leading cause of death, with about 520,000 deaths per year[2]. The limited clinical treatment of lung cancer is the main reason for its poor prognosis. There is a huge demand for new types of lung cancer treatment drugs.

Approximately 85–90% of lung cancers are non-small cell lung cancer (NSCLC) and patients with NSCLC are usually in the advanced stages when diagnosed[3]. According to the Chinese guidelines for the diagnosis and treatment of primary lung cancer, anatomic pulmonary resection is the mainstay of treatment for early stage lung cancers[4]. However, despite surgery, some patients develop distance metastases that eventually lead to death[5]. Surgery is not possible for most patients with clearly diagnosed stage IIIb and IV as well as some patients with stage IIIa NSCLC[4]. Comprehensive treatment based on systemic therapy is used to maximize patient survival, control progressive disease, and improve the quality of life[6].

In recent years, anti-tumor therapies have entered a new era with the emergency of targeted drugs. Some of these targeted drugs have demonstrated satisfactory efficacy in the treatment of advanced NSCLC. These targeted drugs include monoclonal antibodies and tyrosine kinase inhibitors (TKIs), mostly targeting epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF), such as bevacizumab, cetuximab, gefitinib, erlotinib, and icotinib. Monoclonal antibodies have become the drugs of choice in various treatment guidelines due to the good targeting ability, low drug resistance, and good patient tolerability. Bevacizumab combination chemotherapy is a first-line therapy of NSCLC recommended by the National Comprehensive Cancer Network (NCCN)[7]. Additionally, bevacizumab in combination with paclitaxel/carboplatin has also been approved as the first-line therapy of unresectable advanced, metastatic, or relapsed non-squamous NSCLC by China Food and Drug Administration (CFDA) on Jul. 9, 2015[6].

Compared with traditional chemotherapy that directly inhibit or kill tumor cells, anti-angiogenic drugs have the following unique advantages[8]:

- The targets are genetically stable vascular endothelial cells (VECs) rather than highly heterogeneous tumor cells, thus leading to lower drug resistance;
- The number of tumor-induced VECs is far less than that of tumor cells, and the efficacy is preferable targeting on VECs and their cytokines;
- Normal VECs are quiescent, whereas tumor VECs are active in proliferation. Anti-angiogenic therapy targets activated cells and avoids damage to normal VECs, thus leading to better targeting ability;
- Anti-angiogenic therapy can normalize the tumor vessels and thereby reduce the pressure in tumor tissues. This enhances the delivery of chemotherapeutic agents into tumor tissues, thus increasing the efficacy of chemotherapy.

Angiogenesis is a basic biological characteristic of tumors. The growth of both solid and hematologic tumors are depended on angiogenesis regardless of the nature of tumor cells. Therefore, anti-angiogenic therapy is broad-spectrum and applicable to various tumors.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to human VEGF and blocks its biological activity. Bevacizumab consists of a framework region of a human antibody and a humanized murine antigen binding region that can inhibit the binding of VEGF to its receptors on epithelial cells, Flt-1 and KDR. By blocking the activity of VEGF and reducing tumor angiogenesis, tumor growth is inhibited[9].

In a study conducted by the Estern Cooperative Oncology Group (ECOG), compared with chemotherapy alone (paclitaxel/ carboplatin), bevacizumab in combination with paclitaxel/carboplatin significantly increased the overall survival (OS) (median: 12.3 vs. 10.3 months), progression-free survival (PFS) (median: 6.2 vs. 4.5 months), and overall response rate (ORR) (35% vs. 15%) in patients with advanced, metastatic, or relapsed non-squamous NSCLC[10]. In another foreign AVAiL study, different doses of bevacizumab (7 and 15 mg/kg) in combination with chemotherapy (cisplatin and gemcitabine) and placebo combine with chemotherapy were compared for the treatment of non-squamous NSCLC. The study found that the two bevacizumab groups had significantly increased the PFS (median: 6.7 months (7.5 mg/kg combination chemotherapy group) vs. 6.5 months (15 mg/kg combination chemotherapy group) vs. 6.1 months (placebo combination chemotherapy group)) and the ORR (37.8% (7.5 mg/kg combination chemotherapy group) vs. 34.6% (15 mg/kg combination chemotherapy group) vs. 21.6% (placebo combination chemotherapy group)) in patients with locally advanced, metastatic, or relapsed non-squamous NSCLC[11]. In a BEYOND study conducted in China, compared with

placebo in combination with paclitaxel/carboplatin, bevacizumab in combination with paclitaxel/carboplatin significantly increase the PFS (median: 9.2 vs. 6.5 months), OS (median: 24.3 vs. 17.7 months), and the ORR (54% vs. 26%) in patients with advanced or relapsed non-squamous NSCLC[12].

In China, the antibodies and fusion proteins targeting VEGF are research hotspots. However, since 2006, the clinical efficacies of various drugs have not been verified and no products have been marketed. Considering the complexity of macromolecular drugs and the limitations of drug development capability in China, advanced technologies in antibody development, production, and quality control is required to develop high-quality VEGF inhibitors that are safe and effective. IBI305 has showed high similarity to bevacizumab in various pharmaceutical and nonclinical studies (refer to Investigator's Brochure [IB]). Besides, the efficacy and safety of bevacizumab for treatment of locally advanced, metastatic or relapsed lung cancer have been verified. The relevant domestic and external pivotal clinical studies are referable for the protocol design of IBI305 clinical study. In summary, the clinical study of IBI305 for treatment of NSCLC has a solid foundation and relatively low risks. The successful development of IBI305 indicates an additional first-line targeted drug for lung cancer in China, providing doctors and patients with more therapeutic options.

1.1.2 Investigational drug

1.1.2.1 Description of investigational drug

IBI305 is a recombinant humanized anti-VEGF monoclonal antibody injection developed by Innovent Biologics (Suzhou) Co., Ltd. (hereafter as sponsor) that specifically binds human VEGF. The molecular weight of IBI305 is 149 KDa. IBI305 specifically binds to VEGF-A, inhibits the binding of VEGF-A to VEGF-R1 and VEGF-R2, blocks the signaling pathways such as PI3K/Akt/PKB and Ras-Raf-MEK-ERK. IBI305 also inhibits the growth, proliferation, and migration of VECs and angiogenesis, decreases the vascular permeability, blocks blood supply to tumor tissues, inhibits the proliferation and metastasis of tumor cells, and induces the apoptosis of tumor cells, thereby generates anti-tumor effects. The main active ingredient is recombinant humanized anti-VEGF monoclonal antibody and excipients include sodium acetate, sorbitol, and polysorbate 80[13]. Refer to the Investigator's Brochure for the detailed structure and physicochemical properties of IBI305.

1.1.2.2 Preclinical studies

Pharmaceutical studies

The pharmaceutical studies showed that stability, primary structure, higher-order structure, oligosaccharide distribution, charge variant, and product-related impurities of IBI305 are highly similar to those of bevacizumab, and the process-related impurities meet the proposed specification. Therefore, IBI305 is considered to have highly similar protein properties and product quality to bevacizumab[13].

Pharmacodynamic studies

In vitro and in vivo pharmacodynamic (PD) studies of IBI305 showed the following findings:

1) Target: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A with an affinity constant same as that of bevacizumab, indicating that IBI305, the same as bevacizumab, is a specific human VEGF blocker with a clear target.
2) Specificity: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A, medium-affinity binding to canine VEGF-A, but low-affinity binding to human VEGF-B, VEGF-C, VEGF-D, PlGF, suggesting that IBI305 recognizes specific targets and has low off-target toxicity risk; no obvious affinity to mouse VEGF-A_{164} and rat VEGF-A_{164}, suggesting that IBI305 has high species specificity.
3) Mechanism of action: IBI305 specifically binds to VEGF-A and inhibits the activation of VEGFR-2 and ERK1/2, blocks the proliferation and migration of HUVEC, and inhibits the sprouting from rat aortic ring, suggesting that IBI305 antagonizes VEGF-A-induced signaling pathway to block the proliferation and migration of VECs and inhibit angiogenesis, which leads to the reduction of nutritional supply and metastasis of tumor.
4) Anti-tumor effects: IBI305 significantly inhibits the growth of human colon cancer Ls174t and lung cancer NCI-H460 cells in xenografts in nude mice, indicating that IBI305 has significant anti-tumor effects.

Results from in vitro and in vivo studies of IBI305 showed highly similarity with that of bevacizumab designed simultaneously, demonstrating that the target, mechanism of action, and anti-tumor effects of IBI305 are highly similar to bevacizumab[13].

Pharmacokinetic studies

In vitro and in vivo pharmacokinetic (PK) studies of IBI305 showed the following findings:

1) IBI305 showed no significant cross-reactivity with normal human tissues and cynomolgus monkey tissues, and only cross-reacted with the positive-control. i.e. human angiosarcoma tissue, suggesting that IBI305 is highly specific to cancer tissues rather than normal human tissues and has very low on-target toxicity.
2) Linearity: With single dose or repeated doses of IBI305 (2-50 mg/kg) vis intravenous injection in cynomolgus monkeys, the test showed significant PK, thus reducing the suddenly rising toxicity risks with increased clinical doses.
3) Immunogenicity: With single dose or repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed abnormal changes of drug concentration-time curves in several animals. The anti-drug antibody (ADA) test results showed that IBI305 has a medium immunogenicity.
4) Accumulation: With repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed that drug exposure of the last dose was significantly higher than that of the first dose, and the steady-state drug concentration after repeated doses was higher than that after a single dose, suggesting that the drug may be accumulated in body.

The results of tissue cross-reactivity and PK/toxicokinetic studies in cynomolgus monkeys indicated that IBI305 and bevacizumab have similar characteristics in tissue cross-reactivity and PK/toxicokinetics[13].

Toxicological studies

Toxicological studies of IBI305 showed the following findings:

1) Single dose: With single dose of IBI305 (up to 300 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed good tolerability without any abnormal clinical symptoms and toxicity. The dose was about 48 times the proposed clinical dose for human based on body surface area. In the safety pharmacology test, with single dose of IBI305 (50 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed no significant effects on the central nervous system, respiratory system, and cardiovascular system, suggesting that the single dose of IBI305 via intravenous injection has a high safety.

2) Repeated doses: With repeated doses of IBI305 (up to 50 mg/kg) via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, equivalent to 20 times the proposed clinical dose for humans (based on the weight), the test showed extremely mild to mild linear growth arrest of metaphyseal lines at knee joint and disordered chondrocyte proliferation, extremely mild increases in macrophage count in white pulp of spleen, pulmonary (including bronchial) hemorrhage, and deposits of hemosiderin in lymphoid tissue of bronchial mucosa, indicating that the target organ toxicities are mainly in the bone, spleen, and lungs.

3) Immunotoxicity and immunogenicity: With repeated doses of IBI305 via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, the test showed medium immunotoxicity to the spleen. Different doses of IBI305 may result in the production of ADAs, a portion of which are neutralizing antibodies (NAbs), indicating that IBI305 has medium immunotoxicity and immunogenicity.

4) Local irritation test: With repeated dose of IBI305 via intravenous injection in cynomolgus monkeys, the test showed no irritation at the injection site, suggesting that administration of IBI305 via intravenous injection is safe and feasible.

5) In vitro hemolysis assay: With maximum proposed clinical concentration of IBI305 (9 mg/mL), the assay showed no hemolysis, suggesting that IBI305 is suitable for intravenous injection.

IBI305 has high similarity with bevacizumab in safety pharmacology, long-term toxicity, immunotoxicity, immunogenicity, local irritation, and hemolysis[13].

1.2 Study Principles and Risk/Benefit Assessment

1.2.1 Study principles and dose selection

A biosimilar drug refers to a therapeutic biological product that is similar in quality, safety and efficacy with an approved reference drug[14]. IBI305, developed and sold in the market by the sponsor, is a bevacizumab biosimilar, and has the same administration method and indications as bevacizumab.

This study is conducted in accordance with the "Guidelines on Development and Evaluation of Bosimilars (for Trial Version)" issued by the NMPA (formerly CFDA)[14]. The doses of IBI305 selected in this study are based on the preclinical studies that showed highly similarity between IBI305 and bevacizumab in pharmacology, PD, PK and toxicology (refer to the Investigator's Brochure for details). Besides, the efficacy and safety of bevacizumab for treatment of advanced, metastatic or relapsed non-squamous NSCLC have been verified, and the indications have also been approved in China. Therefore, the dose and administration of IBI305 is similar to bevacizumab in this study, that is, 15 mg/kg intravenously on D1 of every 3-week cycle when used in combination with chemotherapy (paclitaxel and carboplatin). In the subsequent maintenance monotherapy therapy, IBI305 will be given intravenously at a dose of 7.5 mg/kg on the first day of every 3-week cycle. This design of this study is to further demonstrate that IBI305 is similar to bevacizumab in clinical efficacy, safety, and immunogenicity in subjects with advanced, metastatic or relapsed non-squamous NSCLC.

1.2.2 Risk/benefit assessment

IBI305 is a bevacizumab biosimilar developed by the sponsor. Based on the clinical pharmacology and toxicology characteristics of IBI305, the risks and benefits of IBI305 are expected to be similar to bevacizumab.

The treatment-related risks of bevacizumab are detailed in its prescribing information. This study is the first human study of IBI305 so that unexpected adverse reactions will be possible. The design of this study ensures the minimized subject risks by close monitoring of the adverse events (AEs) before, during, and after the infusion of the investigational drugs. Once an adverse reaction occurs, the investigator will immediately take appropriate action for the subject safety.

The platinum-based therapy is the standard first-line regimen of advanced NSCLC[4]. This study uses the combination of paclitaxel/carboplatin, ensuring the basic anti-tumor therapy for subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC.

2.2 Secondary Objectives

Secondary objectives include:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) in subjects with advanced or relapsed non-squamous NSCLC treated by IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

2.3 Exploratory Objectives

- To compare the population pharmacokinetics (PPK) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC
- To compare the pharmacodynamics (PD) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC

3 STUDY PLAN

3.1 Overview of Study Design

This is a randomized, double-blind, active-controlled, and multi-center phase III study. A total of 436 subjects across 35 study sites with non-squamous NSCLC will be planned, randomized in a 1:1 ratio into the IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group, and stratified according to age (< 60 vs. ≥ 60 years old) and epidermal growth factor receptor (EGFR) status (wild type vs. unknown type). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first). Then subjects received maintenance monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing maintenance therapy with IBI305 or bevacizumab. The maintenance monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first).

After discontinuing the study drug, subjects will return to the study site 28 days (± 7 days) after the last dose for an end-of-treatment visit. If the subjects discontinue the study treatment for reasons other than PD, subsequent follow-up will be continued until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. If the subjects discontinue the study treatment for PD, the investigator will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival.

A CT or an MRI will be performed every 6 weeks (± 7 days) until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. The method for subsequent imaging examination should be consistent with that at baseline, and the chest, abdomen and pelvis of the subject must be scanned. Each assessment must be completed within 7 days from the most recent visit. The investigators then perform the evaluation based on the RECIST v1.1 criteria to determine whether the subject can continue receiving the next cycle of treatment. Furthermore, the independent tumor evaluation committee (Section 11.1.1) will also evaluate tumor response according to the RECIST v1.1. If the subjects discontinue the study treatment for reasons other than PD, subsequent tumor evaluation should be continued according to the study procedures until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death or, end of study.

The study design is shown in Figure 1.

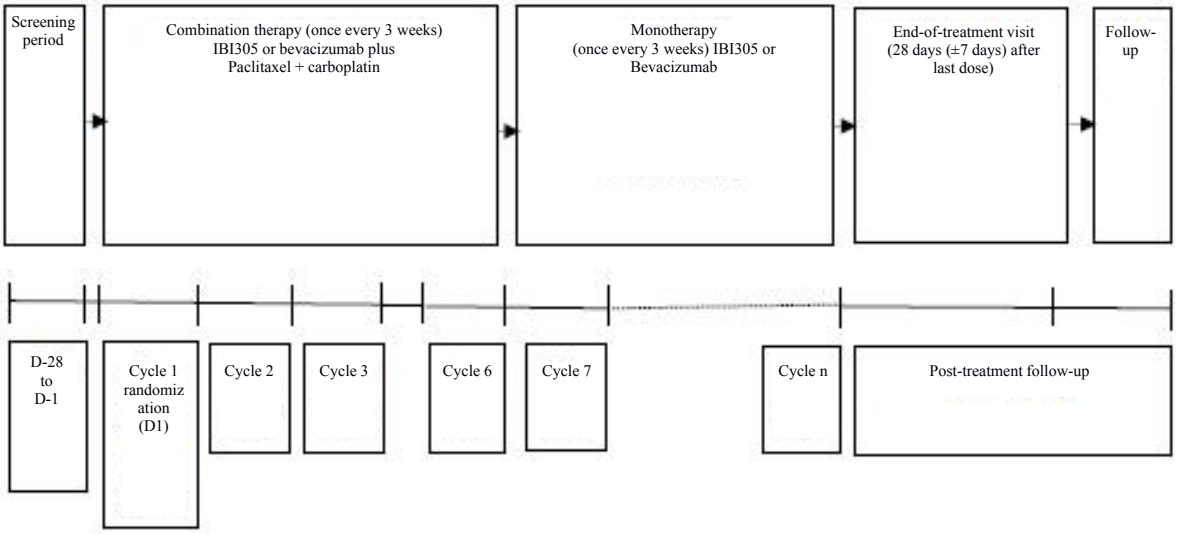

Figure 1. Study design schematic

3.2 Study Design Discussion

This is a randomized, double-blind study, and bias in treatment groups is avoided. Furthermore, the CT/MRI images of each subject will be evaluated by an independent tumor evaluation committee according to the RECIST v1.1 to ensure consistency in evaluation.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled in the study:

1) Sign the informed consent form
2) Male or female ≥ 18 and ≤ 70 years old
3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIb), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types
4) Histologically or cytologically confirmed EGFR wild type
5) Must have at least one measurable target lesion (as per RECIST 1.1)
6) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1
7) Expected survival ≥ 6 months
8) Laboratory results during screening:

   Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L

   Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis

   Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2 + in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline must have undergone 24 h urine collection with total protein content <1 g

   INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment
9) Able to comply with study protocol
10) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug

4.2 Exclusion Criteria

Subjects meeting any of the followings are not enrolled in the study:

1) Prior chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIb not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible
2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component
3) Histologically or cytologically confirmed EGFR mutation type. Subjects with unknown EGFR status for various reasons could be enrolled.
4) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL
5) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava)
6) History of brain metastasis, spinal cord compression, or carcinomatous meningitis, or brain metastasis confirmed by CT or MRI during screening
7) Subjects who received radical thoracic radiation therapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug
8) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study
9) Subject who received minor surgery (including catheterization) within 48 h prior to the first dose of the study drug
10) Currently or recently (within 10 days prior to the first dose of study drug) used aspirin (> 325 mg/day) or other nonsteroidal anti-inflammatory drugs known to inhibit platelet function
11) Currently or recently (within 10 days prior to the first dose of study drug) received treatment with full dose oral or parenteral anticoagulants or thrombolytic agents.

However, anticoagulants for prophylaxis are accepted.

12) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis
13) Uncontrolled hypertension (systolic greater than 150 mmHg and/or diastolic greater than 100 mmHg), history of hypertensive crisis or hypertensive encephalopathy
14) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease
15) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess
16) Subjects with tracheoesophageal fistula
17) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments)
18) Subjects with pulmonary fibrosis history or active pneumonia shown on CT during screening
19) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery
20) Subjects with autoimmune disease
21) Subjects with positive test result of HBsAg, and peripheral blood HBV DNA titer ≥ 1×10^3 copies/L; subjects with positive test result of HBsAg and peripheral blood HBV DNA titer < 1×10^3 copies/L are eligible if the investigator determined that the subject's chronic hepatitis B is table and participation in the study would add no further risks to the subject
22) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis
23) Subjects with known history of allergic diseases or allergic physique
24) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening
25) History of alcohol or drug abuse

26) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study

27) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents

28) Other conditions unsuitable for the inclusion as determined by the investigator

4.3 Screening Failure

Screening failure is that the subject who has signed the informed consent form fails to meet the inclusion criteria. Subjects with screening failure will not get a randomization number. The reasons of screening failure will be documented in the electronic case report forms (eCRFs).

4.4 Subject Restrictions

Female subjects of childbearing age must take effective contraceptive measures during the study and 6 months after the last dose.

Male subjects must take effective contraceptive measures during the study and 6 months after the last dose to avoid the pregnancy of their partners.

Restrictions on the use of medication during the study are shown in Section 5.9.

4.5 Subject Withdrawal and Replacement

All subjects may withdraw from this study at any time, with or without a reason. Subjects who withdraw from the study will not be subjected to discrimination or retaliation, and their medical treatment will not be affected.

Subjects may discontinue the study treatment or withdraw from the study under the following circumstances:

- $\frac{8}{5}$ Unacceptable toxicity
- $\frac{8}{5}$ Progressive disease
- $\frac{8}{5}$ Investigator believes that the subject should withdraw from the study. If an unacceptable adverse event (AE) occurs and the investigator believes that the subject should withdraw from the study, the study treatment should be discontinued and appropriate measures should be taken. In addition, the sponsor or personnel designated by the sponsor should be notified.
- $\frac{8}{5}$ Withdrawal of informed consent form by the subject

- Serious protocol deviation determined by the investigator and/or sponsor
- Poor protocol compliance
- Study termination by the investigator or sponsor for any reason
- Enrollment error* (enrollment of subjects who have violated the inclusion/exclusion criteria)
- Use of prohibited concomitant medications or other medications that the investigator believes that it may result in toxicities or may affect study results
- Subject lost to follow-up
- Death of subject

* If the subject is determined by the investigator and the sponsor's doctor to be medically suitable to continue with the study drugs without any risk or inconvenience, the mistakenly enrolled or randomized subject will continue with the study treatment and assessments.

In any cases, reasons for withdrawal must be documented in the eCRFs. If the subject withdraws from the study prematurely for any reason, the investigator should make every effort to persuade the subject to receive the corresponding assessment, and continue the follow-up of all unresolved AEs based on the AE reports and follow-up requirements (Table 2):

- If the subject withdraws during the study, the series of assessments listed under the End of Treatment Visit (Section 6.9) should be performed
- If the subject withdraws after the end of the treatment visit and has not experienced PD, the series of assessments listed under the Follow-Up for PD (Section 6.10) should be performed (tumor assessment is not required to be repeated if it has been performed within 6 weeks prior to this follow-up)
- If the subject withdraws during the follow-up for survival, the information of subsequent anti-tumor therapies and survival should be collected by telephone follow-up only

Subjects who withdraw their informed consent are not to be contacted again unless they clearly indicate the willingness to be contacted. The sponsor may use the clinical study data obtained before the withdrawal of informed consent.

Subjects who have been randomized will not be replaced.

5 STUDY TREATMENT

5.1 Therapies by Study Drugs

The study drugs of this study are IBI305 and bevacizumab.

In this study, the dose of IBI305 or bevacizumab during combination therapy with chemotherapy is 15 mg/kg, while the dose during maintenance monotherapy is 7.5 mg/kg. The study drugs are administered intravenously on D1 of each 3-week cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

The duration of the first dose of IBI305 or bevacizumab should be 90 min (± 15 min). If the first infusion is well-tolerated by the subject, then the duration of the second infusion can be shortened to 60 min (± 15 min). If the 60 min infusion is also well-tolerated by the subject, then the subsequent infusions can be completed within 30 min (± 15 min).

5.2 Chemotherapy

Paclitaxel will be administered after the IBI305 or bevacizumab infusion is completed, then followed by carboplatin:

Paclitaxel: 175 mg/m² administered via intravenous infusion for 3 h (may be adjusted according to clinical practice of each study site) on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Carboplatin: AUC 6.0, the infusion time is based on the standard practice of each study site, administered on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

The chemotherapeutic agents are supplied by the sponsor.

Formulas for calculating surface area, creatinine clearance and carboplatin dose are shown in Section 13.2.

5.3 Dose Adjustment of Each Study Drug

5.3.1 General principles

The reasons for dose adjustments or delayed administration, measures taken, and results should be documented in the medical records and eCRFs

If the concomitant symptoms exist at baseline, the investigator will determine whether the dose should be adjusted according to the change in severity of toxicity. For example, if the subject has Grade 1 "weakness" at baseline and Grade 2 "weakness" during the study treatment, the dose should be adjusted based on Grade 1 toxicity since the severity has increased by one grade

If several toxic reactions of different grades or severity occur simultaneously, the dose will be adjusted according to the highest observed grade/severity

If a dose adjustment is required solely due to abnormal lab test results, then the dose should be adjusted based on the measured values obtained prior to the start of the treatment cycle

If the investigator determines that the toxicity is unlikely to further develop into a serious or life-threatening event, the current dose will be continued without any adjustments or treatment interruptions. In addition, dose adjustments or treatment interruptions will not be performed for non-hemolytic anemia as the symptoms can be alleviated through blood transfusions.

If the investigator determines that a toxicity is caused by a specific therapeutic drug, then the dose adjustments of other drugs are not required

Discontinuation of one or two therapeutic drugs before PD will not affect the continued treatment with other drugs

Dose reductions or adjustments of IBI305 or bevacizumab are not permitted.

Subsequent therapeutic dose will not be adjusted according to weight change, unless the subject weight has changed by ≥ 10% from baseline

Once the dose of any chemotherapeutic agents is reduced, the original dose should no longer be adopted

If any but not all of the therapeutic drug (IBI305, bevacizumab or chemotherapeutic agents) treatments is interrupted due to toxicity, then this treatment will be considered as a treatment cycle

If the administration of any one of the chemotherapeutic agents is delayed for more than 3 weeks, the subject should permanently discontinue that chemotherapeutic agent

If IBI305/bevacizumab is continued/infused after a delay for more than 3 weeks, the investigator must discuss with the sponsor

5.3.2 Dose adjustments of study drugs

Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments (adjusted to 7.5 mg/kg for maintenance monotherapy) specified in the study protocol. The dose of IBI305 or bevacizumab is calculated according to the subject weight at baseline (prior to the first dose), and remains unchanged throughout the study, unless the subject weight has changed by ≥ 10% from baseline.

If an infusion reaction occurs during a 60-minute infusion, the infusion time should be extended to 90 minutes for all subsequent infusions. Likewise, if an infusion reaction occurs during a 30-minute infusion, the infusion time should be extended to 60 minutes for all subsequent infusions.

IBI305 or bevacizumab in combination with paclitaxel/carboplatin will be administered every 3-week treatment cycle for 6 cycles. If PD is not observed in subject during treatment, then the subject will continue to receive IBI305 or bevacizumab as maintenance monotherapy every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, death, or end of study (whichever comes first).

If IBI305 or bevacizumab is permanently discontinued due to unacceptable toxicity or subject refusal to continue the study drugs during the combination therapy, then the subject will continue to receive the chemotherapy (paclitaxel/carboplatin) until 6 treatment cycles are completed as determined by the investigator. If any one of the chemotherapeutic agents (paclitaxel or carboplatin) is prematurely discontinued due to unacceptable toxicity, the subject can continue to receive IBI305 or bevacizumab treatment until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first).

When a Grade 3 or 4 IBI305- or bevacizumab-related toxicity is observed, the investigators should determine whether to continue or terminate IBI305 or bevacizumab treatment according to the followings:

First occurrence:

IBI305 or bevacizumab administration should be interrupted until toxicity symptoms return to baseline level or are at least reduced to the Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or lower (except for the special circumstances listed below)

Note that when Grade 4 febrile neutropenia and/or thrombocytopenia occur(s), IBI305 or bevacizumab administration should be interrupted until the symptoms return to baseline levels or at least reduced to CTCAE Grade 1 or lower, since these events increase the risk of hemorrhage.

Re-occurrence in re-administration:

If Grade 3 IBI305- or bevacizumab-related toxicity occurs again, the investigator should assess the risk/benefit of study drug continuation for the subject. If such toxicity re-occurs again after re-administration, IBI305 or bevacizumab should be permanently discontinued

If Grade 4 IBI305- or bevacizumab-related toxicity occurs again, IBI305 or bevacizumab should be permanently discontinued

Measures should be taken in the following special circumstances (classified based on CTCAE version 4.03):

Hemorrhage

Subjects with Grade 3 or 4 hemorrhages should be treated accordingly and permanently discontinue the study treatment

Thrombosis/embolism

- Subjects with arterial thrombosis of any severity grades should permanently discontinue the study treatment
- Subjects with Grade 4 venous thrombosis should permanently discontinue the study treatment
- Subjects with Grade 3 venous thrombosis should interrupt the study treatment. If the anticoagulant therapy at the planned therapeutic dose is < 2 weeks, the study treatment should be interrupted until the anticoagulant therapy is completed. If the anticoagulant therapy at the planned therapeutic dose is > 2 weeks, IBI305 or bevacizumab administration should be interrupted for 2 weeks, and the study treatment can be restarted during the anticoagulant therapy if the following criteria are met:
  - INR is within the target range (usually 2-3) prior to restarting of study treatment
  - Subjects must not have experienced Grade 3 or 4 hemorrhage since enrollment
  - No signs of great vessel invasion or adjacency to great vessels from previous tumor assessments

  Note: Therapeutic dose of anticoagulant therapy is defined as the escalating dose of warfarin or other anticogulants until INR is maintained at no less than 1.5 (usually

2-3). The warfarin dose should be documented in the eCRFs, and the INR of subjects receiving anticoagulant therapy should be monitored during the treatment.

Hypertension

BP should be measured frequently to monitor the occurrence and exacerbation of hypertension. Subjects should remain at resting position for at least 5 min before BP measurement.

Grade 1 hypertension: Asymptomatic transient (< 24 h) increase in BP (> 20 mmHg diastolic blood pressure), or > 150/100 mmHg in this measurement, but previous BP was within normal range. No interventions are required.

Grade 2 hypertension: Repeated or sustained (> 24 h) or symptomatic BP increase (> 20 mmHg diastolic blood pressure), or > 150/100 mmHg in this measurement, but previous BP was within normal range. One antihypertensive drug can be used. Once BP is lowered to < 150/100 mmHg, the subject may continue the study treatment.

Grade 3 hypertension: Requires more than one antihypertensive drugs or more potent treatment. Study treatment should be interrupted in case of persistent or symptomatic hypertension; study treatment should be permanently discontinued for uncontrollable hypertension.

Grade 4 hypertension: Life-threatening (i.e. hypertensive crisis). The study treatment should be permanently discontinued in case of Grade 4 hypertension. The dose of all antihypertensive agents used should be documented during each visit.

The dose of antihypertensive agents used should be documented during each visit. If the subject remains hypertensive despite treatment discontinuation, BP and antihypertensive agents used should be monitored every 3 months until BP returns to normal or end of study.

Posterior reversible encephalopathy syndrome (PRES)

There have been a few reports of subjects with signs and symptoms consistent with PRES after study treatment. This is a rare neurological disease and its signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with PRES should permanently discontinue the study treatment.

Proteinuria

Urinalysis dipstick test should be performed prior to each IBI305 or bevacizumab infusion unless 24-h proteinuria test has already been performed.

First occurrence of proteinuria:

The urinalysis dipstick test should be performed if:

Urine protein is < 2+, continue study treatment as scheduled, no additional tests are required.

Urine protein is ≥ 2+ (strip test), continue study treatment as scheduled, and a 24-h urine protein test should be performed within 3 days prior to the next treatment cycle:

- If 24-h urine protein is < 2 g, continue study treatment as scheduled, and perform urinalysis dipstick test before each scheduled dose.
- If 24-h urine protein is > 2 g, the current study treatment is interrupted, and a 24-h urine protein test should be performed within 3 days prior to the next planned dose. Study treatment is delayed until 24-h urine protein is ≤ 2 g, and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24-h urine protein is > 2 g.

Second and subsequent occurrence of proteinuria:

< 3+ (strip test): continue study treatment as scheduled, no additional tests are required.

Urine protein is ≥ 3+ (strip test), continue study treatment as scheduled, and a 24-h urine protein test should be performed within 3 days prior to the next treatment cycle:

- If 24-h urine protein ≤ 2 g, continue study treatment as scheduled.
- If 24-h urine protein is > 2 g, the current study treatment is interrupted, and a 24-h urine protein test should be performed within 3 days prior to the next planned dose. Study treatment is delayed until 24-h urine protein is ≤ 2 g, and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24-h urine protein is > 2 g.

Nephrotic syndrome (Grade 4): Study treatment is permanently discontinued

Gastrointestinal perforation

If gastrointestinal perforation occurs, appropriate measures should be taken and the study treatment should be permanently discontinued.

Wound healing complications

The study treatment should not begin within 28 d after a major surgery, or before the surgical

wound is fully healed. If a complication of wound healing occurs during study treatment, the study treatment should be interrupted until the wound is fully healed. If an elective surgery is required, the study treatment should be interrupted.

Abdominal abscess or fistula

If abdominal abscess or fistula occurs, the study treatment should be discontinued. However, the investigator will determine whether study treatment will be continued if the above AE is resolved.

Infusion-related and allergic reactions:

Infusion-related reactions after first dose of the study drug is uncommon (< 3%), and the incidence of a severe reaction is only 0.2%.

If a mild (grade 1 or 2) reaction (such as fever, chills, headache, and nausea) occurs, pretreatment prior to subsequent administration should be performed and infusion time should not be reduced. If the subject is well-tolerated during infusion after pretreatment, the infusion time can be reduced by 30 minutes (+10 minutes) for subsequent administration with pretreatment. If an infusion-related AE occurs during a 60-minute infusion, the subsequent infusion should be completed within 90 minutes (+15 minutes) with pretreatment. Likewise, if an infusion-related AE occurs during a 30-minute infusion, the subsequent infusion should be completed in 60 minutes (+10 minutes) with pretreatment. If a subject has a grade 3 infusion-related reaction, the study treatment should be interrupted and not be restarted on the same day. However, since there lacks the dose adjustment method for grade 3 infusion-related reactions, the investigators may decide to either discontinue the study drug or perform pretreatment, and complete the infusion within 90 minutes (+15 minutes). If an adverse reaction still occurs during a 90-minute infusion, the infusion should be continued at a slower rate and then gradually returned to a 90-minute infusion. If the investigator is uncertain about the handling, the study treatment should be discontinued. When the study treatment is restarted, the subject should be closely monitored based on routine clinical practice until the possible time of adverse reaction has passed. If a subject has a grade 4 infusion-related reaction, the study treatment should be discontinued.

An allergic reaction is defined as the vascular collapse or shock (systolic BP < 90 mmHg, unresponsive to rehydration) that occurs within 30 minutes of a study drug infusion caused by an allergy, with or without respiratory distress. Skin reactions include pruritus, urticaria, and angioedema. Subjects with allergic reactions should discontinue the study treatment.

5.3.3 Dose adjustments of chemotherapy

Paclitaxel and carboplatin should be administered according to the study site guidelines and local prescribing information. For the specific information for use, preparation, and storage of paclitaxel and carboplatin, refer to the prescribing information and local dosing information. Carboplatin-based chemotherapies have a relatively high incidence of emesis. Therefore, antiemetics for prophylaxis can be used.

Hematological toxicity:

Absolute neutrophil count (ANC; dose can only be reduced when febrile neutropenia occurs. ANC must be $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L on D1 of each treatment cycle)

Table 2. Dose adjustments of paclitaxel and carboplatin (febrile neutropenia)

	Dose Adjustments of Paclitaxel/Carboplatin ANC (D1 of each treatment cycle)	
	< 1.5 x 10^9/L	≥ 1.5 x 10^9/L
Febrile neutropenia (regardless of duration)	0	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5

Platelet count:

Table 3. Dose adjustments of paclitaxel and carboplatin (thrombocytopenia)

	Dose Adjustments of Paclitaxel/Carboplatin Platelet count (D1 of each treatment cycle)	
Lowest Level After Last Dose	< 100 x 10^9/L	≥ 100 x 10^9/L
< 25 × 10^9/L or < 50 × 10^9/L with hemorrhage or requires blood transfusion	0	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5

Once the chemotherapeutic dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 × 10^9/L or < 50 × 10^9/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If dose reduction is required due to another incident of febrile neutropenia or thrombocytopenia, the dose of paclitaxel and carboplatin will be reduced to 100 mg/m^2 and AUC 3.0, respectively. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.

If the dose adjustment is required when ANC and thrombocytopenia occur concurrently, the low-dose chemotherapy should be adopted.

Chemotherapy may be delayed for up to 3 weeks. If after the chemotherapy has been delayed for 3 weeks, ANC does not reach ≥ 1.5 × 10^9/L and platelet count does not reach ≥ 100 × 10^9/L on D1 of the scheduled chemotherapy, the chemotherapy should be permanently discontinued. If the above values have been reached, the next course of chemotherapy should be continued.

The investigator should monitor the subject closely for toxicity with particular attention to early and evident signs of myelosuppression, infection, or febrile neutropenia to timely and appropriately treat the complications.

Subjects should be informed to pay attention to these signs and receive treatment as soon as possible.

If the chemotherapy must be interrupted due to hematological toxicity, the complete blood count should be performed regularly (including WBC differentials) until all the counts reach the minimum requirements for treatment continuation. Thereafter the scheduled treatment plan will be performed.

Dose adjustments are not required for anemia. However, treatment based on guidelines of each clinic should be performed.

Gastrointestinal toxicity

Antiemetics will be used to control nausea and/or emesis. If grade 3 or 4 nausea and/or emesis occur(s) despite of antiemetics, the chemotherapeutic dose should be reduced by 20% for the next treatment cycle. The dose should be returned to the initial level as possible if the subject is tolerated.

If the subject experiences stomatitis on D1 of any treatment cycle, the chemotherapy should be interrupted until the symptoms resolve. If the stomatitis has not resolved after 3 weeks, the chemotherapy should be permanently discontinued (refer to CTCAE version 4.03). If an acute Grade 3 stomatitis occurs, the chemotherapeutic dose should be reduced to 75% of the proposed dose when symptoms resolve.

Hepatotoxicity (Paclitaxel)

The paclitaxel dose should be determined based on the lab values measured on D1 of each treatment cycle.

Table 4. Dose adjustment of paclitaxel (hepatotoxicity)

AST		Total bilirubin	Paclitaxel Dose
≤ 5 x UNL	and	WNL	175 mg/m^2
> 5 x UNL	or	> UNL ~ 1.5 x UN	150 mg/m
		> 1.5 x UN	0

If paclitaxel is interrupted due to hepatotoxicity, carboplatin should also be interrupted until paclitaxel is restarted. Paclitaxel will be interrupted for up to 3 weeks. If the subject's hepatic function does not return to the acceptable ranges in 3 weeks, paclitaxel should be permanently discontinued. The carboplatin dose will not be adjusted when hepatotoxicity occurs.

The investigators should avoid PD due to abnormal hepatic enzyme levels as possible. If PD occurs, all the study drugs should be permanently discontinued, including chemotherapy.

Cardiovascular toxicity (paclitaxel)

The arrhythmia in subjects was infrequent in previous clinical studies. However, most subjects were asymptomatic and electrocardiographic monitoring was not required. Asymptomatic transient bradycardia was observed in 29% of subjects, but significant atrioventricular block was rare. Cardiac events should be treated as follows:

Asymptomatic bradycardia: no intervention indicated

Symptomatic arrhythmia during infusion: Discontinue paclitaxel infusion and perform routine treatment of arrhythmia. Discontinue subsequent paclitaxel treatment. Document this AE in the AE Report Form of eCRF.

Chest pain and/or symptomatic hypotension (< 90/60 mmHg or rehydration therapy required): discontinue the paclitaxel infusion. Perform electrocardiography (ECG). If hypersensitivity reaction is suspected, administer diphenhydramine and dexamethasone via intravenous infusion. If the chest pain is not considered as cardiogenic, epinephrine or bronchodilators will be administered. Document this AE in the AE Report Form of eCRF. Discontinue subsequent paclitaxel treatment and provide symptomatic treatment. Consult a cardiologist if needed.

Neurotoxicity (paclitaxel)

The dose of paclitaxel should be adjusted according to Table when neuropathy occurs. The dose adjustment of carboplatin is not needed when neurotoxicity occurs.

Table 5. Dose adjustment of paclitaxel (neurotoxicity)

Toxicity Grade (CTCAE version 4.03)	Paclitaxel dose adjustment
Grade 1 or below	175 mg/m^2
2	Interrupt treatment until return to grade 1, then reduce dose to 140 mg/m^2 (20% of reduction) and restart infusion
Grade 3 or above	Interrupt treatment until return to grade 1, then reduce dose to 125 mg/m^2 (30% of reduction) and restart infusion.

Once the dose is reduced due to neurotoxicity, the original dose should no longer be adopted.

If the neurotoxicity does not return to grade 1 after paclitaxel interruption for 3 weeks, paclitaxel should be permanently discontinued.

Allergic reactions/hypersensitivity reactions (paclitaxel)

Note: Prophylaxis for hypersensitivity reactions (see below) and close monitoring of vital signs are recommended for subjects with history of mild to moderate hypersensitivity reactions when hypersensitivity reactions reoccur.

Mild symptoms: complete paclitaxel infusion. Close monitoring; no treatment indicated.

Moderate symptoms: Interrupt paclitaxel infusion, administer diphenhydramine 25–50 mg and dexamethasone 10 mg via intravenous infusion. Once symptoms have resolved, resume paclitaxel infusion at a slower rate (20 mL/hour for 15 minutes, then at 40 mL/hour for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete). Document this AE in the AE Report Form of eCRF. If symptoms reoccur, interrupt the paclitaxel infusion and permanently discontinue subsequent paclitaxel infusion.

Severe and life-threatening symptoms: Interrupt paclitaxel infusion, administer diphenhydramine and dexamethasone via intravenous infusion (as above). Use epinephrine or bronchodilators if indicated. Document this AE in the AE Report Form of eCRF. Subsequent courses of paclitaxel infusion should be permanently discontinued.

Moderate or severe hypersensitivity reactions should be documented as AEs.

Other toxicities

If other unmentioned grade 3–4 toxicities occur, the chemotherapy should be interrupted until symptoms resolve or return to grade 1. Thereafter restart the infusion at 50% of the original dose (which should no longer be adopted). If the toxicity does not return to grade 1 after an interruption for 3 weeks, the chemotherapy should be permanently discontinued. Dose adjustments are not recommended for grade 1 and 2 toxicities.

5.4 Study Drug Properties

IBI305 is a bevacizumab biosimilar. The active ingredient of both drugs is recombinant humanized anti-VEGF monoclonal antibody; Bevacizumab is the standard commercially available drug, provided by the sponsor.

Detailed information on the study drugs is shown in Table .

Table 6. Study drugs

Study Drugs	Dosage Form and Strength	Excipient	Appearance	Manufacturer
IBI305	4 mL: 100 mg	Sodium acetate, sorbitol, and polysorbate 80	Sterile solution for intravenous injection pH 5.2 Clear, colorless liquid, no foreign matters, no floc or precipitation	Innovent Biologics (Suzhou) Co., Ltd.
Bevacizumab	4 mL: 100 mg	α,α-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, polysorbate 20, and sterile water for injection	Sterile solution for intravenous injection pH 5.9–6.3 Clear to slight opalescent, colorless to light brown	Roche Pharma (Schweiz) Ltd.

5.5 Preparation and Distribution

IBI305 or bevacizumab is diluted in 0.9% sodium chloride solution by the pharmacist or research nurse before infusion. Check the particles and discoloration prior to administration.

The investigator should ensure that the pharmacist or research nurse administers the study drugs according to study protocol.

5.6 Packaging, Labeling, and Storage

The sponsor should package and label the study drugs according to appropriate local regulations.

All study drugs (IBI305 and bevacizumab) must be stored at 2–8 °C away from light. The study drugs should be stored in a safe zone only accessible by authorized staff prior to dispensation to the subjects.

5.7 Subjects Allocation

After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in the Interactive Web Response System (IWRS) and enter the subject information into the IWRS. The IWRS will allocate a random number to the subject and provide a medication number. Stratified randomization is used in this study. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild vs. unknown type).

5.8 Blinding

This is a randomized, double-blind, and active-controlled study, and only relevant study personnel had access to the randomization numbers. A non-blinded pharmacist or research nurse will prepare the medications since IBI305 and bevacizumab do not have an identical appearance. The pharmacist or research nurse who is responsible for preparing the study drugs is not allowed to disclose any information regarding treatment allocation to the subject, the subject's family members, or other personnel including the physician and the relevant study staff.

Unblinding: Subject unblinding should only be performed after database locking.

Emergency unblinding: In case of an emergency where the investigator must know the medication given to a particular subject, the investigator will unblind the subject via the IWRS and immediately inform the sponsor and CRO. The reasons for unblinding, date, and outcomes should be documented in the source document and eCRF of the subject.

5.9 Concomitant Medications and Treatments

All medications except for the study drugs, including other chemotherapies not specified in the study, Chinese herbal medicines, and other non-traditional therapies, are considered concomitant medications. All concomitant medications used within 30 days prior to screening should be documented in the eCRFs, including the information of generic name, route of administration, start date, end date, and indication.

5.9.1 Prohibited medications

No other anti-tumor therapies or medications with anti-tumor indications, including Chinese herbal medicine, radiotherapy, or other investigational drugs, are allowed during this study other than IBI305, bevacizumab, paclitaxel, and carboplatin.

Severe myelosuppression is possible after chemotherapy. Granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are not allowed to be used prophylactically in the first treatment cycle.

5.9.2 Medications allowed

Prophylactic use of anti-emetics, glucocorticoids, or other treatments targeting toxicities is permitted during the study. Unconventional treatments (such as acupuncture) and vitamins/microelements are permitted if their use does not affect the study endpoints as determined by the investigators.

Starting from the 2nd chemotherapy cycle, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are allowed to be used prophylactically to prevent severe myelosuppression.

5.9.3 Treatment after study treatment

Subsequent therapy after the end of study treatment should be determined by the subject's attending doctor.

5.10 Treatment Compliance

Subjects should receive treatment at the study site. The dose and time of administration of IBI305 or bevacizumab and paclitaxel/carboplatin should be documented in the source records and eCRFs during each treatment cycle. Reasons for dose adjustments, therapy delay, and therapy discontinuation should be documented. Treatment compliance is monitored by medication dispensing and return records, medical records, and eCRFs.

5.11 Drug Return and Destruction

The containers, vials, infusion bags, and syringes of used and partially used drugs can be destroyed on-site according to the appropriate guidelines and operating procedures established by study sites and local agencies.

Unless the contents have significant safety issues requiring immediate destruction in accordance with local regulations, all the unused drugs should be returned and destroyed based on the requirements of sponsor.

5.12 Study Drug-Related Records

The designated personnel of the study sites should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines.

6 STUDY PROCEDURE

The detailed procedures of this study are shown in Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

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6.1 Screening Visits (D -28 to D -1)

Complete the screening visits within 28 days prior to study treatment commencement. The following procedures must be completed during screening to ensure that subject meets the requirements for participating in this study:

- Sign the ICF
- Record the demographics, including age, ethnicity, and gender
- Record the past medical history, including smoking history
- Record the history of anti-tumor therapies
- Record the concomitant medications (within 30 days prior to screening)
- Record the vital signs
- Measure the height and weight (including BMI)
- ECOG score
- Physical examination
- 12-Lead ECG
- Hepatitis B panel, anti-HCV, anti-HIV, and syphilis tests
- Clinical laboratory tests (routine blood test, coagulation test, blood chemistry, and urinalysis)

- Blood pregnancy test (for female subjects of childbearing age only)
- Imaging examinations (CT or MRI: Head, chest, abdomen, and pelvis cavity)*
- EGFR test#
- Review the inclusion/exclusion criteria
- Record the AEs and concomitant medications

* Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging results during screening will be used as the baseline data. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

If the subject has been tested for EGFR of tumor sample at the study site with documentation, the subject will not be required for retest.

6.2 Baseline Visits (D1 of cycle 1)

D1 refers to the day of receiving the first dose of the study drugs. Eligible subjects meeting the inclusion criteria will return to the study site and complete the following procedures:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests * (routine blood test, blood chemistry, and urinalysis)
- Confirm the inclusion/exclusion criteria

* If clinical laboratory screening tests (routine blood test, blood chemistry, urinalysis) are performed within 7 days prior to the first dose, then the results of the screening test can be used as baseline.

If the subject meets the inclusion criteria, the following procedures should be complete:

- Randomization and grouping
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Pharmacokinetic (PK) blood sampling (within 1 h prior to the study drug infusion,

immediately after the study drug infusion [+5 min])

- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Record the AEs and concomitant medications

6.3 Cycle 2 (week 4 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.4 Cycle 3 (week 7 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)

- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.5 Cycle 4 (week 10 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- Immunogenicity test (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.6 Cycle 5 (week 13 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)

- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.7 Cycle 6 (week 16 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- PK blood sampling (within 1 h prior to the study drug infusion)
- VEGF blood sampling (within 1 h prior to the study drug infusion)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.8 Cycle 7 and Subsequent Treatment Cycles (±3 Days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Maintenance monotherapy will start from week 7 and the dose of study drug will be adjusted to 7.5 mg/kg. Subjects should complete the following procedures during each visit:

- Record the vital signs
- Measure the weight
- Physical examination
- 12-Lead ECG

- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.9 End-Of-Treatment Visit

The end of treatment visit in study sites will be conducted in 28 days (±7 days) after the last dose of study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Immunogenicity test
- PD blood sampling
- Blood pregnancy test (for female subjects of childbearing age only)
- Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this visit)
- Subsequent anti-tumor therapy
- Record the AEs and concomitant medications

If the subject has not experienced PD, the subsequent follow-up for PD will be performed (Section 6.10). If the subject has experienced PD, the subsequent follow-up for survival will be performed (Section 6.11).

6.10 Disease Progression Visit

If the study drugs are discontinued for reasons other than PD, the end of treatment visit in study sites will be conducted in 28 days after the last dose of study drug, and tumor assessments should be conducted every 6 weeks (±7 days) until PD if possible (after which, follow-up for survival will be conducted [Section 6.11]), withdraw of informed consent, loss to follow-up, death,

start of other anti-tumor therapies, or end of study. During the visit, vital signs and weight measurements will be performed, and any subsequent anti-tumor therapies will be documented.

6.11 Survival Follow-Up

The investigator will make telephone follow-up every 12 weeks (±7 days) to collect the information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, loss to follow-up, death, or end of study.

6.12 Study Completion

The end of this study will be the18th month after randomization of the last subject. If the subjects continue to receive the study drug treatment before this cut-off time, the treatment should be discontinued and the end of treatment visit should be completed (Section 6.9).

6.13 Tumor Assessment

Imaging tests (CT or MRI) of the brain, chest, abdomen, and pelvis are required at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test was used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

The investigator should perform a tumor assessment based on RECIST v1.1 (Section 13.3) prior to each dose to determine whether the subject should continue with the next round of treatment. An independent review committee will also assess the tumor response (Section 11.1.1). Imaging tests will not be rescheduled if the study drugs or chemotherapeutic agents are interrupted due to toxicities. Every effort should be made to continue the schedule for imaging tests even for subjects who discontinue one or two study treatment(s) due to drug-related toxicities.

If subject experience PD according to the RECIST v1.1 criteria, the attending doctor should discuss with the subject regarding subsequent routine cancer therapies.

6.14 Clinical Laboratory Evaluations

Clinical laboratory tests will be conducted at the laboratories of each study site. Sample collection and analysis should be performed according to the requirements of each laboratory.

The following laboratory tests should be conducted according to the study procedures (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

):

Routine blood test: hemoglobin, hematocrit, WBC and differentials (including

absolute neutrophil and lymphocyte counts), platelets, and RBC

Routine coagulation test (baseline test): INR, aPTT, or PTT

➢ Blood chemistry: Creatinine, blood urea nitrogen, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose, sodium, potassium, chloride, calcium, phosphorus, and magnesium

➢ Urinalysis: Specific gravity, pH, glucose, protein, occult blood, and leukocytes

➢ Pregnancy test: Serum pregnancy tests are performed on women of childbearing age during screening and the end-of-treatment visit.

These tests are carried out at the laboratory of each trial site.

For subsequent visits, all laboratory tests need to be completed within 3 days prior to the administration. During the study, the frequency of these laboratory tests will be increased if safety is a concern. The investigator should review the laboratory test results throughout the study to determine whether the results are clinically significant. The investigator should assess the changes in laboratory test results. If the investigator considers a laboratory test result to be abnormal and of clinical significance, it is considered as an AE.

6.15 Vital Signs, Physical Examinations, and Other Safety Assessments

6.15.1 Vital signs

Vital signs include pulse, BP, temperature, and respiratory rate. The subject must rest for at least 5 minutes prior to each vital sign assessment.

Vital signs will be assessed according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	**Screening period**	**Treatment period (21-day cycles)**							**After treatment**		
		Combination treatment period						**Maintenance therapy**	**End-of-treatment visit (28 days after last dose)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks after PD)**
Cycle (C) and day (D)	**D-28 to D1**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**Cycle 7 to end-of-treatment**			
Time window (day)	**-**	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**-**	**±7**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-N**			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

). During the study, the investigator may increase the frequency of vital sign measurement if

safety is a concern.

6.15.2 Height and weight

Height is only measured during screening. Weight is measure during each visit.

6.1.5.3 Physical examinations

The following organs/systems will be examined according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration		x	x	x	x	x	x	x			

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
(IBI305 or bevacizumab) [j]											
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

): general condition, head (eyes, ears, nose, and throat), neck and thyroid, respiratory system, cardiovascular system, abdomen, nervous system, skeletal muscles and limbs, as well as lymphatic system and skin.

6.15.4 12-Lead ECG

12-lead ECG will be performed during screening. During the study, each medication visit requires an ECG examination. The following ECG parameters should be documented: HR, PR-interval, QRS-complex, QT-interval, and QTc-interval. The subject must be in the supine position for at least 5 minutes prior to undergoing the 12-lead ECG. All ECG are evaluated by qualified physicians. All clinically significant abnormal findings should be reported as AEs.

6.15.5 Immunogenicity assessment

Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples were tested at the designated central laboratory.

6.15.6. Pharmacokinetics/pharmacodynamics

6.15.6.1 Pharmacokinetics

Study sites that are implementing version 2.0 of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 hour prior to the dose in C4, within 1 h prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.

6.15.6.2 Pharmacodynamics

Study sites that are implementing version 2.0 of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and during the end-of-treatment visit. Samples were tested at the designated central laboratory.

6.15.7 EGFR testing

EGFR mutation testing histologically or cytologically will be performed in all subjects (if the subject has been tested for EGFR at the study site histologically or cytologically with documentation, the subject will not be required to be retested). The testing will be conducted at the laboratory of each study site or a qualified third-party laboratory.

7 STUDY ASSESSMENTS

7.1 Efficacy Assessment

7.1.1 Primary efficacy endpoint

- Objective response rate (ORR)

ORR will be assessed using RECIST v1.1. ORR is defined as the proportion of subjects whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved complete response (CR) and partial response (PR). The cutoff date for the primary efficacy endpoint analysis of this study is 6 months after subject randomization.

7.1.2 Secondary efficacy endpoints

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Each endpoint will be assessed using RECIST v1.1.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death before PD; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

PFS is defined as the time from the date of randomization to the date of PD or death; Subjects who do not progress or die will be censored on the date of the last tumor assessment.

DCR is defined as the proportion of patients whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved CR, PR, and SD.

OS is defined as the time from the date of randomization to the date of death of any cause. For subjects that are alive on the date of study completion or are lost to follow-up, their survival time will be censored at the date of last contact.

7.2 Safety Assessments

7.2.1 Adverse events

7.2.1.1 Definition

Adverse event

An AE refers to any untoward medical occurrence in a subject after signing the informed consent form, and does not necessarily have a causal relationship with the treatment. Thus, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether considered drug related.

Abnormalities resulting from PD are not considered as AEs.

Serious adverse event

A SAE refers to an AE meeting at least one of the followings:

(1) Lead to death, except for deaths caused by PD.

(2) Life-threatening (a "life-threatening event" is defined as an AE when the subject is at immediate risk of death at the time, but does not include the case that may lead to death only when the event worsens).

(3) Requires hospitalization or prolonged hospitalization, excluding an emergency or outpatient visit. Subjects with existing diseases or conditions prior to the enrollment that do not worsen during the study, and having hospitalization and/or surgery that was scheduled before the study or during the study do not meet the SAE criterion. Hospitalizations resulting from PD are not considered as SAEs.

(4) Results in permanent or severe disability/incapacity.

(5) Results in congenital anomalies/birth defects.

(6) Other important medical events: The event that does not result in death, is not life-threatening or does not require hospitalization, but may jeopardize the health of subjects and require medical intervention to prevent the SAEs above, is considered as an SAE

7.2.1.2 Severity of adverse events

The severity of AEs is evaluated using the 5-level criteria of NCI CTCAE v4.03.

For AEs not included in CTCAE v4.03, use the following CTCAE general guidelines:

- Grade 1: Mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated.
- Grade 2: Moderate; minimal/local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life (such as cooking, shopping, using the phone, financial management, etc.).
- Grade 3: Severe or clinically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; limited ability of self-care (such as bathing, dressing, undressing, eating, using the toilet, taking medication), but not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

7.2.1.3 Relationship between adverse events and the investigational drug

The relationship between the study drugs and AEs can be determined using the followings:

Table 11. Correlation between AEs and investigational drugs

Correlation	CRITERIA
Related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can more reasonably explain the AE than the other causes (such as the pre-existing disease of the subject, environment, toxicity, or other treatment received); The AE resolves or is alleviated after treatment interruption or dose reduction; The AE is consistent with the known type of AEs of the suspicious drug or similar drugs; The AE occurs again after the drug administration is resumed.
Possibly related	The occurrence of the AE is reasonably related to the time sequence of dosing; The investigational drug can be used to explain the AE with the same level of rationality as other reasons (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE resolves or is alleviated after treatment interruption or dose reduction (if applicable).
Possibly not related	Other reasons can more reasonably explain the AE than the investigational drug (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject); The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear; The AE does not occur again or the situation of the AE is unknown after the drug administration is resumed.

Unrelated	$\frac{4}{3}$	The occurrence of the AE is not reasonably related to the time sequence of dosing, or $\frac{4}{3}$ The AE has other obvious causes (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject).
Cannot be determined	$\frac{4}{3}$	The above information is unclear and cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.

7.2.1.4 Serious adverse event reporting

The investigator should immediately take appropriate medical measures to treat any SAE that occurs during the trial. And the SAE should be recorded in the tables of adverse events and serious adverse events in the eCRF and source documents; regardless of whether the SAE is related to the treatment, the investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.

Contact information for the reporting of SAE/pregnancy to the sponsor:

Fax: 021-31652800

SAE reporting email: drugsafety@innoventbio.com

When submitting the SAE report by email, it is recommended for the investigator to encrypt the report file and send the report file and password in separate emails.

At the same time, the investigator should follow the SAE reporting procedures issued by relevant regulatory authorities or the independent ethics committee.

The investigator should follow up the SAE until it disappears or recovers to a result that the investigator believes it can be explained without further follow-ups, such as clinical stability or improvement. The time limit for the follow-up report and the report of answered queries is the same as that for the initial report.

7.2.1.5 Management and follow-up of adverse events

The investigator is responsible for providing appropriate medical treatment for all AEs (Indicate the actions taken, such as suspension/termination of the investigational drug, dose modification, drug therapy, etc.). When an AE occurs, the investigator should actively take appropriate measures to ensure the safety of the subject. All AEs observed from the signing of the ICF to the time specified in the protocol (Table 2) must be followed.

The investigator should report any SAE that occurs after the time specified in the protocol (Table 2) and is suspected of being related to the investigational drug to the sponsor.

7.2.1.6 Adverse event of special interest and expedited reporting

The AESI for this study include:

- Gastrointestinal perforation
- Procedural and wound healing complications
- Hemorrhage
- Fistula
- Hypertension
- Thrombotic event
- Posterior reversible encephalopathy syndrome (PRES)
- Proteinuria
- Infusion-related reaction
- Ovarian failure
- Cardiac failure congestive

Among them, Grade 2 gastrointestinal perforation, procedural and wound healing complications, hemorrhage, fistula, arterial thrombotic events and proteinuria, and all above adverse events of special interest (AESIs) of Grade 3 and above should be reported as AESIs to the sponsor in accordance with the SAE reporting time limit and procedures (see 7.2.1.4 for details) even if they do not meet the SAE definition.

7.2.1.7 Pregnancy

Bevacizumab may be harmful to the fetus. Subjects or female partners of male subjects must use an effective form of contraception during the 6 months after the last dose. If any female subject or the female partner of any male subject becomes pregnant during the study, the drug should be discontinued immediately and the investigator should be notified. The investigator should report the pregnancy to the sponsor within 24 h of knowing the event by filling out the pregnancy form. The Investigator should also discuss with the subject (and the female partner of the male subject) regarding the risk of continuing pregnancy and its possible impact on the fetus. The investigator should follow up the pregnancy to determine its outcome (including abortion) and the status of the mother and the baby for not less than 8 weeks after delivery, and report the follow-up results as the

pregnancy follow-up report to the sponsor according to the procedure and time limit the same as those for the first report. Complications and termination of pregnancy due to medical reasons should be reported as AE or SAE. A spontaneous abortion should be reported as an SAE. For any congenital abnormalities/birth defects or SAEs of the mother and child during the perinatal period, they should be recorded and reported in accordance with the procedure and time limit for reporting SAEs.

The investigator should pay attention to any pregnancy-related SAE that occurs after study completion. Any SAE that the investigator believes may be related to the study treatment should be reported immediately to the sponsor.

7.2.1.8 Time limits of documenting and reporting AEs

All AEs occurring from the time the subject signs the informed consent form to the time specified in the protocol (Table 2) (including SAEs and non-SAEs), regardless of their severity, must be collected and recorded on the AE page of the eCRF.

Table 12. Reporting and follow-up of adverse events

	Reporting time limit	Visit time limit
AEs	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or explainable stable determined by the investigator
Adverse events of special interest (AESIs)	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or explainable stable determined by the investigator
Serious adverse event	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or explainable stable determined by the investigator
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the outcome of the event is available, and the health conditions of the newborn should be followed up for at least 2 months according to the protocol

7.2.1.9 Precautions for AE documentation

Diagnosis, signs, and symptoms

If a diagnosis is already made, the eCRF should record the diagnosis instead of individual symptoms and signs (such as hepatic failure rather than jaundice, transaminase increased, and asterixis). However, if the signs and symptoms cannot be attributed to a definitive diagnosis, each independent event should be documented in the eCRFs as an AE or SAE. Update the report with visit information if a diagnosis is confirmed later.

AEs secondary to other events

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

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs. The initial severity should be documented, and the information should be updated if the event exacerbates.

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

Abnormalities in laboratory tests/vital signs

Not all abnormalities in laboratory tests/vital signs should be reported as AEs. Only the abnormalities in laboratory tests/vital signs that meet the following criteria are reported as AEs:

- Accompanied with clinical symptoms
- Lead to changes in the dose of the study treatment (such as dose adjustment, dose interruption, or permanent drug withdrawal)
- Require medical intervention or changes in concomitant therapy
- Judged by the investigator as clinically significant

It is the responsibility of the investigator to review all abnormal laboratory test results and vital signs, and to determine whether each abnormal laboratory test result or vital signs should be reported as AEs.

If clinically significant laboratory abnormalities or abnormal vital signs are characteristic of a disease or syndrome (such as increased levels of alkaline phosphatase and total bilirubin caused by cholecystitis that are higher than 5 times the upper limit of normal), only the diagnosis is recorded on the AE report of the eCRF (i.e., cholecystitis). Conversely, the laboratory abnormalities or abnormal vital signs are recorded on the AE report of the eCRF, and it should be indicated that whether the test value is above or below the normal range (for example, it should be recorded as "blood potassium increased" instead of "blood potassium abnormal"). If there is a standard clinical term corresponding to the laboratory abnormalities or abnormal vital signs, the clinical term should be recorded on the eCRF (such as "anemia", instead of "hemoglobin decreased"). The same clinically significant laboratory abnormalities or abnormal vital signs found during multiple follow-ups should not be repeatedly recorded as AEs or SAEs in the eCRF unless there is a change

in its severity or etiology.

Death

During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs and reported to the sponsor timely, regardless of the causality with the investigational drug.

When recording a death event, if there is an AE leading to the death, a single medical concept should be used on the AE report of the eCRF to record the event leading to the death, and the event should be reported as an SAE in an expedited manner; if the cause of the death is unknown at the time of reporting , "Death with Unknown Cause" should be recorded on the AE report of the eCRF. The "Death with Unknown Cause" should be reported as an SAE in an expedited manner before further investigation is carried out to find the exact cause of death.

If the cause of death is confirmed to be PD, then the event should not be documented and reported as an AE/SAE. However, the event should be documented in the Mortality Report Form of the eCRF and reported to the sponsor timely.

Pre-existing medical conditions

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

Hospitalization and prolonged hospitalization, or surgery

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

$\frac{4}{3}$ Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration, efficacy evaluation, etc.)

$\frac{4}{3}$ Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.

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

The investigator should fill in all required information, including AE terms

(diagnostic terms, or the record of symptoms and signs including laboratory test abnormalities if there is no diagnosis), start date, end date, severity level, whether it is an AESI, measures taken for the investigational product, treatment given for the AE, outcome, seriousness, and relationship with the investigational product. If the signs and symptoms cannot be attributed to a definitive diagnosis, each AE should be documented independently.

Progressive disease

For any event, if it can be clearly determined that the event is caused by progressive disease, the event is not reported as an AE. Hospitalization or death caused by progressive disease does not need to be reported in an expedited fashion.

Lack of efficacy

When the disease treated by the study treatment deteriorates, it may not be possible to determine whether it is due to the lack of efficacy or the occurrence of an adverse event. In this case, unless the investigator believes that the deterioration of the condition is related to the study treatment, such changes are all regarded as the lack of efficacy rather than adverse events.

Overdose

When there is an accompanying AE, the AE should be recorded; when there is not accompanying AE, the overdose should be recorded on the eCRF.

8 STATISTICS

8.1 Sample Size Determination

A number of 218 subjects for each group (436 subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin.

The sample size is estimated based on the following assumptions:

- The ORRs between IBI305 and bevacizumab group are equivalent
- The ORR of subjects in the bevacizumab groups is set to 50.0%
- The equivalence margin is taken as (-12.5%, 16.7%)
- The significance level of the two one-side test is 0.05
- 1:1 randomization

Based on the above hypotheses, a number of 218 subjects for each group is required (436 subjects in total). The sample size was estimated using PASS 2013.

8.2 Statistical Population

Intention-to-Treat (ITT): All randomized subjects.

Full Analysis Set (FAS): All randomized subjects who received at least one dose of the study treatment. This dataset is used as the primary analysis set for efficacy assessment.

Per-Protocol (PP): Based on the FAS, subjects with the predetermined minimum drug exposure and without any predetermined major protocol deviations. This dataset is used as the secondary analysis set for efficacy assessment.

Safety set (SS): Includes all randomized subjects who received at least one dose of the study treatment and have safety evaluation data. This data set is used for the safety evaluation of this study.

PK analysis set (PKAS): Includes subjects in the FAS with at least one PPK measured value.

Pharmacodynamic analysis set (PDAS): Includes all subjects in the FAS set with at least one PD measured value.

8.3 General Principles for Statistical Analyses

For continuous variables, descriptive statistics should include the count, mean, standard deviation, median, maximum, and minimum. For categorical variables, descriptive statistics will include the frequency as well as the absolute or relative percentage. Statistical analyses will be carried out using SAS 9.4.

8.4 Statistical Methods

8.4.1 Adjustments for covariates

Not applicable.

8.4.2 Managing dropouts and missing data

The analyses of primary and secondary endpoints will include data from dropouts. The management of missing data is described in the Statistical Analysis Plan.

8.4.3 Multi-center study

Since this is a multicenter study, the primary endpoint (ORR) will be listed according to study sites and treatment groups. However, individual equivalence analysis will not be conducted. Trial sites with fewer than 5 ITT subjects per treatment group will need to be combined for analysis. Details will be discussed in the data review meeting.

8.4.4 Multiple comparisons and adjustments to multiplicity

The α adjustment for multiple comparisons is not considered.

8.5 Statistical Analyses

8.5.1 Subject distribution

Refer to Figure 1: Study design schematic for the schedule of activities. The number and percentage of patients who have completed or dropped out of the study (including the reason for dropouts such as loss to follow-up, AEs, and poor compliance) are summarized based on treatment groups.

The number and percentage of subjects in each analysis set are calculated based on treatment groups.

The number and percentage of protocol deviations are calculated based on treatment groups.

8.5.2 Demographics and other baseline characteristics

Demographic information such as age, height, sex, and weight, and other baseline characteristics such as disease history (including NSCLC diagnosis, staging, previous cancer treatment, and target and nontarget lesions) are summarized using descriptive statistics.

8.5.3 Compliance and drug exposure

The required dose and the actual dose must be documented in the eCRF. Subject compliance is calculated based on the ratio of the actual dose (number of doses) to the required dose (number of doses). Subject compliance is classified into the following categories: < 80%, 80–120%, and > 120%. The number and percentage of subjects in each category will be summarized.

8.5.4 Efficacy

The efficacy analysis will be based on the FAS. Results of the PP set will also be presented.

8.5.4.1 Primary efficacy endpoint

The primary objective of this study is to determine the clinical equivalence between IBI305 + paclitaxel/carboplatin and bevacizumab + paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC). The primary endpoint is objective response rate (ORR). ORR is defined as the incidence of patients with confirmed complete response (CR) or partial response (PR), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions. Subjects without tumor assessments beyond baseline will be considered unresponsive to treatment. Subjects qualified for the evaluation of CR or PR must have at least one measurable lesion according to RECIST v1.1. The evaluation of clinical equivalence will be based on the ORR provided by the independent review committee (IRC). Results provided by the investigator will be used for sensitivity analysis.

Clinical equivalence will be declared if the 90% confidence interval of the difference in ORR between IBI305 and bevacizumab groups falls within the preset margin of (-12.5%, 16.7%). The ORR and corresponding 95% confidence interval of the two treatment groups, the ORR difference and the 90% confidence interval, as well as the ORR ratio between the two groups and the 90% confidence interval will be estimated using the generalized linear model (GLM, which includes treatment groups and stratification factors).

8.5.4.2 Secondary efficacy endpoints

The secondary endpoints for this study include DOR, DCR, progress-free survival (PFS), and overall survival (OS).

DCR is defined as the incidence of patients with confirmed complete response (CR), partial response (PR), and stable disease (SD), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

OS refers to the time from the date of randomization to the date of death (of any cause). For subjects who are still alive at the time of the analysis, their survival time is censored on the last known alive date. PFS refers to the time from the date of randomization to the date of first documented PD or death, whichever occurs first. The investigator will assess PD using RECIST v1.1. Subjects who do not progress or die will be censored on the date of the last tumor assessment. Subjects without tumor assessments after baseline are censored on their date of randomization.

Median OS and its 95% CI will be estimated using the Kaplan-Meier method. The survival curve will be plotted. The hazard ratio (HR) between the two groups and its 95% CI will be estimated using a Cox model. The Cox model includes treatment groups and stratification factors. DOR and PFS will be analyzed using the same method as for OS. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

8.5.4.3 Sensitivity analysis

The center effect (fixed or random) will be considered in the primary and secondary endpoints analysis models (GLM or Cox).

8.5.4.4 Antibody and efficacy analysis

Subjects who develop antibodies during the clinical study will be summarized in detail. The difference in efficacy between subjects with and without antibodies will be compared if necessary.

Changes in PK parameters and steady-state trough concentrations of subjects with positive ADA are analyzed.

8.5.5 Exploratory analysis

Pharmacodynamic parameters: The changes in the serum VEGF level at different time points are described, and inter-group comparisons are carried out when necessary (based on the PD dataset)

Steady-state trough concentrations of the drug: The level of trough concentration is described and inter-group comparisons are carried out when necessary (based on the PPK dataset)

8.5.6 Interim analysis

No interim analysis is planned for this study.

8.5.7 Stratified analysis

Efficacy analysis of different levels of subjects is conducted based on the random stratification factors

8.5.8 Safety analysis

The safety analysis is based on the safety analysis set.

8.5.8.1 Adverse events

All adverse events (AE) will be coded using MedDRA and graded using CTCAE v4.03. All TEAEs, TEAEs ≥ grade 3, SAEs, drug-related TEAEs, drug-related SAEs, TEAEs resulting in the termination of study drugs, TEAEs resulting in the termination of study, and AESIs will be listed based on system organ class, preferred terms, and groups and the corresponding numbers and percentages of subjects will be summarized. In addition, the severity of TEAEs and relevance to the study drugs will also be summarized system organ class, preferred terms, and treatment groups.

8.5.8.2 Laboratory tests

All laboratory test results and changes relative to baseline will be summarized by scheduled time point and treatment group using descriptive statistics. Laboratory abnormalities will be listed.

8.5.8.3 ECG examinations

Results of ECG and changes relative to baseline will be summarized using descriptive statistics.

8.5.8.4 Vital signs, physical examinations, and other safety examinations

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

Results of physical examinations are listed by treatment groups.

8.5.8.5 Concomitant medications

Concomitant medications are non-study medications that meet one of the followings:

(1) Any drug therapy started during or after the first dose of the study treatment;

(2) Any drug therapy started before the first dose of the study treatment and continued after the first dose of the study treatment. Concomitant medications are listed by treatment groups.

9 QUALITY ASSURANCE AND QUALITY CONTROL

According to GCP principles, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems based on standard operating procedures (SOP), to ensure that the implementation of the clinical trial and the collection, documentation, and reporting of trial data is in accordance with the protocol, GCP, and applicable regulatory requirements.

To ensure that the data is reliable and processed correctly, there should be quality control for every step during the data processing.

In addition, the Clinical Quality Assurance (CQA) Department of the sponsor and/or CRO may conduct regular audits of the study process, including but not limited to auditing the study site, on-site visits, central laboratory, suppliers, clinical database, and the final clinical study report. Regulatory authorities may also conduct inspections during the trial or at any time after the trial is completed. The investigator and the research institution must allow the sponsor's representative and regulatory authorities to review source data.

9.1 Clinical Monitoring

The sponsor has authorized Wuxi Clinical Co., Ltd. to conduct clinical monitoring for this study. The clinical research associate (CRA) should follow the SOPs of Wuxi Clinical Co., Ltd. when carrying out monitoring, and has the same rights and responsibilities as the sponsor's monitor. The CRA should maintain regular communication with the investigator and the sponsor.

Before the start of the study, the associate monitor assess the qualifications of each study site, and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the study, the CRA will be responsible for confirming whether written informed consent is obtained from all subjects, and whether data documentation is accurate and complete. At the same time, the CRA will compare data entered in to the eCRF with source data, and notify the investigator of any errors or omissions. The CRA will also verify protocol compliance of the study site, as well as the dispensing and storage of investigational drugs to ensure protocol requirements are met.

The monitoring visit will be conducted in accordance with applicable statutes and regulations. Each site receives regular monitoring visits from the time the subjects are enrolled. The CRA should submit a written report to the sponsor after each monitoring visit to the study site.

9.2 Data Management/Coding

The Data Management and Biostatistics Department of Wuxi Clinical Co., Ltd will process data generated from this study in accordance with relevant SOPs.

This study will use an electronic data capture (EDC) system. Trial data will be entered into the eCRF by the investigator or authorized study personnel. Prior to launching of the study site or data entry, the investigator and authorized study personnel will receive appropriate training, and appropriate safety measures will be taken.

All data are input in Chinese. The eCRF should be completed during or soon after each visit, and should be constantly updated to ensure that it reflects the latest status of the subject. To avoid discrepancies in outcome assessments between different evaluators, ensure that baseline and all subsequent efficacy and safety assessments for the same subject are performed by the same person. The investigator must review trial data to ensure the accuracy and correctness of all data entered into the eCRF. During the study, the investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. The investigator needs to sign all verified data electronically.

The CRA will review the eCRF, and evaluate its completeness and consistency. The CRA will also compare the eCRF with the source documents to ensure the consistency of critical data. Data entry, corrections, or modifications are completed by the investigator or designated staff. The CRA do not have access to data entry. The data in eCRF is submitted to the data server, and any changes to the data will be documented in the audit trail, including the reason for the change, the name of the operator, as well as the time and date of the change. The roles and permissions of study personnel responsible for data entry will be predetermined. The CRA or data manager will submit data queries in the EDC system, and study personnel shall respond to the queries. The EDC system will record the audit trail of each query, including the name of the investigator, as well as the time and date.

Unless otherwise specified, the eCRF should be considered simply as a form for data collection and not a source document. A source file is used by the investigator or hospital, relevant to the subject, and can prove the existence of the subject, inclusion criteria, and all records of participation in the study, including laboratory records, ECG results, memorandum, pharmacy dispensing records, and subject folders.

The investigators are required to maintain all source documents and to offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each subject, regardless of the duration of the subject's participation in the study. The study number and subject number in all supporting documents (such as laboratory records or hospital records) submitted along with the eCRF should be carefully verified. All personal privacy information (including the name of the subject) should be deleted or be made indecipherable in order to protect subject privacy.

The investigator could be automatically added to the eCRF with his/her user ID. The investigators verify that the record have been reviewed and that the data are accurate with an electronic signature. The electronic signature is completed with the investigator's user ID and password. The system automatically attaches the date and time of the signature. The investigator could not share the user ID and password with other personnel. If data in the eCRF need to be modified, the procedures defined by the EDC system have to be followed. All modifications and reasons for the changes are recorded in the audit trail.

Training on the EDC system will be provided to study personnel at the study site.

Adverse events, and concurrent diseases/medical history will be coded. The medical dictionary used for coding will be described in the Clinical Study Report (CSR).

9.3 Audits and Inspections

The sponsor or its representative (WuXi Clinical Co., Ltd) may conduct quality assurance audits on the study site, database, and relevant study-related documents. Also, regulatory authorities may also decide to inspect the study site, database, and relevant study-related documents at its own discretion. The aim of audits and inspections is to systematically and independently check all study-related procedures and documents to ensure that the clinical study is being carried out in accordance with requirements of the trial protocol, GCP, Declaration of Helsinki, and applicable regulations. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

10 ETHICS

10.1 Independent Ethics Committee

The sponsor and its designated personnel will prepare all documents to be submitted to the independent ethics committee (IEC) of each study site. The trial protocol, informed consent form (ICF), investigators brochure, subject recruitment material or advertisements (if applicable), as well as other documents required by regulations must be submitted to the IEC for approval. Prior to the start of the study, written approval from the IEC must be obtained and provided to the sponsor. The IEC approval must clearly state the title, number, and version of the study protocol as well as the version of other documents (e.g. ICF) and the date of approval. The investigator must notify the sponsor of the IEC's written comments concerning delays, suspension and re-approval.

The study site must follow the requirements of the IEC. IEC requirements may include submitting the revised protocol, ICF, or subject recruitment material to the IEC for approval, local regulatory requirements for safety reports, and regular reports, updates, and submitting the final report as per IEC requirements. The above documents as well as the IEC approval must be provided to the sponsor or its designated personnel.

10.2 Implementation of Ethical Principles

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements (CPMP/ICH/135/95), and applicable statutes and regulations related to drugs and data protection in the country in which the study is conducted.

The GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. To protect the rights, safety, and healthy of subjects, this study will be carried out in accordance with GCP and applicable national regulations, as well as ethical principles outlined in the Declaration of Helsinki.

The investigator is required to follow the procedures specified in this protocol and must not change the procedures without the permission from the sponsor. Protocol deviations will be reported in accordance with the requirements of each ethics committee.

10.3 Subject Information and Informed Consent

Prior to undergoing any study procedure, the ICF should be used to explain to potential participants the potential risks and benefits of this study. The informed consent form should be in a language that is simple and be easy to understand. The ICF should state that informed consent is voluntary, emphasize the potential risks and benefits of participating in this study, and that the subject may withdraw from the study at any time. The investigator may only enroll a subject after fully explaining the details of the study, answering questions to the subject's satisfaction, giving the subject sufficient time for consideration, and obtaining written consent from the subject or his/her legal representative. All signed ICF must be retained in the investigator's documents or the subject's folder.

The investigator is responsible for explaining the contents of the ICF and obtaining the ICF signed and dated by the subject or his/her legal representative prior to starting the study. The investigator should provide the subject with a copy of the signed ICF. The investigator must document the informed consent process in the source document of the trial.

10.4 Protection of Subject Data

Information about data protection and privacy protection will be included in the ICF (or in some cases, in a separate document).

Study personnel must ensure that the privacy of clinical trial subjects are protected. In all documents submitted to the sponsor, the clinical trial subjects must only be identified with subject number and not with the full name.

Additional precautions should be taken to ensure the confidentiality of the documents and to prevent the identification of subjects based on genetic data. However, under special circumstances, some personnel may be permitted to see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, designated physician, or investigator will have access to the subject identification code and the subject's genetic data. In addition, regulatory agencies may request access to relevant documents.

11 STUDY MANAGEMENT

11.1 Organizational Structure

Refer to Table 3 for relevant collaborating parties.

Table 13. Organizational structure

Sponsor	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China Telephone: (+86) 0512-69566088
Contract research organization	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000
Data management and biostatistics	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000

11.1.1 Independent review committee

Central imaging evaluation will be performed by Parexel China Co., Ltd. The CT/MRI images of each subject will be evaluated using RECIST v1.1.

11.2 Archiving of Study Documents

Clinical trial documents (protocol and amendments, completed eCRFs, signed ICFs, etc.) must be retained and managed as per GCP requirements. The study site must retain these documents for 5 years after the completion of the study. The sponsor should retain clinical trial data for 5 years after the investigational drug is approved for marketing.

Study documents should be retained properly for future access or data traceability. Safety and environmental risks should be considered when retaining documents.

The documents associated with the study may only be destroyed with the written consent of the sponsor and the investigator. Study documents may be transferred to other parties that comply with or other locations that meet retention requirements only after the sponsor is notified and written consent thereof is obtained.

11.3 Access to Source Data/Documents

Source data refers to source records of subject data obtained from a clinical study. These source records are source documents, which include but are not limited to medical records (hospital records, nursing records, pharmacy dispensing records, etc.), electronic data, screening logs, laboratory test results, as well as medical device test results (ECG, CT/MRI, etc.). All source documents associated with the trial are retained by the study site and the investigator. The original ICFs will be retained according to standard practices developed by the clinical trial institution.

The investigator will prepare sufficient and accurate source documents for each randomized subject in order to document all examination results and other relevant data, and retain these documents properly.

During the study, the CRA will conduct on-site visits to verify protocol compliance, EDC data entry, documentation of subjects' medical history, drug inventory, and whether the study is carried out in accordance with applicable regulations. In addition, regulatory authorities, IRB, IEC, and/or the quality assurance department of the sponsor will verify source data and/or conduct on-site audits or inspections. The investigator should allow direct access to documents associated with the study, including medical records of subjects.

11.4 Protocol Revisions

The sponsor and the investigator must both agree on any appropriate protocol revisions during the course of the study. The sponsor shall ensure that the protocol revision is submitted to the regulatory authority in a timely manner.

All protocol revisions must be submitted to the IEC, and if needed, to regulatory authorities for approval. Revisions may only be implemented after approval from the IEC and regulatory authorities (if needed) is obtained (except for changes to eliminate immediate risks to subjects).

11.5 Investigator's Responsibilities

The investigator will conduct this study in accordance with the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP, and applicable regulations. Details of the investigator's responsibilities are list in Chapter 5 (Investigator's Responsibilities) of the Chinese GCP (NMPA order No. 3).

11.6 Study Termination

The study may be terminated after a discussion between relevant parties if the investigator or the sponsor becomes aware of circumstances or events that could jeopardize the subjects if the study is continued. The sponsor may also decide to terminate the study even without such findings.

Reasons for study termination include but are not limited to:

- Unexpected, serious, or unacceptable risks to enrolled subjects
- Slow recruitment
- The sponsor decides to suspend or discontinue the development of the drug

11.7 Publishing Policies

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish study results. The investigator shall not publish any data relevant to this study (posters, abstracts, papers, etc.) without prior communication with the sponsor. Information on the publishing policies of the sponsor and investigator will be described in the clinical trial agreement.

11.8 Finance and Insurance

The sponsor will purchase insurance for subjects participating in the study in accordance with local regulations, and bear the cost of treatment and corresponding financial compensation for the subjects who suffer injury during the study due to the investigational drug or the study process. Insurance related terms shall be saved in the study folder.

12 REFERENCES

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13 APPENDIX

13.1 Appendix I

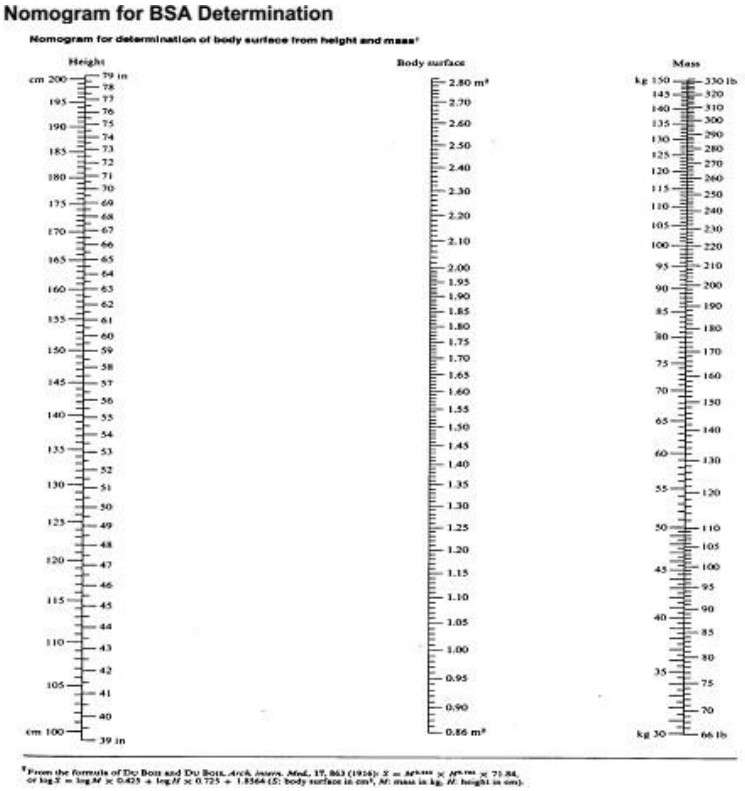
Eastern Cooperative Oncology Group (ECOG) Performance Status Score

Score	Performance Status
0	Fully active, and able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activities but able to move around easily and carry out work of a light or sedentary nature, e.g. light house work or office work
2	Capable of moving around easily and self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or wheelchair more than 50% of waking hours
4	Bedridden and incapable of self-care
5	Death

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

13.2 Appendix II

Calculation of body surface area



Body surface are (m2) = 0.00616 height (cm) + 0.01286 weight (kg) - 0.1529

Creatinine Clearance (Cockroft-Gault Equation)

Ccr (mL/min) = [(140 - age) x weight (kg)]/[72 x Scr (mg/dL)]

Female subjects: results × 0.85

1 mg/dL = 88.41 μmol/L

Carboplatin Dose (Calvert Equation)

Carboplatin dose (mg) = target AUC (mg/mL/min) × [creatinine clearance rate (mL/min) + 25]

13.3 APPENDIX 3

RECIST v1.1

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or not measurable as follows:

1.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be documented as not measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Not measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with a short axis ≥10 and <15 mm) as well as truly not measurable lesions. Lesions considered truly not measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis involving the skin or lungs, abdominal masses/ abdominal organomegaly identified by physical exam but not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding measurable bone lesions, cystic lesions, and lesions with prior locoregional treatment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (such as CT or MRI) can be considered as measurable lesions if the soft tissue components meet the definition of measurability described above.
- Blastic bone lesions are not measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor not measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these noncystic lesions are preferred for selection as target lesions.

Lesions with prior locoregional treatment:

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

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be documented with metric symbols. Calipers should be used if clinical assessments are required. All baseline evaluations should be performed as close as possible to the beginning of the treatment but never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and its diameter is ≥10 mm as assessed using calipers (e.g. skin nodules). For skin lesions, documentation by color photography including a plotting scale to estimate the size of the lesion is recommended. As noted above, when lesions can be evaluated by both clinical examination and imaging evaluation, the latter should be undertaken since it is more objective and may also

be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they have clear boundaries and are surrounded by aerated lung tissues.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound should not be used for measuring lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is recommended. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy: The utilization of these techniques is not recommended for objective tumor evaluation. However, they can be used to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper limit of normal, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into the protocol on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases if required by the protocol (for example, residual lesions in tumor types such as seminoma, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), cytological confirmation of the neoplastic origin of any effusion that appears or worsens during

treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

2.2 Baseline Documentation of "Target" and "Non-Target" Lesions

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those with reproducible repeated measurements. It may be the case that, the largest lesion does not have reproducible measurements, in which circumstance the next largest lesion with reproducible measurements should be selected.

Lymph nodes merit special mention since their normal anatomical structures may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must have a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is invaded by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant measurable node. In this example, 20 mm should be reported as the node measurement. All other pathological nodes (those with a short axis ≥ 10 mm but < 15 mm) should be considered non-

target lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions; short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". In addition, it is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response Criteria

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduced short axis of <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions vs. the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions vs. the smallest sum during the study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also have an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum of diameters during the study as reference.

2.3.2 Special notes on the assessment of lymph nodes which are target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as during the baseline examination), even if the nodes regress to below 10 mm at the time of the study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must have a

short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that are "too small to measure". During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurements of these lesions are potentially non-reproducible, therefore providing this default value will prevent false responses or progressions caused by measurement errors. To reiterate, however, if the radiologist is able to provide an actual measurement, that value should be recorded, even if it is below 5 mm.

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

2.3.3 Evaluation of non-target lesions

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

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

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

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

2.3.4 Special notes on the assessment of progression of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: *When the patient also has measurable lesions*. In this setting, to achieve 'unequivocal progression' on the basis of the non-target lesion, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR of the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A minimal increase in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only lesions that are not measurable. This circumstance arises in some phase III trials when the presence of measurable lesions is not a criterion for study enrollment. The same general concepts apply here as well. However, in this instance there are no measurable lesions to factor into the interpretation of an increase in non-measurable lesion burden. Because worsening in non-target lesion cannot be easily quantified (by definition: if all lesions are truly not measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall lesion burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase of diameter in a measurable lesion). Examples include an increase in pleural effusion from "trace" to "large amount", an increase in lymphangitic lesion from localized to widespread, or a description in the protocol such as "sufficient to require a change in therapy". If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to diseases that are not measurable, the very nature of these diseases makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on the detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumors (for example, some new bone lesions which may be simply healed or flare of pre-existing lesions). This is particularly

important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported by a CT scan as a "new" cystic lesion, while it is actually not.

A lesion identified during a follow-up in an anatomical location that is not discovered during the baseline scan is considered a new lesion and will indicate disease progression. For example, a patient with a visceral disease at baseline has a brain CT or MRI which reveals metastases. The patient's brain metastases are considered evidence of PD even if he/she does not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new lesion. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" lesions). New lesions on the basis of FDG-PET imaging can be identified as follows:

a. A negative FDG-PET at baseline and a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
If the positive FDG-PET at follow-up corresponds to a new lesion site confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new lesion site on CT, additional follow-up CT scans are needed to determine if there is truly progression at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing lesion site on CT that is not progressing according to the anatomic images, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy, so the study protocol should clearly state if post-treatment assessments are to be considered when determining best overall response. The study protocol must specify how any new therapy introduced before progression will affect best response designation. Assignment of best overall response for the patient will depend on the findings of both target and non-target lesions and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the

protocol requirements, confirmatory measurement may also be required. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine which one is the "best overall response".

2.4.1 Time point response

It is assumed that at each time point specified by the study protocol, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2 Missing assessments and non-evaluable targets

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

2.4.3 Best overall response: all time points

The best response is determined once all the data for the patient is obtained.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, the best overall response of a patient who has SD at the first assessment, PR at the second, and PD at the last is PR). When SD is believed to be best response, it must also meet the minimum time from baseline specified by the protocol. If the minimum time is not met, otherwise SD is the best time point response, the patient's best response depends on subsequent assessments. For example, if a patient has SD at the first assessment, PD at the second and does not meet the minimum duration for SD, his/her best response is PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

2.4.4 Special notes on response assessment

When nodal lesions are included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even if the nodes are normal in size in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the case report form (CRF).

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must explain how missing data/assessments will be addressed in the determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response. Instead, it is a reason for stopping the study treatment. The objective response status of this type of patients is to be determined by evaluation of target and non-target lesions as shown in Table 1–3.

Conditions that define "early progression, early death, and non-evaluability" are study specific and should be clearly described in each study protocol (depending on treatment duration and treatment periodicity).

In some circumstances it may be difficult to distinguish a residual lesion from normal tissues. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (by fine needle aspirate/biopsy) before assigning a status of complete response.

Like a biopsy, FDG-PET may also be used to upgrade a response to a CR in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be pre-defined in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Table 1. Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not all were evaluated	No	PR
SD	Non-PD or Not all were evaluated	No	SD
Not all were evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

Table 2. Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all were evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = not evaluable.

a "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since SD is increasingly used as an endpoint for assessment of efficacy in some trials, thus assigning this category in the absence of measurable lesions is not advised.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression is suspected.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided that the minimum duration for SD is met, otherwise PD
CR	PD	SD provided that the minimum duration for SD is met, otherwise PD
CR	NE	SD provided that the minimum duration for SD is met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided that the minimum duration for SD is met, otherwise PD
PR	NE	SD provided that the minimum duration for SD is met, otherwise NE
NE	NE	NE

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

a If CR is truly achieved at the first time point, then any lesions seen at a subsequent time point, even those meeting PR criteria relative to baseline, make the disease PD at that time point (since lesions must have reappeared after CR). Best response would depend on whether the minimum duration for SD is met. However, sometimes CR may be claimed and subsequent scans suggest small lesions are likely still present, while in fact the patient have PR instead of CR at the first time point. Under these circumstances, CR should be changed to PR and the best response is PR.

2.5 Frequency of Tumor Re-Evaluation

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

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

2.6 Confirmation of Measurements/Duration of Response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement errors. This will also permit appropriate interpretation of results in the context of historical data. Response confirmation has been traditionally required in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements after study entry must have met the minimum interval for SD (generally not shorter than 6–8 weeks) defined in the study protocol at least once.

2.6.2 Duration of overall response

The duration of overall response is measured from the time CR/PR measurement criteria are first met CR/PR (whichever is first documented) until the date when recurrent or progressive disease is objectively documented for the first time (using the shortest time to progressive disease documented during the study as reference).

The duration of overall complete response is measured from the time CR measurement criteria are first met until the date when recurrent disease is objectively documented for the first time.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from the date of randomization) until the criteria for progression are met, using the smallest sum during the study as reference (if the baseline sum is the smallest, then it is used as the reference for the calculation of PD).

The clinical relevance of the duration of stable disease varies with different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for the determination of stable disease.

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

14 INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized, double-blind, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin vs. bevacizumab plus paclitaxel/carboplatin in treatment-naive patients with advanced or relapsed non-squamous NSCLC.

Protocol No.: CIBI305A301

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

Instructions for the Investigator: Please sign and date this signature page, type the investigator's name and job title, as well as the name of the study site, and return this document to Innovent Biologics (Suzhou) Co., Ltd.

I have read the entire contents of this study protocol and shall perform the study as required:

Investigator's signature: _____ Date: _____

Name (in Print): _____

Job Title: _____

Name and Address of Study Site: _____

_____

_____

CIBI305A301 STUDY PROTOCOL V2.0 REVISION OVERVIEW

Protocol Version: v2.0
Version Date: Sep. 26, 2016

Original text	After revision	Reason for amendment
Cover: Version Date/No.: Jun. 02, 2016/Version 1.0	**Version Date/No.:** Sep. 26, 2016/Version 2.0 Jun. 02, 2016/Version 1.0	4.3 The revision history of the protocol is added
Cover: Sponsor Contact: Zhou Hui (Medical Director) Tel: (+86) 021-31652896 E-mail: hui.zhou@innoventbio.com Hou Jiagang (Clinical Operations Director) Tel: (+86)0512-69566088-8062 E-mail：jiagang.hou@innoventbio.com	**Sponsor Contact:** Zhou Hui, Medical Director Tel: (+86) 021-31652896 E-mail: hui.zhou@innoventbio.com	4.3 The contact of sponsor is updated
Cover: This document is only for the review of investigators, research consultants or relevant personnel, and independent ethics committee. Without the written approval of the sponsor, the	*Confidentiality Statement* *This document is the confidential information of Innovent*	4.3 The confidentiality statement is updated

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contents of this document shall not be disclosed to any third party.	*Biologics (Suzhou) Co., Ltd.* *The content of this document shall not be disclosed to any person other than the investigators, research consultants or related personnel, and Institutional Review Board/Independent Ethics Committee.* *The information contained in this document must not be used for any purpose, except for the evaluation or conduction of this study, without the written consent of the sponsor.*	
P3: Study Objectives	¾ To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC **Exploratory objectives:** ¾ **To compare the population pharmacokinetics (PPK) of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC** **¾ To compare the PD of IBI305 and bevacizumab in subjects with advanced or recurrent non-squamous NSCLC**	¾ Based on the recommendations of CDE, the pharmacokinetic and pharmacodynamic evaluations are added as the objectives of the exploratory study
P4: Study design	This is a randomized, double-blinded, multi-center phase III study. A total of *436* subjects with non-squamous NSCLC will be	¾ Based on the recommendations of

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CIBI305A301 STUDY PROTOCOL V2.0 REVISION OVERVIEW

This is a randomized, double-blinded, multi-center phase III study. The study planned to enroll and randomize 400 subjects with non-squamous NSCLC in a 1:1 ratio to IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild type vs. mutant type).	enrolled, randomized in a ratio of 1:1 to either IBI305 in combination with paclitaxel/carboplatin group or bevacizumab in combination with paclitaxel/carboplatin group, and the stratification factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild type vs. unknown type).	CDE, the sample size is increased and the stratification factors are updated to include the wild type vs. unknown type
P4: Study design Then subjects received monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The monotherapy continues every 3 weeks.	Then subjects received **maintenance** monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The **maintenance** monotherapy continues every 3 weeks.	4/3 Clarify that monotherapy refers to maintenance monotherapy
P4: Number of Subjects 400 cases	*436* cases	4/3 Based on the recommendations of CDE, the sample size is increased
P5: Diagnosis and main inclusion criteria: 4) Histologically confirmed EGFR wild type 5) Histologically confirmed EGFR mutation type, but subjects who have not received EGFR-TKI treatment due to various	4) Histologically **or cytologically** confirmed EGFR wild type	4/3 Subjects carrying mutant type EGFR are excluded

Note:
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CIBI305A301 STUDY PROTOCOL V2.0 REVISION OVERVIEW

reasons		
P5: Exclusion Criteria None	**3) Histologically or cytologically confirmed EGFR mutation type. Subjects with unknown EGFR status for various reasons could be enrolled**	4/3 Subjects carrying mutant type EGFR are excluded
P7: Investigational Drug, Dosage, and Route of Administration IBI305: 15 mg/kg in combination chemotherapy and 7.5 mg/kg monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)	IBI305: 15 mg/kg in combination chemotherapy and 7.5 mg/kg in **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first)	4/3 Clarify that monotherapy refers to maintenance monotherapy
P7: Control Drug, Dosage, and Route of Administration: Bevacizumab: 15 mg/kg in combination chemotherapy and 7.5 mg/kg monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)	Bevacizumab: 15 mg/kg in combination chemotherapy with and 7.5 mg/kg in **maintenance** monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, intolerable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first)	4/3 Clarify that monotherapy refers to maintenance monotherapy

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CIBI305A301 STUDY PROTOCOL V2.0 REVISION OVERVIEW

Protocol Version: v2.0
Version Date: Sep. 26, 2016

P8: None	**PK/PD Endpoints**: **Population PK parameters, including steady-state trough concentrations after repeated doses** **Changes of serum VEGF at different time points**	Based on the recommendations of CDE, the endpoints for the pharmacokinetic and pharmacodynamic analysis are added
P8：Sample size calculation: A number of 200 subjects for each group (400 subjects in total) will provide over 80% power to confirm the clinical equivalence between IBI305 plus paclitaxel/carboplatin and bevacizumab plus paclitaxel/carboplatin. Estimation of sample size: If the significance level of the two one-sided test is 0.05, the ORR between IBI305 and bevacizumab group is about 54.4%, with an equivalence margin of (-15%, 15%). Based on the above assumptions, 189 subjects are required for each group (378 subjects in total). The sample size is expanded to 200 subjects for each group (400 subjects in total) after taking dropouts into consideration.	A number of *218* subjects for each group (*436* subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin. Estimation **parameters** for sample size: The significance level of the two-sided test is 0.05, the ORR of subjects in the IBI305 and bevacizumab groups is about *50.0*%, and the equivalence margin is taken as (*-12.5*%, *16.7*%). Based on the above hypothesis, each group requires 218 subjects (*436* subjects in total).	Based on the recommendations of CDE, the statistical hypotheses are updated and the sample size is increased
P8：Efficacy analysis: Clinical equivalence will be determined by whether the 90%	Clinical equivalence will be determined by whether the 90%	Based on the recommendations of

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confidence interval (CI) of the difference in ORR between the IBI305 and bevacizumab arms falls within the preset margin of (-15% to 15%).	confidence interval of the difference in ORR between the subjects in the IBI305 and bevacizumab groups falls within the set margin (*-12.5*%, *16.7*%).	CDE, the statistical hypotheses are updated
P8 None	**PK/PD exploratory analysis: Mainly based on description, and inter-group comparison will be carried out if necessary.**	4/3 Based on the recommendations of CDE, the analytical methods for pharmacokinetic and pharmacodynamic evaluations are added
Table 1. Schedule of follow-up visits 12-Lead ECG: C2D1-Progressive disease follow-up; If clinically indicated	12-Lead ECG: *C2D1 C2D1 C3D1 C4D1 C5D1 C6D1* *C7* until the end of treatment	4/3 The frequency of ECG examinations is increased to detect the occurrence of myocardial ischemia
Table 1. Schedule of follow-up visits None	Pharmacokinetics (*PK*): *C1D1 C2D1 C4D1 C5D1 C6D1*	4/3 Based on the recommendations of CDE, pharmacokinetic collection time points are added

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Table 1. Schedule of follow-up visits None	VEGF detection: C1D1 C2D1 C6D1; end-of-treatment	4/3 Based on the recommendations of CDE, pharmacodynamic collection time points are added
Table 1. Schedule of follow-up visits None	l. Study sites that are implementing version 2.0 of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h before the first dose of the study drug (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 h prior to the dose in C4, within 1 hour prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.	4/3 Based on the recommendations of CDE, pharmacokinetic collection time points are added
Table 1. Schedule of follow-up visits None	m. Study sites that are implementing version 2.0 of the study protocol should collect PD samples until 140 subjects in this study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: Within 1 h prior to the first dose of the study	4/3 Based on the recommendations of CDE, pharmacodynamic

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CIBI305A301 STUDY PROTOCOL V2.0 REVISION OVERVIEW

	drug (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and at the end of treatment visit. Samples were tested at the designated central laboratory.	collection time points are added
P14 List of Abbreviations and Definitions None	**ADA Anti-Drug Antibody**	¾ Addition
P15 List of Abbreviations and Definitions None	**PK Pharmacokinetics** **PRES Posterior Reversible Encephalopathy Syndrome**	¾ Addition
P20 Clinical studies This study is the first study of IBI305 in humans.	~~Deleted from the original text~~	¾ Clarification
P20 In the subsequent monotherapy therapy, IBI305 will be given intravenously at a dose of 7.5 mg/kg	The dose is 7.5 mg/kg in the subsequent **maintenance** monotherapy,	¾ Clarify that monotherapy refers to maintenance monotherapy
P21 None	**2.3 Exploratory Objectives** ¾ To compare the population pharmacokinetics (PPK) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC	¾ Based on the recommendations of CDE, the pharmacokinetic and pharmacodynamic

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	4/3 To compare the pharmacodynamics (PD) characteristics of IBI305 and bevacizumab in subjects with advanced or relapsed non-squamous NSCLC	evaluations are added as the objectives of the exploratory study
P22 Overview of Study Design This is a randomized, double-blind, active-controlled, and multi-center phase III study. A total of 400 subjects across 35 study sites with non-squamous NSCLC will be planned,	This is a randomized, double-blind, active-controlled, and multi-center phase III study. This study plans to enroll *436* subjects with non-squamous NSCLC at about 35 study centers in China	4/3 Based on the recommendations of CDE, the sample size is increased
P22 Overview of Study Design Then subjects received monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab.	Then subjects received **maintenance** monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing **maintenance** therapy with IBI305 or bevacizumab. Every treatment cycle of the **maintenance** monotherapy lasts 3 weeks,	4/3 Clarify that monotherapy refers to maintenance monotherapy
P24 Inclusion Criteria 4) Histologically confirmed EGFR wild type 5) Histologically confirmed EGFR mutation type, but subjects who have not received EGFR-TKI treatment due to various reasons	4) Histologically **or cytologically** confirmed EGFR wild type	4/3 Subjects carrying mutant type EGFR are excluded
P24 Inclusion Criteria 6) Must have at least one measurable target lesion (as per	5) Must have **at least** one measurable target lesion (as per RECIST 1.1)	4/3 Correction

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RECIST 1.1)		
P25 Exclusion Criteria None	**3) Histologically or cytologically confirmed EGFR mutation type. Subjects with unknown EGFR status for various reasons could be enrolled.**	4/3 Subjects carrying mutant type EGFR are excluded
P29 Therapies by Study Drugs In this study, the dose of IBI305 or bevacizumab during combination therapy with chemotherapy is 15 mg/kg, while the dose during monotherapy is 7.5 mg/kg.	In this study, the dose of IBI305 or bevacizumab is 15 mg/kg when used in combination with chemotherapeutic drugs and 7.5 mg/kg in the **maintenance** monotherapy,	4/3 Clarify that monotherapy refers to maintenance monotherapy
P29 Chemotherapy Carboplatin: AUC 6.0 administered via intravenous infusion for 15-30 min (may be adjusted according to clinical practice of each study site)	Carboplatin: AUC 6.0, *the infusion time is based on the standard practice of each study site.*	4/3 Because the AUC of carboplatin is 6.0, it may cause adverse events if the infusion is completed within 15–30 min due to the high concentration of the formulated liquid, the provision is changed to operate according to the clinical practice of each center.

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P30 Dose adjustments of study drugs Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments (adjusted to 7.5 mg/kg for monotherapy) specified in the study protocol.	Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments (the dose of **maintenance** monotherapy is adjusted to 7.5 mg/kg) specified in the study protocol.	4/3	Clarify that monotherapy refers to maintenance monotherapy
P30 Dose adjustments of study drugs If PD is not observed in subject during treatment, then the subject will continue to receive IBI305 or bevacizumab as monotherapy every 3-week treatment cycle	If the subject does not experience PD, the **maintenance** monotherapy will be continued every 3-week treatment cycle	4/3	Clarify that monotherapy refers to maintenance monotherapy
P32 Dose adjustments of study drugs Reversible posterior leukoencephalopathy syndrome (RPLS) There have been a few reports with signs and symptoms consist with RPLS after study treatment. RPLS is a rare neurological disease and its signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with RPLS should permanently discontinue the study treatment.	**Posterior reversible encephalopathy syndrome (PRES)** There have been a few reports of subjects with signs and symptoms consistent with **PRES** after study treatment. This is a rare neurological disease and its signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with **PRES** should permanently discontinue the study treatment.	4/3	The description related to PRES is updated according to the latest prescribing information of AVASTIN
P37 Other toxicities Investigator should closely monitor toxicities in subjects during chemotherapy. Before the start of next chemotherapy cycle, the	~~Deleted from the original text~~	4/3	The content has been included in the inclusion/exclusion

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laboratory test results must be: 8/5 ANC ≥ 1.5 × 109/L 8/5 Platelet count ≥ 100 × 109/L 8/5 Serum creatinine < 1.5 × ULN 8/5 Bilirubin ≤ 1.5 × ULN 8/5 ALT and AST ≤ 2.5 × ULN; ALT and AST < 5 × ULN in subjects with liver metastasis		criteria, so the description in the main text is updated
P40 Treatment Compliance The dosage and dosing time of IBI305 or bevacizumab and paclitaxel + carboplatin in each treatment cycle should be documented in the eCRFs. Reasons for dosing delay, dose reduction or missed dossing should also be documented in the eCRFs. Treatment and protocol compliance refers to the subject's voluntary compliance with each aspect of the protocol, including compliance with blood collection for safety evaluation and imaging examination for tumor assessment. If a subject does not return for the scheduled follow-up visits, his/her participation in the study may be terminated based on the opinions of the	Subjects should **receive treatment at the study site**. The dose and time of administration of *IBI305* or bevacizumab and paclitaxel/carboplatin should be documented in the **source records** and eCRFs during each treatment cycle. *Reasons for dose adjustments, therapy delay, and therapy discontinuation should be documented. Treatment compliance is monitored by medication dispensing and return records, medical records, and eCRFs*	4/3 The description related to drug management is updated

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primary investigator or sponsor.		
P40 Study Drug Count The investigator, other relevant stuff, or authorized pharmacists should document the receipt and distribution of study drugs on the study drug count table and ensure that the table is readily available for inspection. The study drugs are only for the use of study subjects. At the end of the trial, all study drugs should be counted and explanations for deviations should be provided in a written document. The investigator shall count all unused study drugs and packaging materials, and return them to the sponsor or the designated third party. Used empty drug bottles/bags will be destroyed on-site according to the institutional standards.	***5.11 Drug Return and Destruction*** *The containers, vials, infusion bags, and syringes of used and partially used drugs can be destroyed on-site according to the appropriate guidelines and operating procedures established by study sites and local agencies.* *Unless the contents have significant safety issues requiring immediate destruction in accordance with local regulations, all the unused drugs should be returned and destroyed based on the requirements of sponsor.* ***5.12 Study Drug-Related Records*** *The designated personnel of the study sites should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines.*	~~4~~ 3 The description related to drug management is updated
P41 Screening Visits (D -28 to D -1) ~~4~~ 3 Record the AEs	~~4~~ 3 Record the AEs and **concomitant medications**	~~4~~ 3 Update based on study visit schedule
P42 Baseline Visits (D1 of cycle 1) ~~8 4~~ 5 3 Record the vital signs	~~4~~ 3 Record the vital signs	~~4~~ 3 Update based on study visit schedule

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~~8 4 5 3~~ Measure the weight ~~8 4 5 3~~ Physical examination ~~8 4 5 3~~ Clinical laboratory tests * (routine blood test, blood chemistry, and urinalysis) ~~8 4 5 3~~ Immunogenicity test (ADAs and neutralizing antibodies) ~~8 4 5 3~~ Confirm the inclusion/exclusion criteria ~~8 4 5 3~~ Record the AEs and concomitant medications * If clinical laboratory screening tests (routine blood test, blood chemistry, urinalysis) are performed within 7 days prior to the first dose, then the results of the screening test can be used as baseline. If the subject meets the inclusion criteria, the following procedures should be complete: ~~8 4 5 3~~ Randomization and grouping ~~8 4 5 3~~ Study drug infusion (IBI305 or bevacizumab) ~~8 4 5 3~~ Chemotherapeutic drug infusion (paclitaxel + carboplatin) ~~8 4 5 3~~ Record the AEs and concomitant medications	~~4 3~~ Measure the weight ~~4 3~~ Physical examination ~~4 3~~ Clinical laboratory tests * (routine blood test, blood chemistry, and urinalysis) ~~4 3~~ Confirm the inclusion/exclusion criteria * If clinical laboratory screening tests (routine blood test, blood chemistry, urinalysis) are performed within 7 days prior to the first dose, then the results of the screening test can be used as baseline. If the subject meets the inclusion criteria, the following procedures should be complete: ~~4 3~~ Randomization and grouping ~~4 3~~ Immunogenicity test (within *1* h prior to the study drug infusion) ~~4 3~~ Study drug infusion (IBI305 or bevacizumab) ~~4 3~~ Chemotherapeutic drug infusion (paclitaxel + carboplatin) ~~4 3~~ **Pharmacokinetic (PK) blood sampling (within 1 h prior to the study drug infusion, immediately after the study drug infusion [+5 min])**	

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	4/3 **VEGF blood sampling (within 1 h prior to the study drug infusion)** 4/3 Record the AEs and concomitant medications	
P42 Cycle 2 (week 4 ± 3 days) 84/53 Record the vital signs 84/53 Measure the weight 84/53 Physical examination 84/53 Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis) 84/53 Study drug infusion (IBI305 or bevacizumab) 84/53 Chemotherapeutic drug infusion (paclitaxel + carboplatin) 84/53 Record the AEs and concomitant medications	4/3 Record the vital signs 4/3 Measure the weight 4/3 Physical examination 4/3 **12-Lead ECG** 4/3 Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis) 4/3 **PK blood sampling (within 1 h prior to the study drug infusion)** 4/3 **VEGF blood sampling (within 1 h prior to the study drug infusion)** 4/3 Study drug infusion (IBI305 or bevacizumab) 4/3 Chemotherapeutic drug infusion (paclitaxel + carboplatin) 4/3 Record the AEs and concomitant medications	4/3 Update based on study visit schedule
P44 Cycle 5 (week 13 ± 3 days)	4/3 Record the vital signs	4/3 Update based on study

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8 4 5 3 Record the vital signs 8 4 5 3 Measure the weight 8 4 5 3 Physical examination 8 4 5 3 Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis) 8 4 5 3 Study drug infusion (IBI305 or bevacizumab) 8 4 5 3 Chemotherapeutic drug infusion (paclitaxel + carboplatin) 8 4 5 3 Record the AEs and concomitant medications	4 3 Measure the weight 4 3 Physical examination 4 3 **12-Lead ECG** 4 3 Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis) 4 3 **PK blood sampling (within 1 h prior to the study drug infusion)** 4 3 Study drug infusion (IBI305 or bevacizumab) 4 3 Chemotherapeutic drug infusion (paclitaxel + carboplatin) 4 3 Record the AEs and concomitant medications	visit schedule
P43 Cycle 3 (week 7 ± 3 days) 4 3 Record the vital signs 8 4 5 3 Measure the weight 8 4 5 3 Physical examination	4 3 Record the vital signs 4 3 Measure the weight 4 3 Physical examination 4 3 **12-Lead ECG**	4 3 Update based on study visit schedule
P43 4 3 Cycle 4 (week 10 ± 3 days)	4 3 Record the vital signs	4 3 Update based on study visit schedule

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⅘ Record the vital signs ⅘ Measure the weight ⅘ Physical examination ⅘ Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis) ⅘ Study drug infusion (IBI305 or bevacizumab) ⅘ Chemotherapeutic drug infusion (paclitaxel + carboplatin) ⅘ Record the AEs and concomitant medications	⅘ Measure the weight ⅘ Physical examination ⅘ **12-Lead ECG** ⅘ Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis) ⅘ **PK blood sampling (within 1 h prior to the study drug infusion)** ⅘ Study drug infusion (IBI305 or bevacizumab) ⅘ Chemotherapeutic drug infusion (paclitaxel + carboplatin) ⅘ Record the AEs and concomitant medications	
P43 **Cycle 6 (week 16 ± 3 days)** ⅘ Record the vital signs ⅘ Measure the weight ⅘ Physical examination ⅘ Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis) ⅘ Study drug infusion (IBI305 or bevacizumab)	⅘ Record the vital signs ⅘ Measure the weight ⅘ Physical examination ⅘ **12-Lead ECG** ⅘ Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)	⅘ Update based on study visit schedule

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4/3 Chemotherapeutic drug infusion (paclitaxel + carboplatin) 4/3 Record the AEs and concomitant medications	4/3 **PK blood sampling (within 1 h prior to the study drug infusion)** 4/3 **VEGF blood sampling (within 1 h prior to the study drug infusion)** 4/3 Study drug infusion (IBI305 or bevacizumab) 4/3 Chemotherapeutic drug infusion (paclitaxel + carboplatin) 4/3 Record the AEs and concomitant medications	
P43 **Cycle 7 and Subsequent Treatment Cycles (±3 Days)** 4/3 Record the vital signs 4/3 Measure the weight 4/3 Physical examination	4/3 Record the vital signs 4/3 Measure the weight 4/3 Physical examination 4/3 **12-Lead ECG**	4/3 Update based on study visit schedule
P43 **End-Of-Treatment Visit** 4/3 Record the vital signs 4/3 Measure the weight 4/3 Physical examination 4/3 Clinical laboratory tests (routine blood test, blood	4/3 Record the vital signs 4/3 Measure the weight 4/3 Physical examination 4/3 Clinical laboratory tests (routine blood test, blood	4/3 Update based on study visit schedule

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chemistry, and urinalysis) 4/3 Immunogenicity test 4/3 Blood pregnancy test (for female subjects of childbearing age only) 4/3 Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this visit) 4/3 Subsequent anti-tumor therapy 4/3 Record the AEs and concomitant medications	chemistry, and urinalysis) 4/3 Immunogenicity test 4/3 **PD blood sampling** 4/3 Blood pregnancy test (for female subjects of childbearing age only) 4/3 Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this visit) 4/3 Subsequent anti-tumor therapy 4/3 Record the AEs and concomitant medications	
P46 Study Completion Completion of this clinical study is defined as 18 months after the enrollment of the last subject.	*The end of this study will be the18th month after randomization of the last subject.*	4/3 The definition of study completion is clarified
P47 12-Lead ECG The subject will undergo a 12-lead ECG during screening, and also during the course of the study if deemed necessary by the investigator.	12-lead ECG will be performed during screening. During the study, each *medication visit requires an ECG examination.*	4/3 Update based on study visit schedule
P48Immunogenicity assessment Blood samples are collected before the first dose, on D1 of Cycle 4, and during the end-of-treatment visit for immunogenicity assessment including testing of anti-drug antibodies and neutralizing antibodies. Immunogenicity testing	*Immunogenicity tests will be performed in all subjects at 3 blood sampling time points: Within 1 hour prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 hour prior to the administration of the study treatment in C4, and during the*	4/3 The description of blood sampling time points for the immunogenicity test is

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will be carried out at the relevant central laboratory. Details regarding sample collection, processing, labeling, storage, transport, and analysis are provided in the Central Laboratory Manual.	*end-of-treatment visit. Blood specimens that are positive for anti-drug antibodies (ADA) after dosing will be further tested for neutralizing antibodies (NAb). Samples were tested at the designated central laboratory.*	added
P48 None	**6.15.6. Pharmacokinetics/pharmacodynamics** **6.15.6.1 Pharmacokinetics** **Study sites that are implementing version 2.0 of the study protocol should collect PK samples until 140 subjects in this study meet the requirements for PPK assessment (based on the written notice of the sponsor). There are 6 PK sampling time points: Within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, immediately after the first infusion (within 5 minutes), within 1 h prior to the dose in C2, within 1 hour prior to the dose in C4, within 1 h prior to the dose in C5, and within 1 h prior to the dose in C6. Serum will be separated from the samples at the study site and the serum samples will be analyzed at the designated central laboratory.** **6.15.6.2 Pharmacodynamics** **Study sites that are implementing version 2.0 of the study protocol should collect PD samples until 140 subjects in this**	4 3 Based on the recommendations of CDE, the description for the sampling at PK and PD blood collection points is added

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	study meet the requirements for VEGF testing (based on the written notice of the sponsor). There are 4 VEGF sampling time points: within 1 h prior to the first dose of the study treatment (IBI305/bevacizumab) in C1, within 1 h prior to the dose in C2, within 1 h prior to the dose in C6, and during the end-of-treatment visit. Samples were tested at the designated central laboratory.	
P53 Adverse events An adverse event is defined as any untoward medical occurrence suffered by the subject of the clinical research, which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational drug, whether or not considered related to the investigational drug	An AE refers to any untoward medical occurrence in a subject *after signing the informed consent form*, and does not necessarily have a causal relationship with the treatment. Thus, an AE can be any unfavorable and *unintended sign* (including an abnormal laboratory finding), symptom, or disease, whether considered drug related. **Abnormalities resulting from PD are not considered as AEs.**	4/3 The definition of adverse events is updated
P53 Serious adverse event A serious adverse event does not necessarily have a causal relationship with the investigational drug. It refers to any untoward medical occurrence that (at any dose of the investigational drug):	*A SAE refers to an AE meeting at least one of the followings:* (1) Lead to death, **except for deaths caused by PD.** (2) Life-threatening (a "life-threatening event" is defined as an *AE* when the subject is at immediate risk of death at	4/3 Definition of serious adverse event is updated

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(1) Results in death. (2) Is life-threatening (The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it is more severe). (3) Requires inpatient hospitalization or prolongation of existing hospitalization: This does not include hospitalization and/or surgical procedures scheduled to be conducted prior to or during the study for a disease or disorder that exists prior to study enrollment and has not worsened during the course of the study. (4) Results in permanent or severe disability/incapacity. (5) Results in congenital anomalies/birth defects. (6) Other important medical events: Medical events that do not necessarily result in death, are not life-threatening, and do not require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the aboves outcomes, are also considered SAEs. Note: Hospitalization as a result of PD is not considered an SAE. Other Definitions An adverse drug reaction (ADR) refers to any untoward response related to the investigational drug after receiving any	the time, but does not include the case that may lead to death only when the event worsens). (3) Requires hospitalization or prolonged hospitalization, excluding an **emergency or outpatient visit**. Subjects with existing diseases or conditions prior to the enrollment that do not worsen during the study, and having hospitalization and/or surgery that was scheduled before the study or during the study **do not meet the SAE criterion**. **Hospitalizations resulting from PD are not considered as SAEs.** (4) Results in permanent or severe disability/incapacity. (5) Results in congenital anomalies/birth defects. (6) Other important medical events: The event that does not result in death, is not life-threatening or does not require hospitalization, but may jeopardize the health of subjects and require medical intervention to prevent the SAEs above, is considered as an SAE.	

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dose. An unexpected adverse drug reaction is any adverse reaction that is not consistent with information known about the investigational drug.		
P53 Severity of adverse events The severity of AEs will be assessed by CTCAE 4.03. The classifications are as follows: - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. - Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.) - Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (e.g. bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not bedridden)	*The severity of AEs is evaluated using the 5-level criteria of NCI CTCAE v4.03.* *For AEs not included in CTCAE v4.03, use the following CTCAE general guidelines:* - Grade 1: Mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated. - Grade 2: Moderate; minimal/local or noninvasive intervention indicated; *limiting age-appropriate instrumental activities of daily life (such as cooking, shopping, using the phone, financial management, etc.)*. - *Grade 3: Severe or clinically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disability; limited ability of self-care (such as bathing, dressing, undressing, eating, using the toilet, taking medication),*	- The description of the NCI CTCAE v4.03 grading principles is updated

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<table>
<tr>
<td>
- Grade 4 Life-threatening; urgent intervention indicated
- Grade 5 Death related to AE
</td>
<td>
but not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE
</td>
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</tr>
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<td>
P54 Relationship between adverse events and the investigational drug

The relationship between the investigational drug and AE can be classified into five categories: definitely related, probably related, possibly related, unlikely related, and definitely unrelated. Specific assessment criteria are as follows:

Table 7. Assessment criteria for causality between an adverse event and the investigational drug
<table>
<tr><td>Parameters</td><td>Definitely related</td><td>Probably related</td><td>Possibly related</td><td>Unlikely related*</td><td>Definitely not related</td></tr>
<tr><td>Reasonable temporal relationship</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No</td></tr>
</table>
</td>
<td>
The relationship between the study drugs and AEs can be determined using the followings:
<table>
<tr><th>Correlation</th><th>CRITERIA</th></tr>
<tr><td>Related</td><td>
- The occurrence of the AE is reasonably related to the time sequence of dosing;
- The investigational drug can more reasonably explain the AE than the other causes (such as the pre-existing disease of the subject, environment, toxicity, or other treatment received);
- The AE resolves or is alleviated after treatment interruption or dose reduction;
- The AE is consistent with the known type of AEs of the suspicious drug or similar drugs;
- The AE occurs again after the drug administration is resumed.
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- Judgment on the correlation between the AE and the investigational product is updated
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CIBI305A301 STUDY PROTOCOL V2.0 REVISION OVERVIEW

Recognized pharmacological phenomenon	Yes	Yes	Yes	No	No
Positive dechallenge	Yes	Yes	Yes or No	Yes or No	No
Positive rechallenge	Yes	?**	?**	?**	No
Other alternative explanations	No	No	Yes	Yes	Yes

* Unlikely related = further observations required to make an assessment;

? ** Rechallenge not permitted due to ethical reasons.

Possibly related	4/3 *The occurrence of the AE is reasonably related to the time sequence of dosing;* 4/3 *The investigational drug can be used to explain the AE with the same level of rationality as other reasons (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject);* 4/3 *The AE resolves or is alleviated after treatment interruption or dose reduction (if applicable).*	
Possibly not related	4/3 *Other reasons can more reasonably explain the AE than the investigational drug (such as the pre-existing disease of the subject, environmental or toxic factors, or other treatments received by the subject);* 4/3 *The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear;* 4/3 *The AE does not occur again or the situation of the AE is unknown after the drug administration is resumed.*	
Unrelated	4/3 *The occurrence of the AE is not reasonably related to the time sequence of dosing, or* 4/3 *The AE has other obvious causes (such as the pre-existing disease of the subject, environmental or toxic factors,*	

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CIBI305A301 STUDY PROTOCOL V2.0 REVISION OVERVIEW

			or other treatments received by the subject).	
	Cannot be determined	$\frac{4}{3}$	*The above information is unclear and cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.*	
P54 Serious adverse event reporting Any SAE that occurs during the trial should be reported in accordance with SAE reporting procedures of regulatory authorities or the ethics committee, regardless of whether the event is related to treatment. The investigator should take the following measures: $\frac{4}{3}$ If necessary, take appropriate treatment measures immediately; $\frac{4}{3}$ Immediately (within 24 hours after becoming aware of the event or obtaining new information about the event) report the event to the sponsor's authorized representative responsible for relevant safety information using a method approved by the sponsor; $\frac{4}{3}$ Document the SAE in the AE and SAE section of the eCRF as well as in the source documents; $\frac{4}{3}$ The investigator must immediately (within 24 hours) submit the signed and dated SAE Report to the independent ethics committee, NMPA (formerly			*The investigator should immediately take appropriate medical measures* to treat any SAE that occurs during the trial. *And the SAE should be recorded in the tables of adverse events and serious adverse events in the eCRF and source documents; regardless of whether the SAE is related to the treatment, the investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.* *Contact information for the reporting of SAE/pregnancy to the sponsor: Fax: 021-31652800* SAE reporting email: *drugsafety@innoventbio.com* *When submitting the SAE report by email, it is recommended for the investigator to encrypt the report file and send the report file*	$\frac{4}{3}$	The time limit and contact information for the reporting of AEs are updated

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CFDA), health administration department, and local drug administration authorities; 4/3 Follow and document the course of the event, until the event resolves or returns to baselines levels, or becomes clinically stable. In addition, the sponsor or its representative (such as CRO) should report the SAE to the corresponding regulatory agencies and other investigators in accordance with the requirements of regulatory agencies and local regulations.	*and password in separate emails.* *At the same time, the investigator should follow the SAE reporting procedures issued by relevant regulatory authorities or the independent ethics committee.* *The investigator should follow up the SAE until it disappears or recovers to a result that the investigator believes it can be explained without further follow-ups, such as clinical stability or improvement. The time limit for the follow-up report and the report of answered queries is the same as that for the initial report.*	
P55 Management and follow-up of adverse events All AEs observed from the signing of the ICF to the time specified in the protocol (Table 8) must be followed. Refer to Section 7.2.1.8 for the specific follow-up time.	Any AE observed from the time the subject signs the informed consent form to the time specified in the protocol (Table 8) should be **recorded, reported, and visited in accordance with the requirements of this protocol**	4/3 The chapter of AEs is updated
P55 Adverse events of special interest The AESI for this study include: 8/5 Hypertension 8/5 Proteinuria 8/5 Gastrointestinal perforation	The AESI for this study include: 4/3 *Gastrointestinal perforation* 4/3 **Procedural and wound healing complications**	4/3 The chapter of AESIs is updated

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8 5 Hemorrhage (cerebral hemorrhage, hematuria, and upper gastrointestinal hemorrhage) 8 5 Cardiotoxicity 8 5 Thrombus An AESI should also be reported as an SAE if the definition of SAE is met.	4 3 *Hemorrhage* 4 3 **Fistula** 4 3 Hypertension 4 3 **Thrombotic event** 4 3 **Posterior reversible encephalopathy syndrome (PRES)** 4 3 Proteinuria 4 3 **Infusion-related reaction** 4 3 **Ovarian failure** 4 3 *Cardiac failure congestive* *Among them, Grade 2 gastrointestinal perforation, procedural and wound healing complications, hemorrhage, fistula, arterial thrombotic events and proteinuria, and all above adverse events of special interest (AESIs) of Grade 3 and above should be reported as AESIs to the sponsor in accordance with the SAE reporting time limit and procedures (see 7.2.1.4 for details) even if they do not meet the SAE definition.*	
P55 Pregnancy Any pregnancy during the study, though not an SAE, must be reported using the Clinical Trial Pregnancy Report. To ensure	**Bevacizumab may be harmful to the fetus. Subjects or female partners of male subjects must use an effective form of contraception during the 6 months after the last dose.** If any	4 3 The record, procedure,

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subject safety, the investigator must submit the report to the sponsor or the sponsor's representative within 24 hours after becoming aware of the event. Pregnancies must be followed to determine the outcome (including early termination) and the condition of the mother and the baby. Complications and termination of pregnancy due to medical reasons should be reported as AE or SAE. A spontaneous abortion should be reported as an SAE.	**female subject or the female partner of any male subject becomes pregnant** during the study, the drug should be discontinued immediately and the investigator should be notified. *The investigator should report the pregnancy to the sponsor within 24 h of knowing the event by filling out the pregnancy form. The Investigator should also discuss with the subject (and the female partner of the male subject) regarding the risk of continuing pregnancy and its possible impact on the fetus. The investigator should follow up the pregnancy to determine its outcome (including abortion) and the status of the mother and the baby for not less than 8 weeks after delivery, and report the follow-up results as the pregnancy follow-up report to the sponsor according to the procedure and time limit the same as those for the first report.* Complications and termination of pregnancy due to medical reasons should be reported as AE or SAE. A spontaneous abortion should be reported as an SAE. **For any congenital abnormalities/birth defects or SAEs of the mother and child during the perinatal period, they should be recorded and reported in accordance with the procedure and time limit for reporting SAEs.**	and time limit of pregnancy report are updated
P55 Summary of adverse event collection, documentation, and reporting All adverse events that occur from the signing of the ICF to the time specified in the protocol (Table 8) must be collected and documented in the AE page of the eCRF regardless of severity	All AEs occurring from the time the subject signs the informed consent form to the time specified in the protocol (Table 8) **(including SAEs and non-SAEs)**, regardless of their severity,	4/3 The reporting and follow-up periods of AEs are updated

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(all SAEs and non-serious AEs).

The investigator must fill out all the required information, including the description of the AE, start date, end date, severity, measures taken, outcome, seriousness, and causality with the investigational drug. Each AE should be documented separately.

Table 8. Reporting and follow-up of adverse events

	Reporting time limit	Visit time limit
AEs	From the signing of the ICF until 28 days after the last dose of the study treatment	Until resolution or 28 days after the last dose of the study treatment
Adverse events of special interest (AESIs)	From the signing of the ICF until 6 months after the last dose of the study treatment	Until resolution or 6 months after the last dose of the study treatment
Serious adverse event	From the signing of the ICF until 6 months after the last dose of the study treatment	Until resolution (treatment-related) or 6 months after the last dose of the study treatment (not treatment-related)
Pregnancy	From the first dose until 6 months after the	Until the end of the event

must be collected and recorded on the AE page of the eCRF.

Table 18 . Report and follow-up of adverse events

	Reporting Time Limit	Visit Time Limit
AEs	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or *explainable stable determined by the investigator*
AESI	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or *explainable stable determined by the investigator*
SAE	From signing of the informed consent form to 3 months after the last dose of the study treatment	Until resolved or *explainable stable determined by the investigator*
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the outcome of the event is available, **and the health conditions of the newborn should be followed up for at least 2 months according to the**

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	last dose of the study treatment	

		protocol	

P55 None	**Precautions for AE documentation** **Diagnosis, signs, and symptoms** **If a diagnosis is already made, the eCRF should record the diagnosis instead of individual symptoms and signs** **(such as hepatic failure rather than jaundice, transaminase increased, and asterixis). However, if the signs and symptoms cannot be attributed to a definitive diagnosis, each independent event should be documented in the eCRFs as an AE or SAE. Update the report with visit information if a diagnosis is confirmed later.** **AEs secondary to other events** **Generally, AEs secondary to other events (such as result of another event or clinical sequelae)** **should be documented as the primary event, unless the event is severe or an SAE. However, clinically significant secondary events should be recorded as independent adverse events in the eCRFs if they occur at different times than the primary event. If the relationship between events is unclear, document them as separate events in the eCRFs.**	$\frac{4}{3}$ The description of adverse event records is added

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	Ongoing or recurrent AEs **An ongoing AE refers to an event that does not resolve** **and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs. The initial severity should be documented, and the information should be updated if the event exacerbates.** **Recurring AEs refer to AE that have resolved between the two time points of** **assessment but subsequently occur. These events should be independently documented in the eCRFs.** **Abnormalities in laboratory tests/vital signs** **Not all abnormalities in laboratory tests/vital signs should be reported as AEs. Only the abnormalities in laboratory tests/vital signs that meet the following criteria are reported as AEs:** **Accompanied with clinical symptoms** **Lead to changes in the dose of the study treatment (such as dose adjustment, dose interruption, or permanent drug withdrawal)** **Require medical intervention or changes in concomitant therapy**	

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	4/3 Judged by the investigator as clinically significant **It is the responsibility of the investigator to review all abnormal laboratory test results and vital signs, and to determine whether each abnormal laboratory test result or vital signs should be reported as AEs.** **If clinically significant laboratory abnormalities or abnormal vital signs are characteristic of a disease or syndrome (such as increased levels of alkaline phosphatase and total bilirubin caused by cholecystitis that are higher than 5 times the upper limit of normal), only the diagnosis is recorded on the AE report of the eCRF (i.e., cholecystitis). Conversely, the laboratory abnormalities or abnormal vital signs are recorded on the AE report of the eCRF, and it should be indicated that whether the test value is above or below the normal range (for example, it should be recorded as "blood potassium increased" instead of "blood potassium abnormal"). If there is a standard clinical term corresponding to the laboratory abnormalities or abnormal vital signs, the clinical term should be recorded on the eCRF** **(such as "anemia", instead of "hemoglobin decreased"). The same clinically significant laboratory abnormalities or abnormal vital signs found during multiple follow-ups should not be repeatedly recorded as AEs or SAEs in the eCRF unless**	

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	there is a change in its severity or etiology. **Death** **During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs and reported to the sponsor timely, regardless of the causality with the investigational drug.** **When recording a death event, if there is an AE leading to the death, a single medical concept should be used on the AE report of the eCRF to record the event leading to the death, and the event should be reported as an SAE in an expedited manner; if the cause of the death is unknown at the time of reporting , "Death with Unknown Cause" should be recorded on the AE report of the eCRF. The "Death with Unknown Cause" should be reported as an SAE in an expedited manner before further investigation is carried out to find the exact cause of death.** **If the cause of death is confirmed to be PD, then the event should not be documented and reported as an AE/SAE. However, the event should be documented in the Mortality Report Form of the eCRF and reported to the sponsor timely.** **Pre-existing medical conditions** **Symptoms/signs presenting during the screening period will**	

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	be recorded and reported as AEs only if their severity, frequency, or property becomes aggravated (except for worsening of the studied disease). The relative change should be documented, such as "increased frequency of headaches". **Hospitalization and prolonged hospitalization, or surgery** **Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, except for the following situations:** **- Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration, efficacy evaluation, etc.)** **- Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.** **However, elective surgery/therapy required because of the exacerbated condition during the study (e.g. surgery/therapy required earlier than scheduled) should be considered as an AE.** **The investigator should fill in all required information, including AE terms** **(diagnostic terms, or the record of symptoms and signs including laboratory test abnormalities if there is no**	

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	diagnosis), start date, end date, severity level, whether it is an AESI, measures taken for the investigational product, treatment given for the AE, outcome, seriousness, and relationship with the investigational product. If the signs and symptoms cannot be attributed to a definitive diagnosis, each AE should be documented independently. **Progressive disease** **For any event, if it can be clearly determined that the event is caused by progressive disease, the event is not reported as an AE. Hospitalization or death caused by progressive disease does not need to be reported in an expedited fashion.** **Lack of Efficacy** **When the disease treated by the study treatment deteriorates, it may not be possible to determine whether it is due to the lack of efficacy or the occurrence of an adverse event. In this case, unless the investigator believes that the deterioration of the condition is related to the study treatment, such changes are all regarded as the lack of efficacy rather than adverse events.** **Overdose** **When there is an accompanying AE, the AE should be recorded; when there is not accompanying AE, the overdose**	

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	should be recorded **on the eCRF.**	
P57 Sample Size Determination It will require 200 subjects in each treatment group (400 in total) to demonstrate clinical equivalence between IBI305 + paclitaxel/carboplatin and bevacizumab + paclitaxel/carboplatin with more than 80% power. The sample size is estimated based on the following assumptions: - The actual difference in ORR between subjects in the IBI305 and bevacizumab arms is 0 - The ORR of subjects in the bevacizumab arm is about 54.4% - The equivalence margin is (-15%, 15%) - The significance level of the two one-side test is 0.05 - 1:1 randomization Based on the above assumptions, 189 subjects are required for each treatment group (378 in total). The sample size is expanded to 200 subjects for each treatment group (400 in total) after taking dropouts into consideration. The sample size was estimated using PASS 2013.	A number of *218* subjects for each group (*436* subjects in total) can provide 80% test power to confirm the clinical equivalence between the treatments of IBI305 in combination with paclitaxel/carboplatin and bevacizumab in combination with paclitaxel/carboplatin. The sample size was estimated based on the following assumptions: - The ORRs between IBI305 and bevacizumab group are *equivalent* - The ORR of subjects in the bevacizumab groups is set to *50.0%* - The equivalence margin is taken as (*-12.5%*, *16.7%*) - The significance level of the two-sided test is 0.05 - The ratio of randomization is 1:1 Based on the above hypotheses, *a number of 218 subjects for each group is required (436 subjects in total)*. The sample size was estimated using PASS 2013.	- Based on the recommendations of CDE, the statistical hypotheses and the sample size are updated

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P57 Statistical Population Intention-to-Treat (ITT): All randomized subjects who received the study treatment.	Intention-to-Treat (ITT): *All randomized subjects.*	4/3 The definition of ITT is clarified
P57 Statistical Population None	**PK analysis set (PKAS): Includes subjects in the FAS with at least one PPK measured value.** **Pharmacodynamic analysis set (PDAS): Includes all subjects in the FAS set with at least one PD measured value.**	4/3 Based on the recommendations of CDE, the definitions of analysis sets of pharmacokinetic and pharmacodynamic evaluations are added for the objectives of the exploratory study
P58 Interim analysis There is no interim analysis planned for this study.	~~Deleted from the original text~~	4/3 Correction
P58 Multiple comparisons and adjustments to multiplicity Not applicable.	*The α adjustment for multiple comparisons is not considered.*	4/3 Clarification
P60 Antibody and efficacy analysis Subjects who develop antibodies during the clinical study will be summarized in detail. The difference in efficacy between subjects with and without antibodies will be compared if necessary.	Subjects who develop antibodies during the clinical study will be summarized in detail. The difference in efficacy between subjects with and without antibodies will be compared if necessary.	4/3 The analytical method of immunogenicity is updated

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	Changes in PK parameters and steady-state trough concentrations of subjects with positive ADA are analyzed.	
P60 None	8.5.5 **Exploratory analysis** **Pharmacodynamic parameters: The changes in the serum VEGF level at different time points are described, and inter-group comparisons are carried out when necessary (based on the PD dataset)** **Steady-state trough concentrations of the drug: The level of trough concentration is described and inter-group comparisons are carried out when necessary (based on the PPK dataset)**	4/3 Based on the recommendations of CDE, the pharmacokinetic and pharmacodynamic evaluations are added as analytical methods for the objectives of the exploratory study
P60 Interim analysis No interim analysis is planned for this study.	No *interim* analysis is planned.	4/3 Correction
P60 None	**8.5.7 Stratified analysis** **Efficacy analysis of different levels of subjects is conducted based on the random stratification factors**	4/3 A stratified analysis is added

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CLINICAL STUDY PROTOCOL

Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Version and Date:	Version 1.0/Jun. 2, 2016
Product Name:	Recombinant anti-VEGF humanized monoclonal antibody injection (IBI305)
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	Zhou Hui (Medical Director) Tel: （+86）0512-69566088-8067 E-mail: hui.zhou@innoventbio.com Hou Jiagang (Clinical Operations Director) Tel: （+86）0512-69566088-8062 E-mail：jiagang.hou@innoventbio.com

SIGNATURE PAGE

Protocol Title: A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer

Protocol No.: CIBI305A301

<Name> <Title>	Signature	Date
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PROTOCOL SYNOPSIS

Sponsor/Company:	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug:	IBI305
Active Ingredient:	Recombinant anti-VEGF humanized monoclonal antibody
Study Title:	A randomized, double-blinded, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin in treatment-naive subjects with advanced or relapsed non-squamous non-small cell lung cancer
Protocol No.:	CIBI305A301
Coordinating Investigator:	Zhang Li
Coordinating Center:	Sun Yat-Sen University Cancer Center

Expected study duration: Each subject will receive treatment every 3-week until progressive disease (PD), unacceptable toxicity, withdrawal of informed consent, lost to follow-up or death (whichever comes first). The end of the study is defined as the 18th month after the randomization of the last subject.	**Phase:** III

Study Objectives:

Primary Objective:

- To compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC)

Secondary Objectives:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

Study design:

This is a randomized, double-blinded, multi-center phase III study. The study planned to enroll and randomize 400 subjects with non-squamous NSCLC in a 1:1 ratio to IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild type vs. mutant).

Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death (whichever comes first). Then subjects receive monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

During the study, a CT or an MRI will be performed every 6 weeks (± 7 days) and be determined whether the study treatment will be continued by investigators at each site through tumor assessments until PD, withdrawal of informed consent, lost to follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for reasons other than PD, tumor assessments will be continued until PD, withdrawal of informed consent, loss of follow-up, death, start of other anti-tumor therapies, or end of study. If subjects discontinue the study treatment for PD, the investigators will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, lost to follow-up, death, or end of study.

Number of Subjects:	400
Diagnosis and main inclusion criteria:	**Inclusion Criteria:** Subjects must meet all of the following inclusion criteria to be enrolled in the study: 1) Sign the formed consent form 2) Male or female ≥ 18 and ≤ 70 years old 3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIb), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types 4) Histologically confirmed EGFR wild type 5) Histologically confirmed EGFR mutation type, but subjects who have not received EGFR-TKI treatment due to various reasons 6) Must have at least one measurable target lesion (as per RECIST 1.1) 7) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1

	8) Expected survival ≥ 6 months 9) Laboratory results during screening: Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2+ in routine urinalysis. Subjects with urine protein ≥ 2+ from urinalysis dipstick at baseline, a 24-h urine should be collected with total protein content < 1 g INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment 10) Able to comply with study protocol 11) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the study and for 6 months after the infusion of the study drug Exclusion Criteria: Subjects meeting any of the followings will not enrolled in the study: 1) Prior chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIb not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible 2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component 3) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time 4) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava) 5) History of brain metastasis, spinal cord compression, or carcinomatous

	meningitis, or brain metastasis confirmed by CT or MRI during screening
	6) Subjects who received radical thoracic radiotherapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug
	7) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study
	8) Subject who received minor surgery (including catheterization) within 48 h prior to the first dose of the study drug
	9) Currently or recently (within 10 days prior to the first dose of study drug) used aspirin (> 325 mg/day) or other nonsteroidal anti-inflammatory drugs known to inhibit platelet function
	10) Currently or recently (within 10 days prior to the first dose of study drug) received treatment with full dose oral or parenteral anticoagulants or thrombolytic agents. However, anticoagulants for prophylaxis are accepted.
	11) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis
	12) Uncontrolled hypertension (systolic greater than 150 mmHg and/or diastolic greater than 100 mmHg), history of hypertensive crisis or hypertensive encephalopathy
	13) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease
	14) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess
	15) Subjects with tracheoesophageal fistula
	16) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments)
	17) Subjects with pulmonary fibrosis history or active pneumonia shown on CT during screening
	18) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after

	radical surgery, ductal carcinoma in situ after radical surgery 19) Subjects with autoimmune disease 20) Subjects with positive test result of HBsAg, and peripheral blood HBV DNA titer ≥ 1×10^3 copies/L; subjects with positive test result of HBsAg and peripheral blood HBV DNA titer < 1×10^3 copies/L are eligible if the investigator determine that the subject's chronic hepatitis B is stable and participation in the study would add no further risks to the subject 21) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis 22) Subjects with known history of allergic diseases or allergic physique 23) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening 24) History of alcohol or drug abuse 25) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study 26) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents 27) Other conditions unsuitable for the inclusion as determined by the investigator
Investigational Drug, Dosage, and Route of Administration:	IBI305: 15 mg/kg in combination chemotherapy and 7.5 mg/kg monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)
Control Drug, Dosage, and Route of Administration:	Bevacizumab: 15 mg/kg in combination chemotherapy and 7.5 mg/kg monotherapy, administered via intravenous infusion on D1 of every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first)
Chemotherapy:	Paclitaxel: 175 mg/m² administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death. Carboplatin: Areas under the concentration-time curve (AUC) = 6.0 administered via intravenous infusion on D1 of every 3-week treatment cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Evaluation criteria:

Efficacy endpoints:

Primary efficacy endpoint:

- Objective response rate (ORR)

Secondary efficacy endpoints:

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Safety endpoints:

- Vital signs
- Physical examination
- Laboratory tests (routine blood test, blood chemistry, and urinalysis)
- 12-Lead ECG
- Adverse event (AE, including treatment-emergent AE (TEAE)), AE of special interest (AESI) (hypertension, proteinuria, gastrointestinal perforation, hemorrhage [cerebral hemorrhage, hematuria and upper gastrointestinal hemorrhage], cardiotoxicity, and thrombosis), and serious adverse event (SAE)
- Immunogenicity: Positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs)

Statistical methods:

Sample size calculation:

A number of 200 subjects for each group (400 subjects in total) will provide over 80% power to confirm the clinical equivalence between IBI305 plus paclitaxel/carboplatin and bevacizumab plus paclitaxel/carboplatin. Estimation of sample size: If the significance level of the two one-sided test is 0.05, the ORR between IBI305 and bevacizumab group is about 54.4%, with an equivalence margin of (-15%, 15%). Based on the above assumptions, 189 subjects are required for each group (378 subjects in total). The sample size is expanded to 200 subjects for each group (400 subjects in total) after taking dropouts into consideration.

Efficacy analysis:

Clinical equivalence will be determined by whether the 90% confidence interval (CI) of the difference in ORR between the IBI305 and bevacizumab arms falls within the preset margin of (-15% to 15%). The ORR and 95% CI of two groups, ORR difference and 90% CI, and ORR ratio and 90% CI will be estimated using the generalized linear model (GLM, including groups and stratification factors).

Median survival (OS) and survival curves will be estimated using the Kaplan-Meier method. The hazard ratio (HR) and 95% CI of two groups will be estimated using the Cox model. DORs and PFSs will be analyzed by the same method as the median survivals. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

Safety analysis:

All adverse events (AE) will be coded using MedDRA and graded according to CTCAE v4.03. All treatment-emergent adverse events (TEAEs), Grade 3 or greater TEAEs, serious adverse events (SAEs), investigational drug-related TEAEs, investigational drug-related SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study termination, and adverse events of special interest (AESIs) will be listed based on system organ class, preferred terms, and groups and the numbers of corresponding subjects and percentages will be summarized. In addition, the severity of TEAEs and the correlation with the study drug will also be summarized by system organ class, preferred terms, and treatment groups.

Measured values and changes from baseline for vital signs, physical examination, laboratory tests and 12-lead ECG will be analyzed using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation.

The number and percentage of subjects who developed anti-drug antibodies and neutralizing antibodies during the study will be summarized by treatment group.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definitions
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AUC	Area under the curve
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CFDA	China Food and Drug Administration (now National Medical Products Administration)
CQA	Clinical quality assurance
CR	Complete response
CRA	Clinical research associate
CRO	Contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data collection
EGFR	Epithelial growth factor receptor
FAS	Full analysis set
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
ITT	Intention-to-treat
NCCN	National Comprehensive Cancer Network

NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PP	Per-protocol
PR	Partial response
RPLS	Reversible posterior leukoencephalopathy syndrome
PTT	Partial thromboplastin time
SAE	Serious adverse event
SD	Stable disease
SOP	Standard operating procedure
SS	Safety set
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

1 INTRODUCTION

1.1 Study Background

1.1.1 Disease background

Lung cancer has the highest incidence and mortality globally among all cancers. According to the 2012 Global Cancer Statistics (GLOBOCAN 2012) published by International Agency for Research on Cancer, there were approximately 1.8 million new lung cancer cases worldwide, which accounted for 13% of the global newly-diagnosed cancers, and 58% of these cases occurred in underdeveloped areas[1]. According to the data released by the National Central Cancer Registry of China in 2015, lung cancer was the most prevalent malignancy in China in 2011, with about 650,000 new cases every year. Lung cancer was also the leading cause of death, with about 520,000 deaths per year[2]. The limited clinical treatment of lung cancer is the main reason for its poor prognosis. There is a huge demand for new types of lung cancer treatment drugs.

Approximately 85–90% of lung cancers are non-small cell lung cancer (NSCLC) and patients with NSCLC are usually in the advanced stages when diagnosed[3]. According to the Chinese guidelines for the diagnosis and treatment of primary lung cancer, anatomic pulmonary resection is the mainstay of treatment for early stage lung cancers[4]. However, despite surgery, some patients develop distance metastases that eventually lead to death[5]. Surgery is not possible for most patients with clearly diagnosed stage IIIb and IV as well as some patients with stage IIIa NSCLC[4]. Comprehensive treatment based on systemic therapy is used to maximize patient survival, control progressive disease, and improve the quality of life[6].

In recent years, anti-tumor therapies have entered a new era with the emergency of targeted drugs. Some of these targeted drugs have demonstrated satisfactory efficacy in the treatment of advanced NSCLC. These targeted drugs include monoclonal antibodies and tyrosine kinase inhibitors (TKIs), mostly targeting epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor (VEGF), such as bevacizumab, cetuximab, gefitinib, erlotinib, and icotinib. Monoclonal antibodies have become the drugs of choice in various treatment guidelines due to the good targeting ability, low drug resistance, and good patient tolerability. Bevacizumab combination chemotherapy is a first-line therapy of NSCLC recommended by the National Comprehensive Cancer Network (NCCN)[7]. Additionally, bevacizumab in combination with paclitaxel/carboplatin has also been approved as the first-line therapy of unresectable advanced, metastatic, or relapsed non-squamous NSCLC by China Food and Drug Administration (CFDA) on Jul. 9, 2015[6].

Compared with traditional chemotherapy that directly inhibit or kill tumor cells, anti-angiogenic drugs have the following unique advantages[8]:

- The targets are genetically stable vascular endothelial cells (VECs) rather than highly heterogeneous tumor cells, thus leading to lower drug resistance;
- The number of tumor-induced VECs is far less than that of tumor cells, and the efficacy is preferable targeting on VECs and their cytokines;
- Normal VECs are quiescent, whereas tumor VECs are active in proliferation. Anti-angiogenic therapy targets activated cells and avoids damage to normal VECs, thus leading to better targeting ability;
- Anti-angiogenic therapy can normalize the tumor vessels and thereby reduce the pressure in tumor tissues. This enhances the delivery of chemotherapeutic agents into tumor tissues, thus increasing the efficacy of chemotherapy.

Angiogenesis is a basic biological characteristic of tumors. The growth of both solid and hematologic tumors are depended on angiogenesis regardless of the nature of tumor cells. Therefore, anti-angiogenic therapy is broad-spectrum and applicable to various tumors.

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to human VEGF and blocks its biological activity. Bevacizumab consists of a framework region of a human antibody and a humanized murine antigen binding region that can inhibit the binding of VEGF to its receptors on epithelial cells, Flt-1 and KDR. By blocking the activity of VEGF and reducing tumor angiogenesis, tumor growth is inhibited[9].

In a study conducted by the Estern Cooperative Oncology Group (ECOG), compared with chemotherapy alone (paclitaxel/ carboplatin), bevacizumab in combination with paclitaxel/carboplatin significantly increased the overall survival (OS) (median: 12.3 vs. 10.3 months), progression-free survival (PFS) (median: 6.2 vs. 4.5 months), and overall response rate (ORR) (35% vs. 15%) in patients with advanced, metastatic, or relapsed non-squamous NSCLC[10]. In another foreign AVAiL study, different doses of bevacizumab (7 and 15 mg/kg) in combination with chemotherapy (cisplatin and gemcitabine) and placebo combine with chemotherapy were compared for the treatment of non-squamous NSCLC. The study found that the two bevacizumab groups had significantly increased the PFS (median: 6.7 months (7.5 mg/kg combination chemotherapy group) vs. 6.5 months (15 mg/kg combination chemotherapy group) vs. 6.1 months (placebo combination chemotherapy group)) and the ORR (37.8% (7.5 mg/kg combination chemotherapy group) vs. 34.6% (15 mg/kg combination chemotherapy group) vs. 21.6% (placebo combination chemotherapy group)) in patients with locally advanced, metastatic, or relapsed non-squamous NSCLC[11]. In a BEYOND study conducted in China, compared with

placebo in combination with paclitaxel/carboplatin, bevacizumab in combination with paclitaxel/carboplatin significantly increase the PFS (median: 9.2 vs. 6.5 months), OS (median: 24.3 vs. 17.7 months), and the ORR (54% vs. 26%) in patients with advanced or relapsed non-squamous NSCLC[12].

In China, the antibodies and fusion proteins targeting VEGF are research hotspots. However, since 2006, the clinical efficacies of various drugs has not been verified and no products have been marketed. Considering the complexity of macromolecular drugs and the limitations of drug development capability in China, advanced technologies in antibody development, production, and quality control is required to develop high-quality VEGF inhibitors that are safe and effective. IBI305 has showed high similarity to bevacizumab in various pharmaceutical and nonclinical studies (refer to Investigator's Brochure [IB]). Besides, the efficacy and safety of bevacizumab for treatment of locally advanced, metastatic or relapsed lung cancer have been verified. The relevant domestice and external pivotal clinical studies are referable for the protocol design of IBI305 clinical study. In summary, the clinical study of IBI305 for treatment of NSCLC has a solid foundation and relatively low risks. The successful development of IBI305 indicates an additional first-line targeted drug for lung cancer in China, providing doctors and patients with more therapeutic options.

1.1.2 Investigational drug

1.1.2.1 Description of investigational drug

IBI305 is a recombinant humanized anti-VEGF monoclonal antibody injection developed by Innovent Biologics (Suzhou) Co., Ltd. (hereafter as sponsor) that specifically binds human VEGF. The molecular weight of IBI305 is 149 KDa. IBI305 specifically binds to VEGF-A, inhibits the binding of VEGF-A to VEGF-R1 and VEGF-R2, blocks the signaling pathways such as PI3K/Akt/PKB and Ras-Raf-MEK-ERK. IBI305 also inhibits the growth, proliferation, and migration of VECs and angiogenesis, decreases the vascular permeability, blocks blood supply to tumor tissues, inhibits the proliferation and metastasis of tumor cells, and induces the apoptosis of tumor cells, thereby generates anti-tumor effects. The main active ingredient is recombinant humanized anti-VEGF monoclonal antibody and excipients include sodium acetate, sorbitol, and polysorbate 80[13]. Refer to the Investigator's Brochure for the detailed structure and physicochemical properties of IBI305.

1.1.2.2 Preclinical studies

Pharmaceutical studies

The pharmaceutical studies showed that stability, primary structure, higher-order structure, oligosaccharide distribution, charge variant, and product-related impurities of IBI305 are highly similar to those of bevacizumab, and the process-related impurities meet the proposed specification. Therefore, IBI305 is considered to have highly similar protein properties and product quality to bevacizumab[13].

Pharmacodynamic studies

In vitro and in vivo pharmacodynamic (PD) studies of IBI305 showed the following findings:

1) Target: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A with an affinity constant same as that of bevacizumab, indicating that IBI305, the same as bevacizumab, is a specific human VEGF blocker with a clear target.
2) Specificity: IBI305 displayed specifically high-affinity binding to recombinant human VEGF-A, medium-affinity binding to canine VEGF-A, but low-affinity binding to human VEGF-B, VEGF-C, VEGF-D, PlGF, suggesting that IBI305 recognizes specific targets and has low off-target toxicity risk; no obvious affinity to mouse VEGF-A_{164} and rat VEGF-A_{164}, suggesting that IBI305 has high species specificity.
3) Mechanism of action: IBI305 specifically binds to VEGF-A and inhibits the activation of VEGFR-2 and ERK1/2, blocks the proliferation and migration of HUVEC, and inhibits the sprouting from rat aortic ring, suggesting that IBI305 antagonizes VEGF-A-induced signaling pathway to block the proliferation and migration of VECs and inhibit angiogenesis, which leads to the reduction of nutritional supply and metastasis of tumor.
4) Anti-tumor effects: IBI305 significantly inhibits the growth of human colon cancer Ls174t and lung cancer NCI-H460 cells in xenografts in nude mice, indicating that IBI305 has significant anti-tumor effects.

Results from in vitro and in vivo studies of IBI305 showed highly similarity with that of bevacizumab designed simultaneously, demonstrating that the target, mechanism of action, and anti-tumor effects of IBI305 are highly similar to bevacizumab[13].

Pharmacokinetic studies

In vitro and in vivo pharmacokinetic (PK) studies of IBI305 showed the following findings:

1) IBI305 showed no significant cross-reactivity with normal human tissues and cynomolgus monkey tissues, and only cross-reacted with the positive-control. i.e. human angiosarcoma tissue, suggesting that IBI305 is highly specific to cancer tissues rather than normal human tissues and has very low on-target toxicity.
2) Linearity: With single dose or repeated doses of IBI305 (2-50 mg/kg) vis intravenous injection in cynomolgus monkeys, the test showed significant PK, thus reducing the suddenly rising toxicity risks with increased clinical doses.
3) Immunogenicity: With single dose or repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed abnormal changes of drug concentration-time curves in several animals. The anti-drug antibody (ADA) test results showed that IBI305 has a medium immunogenicity.
4) Accumulation: With repeated doses of IBI305 or bevacizumab via intravenous injection in cynomolgus monkeys, the test showed that drug exposure of the last dose was significantly higher than that of the first dose, and the steady-state drug concentration after repeated doses was higher than that after a single dose, suggesting that the drug may be accumulated in body.

The results of tissue cross-reactivity and PK/toxicokinetic studies in cynomolgus monkeys indicated that IBI305 and bevacizumab have similar characteristics in tissue cross-reactivity and PK/toxicokinetics[13].

Toxicological studies

Toxicological studies of IBI305 showed the following findings:

1) Single dose: With single dose of IBI305 (up to 300 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed good tolerability without any abnormal clinical symptoms and toxicity. The dose was about 48 times the proposed clinical dose for human based on body surface area. In the safety pharmacology test, with single dose of IBI305 (50 mg/kg) via intravenous injection in cynomolgus monkeys, the test showed no significant effects on the central nervous system, respiratory system, and cardiovascular system, suggesting that the single dose of IBI305 via intravenous injection has a high safety.

2) Repeated doses: With repeated doses of IBI305 (up to 50 mg/kg) via intravenous injection twice weekly for 9 consecutive doses in cynomolgus monkeys, equivalent to 20 times the proposed clinical dose for humans (based on the weight), the test showed extremely mild to mild linear growth arrest of metaphyseal lines at knee joint and disordered chondrocyte proliferation, extremely mild increases in macrophage count in white pulp of spleen, pulmonary (including bronchial) hemorrhage, and deposits of hemosiderin in lymphoid tissue of bronchial mucosa, indicating that the target organ toxicities are mainly in the bone, spleen, and lungs.

3) Immunotoxicity and immunogenicity: With repeated doses of IBI305 via intravenous injection twice weekly for 9 consecutive in cynomolgus monkeys, the test showed medium immunotoxicity to the spleen. Different doses of IBI305 may result in the production of ADAs, a portion of which are neutralizing antibodies (NAbs), indicating that IBI305 has medium immunotoxicity and immunogenicity.

4) Local irritation test: With repeated dose of IBI305 via intravenous injection in cynomolgus monkeys, the test showed no irritation at the injection site, suggesting that administration of IBI305 via intravenous injection is safe and feasible.

5) In vitro hemolysis assay: With maximum proposed clinical concentration of IBI305 (9 mg/mL), the assay showed no hemolysis, suggesting that IBI305 is suitable for intravenous injection.

IBI305 has high similarity with bevacizumab in safety pharmacology, long-term toxicity, immunotoxicity, immunogenicity, local irritation, and hemolysis[13].

1.1.2.3 Clinical studies

This study is the first study of IBI305 in humans.

1.2 Study Principles and Risk/Benefit Assessment

1.2.1 Study principles and dose selection

A biosimilar drug refers to a therapeutic biological product that is similar in quality, safety and efficacy with an approved reference drug[14]. IBI305, developed and sold in the market by the sponsor, is a bevacizumab biosimilar, and has the same administration method and indications as bevacizumab.

This study is conducted in accordance with the "Guidelines on Development and Evaluation of Bosimilars (for Trial Version)" issued by the NMPA (formerly CFDA)[14]. The doses of IBI305 selected in this study are based on the preclinical studies that showed highly similarity between IBI305 and bevacizumab in pharmacology, PD, PK and toxicology (refer to the Investigator's Brochure for details). Besides, the efficacy and safety of bevacizumab for treatment of advanced, metastatic or relapsed non-squamous NSCLC have been verified, and the indications have also been approved in China. Therefore, the dose and administration of IBI305 is similar to bevacizumab in this study, that is, 15 mg/kg intravenously on D1 of every 3-week cycle when used in combination with chemotherapy (paclitaxel and carboplatin). In the subsequent monotherapy therapy, IBI305 will be given intravenously at a dose of 7.5 mg/kg on the first day of every 3-week cycle. This design of this study is to further demonstrate that IBI305 is similar to bevacizumab in clinical efficacy, safety, and immunogenicity in subjects with advanced, metastatic or relapsed non-squamous NSCLC.

1.2.2 Risk/benefit assessment

IBI305 is a bevacizumab biosimilar developed by the sponsor. Based on the clinical pharmacology and toxicology characteristics of IBI305, the risks and benefits of IBI305 are expected to be similar to bevacizumab.

The treatment-related risks of bevacizumab are detailed in its prescribing information. This study is the first human study of IBI305 so that unexpected adverse reactions will be possible. The design of this study ensures the minimized subject risks by close monitoring of the adverse events (AEs) before, during, and after the infusion of the investigational drugs. Once an adverse reaction occurs, the investigator will immediately take appropriate action for the subject safety.

The platinum-based therapy is the standard first-line regimen of advanced NSCLC[4]. This study uses the combination of paclitaxel/carboplatin, ensuring the basic anti-tumor therapy for subjects.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare the objective response rate (ORR) of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC.

2.2 Secondary Objectives

Secondary objectives include:

- To compare the duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) in subjects with advanced or relapsed non-squamous NSCLC treated by IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin
- To compare the safety and immunogenicity of IBI305 plus paclitaxel/carboplatin versus bevacizumab plus paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous NSCLC

3 STUDY PLAN

3.1 Overview of Study Design

This is a randomized, double-blind, active-controlled, and multi-center phase III study. A total of 400 subjects across 35 study sites with non-squamous NSCLC will be planned, randomized in a 1:1 ratio into the IBI305 plus paclitaxel/carboplatin group or bevacizumab plus paclitaxel/carboplatin group, and stratified according to age (< 60 vs. ≥ 60 years old) and epidermal growth factor receptor (EGFR) status (wild type vs. mutant). Each treatment cycle is 3 weeks for both groups. 15 mg/kg IBI305 or bevacizumab is administered on D1 of each cycle along with paclitaxel/carboplatin. Subjects will receive up to 6 treatment cycles of combination therapy until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first). Then subjects received monotherapy, that is, discontinuing paclitaxel/carboplatin while continuing therapy with IBI305 or bevacizumab. The monotherapy continues every 3 weeks. On D1 of each treatment cycle, subjects will be administered 7.5 mg/kg of either IBI305 or bevacizumab until PD, unacceptable toxicity, withdrawal of informed consent, lost to follow-up, death, or end of study (whichever comes first).

After discontinuing the study drug, subjects will return to the study site 28 days (± 7 days) after the last dose for an end-of-treatment visit. If the subjects discontinue the study treatment for reasons other than PD, subsequent follow-up will be continued until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. If the subjects discontinue the study treatment for PD, the investigator will make telephone follow-up every 12 weeks (± 7 days) to collect information of subsequent anti-tumor therapies and survival.

A CT or an MRI will be performed every 6 weeks (± 7 days) until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death, or end of study. The method for subsequent imaging examination should be consistent with that at baseline, and the chest, abdomen and pelvis of the subject must be scanned. Each assessment must be completed within 7 days from the most recent visit. The investigators then perform the evaluation based on the RECIST 1.1 criteria to determine whether the subject can continue receiving the next cycle of treatment. Furthermore, the independent tumor evaluation committee (Section 11.1.1) will also evaluate tumor response according to the RECIST version 1.1. If the subject discontinue the study treatment for reasons other than PD, subsequent tumor evaluation should be continued according to the study procedures until PD, withdrawal of informed consent, start of other anti-tumor therapies, loss of follow-up, death or, end of study.

The study design is shown in Figure 1.

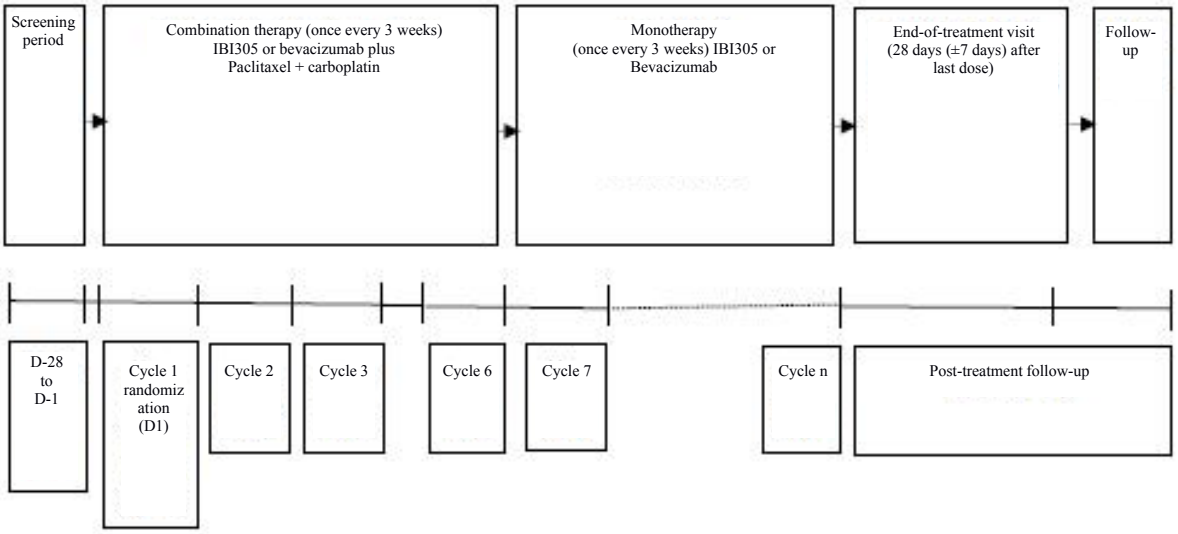

Figure 1. Study design schematic

3.2 Study Design Discussion

This is a randomized, double-blind study, and bias in treatment groups is avoided. Furthermore, the CT/MRI images of each subject will be evaluated by an independent tumor evaluation committee according to the RECIST 1.1 to ensure consistency in evaluation.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled in the study:

1) Sign the informed consent form
2) Male or female ≥ 18 and ≤ 70 years old
3) Histologically or cytologically confirmed unresectable locoregionally advanced (stage IIIb), metastatic (stage IV), or relapsed non-squamous NSCLC; mixed tumors should be categorized according to the main cell types
4) Histologically confirmed EGFR wild type
5) Histologically confirmed EGFR mutation type, but subjects who have not received EGFR-TKI treatment due to various reasons
6) Must have at least one measurable target lesion (as per RECIST 1.1)
7) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1
8) Expected survival ≥ 6 months
9) Laboratory results during screening:

   Routine blood test: WBC ≥ 3.0×10^9/L, ANC ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L

   Hepatic function: TBIL < 1.5 × ULN; ALT and AST < 2.5 × ULN for subjects without liver metastasis, or ALT and AST < 5 × ULN for subjects with liver metastasis

   Renal function: SCr ≤ 1.5 × ULN or CrCl ≥ 50 mL/min, and urine protein < 2 + in routine urinalysis. Subjects with urine protein ≥ 2+ at baseline must have undergone 24 h urine collection with total protein content <1 g

   INR ≤ 1.5 and PTT or aPTT ≤ 1.5 × ULN within 7 days prior to the study treatment

10) Able to comply with study protocol
11) Female and male subjects of childbearing age, and partners of these male subjects must agree to use effective contraceptive measures (such as abstinence, sterilization, oral contraceptives, medroxyprogesterone injections or contraceptive implants) during the

study and for 6 months after the infusion of the study drug

4.2 Exclusion Criteria

Subjects meeting any of the followings are not enrolled in the study:

1) Prior chemotherapy or targeted therapy (such as monoclonal antibody or tyrosine kinase inhibitor) for the treatment of the current stage of disease (Stage IIIb not suitable for multidisciplinary treatment, stage IV or relapsed disease). Prior surgery and radiotherapy are permitted, provided that the criteria outlined in the study protocol are met. Subjects who received prior adjuvant therapy and relapsed within 6 months are not eligible
2) Mixed non-small cell and small cell carcinoma, or mixed adenosquamous carcinoma predominantly containing squamous cell carcinoma component
3) History of hemoptysis within 3 months prior to screening, with a volume of blood greater than 2.5 mL each time
4) Radiographic evidence of tumor invasion in great vessels. The investigator or the radiologist must exclude subjects with tumors that are fully contiguous with, surrounding, or extending into the lumen of a great vessel (such as pulmonary artery or superior vena cava)
5) History of brain metastasis, spinal cord compression, or carcinomatous meningitis, or brain metastasis confirmed by CT or MRI during screening
6) Subjects who received radical thoracic radiation therapy within 28 days prior to enrollment; subjects who received palliative radiation for non-thoracic bone lesions within 2 weeks prior to the first dose of the study drug
7) Subjects with severe skin ulcers or fracture, or having major surgery within 28 days prior to randomization or expecting to have major surgery during the study
8) Subject who received minor surgery (including catheterization) within 48 h prior to the first dose of the study drug
9) Currently or recently (within 10 days prior to the first dose of study drug) used aspirin (> 325 mg/day) or other nonsteroidal anti-inflammatory drugs known to inhibit platelet function
10) Currently or recently (within 10 days prior to the first dose of study drug) received treatment with full dose oral or parenteral anticoagulants or thrombolytic agents. However, anticoagulants for prophylaxis are accepted.
11) Subjects with inherited hemorrhagic tendency or coagulopathy, or history of thrombosis

12) Uncontrolled hypertension (systolic greater than 150 mmHg and/or diastolic greater than 100 mmHg), history of hypertensive crisis or hypertensive encephalopathy

13) Any unstable systemic disease including but not limited to: active infection, unstable angina, cerebrovascular accident or transient cerebral ischemia (within 6 months prior to screening), myocardial infarction (within 6 months prior to screening), cardiac failure congestive (NYHA Class ≥ II), severe arrhythmia requiring medication, and liver, kidney or metabolic disease

14) History of the following diseases within 6 months prior to screening: gastrointestinal ulcers, gastrointestinal perforation, corrosive esophagitis or gastritis, inflammatory bowel disease or diverticulitis, abdominal fistula, or intra-abdominal abscess

15) Subjects with tracheoesophageal fistula

16) Clinically significant third spacing (such as ascites or pleural effusion that are uncontrollable by drainage or other treatments)

17) Subjects with pulmonary fibrosis history or active pneumonia shown on CT during screening

18) History of malignant tumors other than NSCLC within 5 years prior to randomization, except for adequately treated cervical carcinoma in situ, basal or squamous cell skin cancer, locoregional prostate cancer after radical surgery, ductal carcinoma in situ after radical surgery, or papillary thyroid carcinoma

19) Subjects with autoimmune disease

20) Subjects with positive test result of HBsAg, and peripheral blood HBV DNA titer ≥ 1×10^3 copies/L; subjects with positive test result of HBsAg and peripheral blood HBV DNA titer < 1×10^3 copies/L are eligible if the investigator determined that the subject's chronic hepatitis B is table and participation in the study would add no further risks to the subject

21) Subjects who are tested positive for HCV antibody, HIV antibody or syphilis

22) Subjects with known history of allergic diseases or allergic physique

23) Received treatment with other investigational drugs or participated in another interventional study within 30 days prior to screening

24) History of alcohol or drug abuse

25) Female subjects who are pregnant or breastfeeding, or expected to be pregnant or breastfeeding during the study

26) Known allergies to bevacizumab or any of its excipients, or any chemotherapeutic agents

27) Other conditions unsuitable for the inclusion as determined by the investigator

4.3 Screening Failure

Screening failure is that the subject who has signed the informed consent form fails to meet the inclusion criteria. Subjects with screening failure will not get a randomization number. The reasons of screening failure will be documented in the electronic case report forms (eCRFs).

4.4 Subject Restrictions

Female subjects of childbearing age must take effective contraceptive measures during the study and 6 months after the last dose.

Male subjects must take effective contraceptive measures during the study and 6 months after the last dose to avoid the pregnancy of their partners.

Restrictions on the use of medication during the study are shown in Section 5.9.

4.5 Subject Withdrawal and Replacement

All subjects may withdraw from this study at any time, with or without a reason. Subjects who withdraw from the study will not be subjected to discrimination or retaliation, and their medical treatment will not be affected.

Subjects may discontinue the study treatment or withdraw from the study under the following circumstances:

- Unacceptable toxicity
- Progressive disease
- Investigator believes that the subject should withdraw from the study. If an unacceptable adverse event (AE) occurs and the investigator believes that the subject should withdraw from the study, the study treatment should be discontinued and appropriate measures should be taken. In addition, the sponsor or personnel designated by the sponsor should be notified.
- Withdrawal of informed consent form by the subject
- Serious protocol deviation determined by the investigator and/or sponsor

- Poor protocol compliance
- Study termination by the investigator or sponsor for any reason
- Enrollment error* (enrollment of subjects who have violated the inclusion/exclusion criteria)
- Use of prohibited concomitant medications or other medications that the investigator believes that it may result in toxicities or may affect study results
- Subject lost to follow-up
- Death of subject

* If the subject is determined by the investigator and the sponsor's doctor to be medically suitable to continue with the study drugs without any risk or inconvenience, the mistakenly enrolled or randomized subject will continue with the study treatment and assessments.

In any cases, reasons for withdrawal must be documented in the eCRFs. If the subject withdraws from the study prematurely for any reason, the investigator should make every effort to persuade the subject to receive the corresponding assessment, and continue the follow-up of all unresolved AEs based on the AE reports and follow-up requirements (Table 2):

- If the subject withdraws during the study, the series of assessments listed under the End of Treatment Visit (Section 6.9) should be performed
- If the subject withdraws after the end of the treatment visit and has not experienced PD, the series of assessments listed under the Follow-Up for PD (Section 6.10) should be performed (tumor assessment is not required to be repeated if it has been performed within 6 weeks prior to this follow-up)
- If the subject withdraws during the follow-up for survival, the information of subsequent anti-tumor therapies and survival should be collected by telephone follow-up only

Subjects who withdraw their informed consent are not to be contacted again unless they clearly indicate the willingness to be contacted. The sponsor may use the clinical study data obtained before the withdrawal of informed consent.

Subjects who have been randomized will not be replaced.

5 STUDY TREATMENT

5.1 Therapies by Study Drugs

The study drugs of this study are IBI305 and bevacizumab.

In this study, the dose of IBI305 or bevacizumab during combination therapy with chemotherapy is 15 mg/kg, while the dose during monotherapy is 7.5 mg/kg. The study drugs are administered intravenously on D1 of each 3-week cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or end of study (whichever comes first).

The duration of the first dose of IBI305 or bevacizumab should be 90 min (± 15 min). If the first infusion is well-tolerated by the subject, then the duration of the second infusion can be shortened to 60 min (± 15 min). If the 60 min infusion is also well-tolerated by the subject, then the subsequent infusions can be completed within 30 min (± 15 min).

5.2 Chemotherapy

Paclitaxel will be administered after the IBI305 or bevacizumab infusion is completed, then followed by carboplatin:

Paclitaxel: 175 mg/m² administered via intravenous infusion for 3 h (may be adjusted according to clinical practice of each study site) on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

Carboplatin: AUC 6.0 administered via intravenous infusion for 15-30 min (may be adjusted according to clinical practice of each study site) on D1 of every 3-week cycle for up to 6 cycles until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death.

The chemotherapeutic agents are supplied by the sponsor.

Formulas for calculating surface area, creatinine clearance and carboplatin dose are shown in Section 13.2.

5.3 Dose Adjustment of Each Study Drug

5.3.1 General principles

The reasons for dose adjustments or delayed administration, measures taken, and results should be documented in the medical records and eCRFs

If the concomitant symptoms exist at baseline, the investigator will determine whether the dose should be adjusted according to the change in severity of toxicity. For example, if the subject has Grade 1 "weakness" at baseline and Grade 2 "weakness" during the study treatment, the dose should be adjusted based on Grade 1 toxicity since the severity has increased by one grade

If several toxic reactions of different grades or severity occur simultaneously, the dose will be adjusted according to the highest observed grade/severity

If a dose adjustment is required solely due to abnormal lab test results, then the dose should be adjusted based on the measured values obtained prior to the start of the treatment cycle

If the investigator determines that the toxicity is unlikely to further develop into a serious or life-threatening event, the current dose will be continued without any adjustments or treatment interruptions. In addition, dose adjustments or treatment interruptions will not be performed for non-hemolytic anemia as the symptoms can be alleviated through blood transfusions.

If the investigator determines that a toxicity is caused by a specific therapeutic drug, then the dose adjustments of other drugs are not required

Discontinuation of one or two therapeutic drugs before PD will not affect the continued treatment with other drugs

Dose reductions or adjustments of IBI305 or bevacizumab are not permitted.

Subsequent therapeutic dose will not be adjusted according to weight change, unless the subject weight has changed by ≥ 10% from baseline

Once the dose of any chemotherapeutic agents is reduced, the original dose should no longer be adopted

If any but not all of the therapeutic drug (IBI305, bevacizumab or chemotherapeutic agents) treatments is interrupted due to toxicity, then this treatment will be considered as a treatment cycle

If the administration of any one of the chemotherapeutic agents is delayed for more than 3 weeks, the subject should permanently discontinue that chemotherapeutic agent

If IBI305/bevacizumab is continued/infused after a delay for more than 3 weeks, the investigator must discuss with the sponsor

5.3.2 Dose adjustments of study drugs

Dose adjustments of IBI305 or bevacizumab are not permitted except for the adjustments (adjusted to 7.5 mg/kg for monotherapy) specified in the study protocol. The dose of IBI305 or bevacizumab is calculated according to the subject weight at baseline (prior to the first dose), and remains unchanged throughout the study, unless the subject weight has changed by ≥ 10% from baseline.

If an infusion reaction occurs during a 60-minute infusion, the infusion time should be extended to 90 minutes for all subsequent infusions. Likewise, if an infusion reaction occurs during a 30-minute infusion, the infusion time should be extended to 60 minutes for all subsequent infusions.

IBI305 or bevacizumab in combination with paclitaxel/carboplatin will be administered every 3-week treatment cycle for 6 cycles. If PD is not observed in subject during treatment, then the subject will continue to receive IBI305 or bevacizumab as monotherapy every 3-week treatment cycle until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, death, or end of study (whichever comes first).

If IBI305 or bevacizumab is permanently discontinued due to unacceptable toxicity or subject refusal to continue the study drugs during the combination therapy, then the subject will continue to receive the chemotherapy (paclitaxel/carboplatin) until 6 treatment cycles are completed as determined by the investigator. If any one of the chemotherapeutic agents (paclitaxel or carboplatin) is prematurely discontinued due to unacceptable toxicity, the subject can continue to receive IBI305 or bevacizumab treatment until PD, unacceptable toxicity, withdrawal of informed consent, loss of follow-up, or death (whichever comes first).

When a Grade 3 or 4 IBI305- or bevacizumab-related toxicity is observed, the investigators should determine whether to continue or terminate IBI305 or bevacizumab treatment according to the followings:

First occurrence:

IBI305 or bevacizumab administration should be interrupted until toxicity symptoms return to baseline level or are at least reduced to the Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or lower (except for the special circumstances listed below)

Note that when Grade 4 febrile neutropenia and/or thrombocytopenia occur(s), IBI305 or bevacizumab administration should be interrupted until the symptoms return to baseline levels or at least reduced to CTCAE Grade 1 or lower, since these events increase the risk of hemorrhage.

Re-occurrence in re-administration:

If Grade 3 IBI305- or bevacizumab-related toxicity occurs again, the investigator should assess the risk/benefit of study drug continuation for the subject. If such toxicity re-occurs again after re-administration, IBI305 or bevacizumab should be permanently discontinued

If Grade 4 IBI305- or bevacizumab-related toxicity occurs again, IBI305 or bevacizumab should be permanently discontinued

Measures should be taken in the following special circumstances (classified based on CTCAE version 4.03):

Hemorrhage

Subjects with Grade 3 or 4 hemorrhages should be treated accordingly and permanently discontinue the study treatment

Thrombosis/embolism

- Subjects with arterial thrombosis of any severity grades should permanently discontinue the study treatment
- Subjects with Grade 4 venous thrombosis should permanently discontinue the study treatment
- Subjects with Grade 3 venous thrombosis should interrupt the study treatment. If the anticoagulant therapy at the planned therapeutic dose is < 2 weeks, the study treatment should be interrupted until the anticoagulant therapy is completed. If the anticoagulant therapy at the planned therapeutic dose is > 2 weeks, IBI305 or bevacizumab administration should be interrupted for 2 weeks, and the study treatment can be restarted during the anticoagulant therapy if the following criteria are met:
  - INR is within the target range (usually 2-3) prior to restarting of study treatment
  - Subjects must not have experienced Grade 3 or 4 hemorrhage since enrollment
  - No signs of great vessel invasion or adjacency to great vessels from previous tumor assessments

  Note: Therapeutic dose of anticoagulant therapy is defined as the escalating dose of warfarin or other anticogulants until INR is maintained at no less than 1.5 (usually

2-3). The warfarin dose should be documented in the eCRFs, and the INR of subjects receiving anticoagulant therapy should be monitored during the treatment.

Hypertension

BP should be measured frequently to monitor the occurrence and exacerbation of hypertension. Subjects should remain at resting position for at least 5 min before BP measurement.

Grade 1 hypertension: Asymptomatic transient (< 24 h) increase in BP (> 20 mmHg diastolic blood pressure), or > 150/100 mmHg in this measurement, but previous BP was within normal range. No interventions are required.

Grade 2 hypertension: Repeated or sustained (> 24 h) or symptomatic BP increase (> 20 mmHg diastolic blood pressure), or > 150/100 mmHg in this measurement, but previous BP was within normal range. One antihypertensive drug can be used. Once BP is lowered to < 150/100 mmHg, the subject may continue the study treatment.

Grade 3 hypertension: Requires more than one antihypertensive drugs or more potent treatment. Study treatment should be interrupted in case of persistent or symptomatic hypertension; study treatment should be permanently discontinued for uncontrollable hypertension.

Grade 4 hypertension: Life-threatening (i.e. hypertensive crisis). The study treatment should be permanently discontinued in case of Grade 4 hypertension. The dose of all antihypertensive agents used should be documented during each visit.

The dose of antihypertensive agents used should be documented during each visit. If the subject remains hypertensive despite treatment discontinuation, BP and antihypertensive agents used should be monitored every 3 months until BP returns to normal or end of study.

Reversible posterior leukoencephalopathy syndrome (RPLS)

There have been a few reports with signs and symptoms consist with RPLS after study treatment. RPLS is a rare neurological disease and its signs and symptoms include epilepsy, headache, altered mental status, visual impairment, or cortical blindness, with or without hypertension. Subjects with RPLS should permanently discontinue the study treatment.

Proteinuria

Urinalysis dipstick test should be performed prior to each IBI305 or bevacizumab infusion unless 24-h proteinuria test has already been performed.

First occurrence of proteinuria:

The urinalysis dipstick test should be performed if:

Urine protein is < 2+, continue study treatment as scheduled, no additional tests are required.

Urine protein is ≥ 2+ (strip test), continue study treatment as scheduled, and a 24-h urine protein test should be performed within 3 days prior to the next treatment cycle:

- If 24-h urine protein is < 2 g, continue study treatment as scheduled, and perform urinalysis dipstick test before each scheduled dose.
- If 24-h urine protein is > 2 g, the current study treatment is interrupted, and a 24-h urine protein test should be performed within 3 days prior to the next planned dose. Study treatment is delayed until 24-h urine protein is ≤ 2 g, and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24-h urine protein is > 2 g.

Second and subsequent occurrence of proteinuria:

< 3+ (strip test): continue study treatment as scheduled, no additional tests are required.

Urine protein is ≥ 3+ (strip test), continue study treatment as scheduled, and a 24-h urine protein test should be performed within 3 days prior to the next treatment cycle:

- If 24-h urine protein ≤ 2 g, continue study treatment as scheduled.
- If 24-h urine protein is > 2 g, the current study treatment is interrupted, and a 24-h urine protein test should be performed within 3 days prior to the next planned dose. Study treatment is delayed until 24-h urine protein is ≤ 2 g, and a 24-h urine protein test prior to each subsequent dose is performed until urine protein is reduced to ≤ 1 g/24 h. Interrupt study treatment only when 24-h urine protein is > 2 g.

Nephrotic syndrome (Grade 4): Study treatment is permanently discontinued

Gastrointestinal perforation

If gastrointestinal perforation occurs, appropriate measures should be taken and the study treatment should be permanently discontinued.

Wound healing complications

The study treatment should not begin within 28 d after a major surgery, or before the surgical

wound is fully healed. If a complication of wound healing occurs during study treatment, the study treatment should be interrupted until the wound is fully healed. If an elective surgery is required, the study treatment should be interrupted.

Abdominal abscess or fistula

If abdominal abscess or fistula occurs, the study treatment should be discontinued. However, the investigator will determine whether study treatment will be continued if the above AE is resolved.

Infusion-related and allergic reactions:

Infusion-related reactions after first dose of the study drug is uncommon (< 3%), and the incidence of a severe reaction is only 0.2%.

If a mild (grade 1 or 2) reaction (such as fever, chills, headache, and nausea) occurs, pretreatment prior to subsequent administration should be performed and infusion time should not be reduced. If the subject is well-tolerated during infusion after pretreatment, the infusion time can be reduced by 30 minutes (+10 minutes) for subsequent administration with pretreatment. If an infusion-related AE occurs during a 60-minute infusion, the subsequent infusion should be completed within 90 minutes (+15 minutes) with pretreatment. Likewise, if an infusion-related AE occurs during a 30-minute infusion, the subsequent infusion should be completed in 60 minutes (+10 minutes) with pretreatment. If a subject has a grade 3 infusion-related reaction, the study treatment should be interrupted and not be restarted on the same day. However, since there lacks the dose adjustment method for grade 3 infusion-related reactions, the investigators may decide to either discontinue the study drug or perform pretreatment, and complete the infusion within 90 minutes (+15 minutes). If an adverse reaction still occurs during a 90-minute infusion, the infusion should be continued at a slower rate and then gradually returned to a 90-minute infusion. If the investigator is uncertain about the handling, the study treatment should be discontinued. When the study treatment is restarted, the subject should be closely monitored based on routine clinical practice until the possible time of adverse reaction has passed. If a subject has a grade 4 infusion-related reaction, the study treatment should be discontinued.

An allergic reaction is defined as the vascular collapse or shock (systolic BP < 90 mmHg, unresponsive to rehydration) that occurs within 30 minutes of a study drug infusion caused by an allergy, with or without respiratory distress. Skin reactions include pruritus, urticaria, and angioedema. Subjects with allergic reactions should discontinue the study treatment.

5.3.3 Dose adjustments of chemotherapy

Paclitaxel and carboplatin should be administered according to the study site guidelines and local prescribing information. For the specific information for use, preparation, and storage of paclitaxel and carboplatin, refer to the prescribing information and local dosing information. Carboplatin-based chemotherapies have a relatively high incidence of emesis. Therefore, antiemetics for prophylaxis can be used.

Hematological toxicity:

Absolute neutrophil count (ANC; dose can only be reduced when febrile neutropenia occurs. ANC must be $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L on D1 of each treatment cycle)

Table 14. Dose adjustments of paclitaxel and carboplatin (febrile neutropenia)

	Dose Adjustments of Paclitaxel/Carboplatin ANC (D1 of each treatment cycle)	
	< 1.5 x 10^9/L	≥ 1.5 x 10^9/L
Febrile neutropenia (regardless of duration)	0	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5

Platelet count:

Table 15. Dose adjustments of paclitaxel and carboplatin (thrombocytopenia)

	Dose Adjustments of Paclitaxel/Carboplatin Platelet count (D1 of each treatment cycle)	
Lowest Level After Last Dose	< 100 x 10^9/L	≥ 100 x 10^9/L
< 25 × 10^9/L or < 50 × 10^9/L with hemorrhage or requires blood transfusion	0	Paclitaxel = 150 mg/m^2 Carboplatin = AUC 4.5

Once the chemotherapeutic dose is reduced due to febrile neutropenia or thrombocytopenia (platelet count < 25 × 10^9/L or < 50 × 10^9/L with hemorrhage or blood transfusion required), the original dose should no longer be adopted. If dose reduction is required due to another incident of febrile neutropenia or thrombocytopenia, the dose of paclitaxel and carboplatin will be reduced to 100 mg/m^2 and AUC 3.0, respectively. If the dose reduction is required for the third time, the chemotherapy should be immediately discontinued.

If the dose adjustment is required when ANC and thrombocytopenia occur concurrently, the low-dose chemotherapy should be adopted.

Chemotherapy may be delayed for up to 3 weeks. If after the chemotherapy has been delayed for 3 weeks, ANC does not reach ≥ 1.5 × 10^9/L and platelet count does not reach ≥ 100 × 10^9/L on D1 of the scheduled chemotherapy, the chemotherapy should be permanently discontinued. If the above values have been reached, the next course of chemotherapy should be continued.

The investigator should monitor the subject closely for toxicity with particular attention to early and evident signs of myelosuppression, infection, or febrile neutropenia to timely and appropriately treat the complications.

Subjects should be informed to pay attention to these signs and receive treatment as soon as possible.

If the chemotherapy must be interrupted due to hematological toxicity, the complete blood count should be performed regularly (including WBC differentials) until all the counts reach the minimum requirements for treatment continuation. Thereafter the scheduled treatment plan will be performed.

Dose adjustments are not required for anemia. However, treatment based on guidelines of each clinic should be performed.

Gastrointestinal toxicity

Antiemetics will be used to control nausea and/or emesis. If grade 3 or 4 nausea and/or emesis occur(s) despite of antiemetics, the chemotherapeutic dose should be reduced by 20% for the next treatment cycle. The dose should be returned to the initial level as possible if the subject is tolerated.

If the subject experiences stomatitis on D1 of any treatment cycle, the chemotherapy should be interrupted until the symptoms resolve. If the stomatitis has not resolved after 3 weeks, the chemotherapy should be permanently discontinued (refer to CTCAE version 4.03). If an acute Grade 3 stomatitis occurs, the chemotherapeutic dose should be reduced to 75% of the proposed dose when symptoms resolve.

Hepatotoxicity (Paclitaxel)

The paclitaxel dose should be determined based on the lab values measured on D1 of each treatment cycle.

Table 16. Dose adjustment of paclitaxel (hepatotoxicity)

AST		Bilirubin	Paclitaxel Dose
≤ 5 x UNL	and	WNL	175 mg/m^2
> 5 x UNL	or	> UNL ~ 1.5 x UN	150 mg/m
		> 1.5 x UN	0

If paclitaxel is interrupted due to hepatotoxicity, carboplatin should also be interrupted until paclitaxel is restarted. Paclitaxel will be interrupted for up to 3 weeks. If the subject's hepatic function does not return to the acceptable ranges in 3 weeks, paclitaxel should be permanently discontinued. The carboplatin dose will not be adjusted when hepatotoxicity occurs.

The investigators should avoid PD due to abnormal hepatic enzyme levels as possible. If PD occurs, all the study drugs should be permanently discontinued, including chemotherapy.

Cardiovascular toxicity (paclitaxel)

The arrhythmia in subjects was infrequent in previous clinical studies. However, most subjects were asymptomatic and electrocardiographic monitoring was not required. Asymptomatic transient bradycardia was observed in 29% of subjects, but significant atrioventricular block was rare. Cardiac events should be treated as follows:

Asymptomatic bradycardia: no intervention indicated

Symptomatic arrhythmia during infusion: Discontinue paclitaxel infusion and perform routine treatment of arrhythmia. Discontinue subsequent paclitaxel treatment. Document this AE in the AE Report Form of eCRF.

Chest pain and/or symptomatic hypotension (< 90/60 mmHg or rehydration therapy required): discontinue the paclitaxel infusion. Perform electrocardiography (ECG). If hypersensitivity reaction is suspected, administer diphenhydramine and dexamethasone via intravenous infusion. If the chest pain is not considered as cardiogenic, epinephrine or bronchodilators will be administered. Document this AE in the AE Report Form of eCRF. Discontinue subsequent paclitaxel treatment and provide symptomatic treatment. Consult a cardiologist if needed.

Neurotoxicity (paclitaxel)

The dose of paclitaxel should be adjusted according to Table when neuropathy occurs. The dose adjustment of carboplatin is not needed when neurotoxicity occurs.

Table 17. Dose adjustment of paclitaxel (neurotoxicity)

Toxicity Grade (CTCAE version 4.03)	Paclitaxel dose adjustment
Grade 1 or below	175 mg/m^2
2	Interrupt treatment until return to grade 1, then reduce dose to 140 mg/m^2 (20% of reduction) and restart infusion
Grade 3 or above	Interrupt treatment until return to grade 1, then reduce dose to 125 mg/m^2 (30% of reduction) and restart infusion.

Once the dose is reduced due to neurotoxicity, the original dose should no longer be adopted.

If the neurotoxicity does not return to grade 1 after paclitaxel interruption for 3 weeks, paclitaxel should be permanently discontinued.

Allergic reactions/hypersensitivity reactions (paclitaxel)

Note: Prophylaxis for hypersensitivity reactions (see below) and close monitoring of vital signs are recommended for subjects with history of mild to moderate hypersensitivity reactions when hypersensitivity reactions reoccur.

Mild symptoms: complete paclitaxel infusion. Close monitoring; no treatment indicated.

Moderate symptoms: Interrupt paclitaxel infusion, administer diphenhydramine 25–50 mg and dexamethasone 10 mg via intravenous infusion. Once symptoms have resolved, resume paclitaxel infusion at a slower rate (20 mL/hour for 15 minutes, then at 40 mL/hour for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete). Document this AE in the AE Report Form of eCRF. If symptoms reoccur, interrupt the paclitaxel infusion and permanently discontinue subsequent paclitaxel infusion.

Severe and life-threatening symptoms: Interrupt paclitaxel infusion, administer diphenhydramine and dexamethasone via intravenous infusion (as above). Use epinephrine or bronchodilators if indicated. Document this AE in the AE Report Form of eCRF. Subsequent courses of paclitaxel infusion should be permanently discontinued.

Moderate or severe hypersensitivity reactions should be documented as AEs.

Other toxicities

If other unmentioned grade 3–4 toxicities occur, the chemotherapy should be interrupted until symptoms resolve or return to grade 1. Thereafter restart the infusion at 50% of the original dose (which should no longer be adopted). If the toxicity does not return to grade 1 after an interruption for 3 weeks, the chemotherapy should be permanently discontinued. Dose adjustments are not recommended for grade 1 and 2 toxicities.

Investigator should closely monitor toxicities in subjects during chemotherapy. Before the start of next chemotherapy cycle, the laboratory test results must be:

- ANC $\geq 1.5 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Serum creatinine $< 1.5 \times$ ULN

- Bilirubin ≤ 1.5 × ULN
- ALT and AST ≤ 2.5 × ULN; ALT and AST < 5 × ULN in subjects with liver metastasis

5.4 Study Drug Properties

IBI305 is a bevacizumab biosimilar. The active ingredient of both drugs is recombinant humanized anti-VEGF monoclonal antibody; Bevacizumab is the standard commercially available drug, provided by the sponsor.

Detailed information on the study drugs is shown in Table .

Table 18. Study drugs

Study Drugs	Dosage Form and Strength	Excipient	Appearance	Manufacturer
IBI305	4 mL: 100 mg	Sodium acetate, sorbitol, and polysorbate 80	Sterile solution for intravenous injection pH 5.2 Clear, colorless liquid, no foreign matters, no floc or precipitation	Innovent Biologics (Suzhou) Co., Ltd.
Bevacizumab	4 mL: 100 mg	α,α-trehalose dihydrate, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate, polysorbate 20, and sterile water for injection	Sterile solution for intravenous injection pH 5.9–6.3 Clear to slight opalescent, colorless to light brown	Roche Pharma (Schweiz) Ltd.

5.5 Preparation and Distribution

IBI305 or bevacizumab is diluted in 0.9% sodium chloride solution by the pharmacist or research nurse before infusion. Check the particles and discoloration prior to administration.

The investigator should ensure that the pharmacist or research nurse administers the study drugs according to study protocol.

5.6 Packaging, Labeling, and Storage

The sponsor should package and label the study drugs according to appropriate local regulations.

All study drugs (IBI305 and bevacizumab) must be stored at 2–8 °C away from light. The study drugs should be stored in a safe zone only accessible by authorized staff prior to dispensation to the subjects.

5.7 Subjects Allocation

After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in the Interactive Web Response System (IWRS) and enter the subject information into the IWRS. The IWRS will allocate a random number to the subject and provide a medication number. Stratified randomization is used in this study. Stratifying factors include age (< 60 vs. ≥ 60 years old) and EGFR status (wild vs. mutant type).

5.8 Blinding

This is a randomized, double-blind, and active-controlled study, and only relevant study personnel had access to the randomization numbers. A non-blinded pharmacist or research nurse will prepare the medications since IBI305 and bevacizumab do not have an identical appearance. The pharmacist or research nurse who is responsible for preparing the study drugs is not allowed to disclose any information regarding treatment allocation to the subject, the subject's family members, or other personnel including the physician and the relevant study staff.

Unblinding: Subject unblinding should only be performed after database locking.

Emergency unblinding: In case of an emergency where the investigator must know the medication given to a particular subject, the investigator will unblind the subject via the IWRS and immediately inform the sponsor and CRO. The reasons for unblinding, date, and outcomes should be documented in the source document and eCRF of the subject.

5.9 Concomitant Medications and Treatments

All medications except for the study drugs, including other chemotherapies not specified in the study, Chinese herbal medicines, and other non-traditional therapies, are considered concomitant medications. All concomitant medications used within 30 days prior to screening should be documented in the eCRFs, including the information of generic name, route of administration, start date, end date, and indication.

5.9.1 Prohibited medications

No other anti-tumor therapies or medications with anti-tumor indications, including Chinese herbal medicine, radiotherapy, or other investigational drugs, are allowed during this study other than IBI305, bevacizumab, paclitaxel, and carboplatin.

Severe myelosuppression is possible after chemotherapy. Granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are not allowed to be used prophylactically in the first treatment cycle.

5.9.2 Medications allowed

Prophylactic use of anti-emetics, glucocorticoids, or other treatments targeting toxicities is permitted during the study. Unconventional treatments (such as acupuncture) and vitamins/microelements are permitted if their use does not affect the study endpoints as determined by the investigators.

Starting from the 2nd chemotherapy cycle, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor are allowed to be used prophylactically to prevent severe myelosuppression.

5.9.3 Treatment after study treatment

Subsequent therapy after the end of study treatment should be determined by the subject's attending doctor.

5.10 Treatment Compliance

The dosage and dosing time of IBI305 or bevacizumab and paclitaxel + carboplatin in each treatment cycle should be documented in the eCRFs. Reasons for dosing delay, dose reduction or missed dossing should also be documented in the eCRFs.

Treatment and protocol compliance refers to the subject's voluntary compliance with each aspect of the protocol, including compliance with blood collection for safety evaluation and imaging examination for tumor assessment. If a subject does not return for the scheduled follow-up visits, his/her participation in the study may be terminated based on the opinions of the primary investigator or sponsor.

5.11 Study Drug Count

The investigator, other relevant stuff, or authorized pharmacists should document the receipt and distribution of study drugs on the study drug count table and ensure that the table is readily available for inspection.

The study drugs are only for the use of study subjects. At the end of the trial, all study drugs should be counted and explanations for deviations should be provided in a written document. The investigator shall count all unused study drugs and packaging materials, and return them to the sponsor or the designated third party. Used empty drug bottles/bags will be destroyed on-site according to the institutional standards.

6 STUDY PROCEDURE

The detailed procedures of this study are shown in Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

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6.1 Screening Visits (D -28 to D -1)

Complete the screening visits within 28 days prior to study treatment commencement. The following procedures must be completed during screening to ensure that subject meets the requirements for participating in this study:

- Sign the ICF
- Record the demographics, including age, ethnicity, and gender
- Record the past medical history, including smoking history
- Record the history of anti-tumor therapies
- Record the concomitant medications (within 30 days prior to screening)
- Record the vital signs
- Measure the height and weight (including BMI)
- ECOG score
- Physical examination
- 12-Lead ECG
- Hepatitis B panel, anti-HCV, anti-HIV, and syphilis tests
- Clinical laboratory tests (routine blood test, coagulation test, blood chemistry, and urinalysis)

- Blood pregnancy test (for female subjects of childbearing age only)
- Imaging examinations (CT or MRI: Head, chest, abdomen, and pelvis cavity)*
- EGFR test#
- Review the inclusion/exclusion criteria
- Record the AEs

* Retests are not required if the tests have been performed within 28 days prior to the first dose, unless the investigators suspect changes in tumor burden. Imaging results during screening will be used as the baseline data. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

If the subject has been tested for EGFR of tumor sample at the study site with documentation, the subject will not be required for retest.

6.2 Baseline Visits (D1 of cycle 1)

D1 refers to the day of receiving the first dose of the study drugs. Eligible subjects meeting the inclusion criteria will return to the study site and complete the following procedures:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests * (routine blood test, blood chemistry, and urinalysis)
- Immunogenicity test (ADAs and neutralizing antibodies)
- Confirm the inclusion/exclusion criteria
- Record the AEs and concomitant medications

* If clinical laboratory screening tests (routine blood test, blood chemistry, urinalysis) are performed within 7 days prior to the first dose, then the results of the screening test can be used as baseline.

If the subject meets the inclusion criteria, the following procedures should be complete:

- Randomization and grouping
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)

- Record the AEs and concomitant medications

6.3 Cycle 2 (week 4 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.4 Cycle 3 (week 7 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.5 Cycle 4 (week 10 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug.

Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Immunogenicity test
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.6 Cycle 5 (week 13 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.7 Cycle 6 (week 16 ± 3 days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs

- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Chemotherapeutic drug infusion (paclitaxel + carboplatin)
- Record the AEs and concomitant medications

6.8 Cycle 7 and Subsequent Treatment Cycles (±3 Days)

Subjects should return to the study site 3 weeks (±3 days) after the last infusion of the study drug. Monotherapy will start from week 7 and the dose of study drug will be adjusted to 7.5 mg/kg. Subjects should complete the following procedures during each visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Study drug infusion (IBI305 or bevacizumab)
- Record the AEs and concomitant medications

Imaging tests (CT or MRI) should be done every 6 weeks (±7 days), and tumor assessment should be completed within 7 days prior to this visit to determine whether the study treatment should be continued.

6.9 End-Of-Treatment Visit

The end of treatment visit in study sites will be conducted in 28 days (±7 days) after the last dose of study drug. Subjects should complete the following procedures during this visit:

- Record the vital signs
- Measure the weight
- Physical examination
- Clinical laboratory tests (routine blood test, blood chemistry, and urinalysis)
- Immunogenicity test

- ☑ Blood pregnancy test (for female subjects of childbearing age only)
- ☑ Tumor assessment (CT or MRI, completed within 7 days prior to this visit; not required to be repeated if it has been performed within 6 weeks prior to this visit)
- ☑ Subsequent anti-tumor therapy
- ☑ Record the AEs and concomitant medications

If the subject has not experienced PD, the subsequent follow-up for PD will be performed (Section 6.10). If the subject has experienced PD, the subsequent follow-up for survival will be performed (Section 6.11).

6.10 Disease Progression Visit

If the study drugs are discontinued for reasons other than PD, the end of treatment visit in study sites will be conducted in 28 days after the last dose of study drug, and tumor assessments should be conducted every 6 weeks (±7 days) until PD if possible (after which, follow-up for survival will be conducted [Section 6.11]), withdraw of informed consent, loss to follow-up, death, start of other anti-tumor therapies, or end of study. During the visit, vital signs and weight measurements will be performed, and any subsequent anti-tumor therapies will be documented.

6.11 Survival Follow-Up

The investigator will make telephone follow-up every 12 weeks (±7 days) to collect the information of subsequent anti-tumor therapies and survival until withdrawal of informed consent, loss to follow-up, death, or end of study.

6.12 Study Completion

Completion of this clinical study is defined as 18 months after the enrollment of the last subject. If the subjects continue to receive the study drug treatment before this cut-off time, the treatment should be discontinued and the end of treatment visit should be completed (Section 6.9).

6.13 Tumor Assessment

Imaging tests (CT or MRI) of the brain, chest, abdomen, and pelvis are required at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test was used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

The investigator should perform a tumor assessment based on RECIST v1.1 (Section 13.3) prior to each dose to determine whether the subject should continue with the next round of treatment. An independent review committee will also assess the tumor response (Section 11.1.1). Imaging tests will not be rescheduled if the study drugs or chemotherapeutic agents are interrupted due to toxicities. Every effort should be made to continue the schedule for imaging tests even for subjects who discontinue one or two study treatment(s) due to drug-related toxicities.

If subject experience PD according to the RECIST v 1.1 criteria, the attending doctor should discuss with the subject regarding subsequent routine cancer therapies.

6.14 Clinical Laboratory Evaluations

Clinical laboratory tests will be conducted at the laboratories of each study site. Sample collection and analysis should be performed according to the requirements of each laboratory.

The following laboratory tests should be conducted according to the study procedures (Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel +		x	x	x	x	x	x				

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
carboplatin) [k]											
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

):

Routine blood test: hemoglobin, hematocrit, WBC and differentials (including absolute neutrophil and lymphocyte counts), platelets, and RBC

Routine coagulation test (baseline test): INR, aPTT, and PTT

- ➢ Blood chemistry: Creatinine, blood urea nitrogen, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting blood glucose, sodium, potassium, chloride, calcium, phosphorus, and magnesium
- ➢ Urinalysis: Specific gravity, pH, glucose, protein, occult blood, and leukocytes
- ➢ Pregnancy test: Serum pregnancy tests are performed on women of childbearing age during screening and the end-of-treatment visit.

These tests are carried out at the laboratory of each trial site.

For subsequent visits, all laboratory tests need to be completed within 3 days prior to the administration. During the study, the frequency of these laboratory tests will be increased if safety is a concern. The investigator should review the laboratory test results throughout the study to determine whether the results are clinically significant. The investigator should assess the changes in laboratory test results. If the investigator considers a laboratory test result to be abnormal and of clinical significance, it is considered as an AE.

6.15 Vital Signs, Physical Examinations, and Other Safety Assessments

6.15.1 Vital signs

Vital signs include pulse, BP, temperature, and respiratory rate. The subject must rest for at least 5 minutes prior to each vital sign assessment.

Vital signs will be assessed according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or		x	x	x	x	x	x	x			

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
bevacizumab) [j]											
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

). During the study, the investigator may increase the frequency of vital sign measurement if safety is a concern.

6.15.2 Height and weight

Height is only measured during screening. Weight is measure during each visit.

6.1.5.3 Physical examinations

The following organs/systems will be examined according to the Schedule of Activities (Table 1. Schedule of follow-up visits

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history	x										

Stage	Screening period	Treatment period (21-day cycles)							After treatment		
		Combination treatment period						Maintenance therapy	End-of-treatment visit (28 days after last dose)	PD follow-up[a]	Survival follow-up[b] (Once every 12 weeks after PD)
Cycle (C) and day (D)	D-28 to D1	C1D1	C2D1	C3D1	C4D1	C5D1	C6D1	Cycle 7 to end-of-treatment			
Time window (day)	-	-	±3	±3	±3	±3	±3	±3	±7	-	±7
Visit	1	2	3	4	5	6	7	8-N			
(including smoking history)											
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		x	x	x	x	x	x			
Routine blood test [d]	x	x	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry [d]	x	x	x	x	x	x	x	x	x		
Urinalysis [d]	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test [f]	x								x		
Immunogenicity [g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI) [h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing [i]	x										
Randomization		x									
Study drug administration (IBI305 or bevacizumab) [j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin) [k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
Aes	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x
Pharmacokinetic (PK)		x	x		x	x	x				
VEGF testing		x	x				x		x		

): general condition, head (eyes, ears, nose, and throat), neck and thyroid, respiratory system, cardiovascular system, abdomen, nervous system, skeletal muscles and limbs, as well as

lymphatic system and skin.

6.15.4 12-Lead ECG

The subject will undergo a 12-lead ECG during screening, and also during the course of the study if deemed necessary by the investigator.

The following ECG parameters should be documented: HR, PR-interval, QRS-complex, QT-interval, and QTc-interval. The subject must be in the supine position for at least 5 minutes prior to undergoing the 12-lead ECG. All ECG are evaluated by qualified physicians. All clinically significant abnormal findings should be reported as AEs.

6.15.5 Immunogenicity assessment

Blood samples are collected before the first dose, on D1 of Cycle 4, and during the end-of-treatment visit for immunogenicity assessment including testing of anti-drug antibodies and neutralizing antibodies. Immunogenicity testing will be carried out at the relevant central laboratory. Details regarding sample collection, processing, labeling, storage, transport, and analysis are provided in the Central Laboratory Manual.

6.15.6 EGFR testing

All subjects should undergo tumor tissue EGFR testing during screening at the laboratory of each trial site (The test does not need to be repeated if it can be confirmed with relevant reports that the test has already been completed at the trial site).

Table 19. Schedule of follow-up visits

Item	Screening period	Combination treatment period						Monotherapy period	After treatment		
Time point	**D-28 to D-1**	**Cycle 1 (D1)**	**Cycle 2 (±3 days)**	**Cycle 3 (±3 days)**	**Cycle 4 (±3 days)**	**Cycle 5 (±3 days)**	**Cycle 6 (±3 days)**	**Cycle 7 to end-of-treatment (3 weeks/cycle [±3 days])**	**End-of-treatment visit (28 ± 7 days)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks [±7 days] after PD)**
Informed consent	x										
Inclusion/exclusion criteria assessment	x	x									
Demographics	x										
Medical history (including smoking history)	x										
NSCLC treatment history	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	
Height and weight	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	
ECOG score	x										

Item	Screening period	Combination treatment period						Monotherapy period	After treatment		
Time point	**D-28 to D-1**	**Cycle 1 (D1)**	**Cycle 2 (±3 days)**	**Cycle 3 (±3 days)**	**Cycle 4 (±3 days)**	**Cycle 5 (±3 days)**	**Cycle 6 (±3 days)**	**Cycle 7 to end-of-treatment (3 weeks/cycle [±3 days])**	**End-of-treatment visit (28 ± 7 days)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks [±7 days] after PD)**
Physical examination	x	x	x	x	x	x	x	x	x		
12-Lead ECG	x		If clinically indicated								
Routine blood test	x	x[d]	x	x	x	x	x	x	x		
Coagulation test	x										
Blood chemistry	x	x[d]	x	x	x	x	x	x	x		
Urinalysis	x	x[d,e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]		
Pregnancy test[f]	x								x		
Immunogenicity[g]		x			x				x		
HBV, HCV, HIV, and syphilis testing	x										
Imaging assessment (CT or MRI)[h]	x			x		x		x	x	x	
Tumor specimen collection for EGFR testing[i]	x										

Item	Screening period	Combination treatment period						Monotherapy period	After treatment		
Time point	**D-28 to D-1**	**Cycle 1 (D1)**	**Cycle 2 (±3 days)**	**Cycle 3 (±3 days)**	**Cycle 4 (±3 days)**	**Cycle 5 (±3 days)**	**Cycle 6 (±3 days)**	**Cycle 7 to end-of-treatment (3 weeks/cycle [±3 days])**	**End-of-treatment visit (28 ± 7 days)**	**PD follow-up[a]**	**Survival follow-up[b] (Once every 12 weeks [±7 days] after PD)**
Randomization		x									
Study drug administration (IBI305 or bevacizumab)[j]		x	x	x	x	x	x	x			
Chemotherapy (paclitaxel + carboplatin)[k]		x	x	x	x	x	x				
Concomitant medications	x	x	x	x	x	x	x	x	x		
AEs	x	x	x	x	x	x	x	x	x		
Subsequent anti-tumor therapy									x	x	x
Survival follow-up									x	x	x

a. After completing the on-site end-of-treatment visit 28 days after the last dose, subjects who discontinue the investigational drug treatment due to reasons other than PD should continue to undergo tumor assessments once every 6 weeks (±7 days) until PD (and begin post-PD follow-up thereafter), withdrawal of consent, start of another antineoplastic treatment, loss to follow-up, death, or study completion.

b. For subjects with PD, collect survival information once every 12 weeks (84 days, ±7 days) by phone until death, loss to follow-up, withdrawal of informed consent, or study completion. Subsequent antineoplastic treatments should be documented in the eCRF.

c. Only measure weight.

d. Clinical laboratory tests are carried out at the laboratory of each hospital. If screening laboratory tests (routine blood test, blood chemistry, and urinalysis) are performed within 7 days prior to the first dose, the screening results may be used as baseline data. For subsequent visits, all laboratory tests have to be completed within 3 days prior to the dose administration.

e. Prior to each IBI305/bevacizumab infusion, test paper should be used to examine urinary protein.

f. Women of childbearing age should undergo serum pregnancy tests.

g. Immunogenicity testing (for anti-drug antibodies and neutralizing antibodies) is performed at the central laboratory.

h. Image assessments (CT or MRI) of the brain, chest, abdomen, and pelvis should be completed at baseline. If these tests are performed within 28 days prior to the first dose of the study drug, they do not need to be repeated unless the investigator believes that there have been changes in the subject's tumor burden. After the start of treatment, imaging tests are performed once every 6 weeks (±7 days) and have to be completed within 7 days prior to the scheduled visits, until progressive disease, start of other treatment, withdrawal of informed consent, loss to follow-up, death, or study completion. The same method of imaging test is used at baseline and during follow-up. Imaging evaluations of the chest, abdomen, and pelvis are required.

i. All subjects should undergo tumor tissue EGFR testing, but the test does not need to be repeated if it can be confirmed with relevant reports that the test has already been completed at the trial site. EGFR testing will be carried out at the laboratory of each trial site.

j. Each treatment cycle for the investigational drug is 3 weeks long. IBI305 or bevacizumab is administered on D1 of each cycle, at 15 mg/kg during combination treatment with chemotherapy and 7.5 mg/kg during monotherapy, until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, death, or study completion, whichever occurs first. After all assessments are completed, the study drug is administered followed by chemotherapy.

k. Each treatment cycle is 3 weeks long. Chemotherapy (paclitaxel + carboplatin) is administered on D1 of each cycle for up to 6 cycles, or until disease progression (PD), unacceptable toxicity, withdrawal of informed consent, loss to follow-up, or death. Paclitaxel is administered after the infusion of study drug is completed, followed by carboplatin.

7 STUDY ASSESSMENTS

7.1 Efficacy Assessment

7.1.1 Primary efficacy endpoint

- Objective response rate (ORR)

ORR will be assessed using RECIST v1.1. ORR is defined as the proportion of subjects whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved complete response (CR) and partial response (PR). The cutoff date for the primary efficacy endpoint analysis of this study is 6 months after subject randomization.

7.1.2 Secondary efficacy endpoints

- Duration of response (DOR)
- Progression-free survival (PFS)
- Disease control rate (DCR)
- Overall survival (OS)

Each endpoint will be assessed using RECIST v1.1.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death before PD; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

PFS is defined as the time from the date of randomization to the date of PD or death; Subjects who do not progress or die will be censored on the date of the last tumor assessment.

DCR is defined as the proportion of patients whose tumor volume has reduced to a predetermined value for a minimum time limit, including patients who achieved CR, PR, and SD.

OS is defined as the time from the date of randomization to the date of death of any cause. For subjects that are alive on the date of study completion or are lost to follow-up, their survival time will be censored at the date of last contact.

7.2 Safety Assessments

7.2.1 Adverse events

7.2.1.1 Definition

AEs

An adverse event is defined as any untoward medical occurrence suffered by the subject of the clinical research, which does not necessarily have a causal relationship with the treatment.
An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational drug, whether or not considered related to the investigational drug.

Serious adverse event

A serious adverse event does not necessarily have a causal relationship with the investigational drug. It refers to any untoward medical occurrence that (at any dose of the investigational drug):

(1) Results in death.

(2) Is life-threatening (The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it is more severe).

(3) Requires inpatient hospitalization or prolongation of existing hospitalization: This does not include hospitalization and/or surgical procedures scheduled to be conducted prior to or during the study for a disease or disorder that exists prior to study enrollment and has not worsened during the course of the study.

(4) Results in permanent or severe disability/incapacity.

(5) Results in congenital anomalies/birth defects.

(6) Other important medical events: Medical events that do not necessarily result in death, are not life-threatening, and do not require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the aboves outcomes, are also considered SAEs.

Note: Hospitalization as a result of PD is not considered an SAE.

Other Definitions

An adverse drug reaction (ADR) refers to any untoward response related to the investigational drug after receiving any dose.

An unexpected adverse drug reaction is any adverse reaction that is not consistent with information known about the investigational drug.

7.2.1.2 Severity of adverse events

The severity of AEs will be assessed by CTCAE 4.03. The classifications are as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (e.g. bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not bedridden)
- Grade 4 Life-threatening; urgent intervention indicated
- Grade 5 Death related to AE

7.2.1.3 Relationship between adverse events and the investigational drug

The relationship between the investigational drug and AE can be classified into five categories: definitely related, probably related, possibly related, unlikely related, and definitely unrelated. Specific assessment criteria are as follows:

Table 20. Assessment criteria for causality between an adverse event and the investigational drug

Parameters	Definitely related	Probably related	Possibly related	Unlikely related*	Definitely not related
Reasonable temporal relationship	Yes	Yes	Yes	Yes	No
Recognized pharmacological phenomenon	Yes	Yes	Yes	No	No
Positive dechallenge	Yes	Yes	Yes or No	Yes or No	No
Positive rechallenge	Yes	?**	?**	?**	No
Other alternative explanations	No	No	Yes	Yes	Yes

* Unlikely related = further observations required to make an assessment;
? ** Rechallenge not permitted due to ethical reasons.

7.2.1.4 Serious adverse event reporting

Any SAE that occurs during the trial should be reported in accordance with SAE reporting procedures of regulatory authorities or the ethics committee, regardless of whether the event is related to treatment.

The investigator should take the following measures:

- If necessary, take appropriate treatment measures immediately;
- Immediately (within 24 hours after becoming aware of the event or obtaining new information about the event) report the event to the sponsor's authorized representative responsible for relevant safety information using a method approved by the sponsor;
- Document the SAE in the AE and SAE section of the eCRF as well as in the source documents;
- The investigator must immediately (within 24 hours) submit the signed and dated SAE Report to the independent ethics committee, NMPA (formerly CFDA), health administration department, and local drug administration authorities;
- Follow and document the course of the event, until the event resolves or returns to baselines levels, or becomes clinically stable.

In addition, the sponsor or its representative (such as CRO) should report the SAE to the corresponding regulatory agencies and other investigators in accordance with the requirements of regulatory agencies and local regulations.

7.2.1.5 Management and follow-up of adverse events

The investigator is responsible for providing appropriate medical treatment for all AEs (Indicate the actions taken, such as suspension/termination of the investigational drug, dose modification, drug therapy, etc.). When an AE occurs, the investigator should actively take appropriate measures to ensure the safety of the subject. All AEs observed from the signing of the ICF to the time specified in the protocol (Table 2) must be followed. Refer to Section 7.2.1.8 for the specific follow-up time.

The investigator should report any AE that occurs after the time specified in the protocol (Table 2) and is suspected of being related to the investigational drug to the sponsor.

7.2.1.6 Adverse events of special interest

The AESI for this study include:

- Hypertension

- Proteinuria
- Gastrointestinal perforation
- Hemorrhage (cerebral hemorrhage, hematuria, and upper gastrointestinal hemorrhage)
- Cardiotoxicity
- Thrombus

An AESI should also be reported as an SAE if the definition of SAE is met.

7.2.1.7 Pregnancy

Any pregnancy during the study, though not an SAE, must be reported using the Clinical Trial Pregnancy Report. To ensure subject safety, the investigator must submit the report to the sponsor or the sponsor's representative within 24 hours after becoming aware of the event. Pregnancies must be followed to determine the outcome (including early termination) and the condition of the mother and the baby. Complications and termination of pregnancy due to medical reasons should be reported as AE or SAE. A spontaneous abortion should be reported as an SAE.

The investigator should pay attention to any pregnancy-related SAE that occurs after study completion. Any SAE that the investigator believes may be related to the study treatment should be reported immediately to the sponsor.

7.2.1.8 Summary of adverse event collection, documentation, and reporting

All adverse events that occur from the signing of the ICF to the time specified in the protocol (Table 2) must be collected and documented in the AE page of the eCRF regardless of severity (all SAEs and non-serious AEs).

The investigator must fill out all the required information, including the description of the AE, start date, end date, severity, measures taken, outcome, seriousness, and causality with the investigational drug. Each AE should be documented separately.

Table 21. Reporting and follow-up of adverse events

	Reporting time limit	Visit time limit
AEs	From the signing of the ICF until 28 days after the last dose of the study treatment	Until resolution or 28 days after the last dose of the study treatment
Adverse events of special interest (AESIs)	From the signing of the ICF until 6 months after the last dose of the study treatment	Until resolution or 6 months after the last dose of the study treatment
Serious adverse event	From the signing of the ICF until 6 months after the last dose of the study treatment	Until resolution (treatment-related) or 6 months after the last dose of the study treatment (not treatment-related)
Pregnancy	From the first dose until 6 months after the last dose of the study treatment	Until the end of the event

8 STATISTICS

8.1 Sample Size Determination

It will require 200 subjects in each treatment group (400 in total) to demonstrate clinical equivalence between IBI305 + paclitaxel/carboplatin and bevacizumab + paclitaxel/carboplatin with more than 80% power.

The sample size is estimated based on the following assumptions:

- The actual difference in ORR between subjects in the IBI305 and bevacizumab arms is 0
- The ORR of subjects in the bevacizumab arm is about 54.4%
- The equivalence margin is (-15%, 15%)
- The significance level of the two one-side test is 0.05
- 1:1 randomization

Based on the above assumptions, 189 subjects are required for each treatment group (378 in total). The sample size is expanded to 200 subjects for each treatment group (400 in total) after taking dropouts into consideration. The sample size was estimated using PASS 2013.

8.2 Statistical Population

Intention-to-Treat (ITT): All randomized subjects who received the study treatment.

Full Analysis Set (FAS): All randomized subjects who received at least one dose of the study treatment. This dataset is used as the primary analysis set for efficacy assessment.

Per-Protocol (PP): Based on the FAS, subjects with the predetermined minimum drug exposure and without any predetermined major protocol deviations. This dataset is used as the secondary analysis set for efficacy assessment.

Safety set (SS): Includes all randomized subjects who received at least one dose of the study treatment and have safety evaluation data. This data set is used for the safety evaluation of this study.

Intention-to-Treat (ITT): All randomized subjects.

8.3 General Principles for Statistical Analyses

For continuous variables, descriptive statistics should include the count, mean, standard deviation, median, maximum, and minimum. For categorical variables, descriptive statistics will include the frequency as well as the absolute or relative percentage. Statistical analyses will be carried out using SAS 9.4.

8.4 Statistical Methods

8.4.1 Adjustments for covariates

Not applicable.

8.4.2 Managing dropouts and missing data

The analyses of primary and secondary endpoints will include data from dropouts. The management of missing data is described in the Statistical Analysis Plan.

8.4.3 Interim analysis

There is no interim analysis planned for this study.

8.4.4 Multi-center study

Since this is a multicenter study, the primary endpoint (ORR) will be listed according to study sites and treatment groups. However, individual equivalence analysis will not be conducted. Trial sites with fewer than 5 ITT subjects per treatment group will need to be combined for analysis. Details will be discussed in the data review meeting.

8.4.5 Multiple comparisons and adjustments to multiplicity

Not applicable.

8.5 Statistical Analyses

8.5.1 Subject distribution

Refer to Figure 1: Study design schematic for the schedule of activities. The number and percentage of patients who have completed or dropped out of the study (including the reason for dropouts such as loss to follow-up, AEs, and poor compliance) are summarized based on treatment groups.

The number and percentage of subjects in each analysis set are calculated based on treatment groups.

The number and percentage of protocol deviations are calculated based on treatment groups.

8.5.2 Demographics and other baseline characteristics

Demographic information such as age, height, sex, and weight, and other baseline characteristics such as disease history (including NSCLC diagnosis, staging, previous cancer treatment, and target and nontarget lesions) are summarized using descriptive statistics.

8.5.3 Compliance and drug exposure

The required dose and the actual dose must be documented in the eCRF. Subject compliance is calculated based on the ratio of the actual dose (number of doses) to the required dose (number of doses). Subject compliance is classified into the following categories: < 80%, 80–120%, and > 120%. The number and percentage of subjects in each category will be summarized.

8.5.4 Efficacy

The efficacy analysis will be based on the FAS. Results of the PP set will also be presented.

8.5.4.1 Primary efficacy endpoint

The primary objective of this study is to determine the clinical equivalence between IBI305 + paclitaxel/carboplatin and bevacizumab + paclitaxel/carboplatin for the treatment of advanced or relapsed non-squamous non-small cell lung cancer (NSCLC). The primary endpoint is objective response rate (ORR). ORR is defined as the incidence of patients with confirmed complete response (CR) or partial response (PR), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions. Subjects without tumor assessments beyond baseline will be considered unresponsive to treatment. Subjects qualified for the evaluation of CR or PR must have at least one measurable lesion according to RECIST v1.1. The evaluation of clinical equivalence will be based on the ORR provided by the independent review committee (IRC). Results provided by the investigator will be used for sensitivity analysis.

Clinical equivalence will be declared if the 90% confidence interval of the difference in ORR between IBI305 and bevacizumab groups falls within the preset margin of (-15%, 15%).
The ORR and corresponding 95% confidence interval of the two treatment groups, the ORR difference and the 90% confidence interval, as well as the ORR ratio between the two groups and the 90% confidence interval will be estimated using the generalized linear model (GLM, which includes treatment groups and stratification factors).

8.5.4.2 Secondary efficacy endpoints

The secondary endpoints for this study include DOR, DCR, progress-free survival (PFS), and overall survival (OS).

DCR is defined as the incidence of patients with confirmed complete response (CR), partial response (PR), and stable disease (SD), when a validated imaging method and RECIST v1.1 are used to evaluate target and non-target lesions.

DOR is defined as the time from initial tumor response (CR or PR) to PD or death; Subjects with CR or PR who do not progress or die will be censored on the date of the last tumor assessment.

OS refers to the time from the date of randomization to the date of death (of any cause). For subjects who are still alive at the time of the analysis, their survival time is censored on the last known alive date. PFS refers to the time from the date of randomization to the date of first documented PD or death, whichever occurs first. The investigator will assess PD using RECIST v1.1. Subjects who do not progress or die will be censored on the date of the last tumor assessment. Subjects without tumor assessments after baseline are censored on their date of randomization.

Median OS and its 95% CI will be estimated using the Kaplan-Meier method. The survival curve will be plotted. The hazard ratio (HR) between the two groups and its 95% CI will be estimated using a Cox model. The Cox model includes treatment groups and stratification factors. DOR and PFS will be analyzed using the same method as for OS. DCR will be analyzed using the same method for primary efficacy endpoints, but an equivalence test will not be conducted.

8.5.4.3 Sensitivity analysis

The center effect (fixed or random) will be considered in the primary and secondary endpoints analysis models (GLM or Cox).

8.5.4.4 Antibody and efficacy analysis

Subjects who develop antibodies during the clinical study will be summarized in detail. The difference in efficacy between subjects with and without antibodies will be compared if necessary.

8.5.5 Interim analysis

No interim analysis is planned for this study.

8.5.6 Safety analysis

The safety analysis is based on the safety analysis set.

8.5.6.1 Adverse events

All adverse events (AE) will be coded using MedDRA and graded using CTCAE v4.03. All TEAEs, TEAEs ≥ grade 3, SAEs, drug-related TEAEs, drug-related SAEs, TEAEs resulting in the termination of study drugs, TEAEs resulting in the termination of study, and AESIs will be listed based on system organ class, preferred terms, and groups and the corresponding numbers and percentages of subjects will be summarized. In addition, the severity of TEAEs and relevance to the study drugs will also be summarized system organ class, preferred terms, and treatment groups.

8.5.6.2 Laboratory tests

All laboratory test results and changes relative to baseline will be summarized by scheduled time point and treatment group using descriptive statistics. Laboratory abnormalities will be listed.

8.5.6.3 ECG examinations

Results of ECG and changes relative to baseline will be summarized using descriptive statistics.

8.5.6.4 Vital signs, physical examinations, and other safety examinations

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

Results of physical examinations are listed by treatment groups.

8.5.6.5 Concomitant medications

Concomitant medications are non-study medications that meet one of the followings:

(1) Any drug therapy started during or after the first dose of the study treatment;

(2) Any drug therapy started before the first dose of the study treatment and continued after the first dose of the study treatment. Concomitant medications are listed by treatment groups.

9 QUALITY ASSURANCE AND QUALITY CONTROL

According to GCP principles, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems based on standard operating procedures (SOP), to ensure that the implementation of the clinical trial and the collection, documentation, and reporting of trial data is in accordance with the protocol, GCP, and applicable regulatory requirements.

To ensure that the data is reliable and processed correctly, there should be quality control for every step during the data processing.

In addition, the Clinical Quality Assurance (CQA) Department of the sponsor and/or CRO may conduct regular audits of the study process, including but not limited to auditing the study site, on-site visits, central laboratory, suppliers, clinical database, and the final clinical study report. Regulatory authorities may also conduct inspections during the trial or at any time after the trial is completed. The investigator and the research institution must allow the sponsor's representative and regulatory authorities to review source data.

9.1 Clinical Monitoring

The sponsor has authorized Wuxi Clinical Co., Ltd. to conduct clinical monitoring for this study. The clinical research associate (CRA) should follow the SOPs of Wuxi Clinical Co., Ltd. when carrying out monitoring, and has the same rights and responsibilities as the sponsor's monitor. The CRA should maintain regular communication with the investigator and the sponsor.

Before the start of the study, the associate monitor assess the qualifications of each study site, and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the study, the CRA will be responsible for confirming whether written informed consent is obtained from all subjects, and whether data documentation is accurate and complete. At the same time, the CRA will compare data entered in to the eCRF with source data, and notify the investigator of any errors or omissions. The CRA will also verify protocol compliance of the study site, as well as the dispensing and storage of investigational drugs to ensure protocol requirements are met.

The monitoring visit will be conducted in accordance with applicable statutes and regulations. Each site receives regular monitoring visits from the time the subjects are enrolled. The CRA should submit a written report to the sponsor after each monitoring visit to the study site.

9.2 Data Management/Coding

The Data Management and Biostatistics Department of Wuxi Clinical Co., Ltd will process data generated from this study in accordance with relevant SOPs.

This study will use an electronic data capture (EDC) system. Trial data will be entered into the eCRF by the investigator or authorized study personnel. Prior to launching of the study site or data entry, the investigator and authorized study personnel will receive appropriate training, and appropriate safety measures will be taken.

All data are input in Chinese. The eCRF should be completed during or soon after each visit, and should be constantly updated to ensure that it reflects the latest status of the subject. To avoid discrepancies in outcome assessments between different evaluators, ensure that baseline and all subsequent efficacy and safety assessments for the same subject are performed by the same person. The investigator must review trial data to ensure the accuracy and correctness of all data entered into the eCRF. During the study, the investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. The investigator need to sign all verified data electronically.

The CRA will review the eCRF, and evaluate its completeness and consistency. The CRA will also compare the eCRF with the source documents to ensure the consistency of critical data. Data entry, corrections, or modifications are completed by the investigator or designated staff. The CRA do not have access to data entry. The data in eCRF is submitted to the data server, and any changes to the data will be documented in the audit trail, including the reason for the change, the name of the operator, as well as the time and date of the change. The roles and permissions of study personnel responsible for data entry will be predetermined. The CRA or data manager will submit data queries in the EDC system, and study personnel shall respond to the queries. The EDC system will record the audit trail of each query, including the name of the investigator, as well as the time and date.

Unless otherwise specified, the eCRF should be considered simply as a form for data collection and not a source document. A source file is used by the investigator or hospital, relevant to the subject, and can prove the existence of the subject, inclusion criteria, and all records of participation in the study, including laboratory records, ECG results, memorandum, pharmacy dispensing records, and subject folders.

The investigators are required to maintain all source documents and to offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each subject, regardless of the duration of the subject's participation in the study. The study number and subject number in all supporting documents (such as laboratory records or hospital records) submitted along with the eCRF should be carefully verified. All personal privacy information (including the name of the subject) should be deleted or be made indecipherable in order to protect subject privacy.

The investigator could be automatically added to the eCRF with his/her user ID. The investigators verify that the record have been reviewed and that the data are accurate with an electronic signature. The electronic signature is completed with the investigator's user ID and password. The system automatically attaches the date and time of the signature. The investigator could not share the user ID and password with other personnel. If data in the eCRF need to be modified, the procedures defined by the EDC system have to be followed. All modifications and reasons for the changes are recorded in the audit trail.

Training on the EDC system will be provided to study personnel at the study site.

Adverse events, and concurrent diseases/medical history will be coded. The medical dictionary used for coding will be described in the Clinical Study Report (CSR).

9.3 Audits and Inspections

The sponsor or its representative (WuXi Clinical Co., Ltd) may conduct quality assurance audits on the study site, database, and relevant study-related documents. Also, regulatory authorities may also decide to inspect the study site, database, and relevant study-related documents at its own discretion. The aim of audits and inspections is to systematically and independently check all study-related procedures and documents to ensure that the clinical study is being carried out in accordance with requirements of the trial protocol, GCP, Declaration of Helsinki, and applicable regulations. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

10 ETHICS

10.1 Independent Ethics Committee

The sponsor and its designated personnel will prepare all documents to be submitted to the independent ethics committee (IEC) of each study site. The trial protocol, informed consent form (ICF), investigators brochure, subject recruitment material or advertisements (if applicable), as well as other documents required by regulations must be submitted to the IEC for approval. Prior to the start of the study, written approval from the IEC must be obtained and provided to the sponsor. The IEC approval must clearly state the title, number, and version of the study protocol as well as the version of other documents (e.g. ICF) and the date of approval. The investigator must notify the sponsor of the IEC's written comments concerning delays, suspension and re-approval.

The study site must follow the requirements of the IEC. IEC requirements may include submitting the revised protocol, ICF, or subject recruitment material to the IEC for approval, local regulatory requirements for safety reports, and regular reports, updates, and submitting the final report as per IEC requirements. The above documents as well as the IEC approval must be provided to the sponsor or its designated personnel.

10.2 Implementation of Ethical Principles

The study process and the acquisition of informed consent should comply with the Declaration of Helsinki, relevant GCP requirements (CPMP/ICH/135/95), and applicable statutes and regulations related to drugs and data protection in the country in which the study is conducted.

The GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. To protect the rights, safety, and healthy of subjects, this study will be carried out in accordance with GCP and applicable national regulations, as well as ethical principles outlined in the Declaration of Helsinki.

The investigator is required to follow the procedures specified in this protocol and must not change the procedures without the permission from the sponsor. Protocol deviations will be reported in accordance with the requirements of each ethics committee.

10.3 Subject Information and Informed Consent

Prior to undergoing any study procedure, the ICF should be used to explain to potential participants the potential risks and benefits of this study. The informed consent form should be in a language that is simple and be easy to understand. The ICF should state that informed consent is voluntary, emphasize the potential risks and benefits of participating in this study, and that the subject may withdraw from the study at any time. The investigator may only enroll a subject after fully explaining the details of the study, answering questions to the subject's satisfaction, giving the subject sufficient time for consideration, and obtaining written consent from the subject or his/her legal representative. All signed ICF must be retained in the investigator's documents or the subject's folder.

The investigator is responsible for explaining the contents of the ICF and obtaining the ICF signed and dated by the subject or his/her legal representative prior to starting the study. The investigator should provide the subject with a copy of the signed ICF. The investigator must document the informed consent process in the source document of the trial.

10.4 Protection of Subject Data

Information about data protection and privacy protection will be included in the ICF (or in some cases, in a separate document).

Study personnel must ensure that the privacy of clinical trial subjects are protected. In all documents submitted to the sponsor, the clinical trial subjects must only be identified with subject number and not with the full name.

Additional precautions should be taken to ensure the confidentiality of the documents and to prevent the identification of subjects based on genetic data. However, under special circumstances, some personnel may be permitted to see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, designated physician, or investigator will have access to the subject identification code and the subject's genetic data. In addition, regulatory agencies may request access to relevant documents.

11 STUDY MANAGEMENT

11.1 Organizational Structure

Refer to Table 3 for relevant collaborating parties.

Table 22. Organizational structure

Sponsor	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China Telephone: (+86) 0512-69566088
Contract research organization	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000
Data management and biostatistics	WuXi Clinical Development Services (Shanghai) Co., Ltd. 19F, Building A, SOHO Fuxing Plaza, 388 Madang Road, Shanghai Tel: (+86) 21-23158000

11.1.1 Independent review committee

Central imaging evaluation will be performed by Parexel China Co., Ltd. The CT/MRI images of each subject will be evaluated using RECIST v1.1.

11.2 Archiving of Study Documents

Clinical trial documents (protocol and amendments, completed eCRFs, signed ICFs, etc.) must be retained and managed as per GCP requirements. The study site must retain these documents for 5 years after the completion of the study. The sponsor should retain clinical trial data for 5 years after the investigational drug is approved for marketing.

Study documents should be retained properly for future access or data traceability. Safety and environmental risks should be considered when retaining documents.

The documents associated with the study may only be destroyed with the written consent of the sponsor and the investigator. Study documents may be transferred to other parties that comply with or other locations that meet retention requirements only after the sponsor is notified and written consent thereof is obtained.

11.3 Access to Source Data/Documents

Source data refers to source records of subject data obtained from a clinical study. These source records are source documents, which include but are not limited to medical records (hospital records, nursing records, pharmacy dispensing records, etc.), electronic data, screening logs, laboratory test results, as well as medical device test results (ECG, CT/MRI, etc.). All source documents associated with the trial are retained by the study site and the investigator. The original ICFs will be retained according to standard practices developed by the clinical trial institution.

The investigator will prepare sufficient and accurate source documents for each randomized subject in order to document all examination results and other relevant data, and retain these documents properly.

During the study, the CRA will conduct on-site visits to verify protocol compliance, EDC data entry, documentation of subjects' medical history, drug inventory, and whether the study is carried out in accordance with applicable regulations. In addition, regulatory authorities, IRB, IEC, and/or the quality assurance department of the sponsor will verify source data and/or conduct on-site audits or inspections. The investigator should allow direct access to documents associated with the study, including medical records of subjects.

11.4 Protocol Revisions

The sponsor and the investigator must both agree on any appropriate protocol revisions during the course of the study. The sponsor shall ensure that the protocol revision is submitted to the regulatory authority in a timely manner.

All protocol revisions must be submitted to the IEC, and if needed, to regulatory authorities for approval. Revisions may only be implemented after approval from the IEC and regulatory authorities (if needed) is obtained (except for changes to eliminate immediate risks to subjects).

11.5 Investigator's Responsibilities

The investigator will conduct this study in accordance with the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP, and applicable regulations. Details of the investigator's responsibilities are list in Chapter 5 (Investigator's Responsibilities) of the Chinese GCP (NMPA order No. 3).

11.6 Study Termination

The study may be terminated after a discussion between relevant parties if the investigator or the sponsor becomes aware of circumstances or events that could jeopardize the subjects if the study is continued. The sponsor may also decide to terminate the study even without such findings.

Reasons for study termination include but are not limited to:

- Unexpected, serious, or unacceptable risks to enrolled subjects
- Slow recruitment
- The sponsor decides to suspend or discontinue the development of the drug

11.7 Publishing Policies

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish study results. The investigator shall not publish any data relevant to this study (posters, abstracts, papers, etc.) without prior communication with the sponsor. Information on the publishing policies of the sponsor and investigator will be described in the clinical trial agreement.

11.8 Finance and Insurance

The sponsor will purchase insurance for subjects participating in the study in accordance with local regulations, and bear the cost of treatment and corresponding financial compensation for the subjects who suffer injury during the study due to the investigational drug or the study process. Insurance related terms shall be saved in the study folder.

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13 APPENDIX

13.1 Appendix I

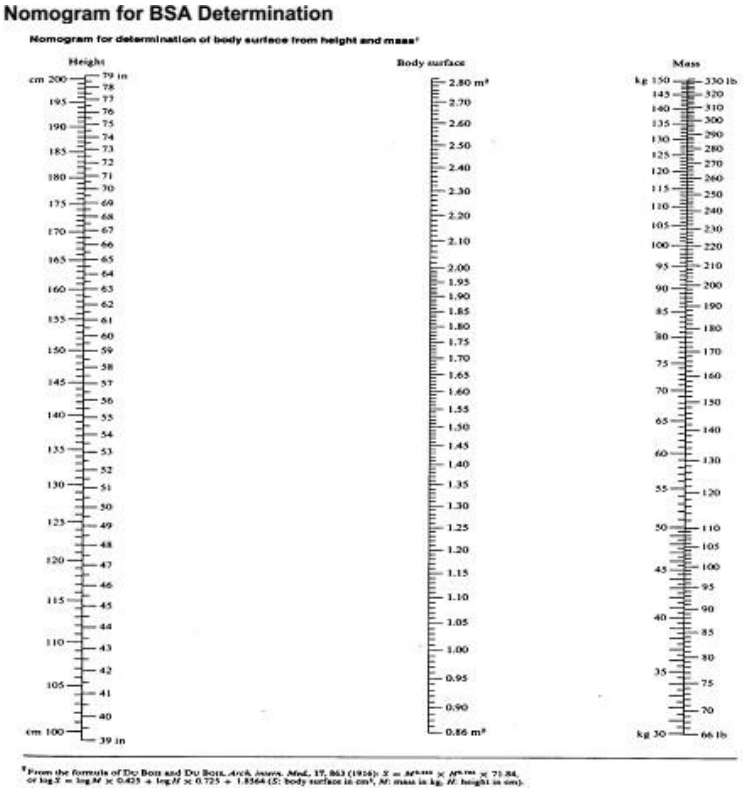
Eastern Cooperative Oncology Group (ECOG) Performance Status Score

Score	Performance Status
0	Fully active, and able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activities but able to move around easily and carry out work of a light or sedentary nature, e.g. light house work or office work
2	Capable of moving around easily and self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or wheelchair more than 50% of waking hours
4	Bedridden and incapable of self-care
5	Death

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

13.2 Appendix II

Calculation of body surface area



Creatinine Clearance (Cockroft-Gault Equation)

Ccr (mL/min) = [(140 - age) x weight (kg)]/[72 x Scr (mg/dL)]

Female subjects: results × 0.85

1 mg/dL = 88.41 μmol/L

Carboplatin Dose (Calvert Equation)

Carboplatin dose (mg) = target AUC (mg/mL/min) × [creatinine clearance rate (mL/min) + 25]

13.3 APPENDIX 3

RECIST v1.1

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or not measurable as follows:

1.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be documented as not measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Not measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with a short axis ≥10 and <15 mm) as well as truly not measurable lesions. Lesions considered truly not measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis involving the skin or lungs, abdominal masses/ abdominal organomegaly identified by physical exam but not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding measurable bone lesions, cystic lesions, and lesions with prior locoregional treatment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (such as CT or MRI) can be considered as measurable lesions if the soft tissue components meet the definition of measurability described above.
- Blastic bone lesions are not measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor not measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these noncystic lesions are preferred for selection as target lesions.

Lesions with prior locoregional treatment:

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

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be documented with metric symbols. Calipers should be used if clinical assessments are required. All baseline evaluations should be performed as close as possible to the beginning of the treatment but never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and its diameter is ≥10 mm as assessed using calipers (e.g. skin nodules). For skin lesions, documentation by color photography including a plotting scale to estimate the size of the lesion is recommended. As noted above, when lesions can be evaluated by both clinical examination and imaging evaluation, the latter should be undertaken since it is more objective and may also

be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they have clear boundaries and are surrounded by aerated lung tissues.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have a slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound should not be used for measuring lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is recommended. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy: The utilization of these techniques is not recommended for objective tumor evaluation. However, they can be used to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper limit of normal, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into the protocol on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases if required by the protocol (for example, residual lesions in tumor types such as seminoma, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), cytological confirmation of the neoplastic origin of any effusion that appears or worsens during

treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. TUMOR RESPONSE EVALUATION

2.1 Assessment of Overall Tumor Burden and Measurable Disease

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

2.2 Baseline Documentation of "Target" and "Non-Target" Lesions

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those with reproducible repeated measurements. It may be the case that, the largest lesion does not have reproducible measurements, in which circumstance the next largest lesion with reproducible measurements should be selected.

Lymph nodes merit special mention since their normal anatomical structures may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must have a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is invaded by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant measurable node. In this example, 20 mm should be reported as the node measurement. All other pathological nodes (those with a short axis ≥ 10 mm but < 15 mm) should be considered non-

target lesions. Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions; short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be recorded as "present", "absent", or in rare cases "unequivocal progression". In addition, it is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response Criteria

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduced short axis of <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions vs. the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions vs. the smallest sum during the study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also have an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum of diameters during the study as reference.

2.3.2 Special notes on the assessment of lymph nodes which are target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as during the baseline examination), even if the nodes regress to below 10 mm at the time of the study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must have a

short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that are "too small to measure". During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurements of these lesions are potentially non-reproducible, therefore providing this default value will prevent false responses or progressions caused by measurement errors. To reiterate, however, if the radiologist is able to provide an actual measurement, that value should be recorded, even if it is below 5 mm.

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

2.3.3 Evaluation of non-target lesions

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

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

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

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

2.3.4 Special notes on the assessment of progression of non-target lesions

The concept of progression of non-target disease requires additional explanation as follows: *When the patient also has measurable lesions*. In this setting, to achieve 'unequivocal progression' on the basis of the non-target lesion, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR of the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A minimal increase in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only lesions that are not measurable. This circumstance arises in some phase III trials when the presence of measurable lesions is not a criterion for study enrollment. The same general concepts apply here as well. However, in this instance there are no measurable lesions to factor into the interpretation of an increase in non-measurable lesion burden. Because worsening in non-target lesion cannot be easily quantified (by definition: if all lesions are truly not measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall lesion burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase of diameter in a measurable lesion). Examples include an increase in pleural effusion from "trace" to "large amount", an increase in lymphangitic lesion from localized to widespread, or a description in the protocol such as "sufficient to require a change in therapy". If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to diseases that are not measurable, the very nature of these diseases makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on the detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumors (for example, some new bone lesions which may be simply healed or flare of pre-existing lesions). This is particularly

important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported by a CT scan as a "new" cystic lesion, while it is actually not.

A lesion identified during a follow-up in an anatomical location that is not discovered during the baseline scan is considered a new lesion and will indicate disease progression. For example, a patient with a visceral disease at baseline has a brain CT or MRI which reveals metastases. The patient's brain metastases are considered evidence of PD even if he/she does not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents a truly new lesion. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional studies, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" lesions). New lesions on the basis of FDG-PET imaging can be identified as follows:

a. A negative FDG-PET at baseline and a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
If the positive FDG-PET at follow-up corresponds to a new lesion site confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new lesion site on CT, additional follow-up CT scans are needed to determine if there is truly progression at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing lesion site on CT that is not progressing according to the anatomic images, this is not PD.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy, so the study protocol should clearly state if post-treatment assessments are to be considered when determining best overall response. The study protocol must specify how any new therapy introduced before progression will affect best response designation. Assignment of best overall response for the patient will depend on the findings of both target and non-target lesions and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the

protocol requirements, confirmatory measurement may also be required. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to determine which one is the "best overall response".

2.4.1 Time point response

It is assumed that at each time point specified by the study protocol, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2 Missing assessments and non-evaluable targets

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

2.4.3 Best overall response: all time points

The best response is determined once all the data for the patient is obtained.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, the best overall response of a patient who has SD at the first assessment, PR at the second, and PD at the last is PR). When SD is believed to be best response, it must also meet the minimum time from baseline specified by the protocol. If the minimum time is not met, otherwise SD is the best time point response, the patient's best response depends on subsequent assessments. For example, if a patient has SD at the first assessment, PD at the second and does not meet the minimum duration for SD, his/her best response is PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

2.4.4 Special notes on response assessment

When nodal lesions are included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even if the nodes are normal in size in order not to overstate progression should it be based on the increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the case report form (CRF).

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must explain how missing data/assessments will be addressed in the determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response. Instead, it is a reason for stopping the study treatment. The objective response status of this type of patients is to be determined by evaluation of target and non-target lesions as shown in Table 1–3.

Conditions that define "early progression, early death, and non-evaluability" are study specific and should be clearly described in each study protocol (depending on treatment duration and treatment periodicity).

In some circumstances it may be difficult to distinguish a residual lesion from normal tissues. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (by fine needle aspirate/biopsy) before assigning a status of complete response.

Like a biopsy, FDG-PET may also be used to upgrade a response to a CR in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be pre-defined in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Table 1. Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not all were evaluated	No	PR
SD	Non-PD or Not all were evaluated	No	SD
Not all were evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

Table 2. Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all were evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = not evaluable.

a "Non-CR/non-PD" is preferred over "stable disease" for non-target disease, since SD is increasingly used as an endpoint for assessment of efficacy in some trials, thus assigning this category in the absence of measurable lesions is not advised.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression is suspected.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided that the minimum duration for SD is met, otherwise PD
CR	PD	SD provided that the minimum duration for SD is met, otherwise PD
CR	NE	SD provided that the minimum duration for SD is met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided that the minimum duration for SD is met, otherwise PD
PR	NE	SD provided that the minimum duration for SD is met, otherwise NE
NE	NE	NE

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

a If CR is truly achieved at the first time point, then any lesions seen at a subsequent time point, even those meeting PR criteria relative to baseline, make the disease PD at that time point (since lesions must have reappeared after CR). Best response would depend on whether the minimum duration for SD is met. However, sometimes CR may be claimed and subsequent scans suggest small lesions are likely still present, while in fact the patient have PR instead of CR at the first time point. Under these circumstances, CR should be changed to PR and the best response is PR.

2.5 Frequency of Tumor Re-Evaluation

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

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

2.6 Confirmation of Measurements/Duration of Response

2.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement errors. This will also permit appropriate interpretation of results in the context of historical data. Response confirmation has been traditionally required in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements after study entry must have met the minimum interval for SD (generally not shorter than 6–8 weeks) defined in the study protocol at least once.

2.6.2 Duration of overall response

The duration of overall response is measured from the time CR/PR measurement criteria are first met CR/PR (whichever is first documented) until the date when recurrent or progressive disease is objectively documented for the first time (using the shortest time to progressive disease documented during the study as reference).

The duration of overall complete response is measured from the time CR measurement criteria are first met until the date when recurrent disease is objectively documented for the first time.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from the date of randomization) until the criteria for progression are met, using the smallest sum during the study as reference (if the baseline sum is the smallest, then it is used as the reference for the calculation of PD).

The clinical relevance of the duration of stable disease varies with different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for the determination of stable disease.

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

14 INVESTIGATOR SIGNATURE PAGE

Protocol Title: A randomized, double-blind, multi-center phase III study comparing the efficacy and safety of IBI305 plus paclitaxel/carboplatin vs. bevacizumab plus paclitaxel/carboplatin in treatment-naive patients with advanced or relapsed non-squamous NSCLC.

Protocol No.: CIBI305A301

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

Instructions for the Investigator: Please sign and date this signature page, type the investigator's name and job title, as well as the name of the study site, and return this document to Innovent Biologics (Suzhou) Co., Ltd.

I have read the entire contents of this study protocol and shall perform the study as required:

Investigator's signature: _____ Date: _____

Name (in Print): _____

Job Title: _____

Name and Address of Study Site: _____

_____

_____